ORIGINAL ARTICLE

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. Morbidity and mortality rates are higher in patients with an ischemic etiology. Moreover, different mechanisms are involved.

Key words: *Heart failure. Systolic function. Ischemic heart disease.*

Insuficiencia cardiaca con función sistólica conservada. Diferencias pronósticas según la etiología

Introducción y objetivos. La insuficiencia cardiaca con función sistólica conservada (ICFSC) parece tener un pronóstico similar al de la insuficiencia cardiaca con función sistólica disminuida. Sin embargo, no se conoce si la ICFSC es una entidad pronóstica homogénea o si su morbimortalidad varía según su etiología.

Métodos. Se ha evaluado a una serie de 95 pacientes diagnosticados consecutivamente de ICFSC, con fracción de eyección mayor del 45%, y hemos comparado los grupos de etiología isquémica (n = 25; 26%) y no isquémica (n = 70; 74%).

Resultados. La edad media fue de 73 ± 6 años, el 60% eran mujeres y la fracción de eyección era del 61 ± 7%, con cifras similares en ambos grupos. Tras un seguimiento de 53 ± 8 meses (límites, 4-69; mediana, 46), el grupo isquémico presentó mayor mortalidad (17,88 frente a 2,37 muertes/100 pacientes/año; p < 0,0001) y mayor incidencia de ingresos cardiovasculares (24,58 frente a 4,14 ingresos/100 pacientes/año; p < 0,0001). La incidencia de muerte por insuficiencia cardiaca crónica (ICC) y de muerte súbita fueron más elevadas en los pacientes isquémicos (7,82 frente a 0,59 y 7,82 frente a 0,30/100 pacientes/año; p < 0,0001). La mayor incidencia de ingresos en el grupo isquémico se debió a la mayor tasa de ingresos por ICC (14,53 frente a 0,89/100 pacientes/año; p < 0,0001) y síndrome coronario agudo (8,94 frente a 1,78; p = 0,003).

Conclusiones. La ICFSC no es una entidad homogénea desde el punto de vista pronóstico. La morbimortalidad es más elevada en los casos de etiología isquémica, y sus mecanismos son también distintos.

Palabras clave: *Insuficiencia cardiaca. Función sistólica. Cardiopatía isquémica.*

INTRODUCTION

Chronic heart failure (CHF) is becoming one of the main morbidity/mortality factors affecting the general population. Its incidence and prevalence continue to rise due to the gradual ageing of the population

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Received July 14, 2005.
Accepted for publication January 17, 2006.

ABBREVIATIONS

LVEF: left ventricular ejection fraction.
CHF: chronic heart failure.

healtha care improvements and survival of patients with chronic diseases. The survival of many heart diseases—of which CHF is the final stage—has also increased.[1,2] It is noteworthy, however, that the CHF morbidity/mortality has not been significantly reduced despite advances in treating heart diseases and the improvements achieved with respect to their long term clinical course. This is probably due to the greater age of the patients with this condition and the comorbidity they commonly experience.[3,4]

It is thought that about 40% of patients with CHF have preserved left ventricular systolic function, a condition more commonly seen in women and older patients.[5,6] Controversy exists over whether such patients have better survival than those with CHF with ventricular systolic dysfunction. Some authors report greater morbidity/mortality among the latter,[5-7] whereas others report no such findings.[8,9] Ojeda et al[10] reported similar survival and hospital readmission rates for cardiac and non-cardiac causes in both types of patient.

From a prognostic point of view it remains to be clarified whether patients with CHF and preserved systolic function are a homogenous group or whether morbidity/mortality varies depending on the etiology of their condition.[11-14] The aim of the present study was to determine whether ischemic or non-ischemic etiology affects the long term prognosis of patients with CHF and preserved systolic function, and to establish whether these etiologies affect the causes and mechanisms of the events suffered.

