HEART FAILURE

Clinical Characteristics and Medium-Term Prognosis of Patients With Heart Failure and Preserved Systolic Function. Do They Differ in Systolic Dysfunction?

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Objectives. To assess the prevalence, clinical profile and medium-term prognosis in patients with heart failure and preserved systolic ventricular function compared to those with systolic dysfunction.

Patients and method. 153 patients were included, 62 with preserved systolic ventricular function (left ventricular ejection fraction $\geq$ 45%) and 91 with impaired systolic ventricular function (left ventricular ejection fraction < 45%). The mean follow-up period was 25 ± 10 months.

Results. Mean age was similar (66 ± 10 vs. 65 ± 10; p = 0.54). There was a higher proportion of women among patients with preserved systolic function (53% vs. 28%; p < 0.01). Ischemic and idiopathic cardiomyopathy were the most common causes of heart failure in patients with systolic dysfunction, whereas valvular disease and hypertensive cardiopathy were the most common in patients with preserved systolic function. Angiotensin-converting enzyme inhibitors and β-blockers were more often prescribed in patients with impaired systolic ventricular function (86% vs. 52%; p < 0.01 and 33% vs. 11%; p < 0.01, respectively). There were no differences between the groups in terms of mortality rate (37% vs. 29%), readmission rate for other causes (29% vs. 23%), readmission rate for heart failure (45% vs. 45%), cumulative survival (51% vs. 62%) and the likelihood of not being readmitted for heart failure (50% vs. 52%). In the multivariate analysis, left ventricular ejection fraction was not a predictor of death or readmission because of heart failure.

Conclusions. In a large proportion of patients with heart failure, systolic ventricular function is preserved. Despite the clinical differences between patients with preserved and impaired systolic ventricular function, the medium-term prognosis was similar in both groups.

Key words: *Heart failure. Prognosis. Survival.*

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Características clínicas y pronóstico a medio plazo de la insuficiencia cardíaca con función sistólica conservada. ¿Es diferente de la insuficiencia cardíaca sistólica?

Objetivos. Analizar la prevalencia, las características clínicas y el pronóstico a medio plazo de los pacientes con insuficiencia cardíaca y función sistólica conservada, y compararlos con los que presentan disfunción ventricular.

Pacientes y método. Se incluyó a un total de 153 pacientes, 62 con función sistólica conservada (fracción de eyección ventricular izquierda $\geq$ 45%) y 91 con disfunción ventricular (fracción de eyección < 45%). El seguimiento medio fue de 25 ± 10 meses.

Resultados. Las edades medias fueron similares (66 ± 10 frente a 65 ± 10 años; p = 0,54). La proporción de mujeres fue mayor entre los pacientes con función sistólica conservada (53 frente a 28%; p < 0,01). Las miocardiopatías isquémica e idiopática fueron las causas más prevalentes en pacientes con disfunción sistólica, y las valvulopatías y la cardiopatía hipertensiva, en los que tenían una función sistólica conservada. Los pacientes con función sistólica deprimida recibieron inhibidores de la enzima de conversión de la angiotensina y bloqueadores beta en mayor proporción (86 frente a 52%; p < 0,01 y 33 frente a 11%; p < 0,01). Las tasas de mortalidad (37 frente a 29%), reingresos por insuficiencia cardíaca (45 frente a 45%) y reingresos por otras causas (29 frente a 23%) fueron similares entre ambos grupos, y tampoco difirieron la supervivencia actuarial (51 frente a 62%) ni la probabilidad de no reingresar por insuficiencia cardíaca (50 frente a 52%). La fracción de eyección ventricular izquierda no fue predictora de mortalidad o reingresos por insuficiencia cardíaca.

Conclusiones. Una importante proporción de pacientes con insuficiencia cardíaca presentan una función ventricular sistólica conservada. Aunque las características clínicas de estos pacientes son distintas de las de aquellos con disfunción ventricular sistólica, el pronóstico a medio plazo fue similar.

