Heart Failure With Preserved Ejection Fraction. Effect of Etiology on Prognosis

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Introduction and objectives. Heart failure with preserved systolic function accounts for almost 40% of heart failure cases. Prognosis is similar to that in patients with a low left ventricular ejection fraction (LVEF). However, it is not clear whether the etiology of heart failure with preserved systolic function has an effect on prognosis.

Methods. We assessed 95 consecutive patients admitted to our hospital with heart failure and a LVEF>45%. Twenty-five (26%) had an ischemic etiology and 70 (74%), a non-ischemic etiology.

Results. The patients’ mean age was 73 (6) years, 60% were female, and their mean LVEF was 61 (7)%. These characteristics were similar in the two etiological groups. After a mean follow-up period of 53 (8) months (4-69 months; median 46 months), mortality was higher in ischemic patients (17.88 vs 2.37/100 patient-years; P<.0001), as was the rate of cardiovascular admissions (24.58 vs 4.14/100 patient-years; P<.0001). The rates of mortality due to heart failure and sudden death were also higher in ischemic patients, at 7.82 vs 0.59/100 patient-years, and 7.82 vs 0.30/100 patient-years, respectively (P<.0001). The higher overall admission rate found in the ischemic group was due to higher rates of admission for heart failure (14.53 vs 0.89/100 patient-years; P<.0001) and acute coronary syndrome (8.94 vs 1.78/100 patient-years; P<.003).

Conclusions. In terms of prognosis, heart failure with preserved systolic function is not a homogeneous disease entity. Mortality and morbidity rates are higher in patients with an ischemic etiology. Moreover, different mechanisms are involved.

Key words: Heart failure. Systolic function. Ischemic heart disease.
It is noteworthy, however, that the CHF or Fishers exact test.

Ojeda et al. Controversy exists over whether such

Patients with CHF and preserved systolic function, and to
determine whether ischemic or non-ischemic

evidence of myocardial infarction, angiographic evidence of significant coronary lesions, and/or showed signs of ischemia in non-invasive tests (echocardiography with dobutamine or myocardial perfusion gammagrapy) during the hospital stay leading to enrollment. When ischemic heart disease was identified, the etiology of the CHF was always attributed to this problem even though other possible causes (e.g., high blood pressure) were present. In patients with no history of ischemic heart disease, echocardiography with dobutamine or myocardial perfusion gammagrapy and/or coronary angiography were performed to rule out coronary disease. When thus coronary artery disease was ruled out, the etiology of the CHF was deemed to be high blood pressure in patients with a known history of hypertension, as well as in those in whom this problem was discovered during their hospital stay.

The incidence of events (morbidity and mortality) was recorded in both the ischemic and non-ischemic etiology groups, and the overall mortality, cardiac mortality, non-cardiac mortality, and readmission to hospital because of heart failure and other causes compared. The causes and mechanisms of the events in both groups of patients were determined. All patients were monitored prospectively during outpatient consultations at our center (the frequency determined by each patient’s needs). When a patient failed to attend an appointment he/she was contacted by telephone. No patients were lost to follow-up. The final consultation (with respect to data collection) took place between June and October of 2005 (either in person or by telephone). The mean follow-up time for the entire group of patients was 5328 months (range, 4-69 months; median, 46 months), 5856 months (range, 8-69 months; median, 55 months) for the non-ischemic etiology patients, and 43211 months (range, 4-67 months; median, 37 months) for those whose condition was of ischemic etiology.

Statistical Analysis

Qualitative variables are shown as percentages and quantitative variables as mean±SD. The former were compared using the χ² or Fisher’s exact test. Continuous variables (all of which showed a normal distribution) were compared using the Student t test.
The probabilities of survival and readmission-free survival, for both the patients as a whole and for the two etiological groups, were estimated by the Kaplan-Meier test and compared using the Mantel log-rank test. Given the different follow-up times of the 2 etiological groups, the incidence of events was adjusted for the total observation time of each; results are expressed as incidence per 100 patients per year of observation. The incidence of events in both groups was compared by the difference in their rates using the Ulm method; the 95% confidence intervals (CI) for these rate differences were determined by the Sahai and Kurshid method. Significance was set at \( P < .05 \).

**RESULTS**

During the enrollment period, 227 patients met the initial inclusion criteria, of whom 95 had an LVEF of >45% (i.e., CHF with preserved systolic function); these formed the study group. Of these 95 patients, the condition of 25 (26%) was of ischemic etiology; that of the remaining 70 (74%) was non-ischemic. Of these latter patients, hypertension was the cause of CHF in 62 patients, hypertrophic cardiomyopathy the cause in 3, and restrictive cardiomyopathy the cause in 1. In the remaining 4, other problems were the cause. In the 62 patients with hypertensive etiology, 42 had a history of high blood pressure (Table 1); the remaining 20 had not been previously diagnosed as hypertensive. In the 70 patients belonging to the non-ischemic group, artery disease was ruled out by coronary angiography in 27, by echocardiography with dobutamine in 5, and by myocardial perfusion gammagraphy in the remaining 38.

