Recent epidemiological studies suggest that 30% to 50% of patients with heart failure (HF) have preserved left ventricular (LV) systolic function. These patients, often presumed to have diastolic heart failure (DHF), appear to have lower short-term but similar long-term mortality when compared to patients with HF and LV systolic dysfunction. Rates of recurrent hospitalization and costs of care appear similar in the two groups of patients. Therefore, DHF may contribute significantly to the burden of disease caused by HF. Exertional breathlessness, the principal symptom of HF, has many causes, including obesity, pulmonary disease and myocardial ischemia. A diagnosis of DHF by exclusion, based on symptoms in the absence of important LV systolic dysfunction or major valve disease, is unsatisfactory. Unfortunately, as yet, no reliable definition with which to make a positive diagnosis of DHF has been agreed on, frequently rendering this diagnosis uncertain. Echocardiography has several limitations, whereas hemodynamic confirmation of DHF by cardiac catheterization is potentially complex and not practically feasible for many patients. Treatment of DHF remains empirical and unsatisfactory because of the lack of large-scale randomized controlled trials in this area. Currently, three large outcome studies on DHF are in progress along with other smaller trials. These should start to provide some of the answers we need to diagnose and effectively treat DHF. (J Am Coll Cardiol 2002;39:138–41) © 2002 by the American College of Cardiology

A number of recent community-based epidemiological studies of heart failure (HF) have suggested that 30% to 50% of cases of HF have preserved left ventricular (LV) systolic function (1–3). It is often assumed that these cases represent diastolic heart failure (DHF). If true, this suggests that DHF contributes significantly to the huge burden of disease caused by HF (4). However, although there has been an intense focus on HF due to LV systolic dysfunction, with considerable evolution in our understanding of the pathophysiology and natural history of the disease and subsequently the development of new treatments (5–7), there has been little parallel progress for DHF. Consequently, if the epidemiological evidence is accurate, a large proportion of the HF population is left with no proven, effective treatment.

The incidence, prevalence and prognosis of DHF form a contentious issue. The Framingham offspring study (1) and the Olmsted County study (3) used a scoring system based on symptoms and signs for the diagnosis of incident HF. Echocardiograms did not form part of the diagnostic criteria and were undertaken subsequently to document ventricular function. Of the 123 Framingham offspring who had a clinical diagnosis of HF, 73 underwent echocardiography. Of these, 51% were found to have preserved LV systolic function. The five-year mortality for these patients was 68% compared to 82% for matched control subjects without HF (p < 0.0001) (1). Similarly, the Olmsted County study (3) found that 43% of cases of incident HF had preserved systolic function on echocardiography; both DHF and systolic heart failure had a similar prognosis over four years of follow-up. Cowie et al. (8), in Hillingdon, UK, used a stricter definition of HF that included both a clinical scoring system and objective evidence of cardiac dysfunction. This study of 220 patients with newly diagnosed HF failed to find an association between the severity of LV systolic dysfunction and survival. In Canada, McAlister et al. (9) found 22% of their 562 patients with congestive heart failure (CHF) to have normal systolic function. One-year mortality did not differ from the group with systolic dysfunction. Studies conducted on elderly patients with CHF found a high prevalence of normal systolic function and similar prognosis for both systolic dysfunction and normal systolic function (10,11). Observational studies of patients discharged from hospital with a diagnosis of HF suggest that short-term mortality may be lower in patients with preserved LV systolic dysfunction, but long-term mortality appears similar (12,13).

Patients who carry a diagnostic label of DHF also have rates of recurrent hospitalization as high as those of patients with HF and LV systolic dysfunction (9,12). These data suggest that DHF may be a real and important entity, albeit poorly defined.

The above studies and others have demonstrated that HF is primarily a disease of the elderly. Older patients with HF...
are more likely to be women and more likely to have preserved systolic function (14). These observations could have major implications for the future, due to the aging of the population (15,16).

PROBLEMS WITH THE DEFINITION OF DHF

Currently, a diagnosis of DHF is often made as a result of a patient presenting with symptoms and signs suggestive of HF in whom LV systolic dysfunction is subsequently excluded. This is unsatisfactory for several reasons. Patients without any cardiac abnormality could be labeled as HF. Studies show considerable differences between clinicians in eliciting the symptoms and signs of HF, making a diagnosis based on these criteria alone unreliable (17). Many patients with HF symptoms and preserved LV systolic function have alternative explanations for their symptoms. Also, LV systolic dysfunction could be transient. This has led some to question the validity of a diagnosis of HF in the presence of preserved systolic function.

