Hospitalized Congestive Heart Failure Patients with Preserved versus Abnormal Left Ventricular Systolic Function

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Objectives. To compare the clinical characteristics of hospitalized patients with congestive heart failure and left ventricular dysfunction versus normal systolic function.

Methods. Clinical records of all admissions with a heart failure diagnostic code over a one-year period were reviewed retrospectively. Of 1,953 admissions, 595 were excluded because they did not fulfill diagnostic criteria.

Results. A total of 1,069 patients had 1,358 admissions with confirmed heart failure (1.27 admissions/patient). Of them, 706 patients (66%) had an echocardiographic study and 381 (54%) had ventricular dysfunction. Ventricular dysfunction was associated with previous myocardial infarction (OR = 5.8), left bundle-branch block (OR = 5.0), male sex (OR = 2.0), and smoking (OR = 1.8). Meanwhile, a negative association existed with age (OR = 0.97), previous valve surgery (OR = 0.46) and atrial fibrillation (OR = 0.49).

Patients with ventricular dysfunction had more hospitalizations in the cardiology department and received more vasodilators, aspirin, and nitrates on discharge. The prescription of angiotensin converting enzyme inhibitors prescription to patients with ventricular dysfunction increased with the severity of ventricular dysfunction and was more frequent in patients admitted to the cardiology department. Systolic dysfunction increased hospital mortality (OR = 2.9).

Conclusions. Patients admitted with heart failure and systolic dysfunction had a different clinical profile than patients with a normal ejection fraction. Seven clinical variables predicted the presence of systolic dysfunction. Patients with ventricular dysfunction had more hospital mortality and were prescribed vasodilators, aspirin, and nitrates more often on discharge.

Key words: Heart failure. Myocardial contraction. Echocardiography.

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Características de los pacientes ingresados por insuficiencia cardiaca según el estado de su función ventricular

Objetivos. Comparar las características de pacientes ingresados por insuficiencia cardiaca con y sin disfunción ventricular.

Métodos. Se revisaron retrospectivamente las historias de todos los ingresos con diagnóstico de insuficiencia cardiaca o relacionados (1,953 ingresos) durante un año. Se excluyeron 595 por no cumplir criterios de insuficiencia cardiaca.

Resultados. Se analizaron los 1,358 ingresos con diagnóstico confirmado de insuficiencia cardiaca en 1,069 pacientes (1,27 ingresos/paciente). En 706 pacientes se realizó un ecocardiograma y 381 (54%) presentaban disfunción ventricular. Se asociaron con disfunción ventricular las siguientes variables en el momento del ingreso: infarto de miocardio previo (odds ratio [OR] = 5.8), bloqueo de rama izquierda (OR = 5.0), sexo masculino (OR = 2.0) y tabaquismo (OR = 1.8). Por el contrario, presentaron una asociación negativa la edad (OR = 0.97), cirugía valvular previa (OR = 0.46) y fibrilación auricular (OR = 0.49).

Los pacientes con disfunción ventricular ingresaban con mayor frecuencia en el Servicio de Cardiología y recibían más vasodilatadores, antiagregantes y nitratos al alta. La tasa de prescripción de inhibidores de la enzima conversiva de la angiotensina en pacientes con disfunción ventricular se incrementó con la gravedad de la disfunción y fue superior en los ingresos en el Servicio de Cardiología. La disfunción ventricular incrementó la mortalidad intrahospitalaria (OR = 2.9).

Conclusiones. El perfil clínico de los pacientes ingresados con insuficiencia cardiaca por disfunción sistólica es claramente distinto del de los pacientes con fracción de eyeción normal. Siete variables clínicas permiten sospechar la presencia o ausencia de disfunción sistólica. Los pacientes con disfunción sistólica tienen una mayor mortalidad intrahospitalaria y reciben más vasodilatadores, antiagregantes y nitratos al alta.

INTRODUCTION

Heart failure (HF) is the only cardiovascular pathology whose incidence, prevalence, and overall mortality are still increasing. Depending on the studies, between 13% and 75% of the patients diagnosed as HF have a normal ejection fraction, although most authors agree that figures of 30% to 50% are probably closer to reality.1-4 This percentage is even higher in persons over the age of 65 years1,3-5,7 and women.1-3,6,7