METHODS

The study subjects were patients discharged consecutively from our unit between January and December 2000 after admission for CHF with preserved systolic function. The diagnosis of CHF was made in agreement with the criteria of the European Society of Cardiology, which include the presence of signs and symptoms of heart failure plus echocardiographic and/or hemodynamic evidence of cardiac structural or functional impairment.[15] The absence of left ventricular systolic dysfunction was determined by echocardiography in all patients. A left ventricular ejection fraction (LVEF) of >45% was required for inclusion (again in agreement with the guidelines of the European Society of Cardiology for the diagnosis of CHF with preserved systolic function).[15] Patients with CHF and preserved systolic function of valvular etiology (a reversible condition requiring surgery-catheterization to correct the cause of decompensation) were excluded, as were those who remained on the heart transplant waiting list.

Patient sociodemographic, clinical, analytical, electrocardiographic and echocardiographic data, plus all treatments administered, were recorded at the time of inclusion and during follow-up. The patients were divided into 2 groups depending on the ischemic or non-ischemic etiology of their condition. This was deemed ischemic when the patient had a history or showed electrocardiographic 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 gammagraphy) 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 gammagraphy 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 53±8 months (range, 4-69 months; median, 46 months), 58±6 months (range, 8-69 months; median, 55 months) for the non-ischemic etiology patients, and 43±11 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 means±SD. The former were compared using the χ^2 or Fishers 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[16]; the 95% confidence intervals (CI) for these rate differences were determined by the Sahai and Kurshid method.[17] 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

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

	Total	Ischemic Etiology	Non-Ischemic Etiology	*P*
Patients, n	95	25	70	
Age, mean±SD, y	73±6	74±7	72±6	.78
Women	55 (58%)	13 (52%)	42 (60%)	.64
Previous admissions for heart failure	48 (51%)	13 (52%)	35 (50%)	.95
CRF				
HBP	57 (60%)	15 (60%)	42 (60%)	.81
Diabetes	28 (29%)	10 (40%)	18 (26%)	.27
Dyslipidemia	33 (35%)	10 (40%)	23 (33%)	.68
Smokers	48 (51%)	13 (52%)	35 (50%)	.95
History of AMI	15 (16%)	15 (64%)	0	<.001
Previous coronary revascularization	6 (6%)	6 (24%)	0	<.001
LVEF, mean±SD, %	61±7	58±8	62±7	.12
Serum creatinine >1.5 mg/dL	25 (26%)	6 (24%)	19 (27%)	.73
Atrial fibrillation	47 (49%)	12 (48%)	35 (50%)	.95
NYHA class III or IV	85 (89%)	22 (88%)	63 (90%)	.58

*LVEF indicates left ventricular ejection fraction; CRF, cardiovascular risk factors; HBP, high blood pressure; AMI, acute myocardial infarction; NYHA, New York Heart Association.

TABLE 2. Treatment Prescribed to Patients With Chronic Heart Failure With Preserved Systolic Function of Ischemic and Non-Ischemic Etiology*

	Total	Ischemic	Non-ischemic	*P*
Patients, n	95	25	70	
Beta-blockers	10 (11%)	9 (36%)	1 (2%)	<.001
Diuretics	95 (100%)	25 (100%)	70 (100%)	1.00
Digoxin	47 (49%)	10 (40%)	37 (53%)	.38
ACEI/ARA-II	55 (58%)	12 (48%)	43 (61%)	.35
Statins	24 (25%)	18 (72%)	6 (8%)	.07
Spironolactone	48 (51%)	10 (40%)	38 (54%)	.32
Calcium antagonists	14 (15%)	6 (25%)	8 (11%)	.23
Nitrates	11 (12%)	10 (40%)	1 (2%)	<.001
Antiaggregants	28 (29%)	25 (100%)	3 (4%)	<.001
Anticoagulants	48 (51%)	10 (40%)	38 (54%)	.32

*ARA-II indicates angiotensin II receptor agonists; ACEI, angiotensin converting enzyme inhibitors.

