Long Term Prognosis of Chronic Heart Failure
—— Reduced vs Preserved Left Ventricular Ejection Fraction ——

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**Background**

Left ventricle diastolic dysfunction is attracting increasing attention of one of the etiologies of chronic heart failure (CHF).

**Methods and Results**

The study sample included 560 patients with CHF who were hospitalized during the 5-year period. They were classified into 2 groups according to the left ventricular ejection fraction (LVEF): reduced group (LVEF<50%, n=431); or preserved group (LVEF≥50%, n=129). The degree of cardiac symptoms did not differ between the 2 groups; however, no difference was found between the 2 groups in the mortality rate (P=0.898), and readmission rates (P=0.674). The results of a multivariate analysis using a Cox proportional hazards model to identify predictors of the prognosis of heart failure revealed no difference in prognosis according to the presence/absence of decreased LVEF, whereas renal dysfunction and anemia were identified as significant prognostic determinants. Also, in the reduced group, the administration of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARB), β-blockers reduced mortality. In the preserved group, ACE-I and/or ARB administration reduced mortality, whereas β-blockers did not.

**Conclusion**

In the present study, the likelihood of LVEF influencing prognosis was considered to be low, with the contribution of non-cardiac factors such as renal function and anemia concluded to be greater. (Circ J 2009; 73: 92–99)

**Key Words:** Chronic heart failure; Ejection fraction; Preserved LV function; Prognosis; Reduced LV function

Chronic heart failure (CHF) is a syndrome with a poor prognosis that can be caused by various cardiac disorders. The number of patients with CHF has been increasing each year in parallel with the aging of society, and its treatment and management have become a social issue. Moreover, left ventricular (LV) diastolic dysfunction has gained increasing attention as a cause of heart failure. In cases of diastolic dysfunction, a decreased LV ejection fraction (LVEF) is characteristically not observed whereas heart failure symptoms such as lung congestion do occur. Our study was undertaken to clarify the clinical characteristics of cases of heart failure with preserved LV function and to determine their prognosis.

**Methods**

**Study Sample**

Patients with CHF who were hospitalized at the Division of Cardiology, Fujita Health University, during the 5-year period from 1 January 2000 to 31 December 2004, were selected as the subjects of the present study. Of 734 consecutive cases, 560 cases were selected after excluding 156 cases of valvular disease and 18 cases of pulmonary embolism or cor pulmonale, to investigate their clinical findings and prognosis retrospectively. Furthermore, to determine prognosis, a 3-year follow-up study was undertaken, in which the patients, or their families, who changed hospitals or stopped coming to our hospital, were contacted with permission by telephone or letter to determine their survival status.

The LVEF was measured at the time of hospitalization with B-mode echocardiography using the modified Simpson method. The subjects were classified into 2 groups: cases with 50% LVEF or higher were classified as the preserved group; and cases with less than 50% LVEF were classified as the reduced group, for comparison and study purposes. In addition, a multivariate analysis using a Cox’s proportional hazard regression model was performed to determine the influence on prognosis of each of the drugs used after admission. Furthermore, heart failure was diagnosed in all cases by cardiologists based on the Framingham diagnostic criteria for heart failure and treated by them.

A rapid deterioration of CHF was defined as a case with heart failure symptoms of II or higher in the New York Heart Association (NYHA) classification, in which some type of underlying heart disorder that had existed for a certain period of time had deteriorated due to the discontinuation of medication or infection, thus resulting in a state in which hospital treatment had become necessary.

Cases with acute heart failure associated with conditions such as acute coronary syndrome (ACS), acute myocarditis and infective endomyocarditis were excluded from the present study.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or previ-
Table 1 Comparison of Clinical Characteristics Between Patients With Reduced and Preserved LVEF

