Differences in Clinical Profile and Outcome in Patients With Decompensated Heart Failure and Systolic Dysfunction or Preserved Systolic Function

Stella M. Macín, Eduardo R. Perna, Juan P. Címbaro Canella, Pablo Alvarenga, Rolando Pantich, Nelson Ríos, Eduardo F. Farias, and Jorge R. Badaracco

Instituto de Cardiología Juana Francisca Cabral, Corrientes, Argentina.

**Objectives.** To compare the clinical characteristics and short- and long-term prognosis for chronic heart failure with left ventricular systolic dysfunction or preserved systolic function.

**Patients and method.** Three-hundred twenty-eight consecutive patients with decompensated chronic heart failure were studied prospectively. Depending on ejection fraction, participants were classified as having systolic dysfunction (group 1, ejection fraction ≤40%) or preserved systolic function (group 2, ejection fraction >40%).

**Results.** Systolic dysfunction was detected in 192 patients (58.5%) and preserved systolic function in 41.5%. Mean age was 62.7 (12.5 years) in group 1 and 65.2 (16.2 years) in group 2 (P=.03), with a male prevalence of 73.3% and 49.3%, respectively (P<.001). Ischemic cardiomyopathy was more frequent in group 1 (44.8% vs 25%; P<.001). In-hospital mortality was similar in patients with systolic dysfunction and preserved systolic function (2.9% vs 1%; P=NS). Twenty-four-month cumulative survival was 61% for patients with systolic dysfunction and 76% for patients with preserved systolic function (log rank test P=NS). In the Cox proportional hazards model, which included age, sex, functional class, hepatomegaly, peripheral hypoperfusion, BUN, sodium level, ejection fraction > 40%, and biventricular heart failure, preserved systolic function was not associated with late mortality. The variables that were independent predictors of late mortality were peripheral hypoperfusion (OR = 3.7; P<.0001), low sodium level (OR=0.9; P=0.09) and male sex (OR=1.9; P=.041).

**Conclusions.** Decompensated chronic heart failure with preserved systolic function was more frequent in women and older patients. Patients with preserved systolic function had a lower prevalence of coronary heart disease. However, these differences had no impact on the short- and long-term prognosis.

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

Full English text available at: www.revespcardiol.org

Características clinicoevolutivas en la insuficiencia cardíaca descompensada con disfunción sistólica y función sistólica preservada

**Objetivos.** Comparar las características clínicas y el pronóstico hospitalario y tardío en la insuficiencia cardiaca crónica con disfunción sistólica o función sistólica preservada.

**Pacientes y método.** Se incluyó a 328 pacientes consecutivos ingresados en el Instituto de Cardiología de Corrientes con insuficiencia cardiaca descompensada. Según la fracción de eyecación evaluada por ecocardiograma bidimensional, la población fue clasificada como con disfunción sistólica (grupo 1, con una fracción de eyecación ≤ 40%) o con función sistólica preservada (grupo 2, con una fracción de eyecación > 40%).

**Resultados.** Se detectó una disfunción sistólica en 192 pacientes (58.5%) y una función sistólica preservada en el 41.5% restante. En los grupos 1 y 2, la edad media fue de 62.7 ± 12.5 frente a 65.2 ± 16.2 años (p = 0.03) y la proporción de varones fue del 73.3 frente al 49.3%, respectivamente (p < 0.001). En el grupo 1 predominó la etiología isquémica (44.8 frente a 25%; p < 0.001), la presencia de tercer ruido (43.2 frente a 25%; p = 0.001) y el bloqueo completo de rama izquierda en el ecocardiograma (40.6 frente a 15.4%; p < 0.001). La mortalidad hospitalaria para los grupos 1 y 2 fue similar (2.9 frente a 1%; p = NS). La supervivencia a los 24 meses fue del 61% en los pacientes con disfunción sistólica y del 76% en los que presentaban una función sistólica preservada (test de rangos logarítmicos; p = NS). En el modelo proporcional de Cox, en el que se incluyó la edad, el sexo, la clase funcional y la presencia de hepatomegala, hipoperfusión periférica, uremia, natriemia, fracción de eyecación > 40% e insuficiencia global, el tipo de disfunción no se asoció con una mortalidad tardía, y fueron predictores independientes la
INTRODUCTION

In the developed world heart failure is a major health problem that mainly affects older people, with a 10% prevalence over 75 years of age. The entity is commonly considered typical when presenting in patients with dilated hearts and impaired systolic function. Consequently, most clinical trials have excluded patients with ejection fraction (EF)>40%, especially among those with normal EF (>50%).

