Inhibition of the Renin-Angiotensin System Prevents Re-Hospitalization of Heart Failure Patients With Preserved Ejection Fraction

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Background  Approximately half of the patients with chronic heart failure (CHF) show preserved systolic function, but less is known about CHF with preserved ejection fraction (EF).

Methods and Results  In a retrospective analysis, patients with CHF who had been admitted to hospital were divided into 2 groups: reduced EF (EF ≤ 40%) and preserved EF (EF > 40%). The rate of preserved EF was 53.5% and those with preserved EF were older, more likely to be female, and had a lower serum hemoglobin concentration than those in the reduced EF group. In the multivariate analysis, only older age was independently related to CHF with preserved EF. CHF patients with preserved EF who were successfully discharged from hospital and then followed at the outpatient clinic were reviewed and re-hospitalization for CHF was examined by Cox hazard univariate analysis, which showed that prior CHF hospitalization, absence of hypertension, and non-use of angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin-receptor blocker (ARB) were predictors. In the multivariate analysis, non-use of ACEI/ARB was the sole predictor for CHF re-hospitalization.

Conclusions  CHF patients with preserved EF are older than those with reduced EF and use of ACEI/ARB prevents their re-hospitalization. (Circ J 2008; 72: 2004–2008)

Key Words: Angiotensin-converting enzyme inhibitor; Angiotensin-receptor blocker; Diastolic function

Approximately half of the patients with chronic heart failure (CHF) show preserved systolic function, and in this type of CHF, diastolic dysfunction is considered to play a dominant role in the pathogenesis.

Blockade of the renin–angiotensin system (RAS) and use of β-blockers have been shown to significantly improve prognosis of the patients with CHF, but almost all the studies, including large cohort studies, examined systolic dysfunction, except for the CHARM-preserved and PEP-CHF studies. The therapeutic approach to patients with preserved ejection fraction (EF) has not been established, so treatment is usually for the underlying heart disease (eg, hypertension, tachycardia, and ischemia).

The purpose of the present study was to investigate the characteristics of patients with CHF with preserved EF, and to evaluate the pharmacological therapy for such patients.

Methods

The study protocol was approved by the Ethics Committee of The Jikei University School of Medicine (20-039 [5229]).

Patients with CHF who had been admitted to hospital from January 2003 through December 2004 were retrospectively examined. CHF was diagnosed by 2 or more cardiologists using the Framingham criteria. CHF complicated with the acute phase of myocardial infarction was excluded. The population of the patients overlapped as previously reported6 Patients who did not undergo echocardiography (UCG) within 24 h after admission were excluded. With these selection criteria, 144 patients were enrolled and divided in 2 groups: those with EF > 40% (preserved EF) and those with EF ≤ 40% (reduced EF).

Estimated glomerular filtration rate was calculated using the MDRD equation7 coefficient modified to Japanese: estimated GFR = 0.741 × 175 × Cr–1.154 × Age−0.203 (ml·min−1·1.73 m−2). If female, the equation was multiplied by a correction factor of 0.742. Age, sex, hypertension, diabetes mellitus (DM), dyslipidemia, coronary artery disease, valvular heart disease, atrial fibrillation, serum hemoglobin, and New York Heart Association category were compared between groups. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or previous history. The diagnostic criteria of DM and dyslipidemia were described previously.8

In the preserved EF group, patients who were successfully discharged and followed up at the outpatient clinic were reviewed and CHF re-hospitalization was examined. In this analysis, patients who were on dialysis or started on dialysis, and who underwent heart surgery during the follow-up period were also excluded. Thus, 58 patients were included. The follow-up period was between 6 and 1,433 days (average, 451 days; median 336 days). The population of this analysis was part of that previously reported6

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(Received July 1, 2008; revised manuscript received July 30, 2008; accepted August 3, 2008; released online October 29, 2008)
Continuous variables are expressed as means±SE and compared with unpaired t-test. Categorical variables are expressed as percentages and compared with chi-square test. The cumulative re-hospitalization-free curve was estimated according to the Kaplan-Meier method. Univariate analysis or multivariate analysis for the predictor of re-hospitalization was performed using the Cox proportional hazard test. Statistical significance was verified at p<0.05.