Recently, Caruana et al. (18) suggested that most patients with symptoms suggestive of HF but preserved systolic function had alternative, often noncardiological reasons for their symptoms, including pulmonary disease, obesity and myocardial ischemia. They suggested that DHF was more often a misdiagnosis than a true entity. However, they did not attempt to determine the predominant pathology for the patients’ symptoms, but rather simply described competing diagnoses. No adequate investigation was attempted with which to refute diastolic dysfunction as a cause of symptoms.

The gold standard for defining diastolic dysfunction is left heart catheterization and evaluation of pressure-volume curves at rest and during exercise (19). However, this is not feasible as an investigational tool for the majority of patients. Echocardiography, although widely available, has considerable limitations. Current European guidelines on the echocardiographic diagnosis of DHF are unsatisfactory because of their complexity, their lack of applicability to patients with atrial fibrillation and the lack of data demonstrating their accuracy (20,21). Atrial fibrillation is common in the population of interest. Techniques for the noninvasive measurement of LV filling pressures are not widely disseminated or validated.

In an attempt to overcome some of these problems, Vasan et al. (21) recently put forward criteria for DHF and allowed for diagnostic uncertainty according to a hierarchy of evidence. Using their criteria, DHF is definitely present if a patient meets the following three conditions in hierarchical fashion: 1) definite evidence of HF, 2) objective evidence of normal LV systolic function in proximity to the HF event, and 3) objective evidence of LV diastolic dysfunction on cardiac catheterization. If the first two criteria are satisfied but information on the third is lacking, probable DHF is present. Possible DHF is present when there is less diagnostic certainty with the first criterion being satisfied, the second criterion partially satisfied (e.g., ejection fraction [EF] not measured in proximity to the HF event) and the third criterion is lacking. This classification accepts diagnostic uncertainty, which is a useful starting point but means that few patients will receive a definite diagnosis of DHF.

A recent report of patients with acute cardiogenic pulmonary edema and hypertension showed a low prevalence of LV systolic dysfunction during the acute episode and on subsequent follow-up, suggesting that transient LV systolic dysfunction is not a common entity, at least in this group of patients (22).

THERAPY FOR DHF

Although many treatments may improve diastolic function in patients with HF secondary to LV systolic dysfunction, there is remarkably little evidence that any treatment is of benefit, symptomatic or prognostic, in patients with DHF. Diuretics should be effective in controlling fluid retention. Subgroup data (n = 218) from the V-HeFT trials suggested that angiotensin-converting enzyme (ACE) inhibitors reduced mortality even in patients with relatively well-preserved LV systolic dysfunction (23), but a similar group of patients in the CONSENSUS study (n = 57) did not appear to benefit (24). One small study of enalapril (25) and another small study using verapamil (26) have demonstrated benefit. Losartan has been shown to improve diastolic dysfunction and exercise tolerance in patients with a hypertensive response to exercise (27). Aronow et al. in 1997 (28) showed that propranolol reduced mortality over 32 months in a study of 158 older (≥62 years) patients with prior myocardial infarction (MI), preserved ventricular function and HF. Propranolol induced a further increase in LV EF and a reduction in LV mass. The DIG (Digitalis Investigation Group) trial (29) included an ancillary study that examined the effects of digoxin in patients with HF and relatively preserved LV systolic function (EF > 45%). As with the main trial, the results in the ancillary study of 988 patients showed no mortality benefit of digoxin, but both the overall rates of hospitalization and worsening heart failure were significantly reduced.

Definition, diagnosis and treatment are integrally linked. Lack of a proper definition of DHF may lead to a failure to show benefit in a randomized controlled outcome study even with an effective intervention, because the wrong patients were recruited. Practical clinical entry criteria em-
ployed in a study with a positive outcome will help shape the future definition of DHF.

**ONGOING TRIALS**

Currently, four large outcome studies are investigating the role of ACE inhibitors, angiotensin receptor blockers and beta-blockers in patients with DHF or HF with preserved LV systolic function (30,31) (Table 1). The PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) (30) is enrolling patients with echocardiographic evidence of diastolic dysfunction and randomizing them to placebo and perindopril. Two placebo-controlled studies of angiotensin II receptor antagonists, the CHARM (Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity [CHARM] study. The other components are confined to patients with left ventricular (LV) systolic dysfunction (ejection fraction [EF] ≤ 40%). CHARM-1 compares placebo and candesartan on top of angiotensin–converting enzyme (ACE) inhibition. CHARM-3 compares placebo and candesartan in patients intolerant of ACE inhibitors. See reference (31) for details. This trial also includes patients with LV systolic dysfunction. ‡See reference (32) for criteria. §See reference (33) for criteria. AF = atrial fibrillation; DHF = diastolic heart failure; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Systolic Function; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with Heart Failure; SWEDIC = Swedish Study in Patients with Diastolic Dysfunction Treated with Carvedilol.

**REFERENCES**