Palabras clave: *Insuficiencia cardíaca. Pronóstico. Supervivencia.*

INTRODUCTION

Heart failure is a particularly important problem and constitutes the final phase in the development of most heart disorders. Heart failure has a high prevalence and incidence and it is predicted that this will increase due, among other factors, to the progressive aging of the population and increased survival rates of patients affected by other illnesses such as cardiac ischemia or hypertension.[1,2] In spite of advances in our knowledge of the pathophysiology of heart failure and the improved prognosis of clinical trials, the effects of pharmacological treatment on the general population of heart failure patients have been limited and mortality and morbidity rates have increased.[3,4]

Between 30% and 50% of heart failure patients have preserved ventricular systolic function, and this is especially common among older patients and women.[5-10] In spite of the high prevalence of this syndrome, the clinical characteristics and associated mortality and morbidity are not well known, and published studies have reported conflicting data with regard to the prognosis. Some authors report lower rates of mortality and readmission in patients with preserved ventricular systolic function than in patients with systolic dysfunction,[7,10-12] whereas others find no differences in the prognosis between these groups.[13-15]

The objectives of this study were to analyze the clinical characteristics and medium-term prognosis in patients with heart failure and preserved ventricular systolic function; to compare these patients with others who had heart failure with systolic dysfunction; and to determine the prevalence of heart failure with preserved ventricular systolic function in the overall population of patients hospitalized for heart failure.

PATIENTS AND METHODS

Patient groups

This is a prospective study of 153 patients consecutively discharged from the Cardiology Unit of a university hospital in Córdoba (Spain) with a principal diagnosis of heart failure. Discharges were recorded from January 1999 to January 2000. The unit

is in a tertiary hospital serving a population of 400 000 inhabitants. Heart failure was diagnosed according to European Society of Cardiology criteria, which are based on the presence of symptoms and signs of heart failure with objective evidence of functional or structural cardiac impairment detected by echocardiography or cardiac catheterization.[16] We excluded patients who died during hospitalization, who were diagnosed with heart failure secondary to a reversible cause, who were recommended for surgery or percutaneous interventions to correct the cause of decompensation, and those on the heart transplant waiting list. The Cardiology Unit received 197 admissions during the study period, and 44 patients were excluded.

Echocardiography was performed on all patients to evaluate left ventricular ejection fraction (LVEF). Patients were then divided into 2 groups: patients with preserved ventricular systolic function (LVEF≥45%) and patients with impaired function (LVEF<45%). We used this cutoff point in accordance with European Society of Cardiology guidelines for the diagnosis of heart failure with preserved ventricular systolic function.[17]

Sociodemographic, clinical, analytical, electrocardiographic, echocardiographic and treatment variables were recorded on inclusion in the study group and during follow-up. We administered the Minnesota Living with Heart Failure Questionnaire to analyze quality of life. This consists of 21 questions about activities and issues pertaining to daily life in which patients score each item from 0 to 5: 0 represents optimal health status, and 5 the worst possible health status.

Average follow-up time was 25±10 months, and patients made 3-monthly visits to the Cardiology Unit outpatient clinic. None of the patients died during the follow-up.

We recorded readmissions for heart failure, readmissions for all other causes, length of hospitalization in days, overall mortality rate, mortality due to heart failure, quality of life score, and New York Heart Association (NYHA) functional class at the end of follow-up.

Statistics

All continuous variables showed a normal distribution. Qualitative variables are expressed in percentages and quantitative variables as mean±1 SD. Qualitative variables with <5% prevalence were compared by chi-squared or Fisher exact test. Relative risk (RR) was calculated for a 95% confidence interval (CI). Quantitative variables were compared by Student's t test. Probability of survival and non-readmission were calculated with Kaplan-Meier curves. Probabilities in the two groups were compared

with the Mantel log-rank test. Multivariate analysis of predictors of death or readmission for heart failure was calculated using the Cox proportional hazards method. All significant variables derived from the univariate analysis were included in the model, as well as those considered necessary in order to adjust the model correctly (e.g, sex, age, heart failure etiology, systolic function, valvular heart disease, NYHA functional class). We calculated risk quotients from the coefficients and established a 95% CI for significant variables. A *P* value <.05 was considered significant. All data were analyzed with SPSS 8.0 software for Windows.