Table 1  Characteristics of the CHF Patients With Preserved EF or Reduced EF

<table>
<thead>
<tr>
<th></th>
<th>Preserved EF</th>
<th>Reduced EF</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>77 (53.5)</td>
<td>67 (46.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>56.2±1.2</td>
<td>29.3±1.0</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>77.0±1.2</td>
<td>66.1±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>59.7</td>
<td>80.3</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>61.0</td>
<td>53.7</td>
<td>NS</td>
</tr>
<tr>
<td>DM (%)</td>
<td>32.5</td>
<td>37.2</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>28.6</td>
<td>38.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>29.9</td>
<td>37.3</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>27.3</td>
<td>13.4</td>
<td>NS</td>
</tr>
<tr>
<td>AF (%)</td>
<td>44.1</td>
<td>41.8</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA ≥III (%)</td>
<td>66.2</td>
<td>68.7</td>
<td>NS</td>
</tr>
<tr>
<td>Prior hospitalization with CHF (%)</td>
<td>28.4</td>
<td>32.3</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated GFR (ml·min⁻¹·1.73 m⁻²)</td>
<td>53.3±3.0</td>
<td>52.0±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum hemoglobin (g/dl)</td>
<td>12.0±0.2</td>
<td>13.4±0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>751±180</td>
<td>1,146±133</td>
<td>NS</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; EF, ejection fraction; DM, diabetes mellitus; AF, atrial fibrillation; NYHA, New York Heart Association; GFR, glomerular filtration rate; BNP, B-type natriuretic peptide.

Table 2  Relationship Between Medication and CHF Re-Hospitalization of CHF Patients With Preserved EF: Univariate Analysis

<table>
<thead>
<tr>
<th>Prescription at discharge</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB (58.6)</td>
<td>0.479</td>
<td>0.238–0.964</td>
<td>0.039</td>
</tr>
<tr>
<td>β-blocker (51.7)</td>
<td>1.274</td>
<td>0.624–2.600</td>
<td>0.505</td>
</tr>
<tr>
<td>Furosemide (74.1)</td>
<td>1.896</td>
<td>0.772–4.657</td>
<td>0.163</td>
</tr>
<tr>
<td>Spironolactone (31.0)</td>
<td>1.899</td>
<td>0.935–3.856</td>
<td>0.067</td>
</tr>
<tr>
<td>Dihydropyridine (59.7)</td>
<td>0.809</td>
<td>0.395–1.658</td>
<td>0.562</td>
</tr>
<tr>
<td>Diltiazem (12.1)</td>
<td>0.202</td>
<td>0.028–1.481</td>
<td>0.116</td>
</tr>
<tr>
<td>Digoxin (15.5)</td>
<td>0.815</td>
<td>0.284–2.333</td>
<td>0.703</td>
</tr>
</tbody>
</table>

Prescription rate of each drug at discharge is shown in parentheses. CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers. Other abbreviations see in Table 1.

Fig 1. Kaplan-Meier curve of chronic heart failure (CHF) re-hospitalization in CHF patients with preserved ejection fraction (EF) taking or not taking angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin-receptor blockers (ARB). Inset, Kaplan-Meier curve of CHF re-hospitalization in CHF patients with reduced EF.
Results

The characteristics of the preserved EF and reduced EF groups are shown in Table 1. Patients with preserved EF were older, more likely to be female and had a lower serum hemoglobin concentration. Plasma BNP on admission was lower in the preserved EF group, but was not statistically significant, probably because BNP was measured in only a limited number of patients. In the multivariate analysis, age was independently related to CHF with preserved EF, whereas gender and serum hemoglobin were not (Table 1).

Fig 1 shows the re-hospitalization-free Kaplan-Meier curve for CHF patients with preserved EF taking or not taking angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin-receptor blockers (ARB). The characteristics of the patients taking or not taking ACEI/ARB did not differ (data not shown). Other factors for CHF re-hospitalization of CHF patients with preserved EF are shown in Tables 2 and 3. Predictors for CHF re-hospitalization identified with univariate analysis were subjected to multivariate analysis, which identified non-use of ACEI/ARB as the only independent predictor for CHF re-hospitalization (Table 4).

We also compared the EF of the first CHF hospitalization with preserved EF in 2003–2004, with that at the next re-hospitalization and in 75% of patients EF was preserved (Fig 2).

Discussion

Diastolic dysfunction may play an important role in the pathogenesis of CHF with preserved EF, but diastolic heart failure (HF) and CHF with preserved EF are not always the same. Diastolic function is difficult to measure non-invasively. Recently, E/E' in UCG was suggested as a good index for diastolic function, but in the present study, E/E' was not routinely measured. Moreover, systolic dysfunction and diastolic dysfunction sometimes overlap. Therefore, in the present study, “CHF with preserved EF” was used rather than “diastolic HF”.