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Reduced group</th>
<th>Preserved group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>431 (77.0%)</td>
<td>129 (23.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>32.9</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>67.7±14.3</td>
<td>70.2±13.8</td>
<td>0.071</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>885±343</td>
<td>882±347</td>
<td>0.932</td>
</tr>
<tr>
<td>Total death (%)</td>
<td>29.5</td>
<td>30.2</td>
<td>0.898</td>
</tr>
<tr>
<td>Rehospitalization (%)</td>
<td>55.2</td>
<td>53.9</td>
<td>0.674</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM (%)</td>
<td>43.2</td>
<td>36.4</td>
<td>0.174</td>
</tr>
<tr>
<td>HT (%)</td>
<td>58.9</td>
<td>62.0</td>
<td>0.531</td>
</tr>
<tr>
<td>HL (%)</td>
<td>35.0</td>
<td>27.9</td>
<td>0.132</td>
</tr>
<tr>
<td>eGFR &lt;60 ml·min⁻¹·1.73 m⁻² (%)</td>
<td>53.5</td>
<td>62.2</td>
<td>0.077</td>
</tr>
<tr>
<td>Hb &lt;12.0 g/dl (%)</td>
<td>40.8</td>
<td>54.3</td>
<td>0.007</td>
</tr>
<tr>
<td>AF (%)</td>
<td>27.8</td>
<td>34.9</td>
<td>0.124</td>
</tr>
<tr>
<td>VT and/or VF (%)</td>
<td>15.1</td>
<td>7.8</td>
<td>0.032</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Killip</td>
<td>3.5±0.6</td>
<td>3.4±0.6</td>
<td>0.107</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>138±34</td>
<td>148±32</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±21</td>
<td>72±19</td>
<td>0.015</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>101±25</td>
<td>90±26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>61.1±6.3</td>
<td>60.9±7.4</td>
<td>0.729</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>26.8±15.7</td>
<td>27.9±18.7</td>
<td>0.475</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73 m⁻²)</td>
<td>54.6±36.8</td>
<td>54.1±33.3</td>
<td>0.819</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.4±2.4</td>
<td>11.6±2.4</td>
<td>0.0005</td>
</tr>
<tr>
<td>BNP·hospitalization (pg/ml)</td>
<td>1.096±1.025</td>
<td>677±727</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP·discharge (pg/ml)</td>
<td>328±506</td>
<td>367±830</td>
<td>0.574</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>31.0±8.9</td>
<td>57.9±7.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>55.1±10.0</td>
<td>65.3±9.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>46.9±10.2</td>
<td>32.5±9.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>10.6±3.0</td>
<td>12.3±3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>11.5±2.7</td>
<td>12.6±2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5±1.0</td>
<td>1.4±0.9</td>
<td>0.643</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>15±57</td>
<td>190±72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>185±68</td>
<td>168±77</td>
<td>0.003</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction; DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CTR, cardiothoracic ratio; BUN, blood urea nitrogen; Cr, creatinine; LVDD, left ventricle end-diastolic diameter; LVDs, left ventricle end-systolic diameter; IVS, intraventricular septal thickness; PW, posterior wall; E/A, early rapid filling/atrial contraction; DT, deceleration time; LV, left ventricular.

Results

Clinical Findings

Number of Cases, Sex Ratio, and Average Age of Each Group Of the 560 cases, the reduced group comprised 431 cases (77.0%) [females: 142 cases (32.9%), 67.7±14.3 years old], and the preserved group 129 cases (23.0%) [females: 67 cases (51.9%), 70.2±13.8 years old] (Table 1). In the preserved group, the proportion of females was higher than in the reduced group (P<0.0001). Moreover, the average age showed no significant difference between the 2 groups, although the age of the preserved group tended to be higher than that of the reduced group (P=0.071).

Basal Heart Disease Regarding the causes of heart failure, the frequency of ischemic heart disease was higher in the reduced group (58.9%: P<0.0001), while the frequency of hypertensive heart disease was higher in the preserved group (28.7%: P<0.0001) (Fig 1). Furthermore, in the preserved group, no case of dilated cardiomyopathy was observed.

Comorbidities In both groups, hypertension was the most frequently observed comorbidity. The frequencies of diabetes mellitus, hypertension, hyperlipidemia, renal
dysfunction (defined as glomerular filtration rate (GFR) <60 ml·min⁻¹·1.73 m⁻²) and atrial fibrillation did not differ significantly between the 2 groups, while ventricular tachycardia and ventricular fibrillation showed higher frequencies in the reduced group (P=0.032). Significantly more patients in the preserved group had anemia with Hb level less than 12.0 g/dl (P=0.007) (Table 1).

Clinical Findings at the Time of Hospitalization The severity of heart failure symptoms at the time of hospitalization according to the NYHA classification and Killip classification showed no significant difference between the 2 groups (P=0.032). Significantly more patients in the preserved group had anemia with Hb level less than 12.0 g/dl (P=0.007) (Table 1).

Comparison of Treatment

The treatment in the acute phase and drugs at administered discharge are shown in Table 2. In the acute phase, carperitide was most frequently administered to both groups, but at a higher rate in the reduced group (P=0.0002). Catecholamine was administered at a high rate in the reduced group (P=0.028). PDE-III inhibitors and IABP were not used.
in any case of the preserved group. No statistically significant difference was observed, but calcium channel blocker was administered more frequently in the acute phase in the preserved group.

With regard to internal drugs at discharge, loop diuretics were the most frequently used in both groups, but were used more in the reduced group (P=0.016). Angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARB) were also used frequently, with no significant difference observed between the 2 groups. Spirotonolactone was administered more frequently in the reduced group (P=0.0002). Beta-blockers were used in 69.0% of the reduced group, in contrast to 45.2% of the preserved group (P<0.0001). Pimobendan and amiodarone were used frequently in the reduced group.