RESULTS

Clinical characteristics

Of 153 patients studied, 62 had preserved ventricular systolic function (LVEF≥45%) and 91 ventricular systolic dysfunction (LVEF<45%). Table 1 shows baseline clinical characteristics of the 2 groups. Average age was similar in both groups (66±10 and 65±10 years; *P*=.54), and women were in the majority among patients with preserved ventricular systolic function (53% vs 28%; *P*<.01). We found no differences in terms of cardiovascular risk factors, history of prior admission for cardiac decompensation, NYHA functional class or average Minnesota Living with Heart Failure Questionnaire score. However, heart failure etiology clearly differed between the ischemia and idiopathic cardiomyopathy groups, and were the most prevalent causes in patients with systolic dysfunction; valvular heart disease and hypertension were the most prevalent in patients with preserved LVEF. Among patients with valvular heart disease we included those who presented conditions for which surgical interventions were not needed and those who had previously undergone surgery (e.g., valve implant, commissurotomy, valvoplasty).

Medical treatment

Table 2 compares treatments at discharge in patients in the two groups. We found no differences in the prescription of diuretics, spironolactone and angiotensin II AT1 receptor antagonists (ARA-II). Patients diagnosed as having depressed LVEF were more frequently prescribed angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, nitrates and antiaggregating agents, in line with results of clinical trials and the greater percentage of ischemic heart disease in this group. Overall, no differences were found in treatment with calcium antagonists except that centrally acting calcium antagonists were prescribed for patients with preserved ventricular systolic function and peripherally acting calcium

TABLE 1. Baseline clinical characteristics of groups studied

	LVEF≥45% (n=62)	LVEF<45% (n=91)	P
Age, years	66±10	65±10	.54
Women	33 (53%)	26 (28%)	<.01
Previous hospitalization for HF	33 (53%)	47 (52%)	.84
Hypertension	34 (55%)	52 (57%)	.78
Diabetes mellitus	18 (29%)	34 (37%)	.38
Hyperlipemia	22 (35%)	35 (38%)	.46
NYHA III and IV	56 (90%)	87 (96%)	.19
Serum sodium, mEq/L 136±4	135±4		.21
Creatinine, mg/dL	1.1±0.3	1.3±0.5	<.01
Atrial fibrillation	40 (65%)	29 (32%)	<.01
Etiology			
Ischemic heart disease	10 (16%)	40 (44%)	<.01
Idiopathic dilated cardiomyopathy	0%	33 (34%)	<.01
Valvular heart disease	26 (42%)	5 (5%)	<.01
Hypertension	16 (26%)	10 (11%)	.02
Other*	10 (16%)	3 (6%)	.01
LVEF, %	56±7	30±7	-

*Hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease.
LVEF indicates left ventricular ejection fraction; HF, heart failure; NYHA, New York Heart Association functional class.

antagonists were prescribed for patients with systolic dysfunction. A greater percentage of patients with preserved LVEF were treated with digoxin (60% vs 45%; *P*=.08), which was probably associated with the greater rate of auricular fibrillation in this group.

Morbidity and mortality

We found no differences in readmission rates for cardiac decompensation (45% in both groups; RR=1; 95% CI, 0.5-1.9; *P*=.99) or in readmission for other

TABLE 2. Treatment prescribed on discharge for patients with heart failure: preserved ventricular systolic function versus depressed systolic function

	LVEF≥45% (n=62)	LVEF<45% (n=91)	P
Diuretics	62 (100%)	91 (100%)	.80
Spironolactone	31 (50%)	49 (54%)	.64
Digoxin	37 (60%)	41 (45%)	.08
ACEI	32 (52%)	78 (86%)	<.01
ARA-II	12 (19%)	13 (14%)	.37
Beta-blockers	7 (11%)	30 (33%)	<.01
Calcium antagonists	11 (18%)	13 (14%)	.56
Nitrates	8 (13%)	45 (49%)	<.01
Antiplatelet drugs	19 (31%)	58 (64%)	<.01

ARA-II indicates angiotensin II AT1 receptor antagonists; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitors.