Prevalence of CHF With Preserved EF

The prevalence of CHF with preserved EF was approximately half of all the patients hospitalized with CHF, which is comparable to previous reports. We used 40% as the cut off value of EF, as in the CHARM-preserved and PEP-
CHF studies. Previous studies have used 40% or 50% as the cut-off value of EF;1–4 but the number of CHF patients with an EF between 40% and 50% was quite small. Thus, this difference in the cut-off value would not severely affect the characteristics of the patients with CHF with preserved EF.

As suggested by Owan et al, the prevalence of CHF with preserved EF increases over time, establishing the concept of "CHF with preserved EF". Thus it is very important to know the characteristics and treatment of CHF with preserved EF, as well as that of CHF with reduced EF.

In the present study, the CHF patients with preserved EF were older than those with reduced EF, which is consistent with previous reports.1–3 Aging induces fibrosis, and the long-term presence of hypertension would induce hypertrophy, thus increasing the passive chamber stiffness.

In our univariate analysis, more women had CHF with preserved EF, and all the previous reports show a higher rate of females (51–63%).1–3 It may be because of the small samples that gender did not reach statistical significance in multivariate analysis in the present study.

Serum hemoglobin was lower in patients with CHF with preserved EF in our univariate analysis, but not in the multivariate analysis. Serum hemoglobin might be influenced by age, but anemia would induce a hyperkinetic state, so anemia might be a risk in CHF with preserved EF.5

Treatment of CHF With Preserved EF

The present study results showed that ACEI/ARB therapy is beneficial for CHF with preserved EF. Almost all studies of the treatment of CHF have been in patients with CHF with reduced EF. Lean is known about the treatment of CHF with preserved EF.5,6

In the CHARM-preserved study, candesartan prevented CHF hospitalization but did not affect the mortality rate of CHF patients with EF more than 40%. In the PEP-CHF study, perindopril prevented CHF hospitalization at 1 year, but did not affect the death of CHF patients with preserved EF and age ≥70 years. Both studies showed that inhibition of the RAS prevented CHF hospitalization, consistent with the results of the present study.

The AT1 receptor plays an important role in the alteration of collagen type I metabolism and subsequent fibrosis. In hypertensive patients, ARB induces regression of fibrosis, which is associated with a decrease in left ventricular stiffness.11 Cardiac hypertrophy is also improved by ACEI/ARB therapy in hypertensive patients.11,12 In a rat model of hypertensive CHF, in which fractional shortening is preserved, the left ventricular end-diastolic pressure increases, and ACEI13 or ARB14 treatment restores it. Thus, it is reasonable that ACEI/ARB therapy is favorable for CHF patients with preserved EF.

As shown in Fig 1, in the present study having ACEI/ARB treatment did not benefit CHF patients with reduced EF. As is probably because of the limited number of patients. A beneficial effect of ACEI/ARB therapy has been established in CHF with reduced EF.

Other Factors Affecting Re-Hospitalization

In our univariate analysis, absence of hypertension was a risk for CHF re-hospitalization. It may be that hypertensive patients tend to have ACEI/ARB therapy, although the rate of prescription of ACEI/ARB did not differ between patients with hypertension and without hypertension in this study and we could not check the dosages of these drugs.

The effect of ACEI/ARB might be dose-dependent and it is possible that patients with hypertension were given higher doses of ACEI/ARB.

Univariate analysis also showed that prior hospitalization was a risk for CHF re-hospitalization and this was the strongest predictor for CHF re-hospitalization if CHF with preserved EF and CHF with reduced EF were mixed. Hospitalization is a result of progression of CHF, and repeated hospitalization itself may worsen prognosis.15 However, in the multivariate analysis, prior CHF hospitalization did not reach statistical significance as a predictor of CHF re-hospitalization. Interestingly, as shown in Fig 2, in CHF patients with preserved EF, the decline in EF was not large. Preservation of EF during the course of repeated hospitalization might explain why prior CHF hospitalization was not independently related to CHF re-hospitalization.

In contrast to our previous report in which CHF with preserved EF and CHF with reduced EF were mixed, in this study renal dysfunction and age were not related to CHF re-hospitalization. Re-hospitalization of CHF patients with preserved EF might not be closely related to renal function or age, although that result might be related to the small sample size.

Conclusion

CHF patients with preserved EF are older and ACEI/ARB therapy is beneficial for them.

References


Circulation Journal Vol.72, December 2008