However, a gradual increase in the proportion of older patients with heart failure who have preserved systolic function (PSF) has been reported. In different series the percentage ranges from 13% to 40%. Such a wide range may be explained by the fact that most data are from observational studies with less stringent inclusion criteria.

Diastolic dysfunction is the most common pathophysiologic feature in patients with heart failure and EF>40%, especially among those with normal EF (>50%). Recently, the terms diastolic dysfunction and PSF have been used interchangeably despite the fact that they should not be interpreted as synonyms. Primary diastolic failure is frequently found in arterial hypertension, valvular heart disease, restrictive or hypertrophic cardiomyopathy and other clinical situations such as tachycardia or ischemia.

The evolution of patients with systolic dysfunction (SDF) and of patients with PSF is controversial as some series indicate a comparatively worse prognosis for SDF but others indicate similar prognoses for both groups. However, data on patients hospitalized for heart failure are limited, especially for Hispanic populations. The objective of this study is to evaluate according to dysfunction type the prevalence, clinical characteristics and short- and long-term prognosis in a cohort of Latin-American patients with heart failure, hospitalized due to the deterioration of their condition.

PATIENTS AND METHODS

Population

Between October 1997 and April 2000 we conducted a prospective observational study of 328 consecutive patients with chronic heart failure that had evolved over >30 days after admission to a cardiology center (the Instituto de Cardiología, Corrientes, Argentina). All patients had been diagnosed with decompensated heart failure and met the following inclusion criteria: age >18 years and presence of 2 or more of the adapted Framingham major criteria or presence of one major criterion and two minor criteria. Major criteria included the presence of signs or symptoms of paroxysmal nocturnal dysnea, increased jugular venous pressure, crepitations, cardiomegaly, pulmonary edema, third heart sound and hepatojugular reflux. Minor criteria were peripheral edema, nocturnal cough, exertional dyspnea, hepatomegaly, heart rate >120 beats/min and pleural effusion. Exclusion criteria were heart failure associated with acute coronary syndrome (acute myocardial infarction or unstable angina) and difficulty in completing the follow-up.

Protocol

The protocol was approved by the Research and Teaching committee of our center. All patients gave written informed consent prior to enrolment.

Patients were hospitalized in the heart unit or intensive care. A full clinical history was taken and patients underwent physical examination, 12-lead electrocardiogram, chest x-ray and standard blood and urine analysis. Two-dimensional echocardiograms were performed by an experienced echocardiographer within 48 hours of admission using a Siemens Sonoline SI 1200 system (Siemens Ultrasound Incorporated, San Ramon, California, US). Ejection fraction was calculated using Simpson’s rule.

Definitions

Left ventricular systolic dysfunction was defined as EF>40%.

When calculating EF proved difficult, a subjective judgment of moderate to severe deterioration was considered equivalent. Preserved systolic function was...
defined as EF > 40% or as mild deterioration or normal functioning when judged subjectively (2 patients).

Baseline New York Heart Association (NYHA) functional class was evaluated with reference to the 30 days prior to hospitalization. Combined right and left heart failure was defined by the presence of signs and symptoms of biventricular cardiac failure. Peripheral hypoperfusion was defined by the observation of at least two of the following criteria: systolic arterial pressure < 90 mm Hg, proportional pulse pressure < 25%, altered sensorium, oliguria or abnormalities in peripheral circulation. Ischemic heart disease etiology was defined as evidence of previous infarction, functional ischemic heart disease or stenosis ≥ 50% in at least one coronary artery, prior myocardial revascularization with angioplasty or aortocoronary bypass surgery.

**Follow-up and outcomes**

Follow-up was conducted 6 months after the inclusion of the last patient. We analyzed the medical records held at our center where 30% of the patients were evaluated in the heart failure clinic and 50% by their local health center cardiologist. The remaining 20% were contacted by telephone or via clinicians in other centers. Mean follow-up was 10±6 months (range, 0-29 months). The outcome was all-cause death during follow-up.

**Statistical analysis**

Statistical analysis was carried out by χ², or Fisher exact test when the number was insufficient for χ². Results are expressed as percentages. Quantitative variables are expressed as mean±SD and normally distributed variables were evaluated for ANOVA. Differences with a probability of error < 5% were considered significant. Kaplan-Meier survival curves were constructed and compared with the log-rank test. Cox proportional hazards analysis was used to identify independent predictors of mortality among the following variables: age, sex, functional class, hepatomegaly, peripheral hypoperfusion, BUN, sodium level, EF > 40%, and combined right and left heart failure. Epi Info 6.0 and SPSS 10.0 for Windows (SPSS Inc., Chicago, Illinois, US) were used in the analysis.