TABLE 3. **Follow-up mortality and morbidity (25±10 months) in patients with heart failure: preserved ventricular systolic function versus depressed systolic function**

	LVEF≥45% (n=62)	LVEF<45% (n=91)	RR (95% CI)	P
Readmissions for heart failure	28 (45%)	41 (45%)	1 (0.5-1.9)	.99
Readmissions for other causes	14 (23%)	27 (29%)	0.7 (0.3-1.4)	.33
Average length of hospitalization, days	4.2 ± 8.2	5.4 ± 12	-	.51
Overall mortality	18 (29%)	34 (37%)	0.7 (0.3-1.5)	.32
Deaths due to heart failure	13 (21%)	27 (29%)	0.6 (0.3-1.3)	.21

LVEF indicates left ventricular ejection fraction; CI, confidence interval; RR, relative risk.

Fig. 1. Survival free from readmission for heart failure in patients with preserved ventricular systolic function versus patients with systolic dysfunction

Fig. 2. Actuarial survival at 3 years in patients with heart failure and preserved ventricular systolic function versus systolic dysfunction.

causes (23% in patients with LVEF≥45% and 29% in patients with LVEF<45%; RR=0.7; 95% CI, 0.3-1.4; P=.33) (Table 3). Similarly, we found no difference in average length of hospitalization (4.2±8.2 days in patients with preserved ventricular systolic function versus 5.4±12 days in patients with systolic dysfunction; P=.51). Overall mortality rates were 29% in patients with preserved ventricular systolic function and 37% among patients with ventricular systolic dysfunction (RR=0.7; 95% CI, 0.3-1.5; P=.32)—figures that also indicates little difference between the groups. In most of the patients in both groups death was due to heart failure. Of these deaths, a cause other than heart failure was identified in only 28% of the patients with preserved ventricular systolic function and 21% of the patients with ventricular dysfunction.

Probability of non-readmission for heart failure was 52% in patients with preserved ventricular systolic function and 50% in patients with ventricular systolic dysfunction (P=.93) (Figure 1). Survival curves for the two groups are shown in Figure 2. Actuarial survival at 3 years was 62% in patients with preserved ventricular systolic function and 51% in patients with LVEF<45% (P=.19).

Even when patients with a heart failure of valvular etiology were excluded from our analysis, we still failed to identify differences between the groups. Similar rates were found for all-cause mortality (28% in patients with preserved ventricular systolic function and 36% in patients with systolic dysfunction; RR=0.68; 95% CI, 0.3-1.6; P=.38) and for readmission due to heart failure (39% vs 44%; RR=0.8; 95% CI, 0.4-1.8; P=.59).

