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Diagnosis and Therapy for Diastolic Heart Failure

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Diastolic heart failure (heart failure with preserved systolic function) causes 30% to 50% of all cases of heart failure, and its prognosis is almost as ominous as that of systolic heart failure. Currently, it is diagnosed when clinical criteria for heart failure are present and left ventricular ejection fraction is preserved (higher than 40% to 50%). However, determinations of brain natriuretic peptides may play an important role in the future. Because we have no evidence from clinical trials, with the exception of the slight benefit obtained with candesartan in reducing hospitalizations in the CHARM Study, treatment of diastolic heart failure is based on the identification and treatment of the causal factor (hypertension, coronary heart disease), control of heart rate, and relief of fluid congestion. Thus, combined therapy with low-dose diuretics, antihypertensive drugs for bradycardia (beta blockers, calcium antagonists) and angiotensin antagonists seems now to be the best therapeutic strategy.

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

Diagnóstico y tratamiento de la insuficiencia cardíaca diastólica

La insuficiencia cardíaca diastólica, o con función sistólica conservada, representa entre el 30 y el 50% de todos los casos de insuficiencia cardíaca, y su pronóstico es casi tan desfavorable como el de los pacientes con insuficiencia cardíaca crónica (ICC) con función sistólica deprimida. En la actualidad sólo se exige para su diagnóstico la presencia de criterios clínicos estrictos de insuficiencia cardíaca y una fracción de eyección del ventrículo izquierdo (FEVI) conservada (mayor del 40-50%), aunque la determinación de los valores de péptido natriurético cerebral puede tener interés para el diagnóstico en el futuro. Puesto que no hay evidencia derivada de ensayos clínicos importantes, salvo el ligero beneficio obtenido con candesartán en el estudio CHARM en la reducción de los reingresos, su tratamiento se basa en la identificación y el tratamiento de su etiología (hipertensión arterial, cardiopatía isquémica), el control de la frecuencia cardíaca y el alivio de la congestión, por lo que la combinación de diuréticos a dosis bajas, antihipertensivos bradicardizantes (bloqueadores beta, antagonistas del calcio) y antagonistas de la angiotensina en la actualidad parece ser la mejor estrategia terapéutica.

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

INTRODUCTION

Chronic heart failure (CHF) is the final outcome common to most heart diseases. For a variety of reasons—the aging population, increased survival rate among patients with illnesses such as coronary heart disease or hypertension—the prevalence of CHF has increased. Pharmacological treatment of heart failure has advanced and most clinical trials show improved prognosis but the effects of pharmacological therapy on the general population of patients with CHF have been modest and high rates of mortality and morbidity persist.[1,2] One possible explanation is that most clinical trials have included patients with reduced left ventricular ejection fraction (LVEF) (systolic dysfunction) whereas 30%-50% of patients with CHF in population studies[3] and hospital registries[4,5] have preserved LVEF. In these patients, the effect of a range of drugs used in CHF therapy has only recently been evaluated. Chronic heart failure with preserved systolic function is more frequent in older patients and women,[3,6,7] which may partly explain the poor prognosis. In recent years, both epidemiologic and clinical aspects of the problem and its treatment have received much attention and the objective of this paper is to review major results in the literature.

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CONCEPT

Initially, the term used to classify patients with heart failure and normal or nearly normal contractility was "diastolic heart failure." However, this is now thought controversial and most authors prefer "heart failure with preserved systolic function." In routine clinical practice, both terms represent a concept that probably identifies the same patients although their pathophysiologic reality may differ. Diagnosis of diastolic heart failure requires the presence of a clinical syndrome of CHF together with objective demonstration of isolated or dominant diastolic dysfunction.[8] In contrast, heart failure with preserved systolic function is diagnosed in patients with a clinical syndrome of CHF and normal or nearly normal LVEF, without the need to demonstrate diastolic abnormality. Given the countless limitations of noninvasive study (Doppler echocardiogram, isotopic ventriculography) of diastolic function and the wide range of variables in the parameters currently used to quantify these (quantification of age-, preload-, and afterload-related cardiac situation, heart rate, etc), it seems more reasonable to use the term "CHF with preserved systolic function," without insisting on an objective demonstration of diastolic abnormality. In fact, some studies show that among patients with CHF diagnosed according to Framingham criteria and LVEF >50% who undergo a hemodynamic study and Doppler echocardiogram, 92% present at least one diastolic abnormality in the hemodynamic study; 94% present at least one diastolic abnormality in the Doppler, and 100% present at least one diastolic abnormality identified by one or other of these methods.[9] Consequently, the study of diastolic function serves to confirm the diagnosis of diastolic CHF rather than establish it.