**Prognosis**

In Fig 2a, the cumulative survival rates of the 2 groups are shown using a Kaplan–Meier curve, with no significant difference observed between the 2 groups (P=0.898). In the 3-year follow-up survey, the mean observation period in the reduced and preserved groups was 885±343 days and 882±347 days, respectively, with this difference not significant (P=0.932). Total mortality during the observation period showed no significant difference between the 2 groups (reduced group: 29.5% vs preserved group: 30.2%). Heart failure was the most frequent cause of death in both groups, but no significant difference was observed between the 2 groups.

In Fig 2b, the rehospitalization rates due to the occurrence of a cardiac event after hospital discharge are shown using a Kaplan–Meier curve, with no significant difference observed between the 2 groups (P=0.674). The rate of occurrence of cardiac events was 55.2% in the reduced group and 53.9% in the preserved group, being high in both.

The results of a multivariate analysis using Cox’s proportional hazards model to identify predictors of the prognosis of heart failure revealed no difference in prognosis according to the presence/absence of decreased left ventricular ejection fraction (LVEF), whereas renal dysfunction and anemia were identified as significant prognostic determinants (Fig 3).

The influence on mortality of the administered drugs in...
the 2 groups is shown in Table3. In the reduced group, similar to previously reported findings, the administration of ACE-I and/or ARB, and β-blockers reduced mortality. In the preserved group, ACE-I and/or ARB administration reduced mortality, whereas β-blockers did not (Table3).

Table4 lists the causes of death in the 2 groups. Heart failure was the most common cause in both groups, with no significant difference seen in the proportions of causes of death between the 2.

### Discussion

It was assumed in the past that a decreased LVEF was a prerequisite for the clinical diagnosis of heart failure, but in recent years, it has been reported that heart failure with preserved LVEF also exists.8–13 In addition, it has been assumed that LV diastolic dysfunction is the cause of heart failure when the LVEF is maintained, and so such cases have been used for studies on diastolic dysfunction. However, studies...
on CHF with preserved LVEF have been mostly conducted in the United States and Europe, and there have only been a few such reports from Japan. Moreover, it was thought that the present study would be useful because few studies have been conducted at a single center and on a large number of cases.

In most large-scale clinical studies, elderly patients and those with severe renal impairment have been excluded, with only a limited proportion of the total cases being investigated. In this way, the type of cases focused on is likely to differ considerably from those encountered in the actual clinical setting.

However, since the present study was conducted at a single institution, and all diagnoses and treatments were performed by cardiologists, we consider that the case selection well reflects the current clinical reality.

The criteria for the preserved group vary according to individual studies. The cases are usually divided according to an LVEF of 50% or higher, or 40% or more in most articles, but in the present study, the preserved group was defined as cases with 50% LVEF or higher so as to exclude cases with even a slight contractile disorder.

The best method for assessing left ventricle diastolic dysfunction is to insert a pressure manometer into the left ventricle and directly measure the end-diastolic pressure. However, this method is invasive and cannot be conducted in all acute cases. Noninvasive indices currently used to assess diastolic dysfunction include E/A ratio measured from the LV inflow velocity waveform by Doppler echocardiography, deceleration time of E wave and pulmonary venous blood flow waveform. In the present study, these 2 indices were used as indices of LV diastolic function.

Clinical Findings. The frequency of diastolic dysfunction and long-term prognosis of heart failure vary in individual reports. The reasons for this include differences in the methods of selecting subjects. Many studies exclude only severe valvular disease but include moderate and mild valvular disease. However, we assumed that it would be genuinely difficult to assess LV diastolic dysfunction if affected by long-term valvular disease in the subjects. Furthermore, we excluded all cases of valvular disease and pulmonary vascular disease from the present study.

Consequently, the proportion of the preserved group was 23.0%, being roughly equal to the findings of previous reports, namely 13–51% (30% on average). Klapholz et al reported that cases of heart failure with preserved LVEF were observed more frequently among older females, with the frequency of hypertensive heart failure being high. In the reports of Tsutsui et al and the Sado Heart Failure Study, the proportion of women was 51% and 42%, respectively, and the mean age was 69 years. The proportion of cases with hypertension was high at 66% and 46%, respectively (Table 5).

In the present study, the frequency among females was 51.9%, and the sex ratio was nearly 1:1, but it tended to be higher among females in comparison to the reduced group. The average age was higher in the preserved group, but no significant difference was observed (P=0.071). All of the cases of valvular disease were excluded from the present study, so it is assumed that many cases of valvular disease in older females with a preserved LVEF were excluded. The frequency of hypertension was also significantly higher in the preserved group in this study, which is consistent with the reports of Klapholz et al, Tsutsui et al and the Sado Heart Failure Study.

Treatment. The influence of administered drugs at discharge, in particular ACE-I and/or ARB and β-blockers, on mortality is noted in Table 3.