At the end of follow-up, 79% of the survivors with preserved ventricular systolic function were in NYHA functional class II, as were 78% of those with systolic dysfunction (P=.68). Similarly, there were no differences in average score on the quality of life questionnaire (1.5±0.9 for patients with preserved
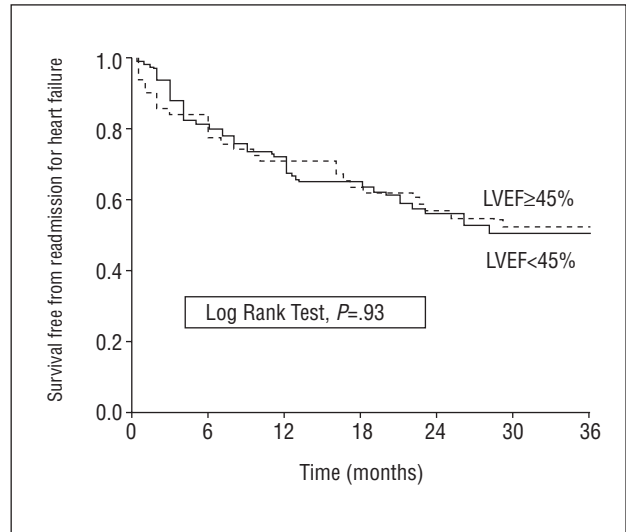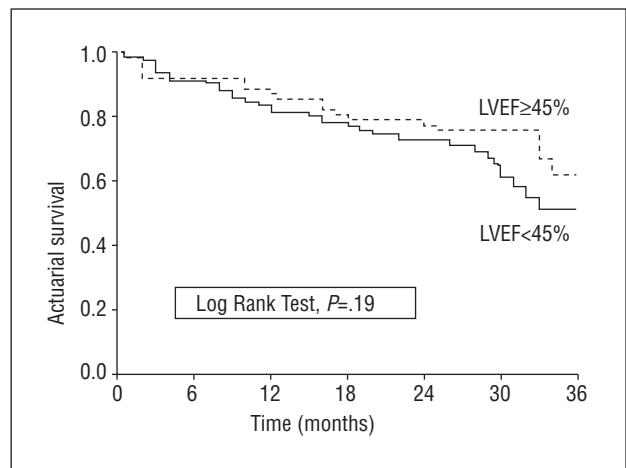
LVEF and 1.8±0.9 for patients with impaired function; P=.10).

In the multivariate analysis (Table 4), the independent predictors of mortality were age, hyponatremia on admission (serum sodium <136 mEq/L) and renal failure (serum creatinine at admission >1.6 mg/dL). Independent predictors of readmission for heart failure were age, prior hospitalization for heart failure, renal failure and quality of life questionnaire score (Table 5). Systolic function and valvular etiology of heart failure did not predict death or readmission for heart failure in the univariate or multivariate analysis.

DISCUSSION

Prevalence of heart failure with preserved ventricular systolic function

In this study, 40% of the patients presented with heart failure with preserved ventricular systolic function. This prevalence is similar to that reported by other authors.[6-8,12,14,15,18,19] In a prospective study of 172 consecutive patients hospitalized for heart failure, Tsutsui et al[14] found that 35% had preserved ventricular systolic function (LVEF>50%). In a substudy of the Framingham trial, Vasan et al[7] reported figures in the region of 50%; and in the Minnesota study,[6] 43% of the patients had LVEF>50%. In Spain, the prevalence of heart failure with preserved ventricular systolic function would appear to be similar[8,12,15] although little research has been published to date.

Clinical characteristics and treatment

We found no difference between groups in terms of age, probably because the patients we recruited were younger than those in other studies.[11] The vast majority of studies point to a greater frequency of heart failure with preserved ventricular systolic function in women.

We found no differences between groups in terms of the severity of heart failure when classified by NYHA functional class, or cardiovascular risk factors, for which we recorded similar percentages of hypertension, diabetes and hyperlipemia. Our data are similar to those reported in other studies.[10,11,14,15] However, the etiology of heart failure clearly differed between the 2 groups: ischemic heart disease and dilated cardiomyopathy were the most frequent causes in patients with ventricular systolic dysfunction, and valvular heart disease and hypertension were the most frequent causes in patients with preserved ventricular systolic function.

Treatment received by these patients has been analyzed. Authors such as Ahmed et al[10] have found no differences between the groups, but most agree that ACE inhibitors are more frequently prescribed in patients with diminished LVEF, in accordance with scientific committee recommendations.[14,15,20] In our study, the proportion of beta-blockers, antiplatelet drugs and nitrates prescribed for patients with ventricular dysfunction was comparatively greater than warranted by the rate of ischemic heart disease.

Morbidity and mortality

In this study the prognosis of patients with heart failure was not influenced by LVEF, and similar overall mortality and readmission rates were found in

TABLE 4. Independent predictors of mortality from all causes during follow-up (25 ± 10 months) in patients with heart failure. Cox proportional hazards method

	RR	95% CI
Age	1.05	1.01-1.08
Creatinine>1.6 mg/dl	1.92	1.23-2.96
Sodium<136 mEq/l	2.56	1.34-4.63

CI indicates confidence interval; RR, relative risk.