**RESULTS**

**Patient Characteristics**

The population consisted of 328 patients. Preserved systolic function was found in 136 patients (41.5%). The average age of patients with SDf was 62.7±12.5 years whereas the average age of patients with PSF was 65.2±16.2 years (P=.03). Women represented 26.7% and 50.7% of the groups, respectively. Table 1 shows the demographic characteristics of both groups. In Group 1, we found a higher proportion of previous infarctions. In the population as a whole, two thirds had been previously diagnosed with heart failure and almost half had been hospitalized during the previous year but no differences existed between the groups.

Baseline NYHA functional class was similar in both groups with two thirds of patients in class II. Ischemic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Patients</th>
<th>SDf (Group 1)</th>
<th>PSF (Group 2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>328 (100%)</td>
<td>192 (58.5%)</td>
<td>136 (41.5%)</td>
<td>–</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>63.8±16.2</td>
<td>62.7±12.5</td>
<td>65.2±16.2</td>
<td>.03</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>202 (61.6%)</td>
<td>135 (73.3%)</td>
<td>67 (49.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>218 (66.7%)</td>
<td>134 (69.8%)</td>
<td>134 (62.2%)</td>
<td>.19</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>67 (20.4%)</td>
<td>45 (23.4%)</td>
<td>22 (16.2%)</td>
<td>.14</td>
</tr>
<tr>
<td>Previous AMI, n (%)</td>
<td>71 (21.6%)</td>
<td>53 (27.6%)</td>
<td>18 (13.8%)</td>
<td>.002</td>
</tr>
<tr>
<td>Previous diagnosis of heart failure, n (%)</td>
<td>206 (62.8%)</td>
<td>123 (64.1%)</td>
<td>83 (61%)</td>
<td>.65</td>
</tr>
<tr>
<td>Previous hospitalization, n (%)</td>
<td>151 (46%)</td>
<td>93 (48.4%)</td>
<td>48 (42.6%)</td>
<td>.61</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>198 (60.4%)</td>
<td>112 (55.2%)</td>
<td>86 (71.7%)</td>
<td>.36</td>
</tr>
<tr>
<td>III-IV</td>
<td>94 (28.6%)</td>
<td>60 (34.8%)</td>
<td>34 (28.3%)</td>
<td>.36</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>120 (36.8%)</td>
<td>86 (44.8%)</td>
<td>34 (25%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>84 (25.6%)</td>
<td>50 (26%)</td>
<td>34 (25%)</td>
<td>.93</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>59 (17.9%)</td>
<td>19 (9.9%)</td>
<td>40 (29.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other</td>
<td>65 (19.8%)</td>
<td>37 (19.3%)</td>
<td>28 (20.6%)</td>
<td>.96</td>
</tr>
</tbody>
</table>

*SD indicates standard deviation; AMI, acute myocardial infarction; SDf, systolic dysfunction; PSF, preserved systolic function.*
heart disease was the most frequent etiology in Group 1 (44.8% vs 25%; \( P < .001 \)) whereas valvular heart disease was most frequent in Group 2 (9.9% vs 29.4%; \( P < .001 \)) (Table 1).

Results of physical examinations and details of symptoms described by patients on admission produced statistically significant differences between the groups regarding presence of third heart sound (43.2% vs 25%; \( P = .001 \)) and paroxysmal nocturnal dyspnea (65.1% vs 49.3%; \( P = .005 \)) (Table 2).

Results of Laboratory Analyses, Electrocardiograms and Echocardiograms

Table 3 shows higher hematocrit in Group 1 than in Group 2 (41.9% vs 39.7%; \( P = .0003 \)), a greater frequency of left bundle branch block in Group 1 (40.6% vs 15.4%; \( P < .001 \)) and a greater frequency of Q waves in Group 1 (31.3% vs 20.6%; \( P = .04 \)).

M-mode and two-dimensional echocardiogram tracings recorded greater ventricular dimensions and volumes in Group 1. Ejection fraction was 26.6% and 57.5% (\( P < .001 \)) in patients with SDf and PSF, respectively.