The mean age of the patients as a whole was 73±6 years; women represented 60% of the sample. The mean LVEF was 61±7%. No significant baseline differences were seen between the ischemic and non-ischemic groups with respect to age, sex, LVEF, or the presence of cardiovascular risk factors such as diabetes, high blood pressure, dyslipidemia, or use of tobacco (Table 1). As expected, the ischemic etiology patients showed a higher frequency of previous myocardial infarction and of having undergone coronary revascularization (Table 1).

Table 2 shows there were no significant differences between the 2 groups with respect to the therapy prescribed, except for the use of antiplatelet agents, lipid reducing drugs, beta-blockers and nitrates, which were used significantly more often in patients of the ischemic etiology group.

After a mean follow-up time of 53±8 months (range, 4-69 months; median, 46 months), the mortality rate for the patients as a whole was 5.72/100 patients per year (24 cases), the incidence of readmission for cardiovascular causes was 8.6/100 patients per year (36 admissions), and the incidence of readmission because of heart failure 3.81/100 patients per year (16 readmissions). Five year survival probability for the patients as a whole was 60%; the probability of readmission-free survival was 32%.

The ischemic etiology patients had a higher mortality rate than those belonging to the non-ischemic etiology group; the 5 year survival probabilities of the 2 groups were 28% and 72% respectively (\( P < .001 \); Figure). Table 3 shows the results of the event incidence (death and readmission) analysis for both etiology groups (expressed as numbers per 100 patients per year of observation). Total mortality was significantly lower in the non-ischemic etiology group.

**TABLE 1. Patient Characteristics at Enrollment According to Whether They Had Chronic Heart Failure With Preserved Systolic Function of Ischemic or Non-Ischemic Etiology**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Ischemic Etiology</th>
<th>Non-Ischemic Etiology</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>95</td>
<td>25</td>
<td>70</td>
<td>.78</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>73±6</td>
<td>74±7</td>
<td>72±6</td>
<td>.78</td>
</tr>
<tr>
<td>Women</td>
<td>55 (58%)</td>
<td>13 (52%)</td>
<td>42 (60%)</td>
<td>.64</td>
</tr>
<tr>
<td>Previous admissions for heart failure</td>
<td>48 (51%)</td>
<td>13 (52%)</td>
<td>35 (50%)</td>
<td>.95</td>
</tr>
<tr>
<td>CRF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBP</td>
<td>57 (60%)</td>
<td>15 (60%)</td>
<td>42 (60%)</td>
<td>.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (29%)</td>
<td>10 (40%)</td>
<td>18 (26%)</td>
<td>.27</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33 (35%)</td>
<td>10 (40%)</td>
<td>23 (33%)</td>
<td>.68</td>
</tr>
<tr>
<td>Smokers</td>
<td>48 (51%)</td>
<td>13 (52%)</td>
<td>35 (50%)</td>
<td>.95</td>
</tr>
<tr>
<td>History of AMI</td>
<td>15 (16%)</td>
<td>15 (64%)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>6 (6%)</td>
<td>6 (24%)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVEF, mean±SD, %</td>
<td>61±7</td>
<td>58±8</td>
<td>62±7</td>
<td>.12</td>
</tr>
<tr>
<td>Serum creatinine&gt;1.5 mg/dL</td>
<td>29 (26%)</td>
<td>6 (24%)</td>
<td>23 (27%)</td>
<td>.73</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>47 (49%)</td>
<td>12 (48%)</td>
<td>35 (50%)</td>
<td>.95</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>85 (89%)</td>
<td>22 (88%)</td>
<td>63 (90%)</td>
<td>.56</td>
</tr>
</tbody>
</table>

*LVEF indicates left ventricular ejection fraction; CRF, cardiovascular risk factors; HBP, high blood pressure; AMI, acute myocardial infarction; NYHA, New York Heart Association.*
higher among the ischemic etiology patients, as was sudden death and heart failure mortality ($P < .0001$) (Table 3). Death due to myocardial infarction or other causes was similar in both groups (Table 3). Sudden death or death due to heart failure accounted for 82% of all deaths among the ischemic etiology patients (14 out of 16 patients), while this was the cause of death in only 37% (3 out of 8) of the non-ischemic etiology patients. The incidence of readmission due to cardiovascular problems was significantly higher in the ischemic etiology group (24.58 compared to 4.14 per 100 patients per year for the non-ischemic etiology patients; $P < .0001$); this was particularly true with respect to readmission for CHF decompensation problems (14.53 compared to 0.89; $P < .0001$) (Table 3). The incidence of readmission due to an acute coronary syndrome was also significantly higher among the ischemic etiology patients ($P = .0033$), although the difference between the rates was less great (Table 3). No significant differences were seen with respect to readmission for other cardiovascular reasons. Among the ischemic etiology patients, 59% of all readmissions for cardiovascular reasons were due to heart failure (13 out of 22); this was the case for 21% among the non-ischemic etiology patients (3 out of 14).