TABLE 5. Independent predictors of readmission for heart failure during follow-up (25±10 months) in patients with heart failure. Cox proportional hazard method

	RR	95% CI
Age	1.03	1.01-1.06
Previous hospitalization for HF	1.10	1.02-1.24
Serum creatinine>1.6 mg/dl	1.86	1.19-3.28
Quality of life (average score >2)	1.50	1.14-2.13

CI indicates confidence interval; RR, relative risk; HF, heart failure.

patients with preserved ventricular systolic function and those with systolic dysfunction. Relative risk (RR) for mortality from all causes was 0.70, (95% CI, 0.3-1.5; *P*=.32), which was not statistically or clinically significant (Table 3). We found no significant differences in the probability of readmission for heart failure. Kaplan-Meier curves showed a slightly more favorable actuarial survival for patients with preserved LVEF, although this was not statistically significant.

Although these findings may seem controversial, they are in agreement with reports by other authors. McDermott et al[21] found that the cumulative survival of 412 patients hospitalized for heart failure was similar in patients with preserved ventricular systolic function and patients with systolic dysfunction. Tsutsui et al[14] found no differences in survival and readmission rates for patients with preserved, intermediate or depressed ventricular systolic function. In our setting in Spain, Varela-Román et al[15] reported no significant differences in mortality rates at 1, 3 and 5 years (20.3%, 39.9%, and 54.7%, respectively, in patients with systolic dysfunction; 17.2%, 33.9%, and 44.2%, respectively, in patients with preserved ventricular systolic function). However, other authors have reported that preserved ejection fraction indicates a better prognosis in patients with heart failure.[7,8,10] In a population of 438 patients, Ahmed et al[10] found significantly greater mortality and readmission rates in patients with systolic dysfunction.

Univariate and multivariate analysis of predictors of

cardiovascular events (death or readmission for heart failure) did not identify greater risks associated with LVEF or valvular etiology of heart failure. In their study of the baseline characteristics and prognosis in patients with heart failure, Permanyer Miralda et al[22] reported that normal systolic function was less important for prognosis than clinical variables such as age or associated comorbidity. The reasons behind this are unclear, but variations in the patients, clinical profiles, different methods of calculating ventricular function and the different cutoff points used to define preserved ventricular systolic function may have influenced results.

Limitations

One of the main limitations of this study is that the size of our sample may be too small to detect statistically significant differences. The fact that we excluded from our analysis patients who died during hospitalization and included only data on those discharged may have influenced our results. However, the objective of our study was to evaluate the medium-term prognosis for these patients, which obliged us to exclude data recorded during hospitalization. In fact, the number of patients who died during hospitalization was similar in both groups, in contrast to other studies.[12]

This study included only patients discharged from the Cardiology Unit with clinical characteristics and treatments that differed from those of patients hospitalized in other departments, according to other authors.[8] This may bias results but it does offer the advantage of greater homogeneity in the clinical management and treatment of patients, two factors that clearly influence the prognosis of heart failure.

Despite these limitations, we consider that our study provides important information on the clinical characteristics and prognosis of patients with heart failure and preserved ventricular systolic function—information which suggests that this condition is not necessarily synonymous with a «better» prognosis.

CONCLUSIONS

Our study demonstrates that:

1. A substantial proportion of patients with heart failure have preserved ventricular systolic function.

2. Clinical characteristics of patients with heart failure and preserved ventricular systolic function differ from those of patients with heart failure and systolic dysfunction, and there is a greater incidence of valvular heart disease and hypertension etiologies, and a greater proportion of women among the former.

3. Medical treatment prescribed differs as a function of ejection fraction and the etiology of heart failure.

Patients with systolic dysfunction are more often prescribed ACE inhibitors, beta-blockers, nitrates and antiplatelet drugs.

4. In spite of these differences in clinical characteristics and treatment, the medium-term prognosis in both groups of patients is not significantly different in terms of mortality or readmission. Left ventricular ejection fraction is not independently associated with greater or lesser risk of cardiovascular events during follow-up.

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