In spite of this high frequency, studies comparing the clinical profile of patients hospitalized with HF due to systolic dysfunction and those with a normal left ventricular ejection fraction (LVEF) are scarce and limited by the inclusion of only men,8 a small number of patients with normal LVEF,2,9-11 or a different from usual cutoff point for normal LVEF.1 On the other hand, although some studies indicate that patients with systolic dysfunction have a worse prognosis,3,6,8,12,13 others have found no differences in survival between patients with and without ventricular dysfunction.11,14-16 This discrepancy in the prognostic effect of the normal LVEF could be due to the use of different patient selection criteria, since in many cases they have been limited to subgroups of ischemic heart disease,5,12,14 older people12,16, or men.5,8,16

It is important to distinguish patients with normal LVEF from those with systolic dysfunction, not only because of the possible effect on prognosis but, above all, because treatment recommendations differ.17,18 In addition, the beneficial effect of medical treatment on survival has been demonstrated only in patients with impaired LVEF. Angiotensin II-converting enzyme inhibitors (ACEI) are the first drugs that have been shown to increase survival in patients with HF and systolic dysfunction. Confirmation of this beneficial effect has led to their unanimous recommendation by experts and societies.18-20 Nevertheless, recent studies demonstrate that ACEIs are underused in patients with HF and impaired LVEF.21

The aims of the present study are: a) to ascertain what percentage of patients hospitalized for HF have a normal LVEF and to compare the clinical characteristics, intrahospital mortality, and treatment at discharge of patients with ventricular dysfunction compared with patients with normal left ventricular systolic function, and b) to study the factors that increase or decrease ACEI prescription in patients with ventricular dysfunction.

METHODS

The data came from the HOLA project (Heart Failure: Observation of Local Admissions). This registry covered all the medical departments of the Hospital Gregorio Marañón, a 1917-bed tertiary hospital with a healthcare area of 636 302 inhabitants (area 1 of Madrid), of which 537 666 inhabitants were over 15 years old.22 The project analyzed all admissions to the Gregorio Marañón University Hospital in 1996 with the main or secondary diagnosis of HF and unspecified cardiomyopathy, according to ICD-9 codes (International Classification of Diseases 9th Revision–Clinical Modification) (Table 1). The clinical histories of 1953 patients admitted with diagnostic codes were reviewed retrospectively, and demographic and medical data were recorded.

Inclusion criteria

The admissions of patients of 15 years old or older who met the following diagnostic criteria for HF were included:

a) In patients with moderate-to-severe ventricular dysfunction or cardiac valve disease, the diagnostic criteria of the European Society of Cardiology.23 b) In patients without ventricular dysfunction or cardiac valve disease in the echocardiogram, at least one symptom (oliguria, dyspnea, or edema), one sign (edema, increased jugular venous pressure, or crepitations), and evidence of HF in the chest radiograph (cardiomegaly or lung congestion/pleural effusion). c) In patients for whom no echocardiogram was available, at least one symptom and one sign or one finding of HF in the chest radiograph.
Exclusion criteria

The patients admitted were excluded if: a) the presence of HF could not be confirmed using the above criteria (454 admissions; 23.3%); b) acute myocardial infarction was the main diagnosis (the cause of admission was myocardial infarction and HF was a complication) (69 admissions; 3.5%), or c) patient data was unavailable (72 admissions; 3.7%).

Echocardiogram

The remaining 1358 admissions, corresponding to 1069 patients, were analyzed (1.27 admissions per patient). An echocardiogram was made in 706 patients (66%) and two groups were classified according to the presence (LVEF=50%) or absence of ventricular dysfunction (LVEF>50%). The ejection fraction was measured using the Teichholz formula and the subjective judgment of the echocardiography specialist. The criterion for performing echocardiography was the request of the responsible physician.

Review of clinical histories

All data were collected by two cardiologists (M.M.S. and J.A.G.R.). Cases were only included if both investigators agreed that the criteria defined had been satisfied. The reproducibility of decision-making, evaluated by randomized re-evaluation of 9% of the cases, was good, with k=0.89 (95% confidence interval, 0.77-0.99).

Statistical methods

For the comparison of groups with and without systolic dysfunction, the Chi-square test or Fisher exact test (as indicated) was used for categorical variables and the Student t test for continuous variables, after confirming the assumption of a normal distribution.

In order to determine if systolic dysfunction was an independent predictor of intrahospital mortality, a multivariate analysis with logistic regression was carried out by stepwise retrograde elimination, in which the variables found to be predictive of mortality in the univariate analysis with $P<.15$ were included.

The predictors of systolic dysfunction at admission were studied by multivariate analysis with logistic regression and retrograde stepwise elimination in which the variables recorded at admission that were predictive of systolic dysfunction in univariate analysis with $P<.15$ were included. In order to assess the discriminatory capacity of the model, the ROC procedure for logistic regression based on generating the predicted variable was also used, which estimated the probability of each subject of not receiving ACEIs.