DIAGNOSTIC CRITERIA

We will now summarize the evolution of diastolic CHF diagnosis. The European Society of Cardiology Study Group on Diastolic Heart Failure proposed that 3 obligatory criteria that should be simultaneously present[10]: *1)* presence of signs or symptoms of CHF; *2)* presence of normal or only mildly abnormal left ventricular systolic function, and *3)* evidence of abnormal left ventricular relaxation, filling, diastolic distensibility or diastolic stiffness. These criteria have received their share of criticism. Firstly, clinical diagnosis of CHF (via signs and symptoms) lacks sensitivity and specificity, apparently making fulfillment of the Framingham criteria (Table 1), or of those of any other equally validated classification, essential. Secondly, the limit on "normal" LVEF has varied greatly (40%-50%); the European Study Group chose 45% but it is arguable that ejection fraction in the 40%-50% range could be considered normal. Moreover, ejection fraction can vary according to when it is determined. For example, in heart failure secondary to acute transitory myocardial ischemia or hypertensive crisis, LVEF determined during the first hours can be reduced but at 24 hours it is normal. Studies show that in patients with heart failure and uncontrolled hypertension differences between LVEF determined in the emergency department and LVEF measured at 72 hours were not significant in those patients who were already clinically stable.[11] Thus, it is not usually essential to determine LVEF during initial decompensation as values obtained in the following days are reliable; the only exception to this rule may be in patients with acute ischemia. The third criticism of the European criteria is related to the low reliability, sensitivity and specificity of the determination of abnormalities in diastolic function, as mentioned earlier.

Vasan and Levy[12] use 2 types of criteria to classify diastolic CHF diagnosis into 3 categories: definitive, probable, and possible (Table 2). The clinical application of these criteria is limited due to their complexity and the fact that both types are empirical and demand demonstrable abnormalities in diastolic function. Consequently, as mentioned earlier, most authors now tend to obviate the need to study diastolic function and define as diastolic CHF cases of clinical criteria of heart failure and LVEF >50% or >45%[9]. Even in the CHF with preserved systolic function component of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trials, the ejection fraction criterion was reduced to 40%.[13]

TABLE 1. **Framingham Criteria for the Diagnosis of Heart Failure***

Major criteria
Paroxysmal nocturnal dyspnea
Orthopnea
Elevated jugular venous pressure
Crepitations
Third heart sound
Radiological evidence of cardiomegaly
Radiological evidence of pulmonary edema
Minor criteria
Extremity edema
Night cough
Exertional dyspnea
Hepatomegaly
Pleural effusion
Heart rate >120
Loss of >4.5 kg in 5 days following diuretic treatment

*Diagnosis of heart failure requires the presence of 2 major criteria or 1 major and 2 minor criteria.

DIAGNOSTIC METHODS

Diagnostic use of isolated symptoms and clinical signs of heart failure is limited and improves when they are grouped as in the Framingham criteria. However, the reliability of these signs and symptoms to distinguish systolic CHF from diastolic CHF is weak (Table 3). McDermott et al[14] found no significant differences in prevalence of symptoms, signs or radiological data between patients with LVEF <50% or >50%. Despite expectations, not even radiological evidence of cardiomegaly distinguished between cases. Similarly, electrocardiograms fail to differentiate between CHF with preserved or reduced systolic function although a normal electrocardiogram does make diagnosis of heart failure unlikely. Therefore, when clinical criteria indicate suspected heart failure it is essential to perform Doppler echocardiography or an alternative study of ventricular function (isotopic ventriculography) to determine ejection fraction with precision. Moreover, echocardiography provides information on the existence or not of left ventricular hypertrophy and can give indications as to diastolic function (although, as said earlier, this is not essential to the diagnosis of CHF with preserved systolic function). The hemodynamic study, the "gold standard" for the diagnosis of diastolic CHF, is reserved for specific cases or when other indications exist. In the future, new techniques such as cardiac magnetic resonance may play an important role in the evaluation of anatomy and cardiac function (although currently their use is limited due to lack of availability).

In recent years, determination of brain natriuretic peptides (BNP and NT-proBNP) has become highly important in CHF diagnosis[15]. In patients with diastolic dysfunction, BNP concentrations are high although some studies find that peptide levels are higher in patients with systolic dysfunction and patients with mixed systolic and diastolic dysfunction. Levels of BNP correlate with abnormality in indices of diastolic function. Other studies indicate that diagnostic BNP levels are similar in diastolic CHF and systolic CHF[16]. Recently, Bay et al[17] found that an isolated determination of NT-proBNP in patients with CHF on admission can distinguish between patients with LVEF >40% and <40%. With a cut-off value of 357 pmol/L, the sensitivity of the test to identify patients with LVEF <40% was 73%, specificity 82%, and negative predictive value 98%. Moreover, they found a correlation between LVEF and natriuretic peptide values.