In both the reports of Tsutsui et al. and the Sado Heart Failure Study, the frequency of administration of ACE-I, ARB, β-blockers and diuretics was low as compared with the present study. The rate of calcium channel blocker use was high (Table 5). These differences in drug usage are attributable to differences in the year in which the respective studies were conducted. The influence on mortality of the administered drugs in the 2 groups is shown in Table 3.

In the reduced group, consistent with previous reports, ACE-I and/or ARB and β-blocker administration had a favorable impact on mortality. In contrast, in the preserved group, only ACE-I and/or ARB administration reduced mortality, whereas β-blockers did not. The OPTIMIZE-HF Registry is a report on the short period from 60 to 90 days after discharge, and although differences in the frequency of drug use were present, in the preserved group neither ACE-I/ARB nor β-blocker administration was found to favorably affect mortality or mortality and rehospitalization.

The ACC/AHA guidelines also specify that a β-blocker should be administered in cases with decreased LVEF, explaining its frequent use in the reduced group. Cases with a preserved LVEF mostly had improvement of heart failure symptoms with the administration of a diuretic only, and so it is believed that some patients were discharged from hospital before the introduction of a β-blocker. In Japan, an extensive clinical trial (J-DHF) regarding the benefit of β-blockers for LV diastolic dysfunction is currently in progress.

Prognosis. The cumulative survival rate considering all cases of mortality showed no significant difference between the 2 groups (P=0.898). Some studies of prognosis have been based on the presence or absence of a decreased LVEF, but there are also reports in which either almost no difference was observed or the prognosis of the preserved group was slightly better. In studies in which the results differed from ours, differences in the selection of subjects and in the criteria for the definition of LVEF may have played a role. In the present study, all cases with valvular disease were excluded from the subject group. This is thought to have been one factor accounting for the difference in prognosis noted in the late phase.

In these studies, the subjects were classified into 2 groups according to LVEF, but there is a high probability that a difference would be observed between the cases with an LVEF of 50% similar to the present study and cases with an LVEF of 40%. Nevertheless, no studies have identified a clear difference in the prognosis of such groups, and so the reliance in the past on LVEF as the best index for classifying the severity of heart failure cannot be considered suitable for predicting prognosis.

In any case, since no study has detected a clear difference in prognosis between 2 such groups, LVEF, which had hitherto been deemed the most appropriate index to express the degree of heart failure, can be concluded as not being useful in predicting prognosis, whereas renal dysfunction and anemia were demonstrated to be major determinants.

Reports that the presence or absence of decreased LVEF results in a difference in prognosis are occasionally apparent. In such reports, drugs such as β-blockers or spironolactone, which are reported to improve long-term prognosis, were actively and frequently used in cases with preserved LVEF. In the present study, the frequency of use,
especially of these drugs, was low in the preserved group. Evidence of treatment for heart failure with a preserved LVEF has not yet been established, but it is reasonable to assume that the prognosis might differ if the frequency of use of these drugs were also high in the preserved group.

In the present study, in parallel with the lack of any differences in the cumulative survival rate or re-hospitalization rate, no differences were noted in the causes of death between the 2 groups. The majority of heart failure cases are elderly and they have various comorbidities as well. In addition to cardiac deaths, many patients die of conditions such as pneumonia and malignancies. In the preserved group, the frequency of cardiac deaths was approximately 70%, being similar to that of the reduced group. Comparing the causes of death in the preserved group in the report of Tsutsui et al, cardiac death accounted for 74%, similar to the high rate noted in the present study, whereas in the Sado Heart Failure Study, cardiac death accounted for only 24% (Table 5). This marked discrepancy is likely due to differences in the proportions of patients with decompensated and stable heart failure included in the respective studies.

Although no evidence has yet established the efficacy of such interventions in heart failure with preserved LVEF, we speculate that if the use of such agents was increased in the preserved group, a difference in prognosis might become apparent.

Study Limitations

Limitations of the present study include the fact that it was conducted at a single institution and was restricted to admitted patients, which may have introduced some bias. Heart failure affects the elderly most frequently, and many of these cases also suffer from diverse non-cardiac comorbidities, which are difficult to investigate in detail. Moreover, although cardiologists diagnosed and treated all cases, since only a single institution was involved in the present study the therapeutic strategies selected may have been biased. Also, since the present study focused on cases with acute exacerbation of heart failure, the results obtained may not be reflective of the entire heart failure population.

Conclusion

A decreased LVEF is assumed to be important as an index for predicting the prognosis of heart failure, but no difference in prognosis was observed between the 2 groups according to the presence or absence of decreased LVEF. Many reports from Japan and other countries have similarly detected any differences between these 2 groups.

In the present study, the likelihood of LVEF influencing prognosis was considered to be low, with the contribution of non-cardiac factors, such as renal function and anemia, concluded to be greater.

References