Treatment

Table 4 compares drugs prescribed on discharge by group. Group 1 patients were more frequently prescribed renin-angiotensin system blockers (83.9% vs 68.4%; \( P = .001 \)), furosemide (84.4% vs 60.3%; \( P < .001 \)), and digoxin, amiodarone, and aspirin.

Survival Analysis

In-hospital mortality was 2.9% in Group 1 (4 patients) and 1% in Group 2 (2 patients; \( P = \text{NS} \)). Follow-up was completed for 98% of the population for an average of 10±6 months and survival rate was 61% in Group 1 versus 76% in Group 2 (Log rank test, \( P = \text{NS} \); Figure 1).

Predictors of Mortality

Cox proportional hazards analysis did not associate...
Follow-up mortality with dysfunction type. However, peripheral hypoperfusion (OR=3.7; \(P<.0001\)), low sodium level (OR=0.9; \(P=0.009\)) and male sex (OR=1.9; \(P=.041\); Table 5) were all independent predictors.

**DISCUSSION**

This study shows that a large proportion of unselected patients hospitalized with decompensated heart failure present PSF (41.5%) and that figures for in-hospital and longer-term mortality in this subgroup were similar to those for patients with systolic dysfunction.

In this cohort of consecutive patients, 41.5% of patients with heart failure had PSF. This figure falls within the 13%-74% range for unselected series \(^5\text{,6,10}\) in which higher percentages correspond to series of older patients. \(^20\) Dauterman et al find 55% prevalence, which is greater than that in most registries. \(^21\)

Patients with PSF tend to be older and more often are women with a high prevalence of hypertension. \(^22\text{-}25\) The results of the present study support these findings. The increased incidence of heart failure with PSF in older people probably reflects the replacement of myocytes by fibrous tissue and the high frequency of hypertension associated with left ventricular hypertrophy and ischemic heart disease. \(^22\text{-}23\) These pathophysiologic mechanisms would explain the detection of lower increases of troponin T in these patients, as reported recently. \(^26\) In patients with diastolic dysfunction, small increases in end-diastolic volume may be associated with a substantial increase in diastolic arterial pressure due to a reduction in left ventricular distensibility. \(^27\)

**Short- and Long-Term Mortality**

In this study, in-hospital mortality was low and no statistically significant differences were found when comparing patients with SDf (Group 1) and patients with PSF (Group 2). However, we would stress that the percentage of deaths was 3 times greater among Group 1 patients (2.9% vs 1%) which means we cannot ignore the influence the sample size may have had on results. Available mortality data vary widely. In some series, mortality has been lower among patients with PSF than patients with lower EF. This difference is notable in long-term follow-ups such as that of the Framingham study (8.7% vs 18.9% at 1 year) \(^18\text{,21}\) and the V-HeFT study subgroup (8% vs 19% at 2.3 years). \(^28\)

In contrast, Dauterman et al, \(^21\) Aronow et al \(^29\) and Perenkel et al \(^7\) report similar annual mortality rates for both groups. Their findings coincide with the data presented here which show no significant differences between groups at 24 months (61% vs 76%). Despite these end-of-follow-up percentages, two aspects of methodology could explain the lack of statistical significance. Firstly, survival curves are parallel up to 18 months and only then diverge, which implies a small population. Secondly, we should take into account the effect of the sample size. However, these findings could have a medical explanation. Systolic dysfunction has a worse prognosis which is related to its clinical profile: SDf is more frequent in men and ischemic heart disease occurs more often in younger patients. In contrast, heart failure with PSF affects older people, women, and those who present with a higher rate of comorbidities.

Data on the presence or absence of ischemic heart disease are controversial. \(^5\) Vasan et al reported that valvular heart disease etiologies (aortic stenosis or regurgitation) and PSF imply high annual mortality (as much as 25%) if surgery is not carried out. \(^30\text{,}31\)