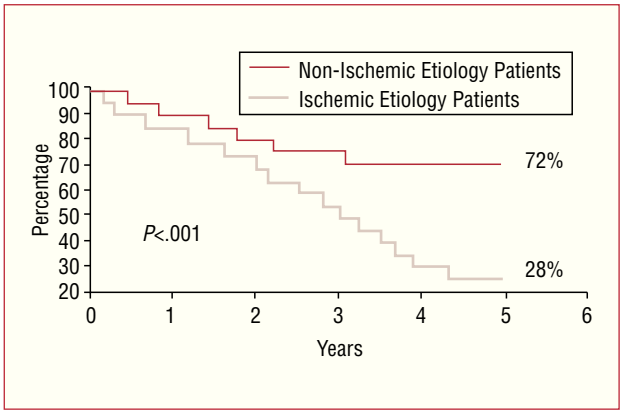

Figure. Actuarial survival of ischemic and non-ischemic etiology patients. Five year survival was 72% for the non-ischemic etiology group, and 28% for the ischemic etiology group (*P*<.001).

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 true 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.

TABLE 3. Incidence of Events per 100 Patients per Year of Observation in Ischemic and Non-Ischemic Etiology Patients*

	Total	Ischemic Etiology†	Non-Ischemic Etiology†	Difference in rates‡	*P*
Total deaths	24 (5.72)	16 (17.88)	8 (2.37)	15.51 (9.99-21.03)	<.0001
Death due to CHF	9 (2.14)	7 (7.82)	2 (0.59)	7.23 (3.85-10.61)	<.0001
Sudden death	8 (1.91)	7 (7.82)	1 (0.30)	7.53 (4.34-10.71)	<.0001
Death due to AMI	4 (0.95)	1 (1.12)	3 (0.89)	0.23 (–2.02 to 2.48)	.8416
Non-cardiac death	3 (0.71)	1 (1.12)	2 (0.59)	0.53 (–1.43 to 2.48)	.5976
Readmissions due to CV	36 (8.6)	22 (24.58)	14 (4.14)	20.44 (13.68-27.20)	<.0001
Readmissions due to CHF	16 (3.81)	13 (14.53)	3 (0.89)	13.64 (9.13-18.14)	<.0001
Readmissions due to ACS	14 (3.35)	8 (8.94)	6 (1.78)	7.16 (2.95-11.38)	.0033
Readmissions due to SVT	6 (1.43)	1 (1.12)	5 (0.76)	0.36 (–3.12 to 2.40)	.9999

*CHF indicates chronic heart failure; AMI, acute myocardial infarction; CV, cardiovascular events; ACS, acute coronary syndrome; SVT, supraventricular tachycardia.
†Expressed as the number of events and (in parentheses) the incidence of events per 100 patients per year of observation.
‡Expressed as the difference in rate between groups plus (in parentheses) the 95% confidence interval.

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.[18] In a study involving 2498 patients, O'Connor et al.[19] 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±6 years) and not all had symptoms of heart failure. Varela-Román et al[9] reported a 3 year mortality of 33.9% in Spanish patients with CHF, while Ojeda et al[10] reported 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 underscores 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 gammagraphy) 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[19] observed that the severity of ischemic disease was an independent risk factor with respect to the mortality of such patients, whether left ventricular systemic 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).[19] In contrast, other studies report no differences in prognosis associated with ischemic and non-ischemic etiologies.[11-13] 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.[12] In addition, Setaro et al found that mortality at 7 years in patients with ischemic and non-ischemic etiology was the same (46%).[13] In a more recent study involving patients with acute myocardial infarction, the impairment of diastolic function was not found to influence prognosis.[14] 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.

In conclusion—and taking into account the limitations of the small number of patients and the possible biases mentioned—this work shows that the ischemic or non-ischemic etiology of CHF with preserved systolic function has an important influence on morbidity and mortality. Patients with this condition should not be considered a homogeneous group from a prognostic point of view since an ischemic etiology has a negative influence on survival and readmission to

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.

ACKNOWLEDGEMENTS

The authors thank Dr. Nieves Martínez Alzamora for her kind help with the statistical analysis.

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