The odds ratios are expressed with their 95% confidence interval. The SPSS statistical program version 10.0 for Windows was used for statistical analysis (SPSS Inc., Chicago, Illinois, U.S.).

RESULTS

Clinical profile

From 1 January to 31 December we identified 1069 patients with 1358 admissions for confirmed HF (1.27 admissions/patient). Seven hundred and six patients (66%) with an echocardiogram were included in the present study. Echocardiograms were made less frequently in women and older persons (Figure 1). LVEF was 0.5 or less in 381 patients (54%), whereas 325 patients (46%) had a normal LVEF. The proportion of patients with a normal LVEF was greater in women (64% versus 29% in men) and older persons (55% in=75 versus 39% in <75 years), both being significant differences, with $P<.001$ (Figure 2). In Table 2 is shown the univariate analysis of the comparison of the clinical profile of the two groups: the patients with normal LVEF were older, more frequently women, and presented more valvular disease. However, they had less ischemic heart disease and less comorbidity than the patients who presented systolic dysfunction.
In Table 3 are listed the variables recorded at the time of admission that were independent predictors of ventricular dysfunction: presence of left bundle-branch block in the electrocardiogram, history of myocardial infarction, smoking, and male sex, all of which had a positive association. On the contrary, advanced age, previous valvular surgery, and atrial fibrillation had a negative association with ventricular dysfunction. With these 7 clinical variables at admission, the presence of LVEF=0.5 was predicted with an area under the ROC curve of 0.80 (95% confidence interval, 0.76-0.83).

**Hospital mortality**

There were no significant differences in intrahospital mortality between the two groups in univariate analysis (ventricular dysfunction 7% versus normal LVEF 4%; \( P=.07 \)). However, multivariate analysis in which age and other confusion variables were controlled demonstrated that the presence of ventricular dysfunction independently increased intrahospital mortality by 2.9 times (\( P<.01 \)), with a 95% confidence interval of 1.2-7.0.

**Treatment**

In the 662 patients discharged alive (94%), the treatment received at hospital discharge was analyzed. In Table 4, the pharmacological treatment of patients is compared in relation to normal or abnormal ejection fraction. The patients with ventricular dysfunction received more drugs at discharge, mainly ACEIs and other vasodilators, antiplatelet aggregants, and nitrates.

**Angiotensin I converting enzyme inhibitors**

Patients with severe ventricular dysfunction (LVEF <0.3) received ACEI more frequently than those with moderate dysfunction (LVEF, 0.3-0.4), patients with moderate dysfunction more frequently than those with mild dysfunction (LVEF, 0.41-0.5), and patients with mild dysfunction more frequently than those with a normal LVEF (77%, 66%, 49% and 45%, respectively; \( P<.001 \)). In patients with LVEF=0.4, ACEI use was greater in the cardiology department than in other departments, whereas in patients with LVEF>0.4, the opposite occurred (Figure 3).

![Fig. 2. Distribution of the left ventricular ejection fraction (LVEF) in different groups by age and sex.](https://www.revespcardiol.org/)

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In order to identify the factors that determined the non-prescription of ACEIs in patients with ventricular dysfunction, a multivariate analysis was made, the result of which is shown in Table 5. Less severe ventricular dysfunction, kidney failure, and aortic stenosis was associated with less ACEI prescription.

**DISCUSSION**

**Percentage of patients with normal LVEF**

In our study, 46% of the patients in which an echocardiogram was made had normal ejection fraction. This figure is comparable to that obtained by other authors in population studies of HF or in hospitalized patients. In the substudy of Framingham made by Vasan et al., approximately half of the patients with HF had normal LVEF (>0.5). In the Minnesota study, 43% had a conserved LVEF (>0.5). On the other hand, in older patients the percentage of cases of HF with conserved systolic function increased, reaching or surpassing 50% in patients over 65 years, which also seemed to occur in women. It is interesting to note that in our study, as in other series, one-third of the patients were excluded from the analysis because no LVEF evaluation was available. The fact that the number of patients without an echocardiogram is higher in women and older patients (Figure 1), and that these subgroups presented more HF with normal LVEF (Figure 2), probably indicates that the figure of 46% of patients hospitalized for HF with normal LVEF is an underestimate.
TABLE 4. Pharmacological treatment of patients in relation to ejection fraction