**DISCUSSION**

Although limited by the small number of patients, the present study shows that, from a prognostic point of view, CHF with preserved systolic function is not a homogeneous condition: patient prognosis depends on its etiology. When coronary disease is present the prognosis is generally poor; 5 year survival is low (around 28%) and the readmission rate is high. In contrast, when the etiology is non-ischemic (usually due to high blood pressure), the prognosis is generally good; 5 year survival is 72% and the readmission rate is lower.
The overall mortality rate of 40% at 5 years of follow-up was similar to that recently described in patients with symptomatic CHF with preserved systolic function. In a study involving 2498 patients, O'Connor et al. reported a 5-year mortality of 28%, although the mean age of their patients was 63 years, significantly lower than that of the present patients (73.46 years) and not all had symptoms of heart failure. Varela-Román et al. reported a 3-year mortality of 33.9% in Spanish patients with CHF, while Ojeda et al. found an overall mortality of 29% in patients with a mean age of 65 years at 25 months of follow-up.

In the present study, no significant differences were seen between the 2 etiological groups with respect to the baseline presence of diabetes, high blood pressure, dyslipidemia, or use of tobacco. It should be noted that a high proportion of patients in whom CHF was due to high blood pressure did not know they were hypertensive (20 out of 62). This reveals the need for people to underscore the importance of high blood pressure and its control in the prevention of CHF. No important differences were seen in the treatments prescribed for the patients of either etiological group, although the ischemic etiology patients were more commonly prescribed antiplatelet agents, lipid lowering drugs, nitrates, and beta-blockers. Thus, the better survival of the non-ischemic etiology patients cannot be attributed to differences in baseline demographic or risk factors, nor to differences in the pharmacological treatment received (indeed, the ischemic etiology patients theoretically received “better treatment” than their non-ischemic counterparts given the quantities of beta-blockers, statins and antiplatelet agents administered).

Some factors related to the inclusion criteria and the assignment of etiology (ischemic or non-ischemic) could have introduced a bias towards a higher mortality and readmission rate among patients of the ischemic etiology group. It is possible that the exclusion of patients in whom coronary revascularization was performed during their hospital stay may have led to the selection of patients with a greater risk of events during follow-up. The same could be true with respect to the assignment of an ischemic etiology when high blood pressure or coronary artery disease was present. Further, it cannot be ruled out that some patients assigned to the non-ischemic group might also have had some coronary lesion. However, this is unlikely given the systematic imaging (echocardiography with dobutamine or myocardial perfusion scintigraphy) and coronary angiography studies performed; any influence on the results is likely to have been very small. It is therefore improbable that these limitations (which are inherent in clinical studies), or those associated with the small number of patients, explain the significant differences in the incidence results shown in Table 3, although they may have a small qualifying effect.

Some authors have underlined the effect of ischemic disease on the survival of patients with CHF. O'Connor et al. observed that the severity of ischemic disease was an independent risk factor with respect to the mortality of such patients, whether left ventricular systolic function was preserved or not. In addition, when these authors compared survival rates of patients with CHF and diminished systolic function to that of patients with CHF but with preserved systolic function, the difference disappeared when adjustment was made for the presence of coronary ischemia (among other variables). In contrast, other studies report no differences in prognosis associated with ischemic and non-ischemic etiologies. In a study by the DIG group of researchers involving patients with CHF with preserved systolic function, the factors found to influence patient prognosis were age, males, the glomerular filtration rate and functional class III-IV, but not ischemic etiology. In addition, Setaro et al. found that mortality at 7 years in patients with ischemic and non-ischemic etiology was the same (46%). In a more recent study involving patients with acute myocardial infarction, the impairment of diastolic function was not found to influence prognosis. According to the results of the present study, however, CHF with preserved systolic function of ischemic etiology is associated with higher mortality than that of non-ischemic etiology at 5 years of follow-up (Figure), and with a higher rate of hospital readmission. The exclusion of patients who underwent coronary revascularization may have led to select a group of ischemic etiology patients at higher risk, but the differences between the results for the 2 groups are very large. Moreover, the mechanisms and causes of the events registered (death and readmission) in the 2 groups are different (Table 3); those with ischemic etiology predominantly suffered complications related to heart failure itself and sudden death, while those of the non-ischemic etiology group suffered other events as well, such as acute coronary syndrome and supraventricular tachyarrhythmias. Although the incidence of acute coronary syndrome was higher in the ischemic etiology group, it was certainly not negligible among the non-ischemic etiology patients (Table 3). It is possible that differences in treatment are important in this respect since the less common use of antiplatelet agents, statins and beta-blockers in the non-ischemic etiology patients could condition a greater incidence of acute coronary events and tachyarrhythmias.
hospital. It is recommended that tests for myocardial ischemia be performed on all patients presenting with CHF with preserved systolic function in order to identify those with coronary heart disease and to establish the most adequate treatment, including possible coronary revascularization.

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REFERENCES