**TABLE 5. Predictors of Mortality During Follow-Up**

<table>
<thead>
<tr>
<th>Variables</th>
<th>(P)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, yes/no</td>
<td>.041</td>
<td>1.957</td>
<td>1.026-3.732</td>
</tr>
<tr>
<td>Age, years</td>
<td>.465</td>
<td>1.008</td>
<td>0.987-1.029</td>
</tr>
<tr>
<td>Baseline NYHA functional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class, I-IV</td>
<td>.083</td>
<td>1.632</td>
<td>0.938-2.838</td>
</tr>
<tr>
<td>Hepatomegaly, yes/no</td>
<td>.436</td>
<td>1.314</td>
<td>0.661-2.612</td>
</tr>
<tr>
<td>Hypoperfusion, yes/no</td>
<td>.0001</td>
<td>3.747</td>
<td>1.880-7.470</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>.283</td>
<td>1.659</td>
<td>0.658-4.179</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>.009</td>
<td>0.927</td>
<td>0.876-0.982</td>
</tr>
<tr>
<td>EF&lt;40%, yes/no</td>
<td>.333</td>
<td>1.343</td>
<td>0.739-2.439</td>
</tr>
<tr>
<td>Combined right and left</td>
<td>.770</td>
<td>0.904</td>
<td>0.460-1.777</td>
</tr>
<tr>
<td>heart failure, yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*EF indicates ejection fraction; CI, confidence interval.*

![Figure 1. Kaplan-Meier survival curves at 24 months for patients with systolic dysfunction (SDf) and patients with preserved systolic function (PSF).](image-url)
Treatment on Discharge

In contrast to the treatment of heart failure in patients with reduced EF, limited data are available on patients with PSF.\textsuperscript{32-34} Although an ideal treatment has yet to be established, heart failure guidelines suggest controlling risk factors and applying specific treatment regimes.\textsuperscript{33-37} Agents such as calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), diuretics and nitrates can improve symptoms in patients with heart failure and PSF. However, few data are available analyzing their impact on survival.\textsuperscript{38-41}

Treatment regimes recommended for patients with heart failure and SDf or PSF were similar. Currently, evidence does not exist to justify this strategy. However, pathophysiologic data and retrospective study reports might indirectly support the use of some of these drugs. Among these are ACEIs-angiotensin II antagonists (ATII), which reduce and prevent the development of left ventricular hypertrophy,\textsuperscript{38,41,42} and improve arterial hypertension and ventricular relaxation.\textsuperscript{42} The clinical administration of these drugs for diastolic dysfunction has produced controversial results in non-randomized trials. In the series reported by Dauterman et al\textsuperscript{12,21} the use of ACEIs was not associated with a reduction in mortality or readmissions at 1 year. However, Philbin found a significant reduction in all-cause mortality (odds ratio [OR]=0.61) and heart failure mortality (OR=0.55).\textsuperscript{39} In the HOPE study, ramipril improved results in patients with multiple cardiovascular risk factors and preserved EF.\textsuperscript{43}

In both groups reported here, the use of beta-blockers at the time of discharge was less than in current registries. This is probably because the study took place between 1997 and 1999, prior to the publication of new studies on these drugs in patients with an impaired function.\textsuperscript{44}

Predictors of Mortality

It is surprising that sodium level, which reflects the activation of the renin-angiotensin-aldosterone system, should contribute to increased risk in these patients.\textsuperscript{45} The identification of peripheral hypoperfusion as a marker of high risk, perhaps due to greater adrenergic drive indicating a progression of the associated illness giving rise to structural changes is not unexpected.\textsuperscript{46}

The Framingham study showed that sex was an independent prognostic predictor\textsuperscript{18,44} with a higher percentage of survivors at 10 years among women. In the present study, male sex equates with a 1.9-fold increase in risk.

Ejection fraction is one of the most potent indicators of risk although PSF was not an independent prognostic marker in this study.

Limitations

This single-center study may not reflect the real incidence of heart failure with PSF in the community and probably only shows the profile of patients hospitalized in our center.

Clinical Implications

This study confirms that heart failure with PSF represents a major epidemiological problem, even among patients hospitalized for decompensated chronic heart failure. This entity is characterized by higher prevalence in older patients and women, a low prevalence of ischemic heart disease and no difference in a short- and long-term course from those patients with SDf.

These findings underline the need for change both in the perspective of clinicians who treat these patients and in the search for effective treatments that demonstrate their efficiency in large-scale randomized trials. These trials should include drugs previously trialed for heart failure with systolic dysfunction (ACEIs, beta-blockers) and the new agents. The focus should include therapeutic strategies aimed at preventing the development of this entity, tools for effective early diagnosis\textsuperscript{22,46} and the application of an adequate therapy regime even in the initial phases of the illness. This would avoid irreversible structural damage\textsuperscript{47} caused because diastolic dysfunction can be present for several years prior to the appearance of symptoms and represents the first stage of heart failure.\textsuperscript{22,37} With the data currently available, patients with heart failure and PSF should be treated in a manner similar to that used to treat patients who present with SDf.

REFERENCES

function in patients > 65 years of age. Am J Cardiol 2001;87:413-9.