<table>
<thead>
<tr>
<th>Treatment at discharge</th>
<th>LVEF&gt;0.5</th>
<th>LVEF&lt;0.5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of drugs</td>
<td>3</td>
<td>4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>23</td>
<td>34</td>
<td>.0013</td>
</tr>
<tr>
<td>ACEIs</td>
<td>45</td>
<td>69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>43</td>
<td>55</td>
<td>.0010</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>3</td>
<td>8</td>
<td>.0014</td>
</tr>
<tr>
<td>Diuretics</td>
<td>81</td>
<td>82</td>
<td>.89</td>
</tr>
<tr>
<td>Digoxin</td>
<td>50</td>
<td>47</td>
<td>.42</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>6</td>
<td>6</td>
<td>.96</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>15</td>
<td>12</td>
<td>.16</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>32</td>
<td>35</td>
<td>.38</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>3</td>
<td>3</td>
<td>.52</td>
</tr>
</tbody>
</table>

Data are expressed as percentages, except for the number of drugs (mean). ACEI indicates angiotensin II converting enzyme inhibitors.

TABLE 5. Factors that determine non-prescription of angiotensin converting enzyme inhibitors (ACEIs)

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney failure</td>
<td>3.1 (1.9-5.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Aortic stenosis*</td>
<td>1.5 (1.2-1.9)</td>
<td>.0006</td>
</tr>
<tr>
<td>Ventricular dysfunction**</td>
<td>0.6 (0.5-0.7)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. *Coded as «without aortic stenosis»=0, to «severe aortic stenosis»=3; **coded as mild=1 to severe=3. These factors allowed us to describe relations that were not well-known before now. Nevertheless, we found no relevant differences in the presence of cerebrovascular accidents (12% in patients with normal LVEF versus 11% in patients with ventricular dysfunction; P=.79) or hypertension (46% in patients with normal LVEF versus 43% in patients with ventricular dysfunction; P=.31), which suggests to us that no differences exist between patients hospitalized for HF with and without ventricular dysfunction in an unselected population.

Profile of patients in relation to the presence or absence of ventricular dysfunction

Few studies have compared patients hospitalized for HF according to whether or not they have systolic dysfunction using a large enough number of patients to detect differences in the clinical profile of groups. In addition, previous comparisons of the clinical characteristics of patients hospitalized for HF with or without systolic dysfunction included few patients with a normal LVEF. The study by Dougherty et al19 of 72 patients with HF (17 with a normal LVEF) demonstrated a greater prevalence of hypertension in patients with a normal LVEF. Echeverria et al8 studied 50 patients with HF (20 with a normal LVEF) and found a greater prevalence of coronary artery disease in patients with systolic dysfunction.

The V-HeFT study5 compared 83 men with normal LVEF to 540 men with ventricular dysfunction. The men with normal LVEF had less coronary artery disease and more hypertension than the men with ventricular dysfunction. McDermott et al6 studied 298 patients with HF, of which 92 had a normal LVEF. The patients with a normal LVEF were older, more frequently women, and more often had stroke and hypothyroidism. The patients with systolic dysfunction presented more coronary artery disease and had cardiomegaly more frequently in the chest radiograph made on admission. Cohen-Solal et al1 studied 739 patients (394 with LVEF<0.4) and found that these patients were older, more frequently women, had hypertension and atrial fibrillation more often, and received more calcium antagonists. On the contrary, they presented less coronary artery disease and received less ACEIs, diuretics, digoxin, nitrates, and beta-blockers than patients with LVEF<0.4. The intrahospital mortality was superior in patients with ventricular dysfunction.

In relation to previous studies, our study analyzed an unselected population and a larger number of patients, particularly patients with LVEF>0.5. This has allowed us to describe relations that were not well-known before now. Nevertheless, we found no relevant differences in the presence of cerebrovascular accidents (12% in patients with normal LVEF versus 11% in patients with ventricular dysfunction; P=.79) or hypertension (46% in patients with normal LVEF versus 43% in patients with ventricular dysfunction; P=.31), which suggests to us that no differences exist between patients hospitalized for HF with and without ventricular dysfunction in an unselected population.

In our population, a normal ejection fraction was more common in older people and women and less frequent in patients with ischemic heart disease/myocardial infarction. This finding coincides with the findings of studies of patients hospitalized for HF12 or in community at large.3 The relation between ventricular dysfunction and coronary artery disease is sustained by the pathophysiological substrate of impaired ventricular contraction induced by myocardial necrosis and/or ischemia.