In conclusion, it seems that determination of brain natriuretic peptide levels may play an important future role in the study of CHF with preserved systolic function. This is already being evaluated in clinical trials (I-Preserve).

TABLE 2. **Vasan and Levy's Criteria for the Diagnosis of Diastolic Heart Failure[12]**

Definitive diagnosis
Definitive clinical evidence of heart failure, and
Normal left ventricular systolic function with ejection fraction >50% determined in the 72 hours following clinical decompensation and
Objective evidence of diastolic dysfunction in the hemodynamic study (increase in diastolic pressure with normal or reduced diastolic volume)
Probable diagnosis
Definitive clinical evidence of heart failure, and
Normal left ventricular systolic function with ejection fraction >50% determined in the 72 hours following clinical decompensation
Possible diagnosis
Definitive clinical evidence of heart failure, and
Normal left ventricular systolic function with ejection fraction >50% determined outside of the 72 hours following clinical decompensation

TABLE 3. **Prevalence of Most Frequent Signs and Symptoms of Heart Failure in Patients With Systolic and Diastolic Heart Failure[14]**

	Diastolic (%)	Systolic (%)
Exertional dyspnea	85	96
Paroxysmal nocturnal dyspnea	55	50
Orthopnea	60	73
Crepitations	72	70
Third heart sound	45	65
Fourth heart sound	45	66
Edemas	30	40
Elevated jugular venous pressure	35	46
Hepatomegaly	15	16
Displaced apex beat	50	60
Radiological evidence of cardiomegaly	90	96
Venous pulmonary hypertension	75	80

Differences not statistically significant.

PROGNOSIS

Although it was traditionally thought that CHF prognosis was closely linked to ejection fraction and that mortality in patients with CHF and reduced systolic function was much greater, a number of recent studies have questioned this. In the classic study by Senni,[3] 6 year survival was not significantly different among patients with CHF and LVEF <50% or >50% and between 60% and 70% of all patients died in this period. In both cases, survival was much lower than expected in the general population of the same age and gender (P<.0001). In Spain, similar results have been published by Varela-Román et al[18] and by our own group[5]. Varela-Román et al found that 5 year mortality was 54% in patients with systolic dysfunction and 44% in patients with preserved LVEF (a nonsignificant

difference). In our study, 3 year mortality was 49% in patients with CHF and LVEF <45% and 38% in patients with CHF and LVEF >45% (*P*=.19, nonsignificant). Readmission rates were also similar for both groups (48% and 50% respectively). Both Permanyer-Miralda et al[19] and our own study[5] found LVEF is not an independent predictor of mortality and that factors such as age or comorbidity are more relevant to prognosis.

All these data seem to show that prognosis of CHF with preserved systolic function is slightly less ominous than that of CHF with reduced systolic function. Annual mortality of patients with diastolic CHF is 5%-8% versus 10%-15% among patients with systolic CHF.[8] Mortality in the general population without CHF and of a similar age is 1% per year. Presence of coronary disease, age and the LVEF cut-off value are important factors in the prognosis. When patients with ischemic heart disease are excluded, annual mortality for diastolic CHF falls to 2%-3%.[20] In patients >70 years with CHF, mortality is very similar, independently of LVEF.[21]

However, other studies have found mortality and readmission rates significantly greater in patients with preserved or reduced LVEF.[22] In Spain, Martínez-Sellés et al[23] recently found an interrelation between gender and LVEF with regard to prognosis. In women with CHF, survival does not vary with respect to LVEF but it is significantly lower in men with LVEF <30%. In other words, survival is similar for men and women when LVEF is >30%, but better in women when LVEF is <30%. Data from the CHARM study add more confusion to the comparative prognosis of CHF with preserved or reduced systolic function. In CHARM, patients with LVEF >40% had a surprisingly low mortality rate, lower than patients with LVEF <40%, which might explain the lack of an observable difference in mortality rates between patients taking candesartan and patients taking the placebo.[13] These differences and the variability observed in the studies may be connected to the different clinical profiles of patients, methods and cut-off values used to determine ventricular function and the different research designs applied.[5] Moreover, patients with systolic CHF are usually treated with a greater percentage of drugs with favorable prognostic effects, such as ACE inhibitors, spironolactone, and beta-blockers.[5,13,18]