Prognostic value of LVEF

Our study also confirmed the less favorable intrahospital prognosis of patients with ventricular dysfunction, who had a 3-fold greater mortality. Although patients with ventricular dysfunction were found to have a shorter survival in population studies like the Framingham study,3 V-HeFT,8 or the study of hospitalized patients by the French Society of Cardiology,4 other studies have not found a clear effect of ventricular dysfunction on prognosis.11 These differences could be due to the different selection criteria of the studies, since some were limited to studying subgroups of patients with HF and ischemic heart disease, older people, or men. In addition, in most of the studies the information about ventricular function was not available for all of the patients.

Treatment

Several clinical trials have demonstrated that ACEIs increase survival in patients with HF and ventricular dysfunction.
dysfunction. The first was published more than 10 years before the admissions studied here. Nevertheless, only 69% of the patients with ventricular dysfunction in our study received ACEIs at discharge. Some recent studies indicate that ACEIs are underused, pointing to a lack of information among physicians as the cause. Another explanation is that the information obtained in clinical trials is not always applicable to unselected populations of patients with HF, which have an older mean age, more women, frequent comorbidity, and a higher incidence of HF with normal LVEF. The fact that 31% of the patients with ventricular dysfunction in our study did not receive ACEIs could have been due, at least in part, to presence of contraindications (aortic stenosis and kidney failure), which, together with the degree of ventricular dysfunction, were the only predictors of ACEI non-prescription.

Although our rate of use of ACEIs cannot be extrapolated to other geographic areas, in a recent study that analyzed differences in the treatment of HF in different European countries, Spain occupied second place, after the United Kingdom, in the use of ACEIs at suitable doses (more than 75 mg daily of captopril or more than 20 mg daily of enalapril or lisinopril). Surprisingly, 45% of the patients with normal LVEF received ACEIs. This finding could be due, at least in part, to the fact that these drugs are authorized in Spain for the treatment of HF, without considering ventricular function, although all the studies of ACEIs were made in patients with LVEF<40%. An important proportion of patients with hypertension or diabetes is a possible explanation, although the fact is that cardiologists treat patients with LVEF=0.4 with ACEIs more frequently than non-cardiologists do. The opposite occurs in patients with LVEF>0.4 and suggests, as has been observed elsewhere, that cardiologists follow published recommendations and the results of clinical trials.

We also found less use of platelet antiaggregants and nitrates in patients with a normal ejection fraction, which was related to the association of ventricular dysfunction with ischemic heart disease that has already been mentioned. The low percentage of beta-blockers used is probably due to the fact that the admissions date from 1996, when the benefit of these drugs in the treatment of HF was not so well known. In addition, the present study examines treatment at discharge whereas drug administration often begins on an outpatient basis, after the acute episode concludes.

**Limitations**

The exclusion of one-third of the patients because no echocardiogram was available is a limitation that may bias our sample of patients, since the subgroup of patients in which the echocardiogram was not made were older, contained more women and, possibly, had more comorbidity. This limitation is common to all series of unselected patients hospitalized for HF, in which the percentage of patients without an echocardiogram is 23% to 46%. Choosing the LVEF value (a filling-dependent measurement) as an index of left ventricular function is also questionable because the LVEF is based on two volume measurement errors that are susceptible to measurement errors and have only a moderate reproducibility. The cutoff point of 0.5 to separate normal LVEF from ventricular dysfunction can also be criticized. We chose this value because it is the value most often used in studies to separate normal LVEF from ventricular dysfunction. The use of only echocardiographic data and not that of the radionuclide or iodine contrast ventriculography, which were available for some patients, was an attempt to increase the homogeneity of the sample by using only data obtained with a single technique, the technique most widely used at our center. In addition, echocardiographic results were available for all the patients that had a ventriculography. Nevertheless, few studies have compared the clinical characteristics of patients hospitalized with HF and a normal LVEF versus those with ventricular dysfunction by comparing a sufficient number of patients in unselected populations. Our study contributes important information on the association between age, sex and other variables with ventricular dysfunction.

**CONCLUSIONS**

1. Systolic dysfunction increases the mortality of patients hospitalized for HF.

2. The clinical profile of patients with systolic dysfunction is different from that of patients with a normal ejection fraction. The risk of systolic dysfunction increases with the presence of previous myocardial infarction, complete left bundle-branch block, smoking, and male sex, whereas it decreases with age, previous cardiac valve surgery, and the presence of atrial fibrillation.

3. Patients with ventricular dysfunction received more drugs at discharge, particularly vasodilators, platelet aggregation inhibitors, and nitrates.

4. Cardiologists treat patients with LVEF=0.4 with ACEIs more often than non-cardiologists do, and they treat patients with LVEF>0.4 less often than cardiologists do.

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