TREATMENT

To date, only one large scale monitored randomized clinical trial has taken place to compare drug versus placebo administration in patients with CHF and preserved systolic function (the "preserved" component of the CHARM study).[13] This trial compared the efficacy of a daily 32 mg dose of candesartan versus a placebo in 3023 patients with CHF and LVEF>40%. After a 36.6 month mean follow-up, primary combined outcome incidence (death by cardiovascular cause or admission for CHF) was similar in both groups, with a tendency in favor of candesartan at the expense of a significant reduction in admissions for CHF (16%; *P*=.047). Data for cardiovascular mortality was very similar. Annual mortality and cardiovascular event rates fell, as mentioned earlier, and annual incidence of cardiovascular death or admission for CHF was only 8.1% in the candesartan group and 9.1% in the placebo group, which raises doubts about the applicability of these results to patient populations at greater risk of events.[5,18]

Other studies of angiotensin receptor antagonists (the I-Preserve study of irbesartan), ACE inhibitors (the PEP-CHF study of perindopril), or beta-blockers, are currently under way. The number of patients enrolled and long follow-up makes I-Preserve the most important of these. This study is comparing the efficacy of a 300 mg/day dose of irbesartan versus a placebo in 3600 patients with CHF and LVEF>45%[24]. Until data from randomized clinical trials become available, treatment of diastolic CHF or CHF with preserved systolic function is simply symptomatic and etiologic, although the benefits of candesartan in reducing readmissions shown by the CHARM study[13] cannot be ignored. Guidelines and general objectives of diastolic CHF treatment appear in Table 4. European and North American guidelines on CHF treatment focus on the principals set out in Table 5.[25,26] Monitoring blood pressure and ventricular frequency is important, as is left ventricular hypertrophy regression and monitoring myocardial ischemia. Consequently, the drugs recommended may well be the same as those administered for systolic dysfunction even though the pathophysiologic objectives of their use differ. Studies have shown that beta-blockers, calcium antagonists and angiotensin antagonists act positively on the symptoms and functional capacity of patients with diastolic CHF.[27,28] The effect of digitalis on patients in sinus rhythm is dubious; in cases of ischemia it can be negative and produce calcium overload during diastole although in the DIG study, patients with LVEF >45% who were administered digitalis had fewer admissions and fewer symptoms than those who were not[27,28]. Diuretics are important in order to reduce congestion and improve symptoms but have to be used with caution and at low dosage to avoid hypotension and other symptoms of low cardiac output. Indications for anticoagulation and administering antiplatelet agents are the same as for patients with systolic CHF.[26]

In the absence of new results from current clinical trials and following guidelines (Tables 4 and 5), the combination of diuretics, "bradicardizing" antihypertensive drugs (beta-blockers or calcium antagonists)

TABLE 4. **Principal and General Objectives Diastolic Heart Failure Treatment**

Treatment of symptoms
Reduction of pulmonary congestion
Maintenance of atrial contraction
Prevention of tachycardia
Reduction of plasma volume
Improvement in exercise tolerance
Nonpharmacologic measures:
Moderate restriction of sodium
Moderate restriction of liquids
Prescription of moderate aerobic physical exercise
Pharmacologic treatment
Low dose inotropic diuretics used with caution
Nitrates
Beta-blockers
Calcium antagonists
Angiotensin-aldosterone system antagonists
Etiology specific treatment
Myocardial ischemia (prevention/treatment)
Left ventricular hypertrophy (prevention/regression)

TABLE 5. **Recommendations of the ACC/AHA for the Treatment of Patients With Heart Failure With Preserved Systolic Function***

1. Monitoring of arterial hypertension in agreement with recommendations (class I)
2. Monitoring of ventricular frequency in patients with atrial fibrillation (class I)
3. Diuretics to improve congestive symptoms (dyspnea and edemas) (class I)
4. Coronary revascularization in patients with coronary heart disease in which ischemia is thought to influence the development of heart failure (class IIa)
5. Restoration of sinus rhythm in patients in atrial fibrillation (class IIb)
6. Use of beta-blockers, calcium antagonists, ACE inhibitors or angiotensin receptor antagonists to reduce symptoms of heart failure in patients with controlled hypertension (class IIb)

*ACC indicates American College of Cardiology; AHA, American Heart Association.

and angiotensin antagonists seems the best pharmacologic strategy in these patients[26-28] together with the identification and correct treatment of the underlying processes (the most frequent of which are myocardial ischemia and hypertension).

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