REVIEW ARTICLES

Heart Failure With Preserved Systolic Function
A Different Natural History?

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Three well-controlled epidemiology studies in the U.S. have reported that 40% of incident congestive heart failure (CHF) cases and 50% to 60% of prevalent CHF cases occur in the setting of preserved systolic function. This condition has been termed "diastolic heart failure" (DHF). Despite minor differences in the types of populations examined, these community-based studies have established DHF as a major health problem in the U.S., particularly among the elderly. Although extensive data are available concerning the natural history of CHF associated with reduced systolic dysfunction (systolic heart failure; SHF), the natural history of DHF is not well-characterized. Indeed, it remains unclear whether patients with DHF share the grim prognosis described for patients with SHF. In this review we examine the available studies comparing survival observed in patients with DHF to that observed in patients with SHF. Although there are insufficient data at present to make definitive conclusions, careful examination of the available studies raises the possibility that the natural history of patients with DHF may not be different from that observed in patients with CHF and reduced systolic function. (J Am Coll Cardiol 2001;38:1277–82) © 2001 by the American College of Cardiology

The Framingham study documented that a clinical diagnosis of congestive heart failure (CHF) is associated with a marked reduction in survival (1,2). The diagnostic criteria for CHF utilized in the Framingham Study were based on the history, physical examination, chest radiograph and response to diuretic therapy and did not include documentation of reduced systolic function. Since this landmark study, noninvasive techniques to measure systolic function have become widely available, and reduced systolic function has rapidly become incorporated into the "diagnostic criteria" for CHF, at least in the context of clinical trials and most observational studies. However, at the same time a number of reports describing patients with clinical CHF and preserved systolic function emerged. These uncontrolled, largely hospital-based studies varied widely in their estimates of the prevalence of preserved systolic function among patients with CHF and in their descriptions of the clinical profile of this group of patients (3). More recently, three well-controlled population-based studies in the U.S. have reported that 40% of incident CHF cases and 50% to 60% of prevalent CHF cases occur in the setting of preserved systolic function (4–6). This condition has been termed "diastolic heart failure" (DHF). Despite minor differences in the types of populations studied, these epidemiology studies have established DHF as a major health problem in the U.S., particularly among the elderly.

HEART FAILURE WITH NORMAL SYSTOLIC FUNCTION

In the face of these reports have come efforts to standardize the diagnostic criteria for DHF (7,8)—an important step in the more systematic study of this syndrome. Clearly, there is a need for more observational data characterizing these patients, as questions remain about the clinical profile and natural history of the disorder. Though extensive data are available concerning the natural history of CHF associated with reduced systolic function (systolic heart failure; SHF), the natural history of DHF is not well characterized. Indeed, it remains unclear whether patients with DHF have a natural history that is different from the grim prognosis described in population-based studies for those with CHF (1,2). In this review we examine the available studies that compared survival in patients with DHF to that observed in SHF. Although there are insufficient data at present to make definitive conclusions, careful examination of the available studies raises the possibility that the natural history of patients with DHF may not be different from that of patients with CHF and reduced systolic function.

THE PROGNOSIS OF PATIENTS WITH DHF IS BETTER THAN THAT OF PATIENTS WITH SHF

It has become widely accepted that patients with DHF have a better prognosis than CHF associated with systolic dysfunction (9). This consideration is derived in part from the established observation that mortality is inversely related to the left ventricular (LV) ejection fraction among large numbers of patients with CHF and variable degrees of reduced systolic function (10). The initial studies describing

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Abbreviations and Acronyms

CAD	=	coronary artery disease
CHF	=	congestive heart failure
DHF	=	diastolic heart failure
LV	=	left ventricular, left ventricle
SHF	=	systolic heart failure
VA	=	Veterans Administration
V-HeFT	=	Veterans Administration Cooperative Study

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the prognosis of patients with DHF reported annual mortality ranging between 1.3% and 17.5% (3). Moreover, early studies published in the 1980s and early 1990s comparing outcomes in CHF patients with preserved versus reduced systolic function (Table 1) reported that patients with DHF had a better prognosis than patients with reduced systolic function. Kinney and Wright (11) reported on 91 patients (mean age 64 years) referred to an echocardiography laboratory with a diagnosis of CHF. In that study, patients with decreased fractional shortening had a significantly shorter median survival (11 months) compared to those with normal shortening fraction (26 months) (11). Cohn and Johnson (12) reported that in the Veterans Administration Cooperative Study (V-HeFT) of middle-aged males (mean age 60 years) with chronic CHF or impaired exercise tolerance, annual mortality was 8% in patients with normal LV ejection fraction compared to 19% in patients with reduced ejection fraction. In the V-HeFT trial, patients were considered to have CHF if the diagnosis had been made in the past or if they exhibited "reduced exercise tolerance and evidence of cardiac enlargement or left ventricular dysfunction." Ghali et al. (13) studied 78 patients (mean age 60 years) admitted to an inner-city hospital with a diagnosis of CHF. The diagnosis of CHF was based on the presence of two or more major criteria or the presence of one major criteria and two minor criteria similar but not identical to the Framingham criteria (13). Patients with CHF and preserved LV systolic function were more frequently women, and unadjusted survival was better when compared to those with impaired function.

In a prospective study of long-term health care facility residents, Aronow et al. (14) reported that LV ejection fraction was the most important prognostic factor for mortality among patients with CHF and coronary artery disease. Heart failure was diagnosed if pulmonary rales were heard and pulmonary vascular congestion was present on chest roentgenogram. Although the mean age of both groups was >80 years, patients with preserved ejection fraction were slightly older than patients with reduced ejection fraction. Unadjusted mortality for patients with CHF and preserved ejection fraction was lower than that of patients with reduced systolic function. Mortality rates for the 81 patients with CHF in their series (14) who did not have coronary disease were not reported. Thus, these early studies suggest that patients with CHF and preserved

systolic function have a more favorable prognosis than patients with CHF and reduced ejection fraction.

THE PROGNOSIS FOR PATIENTS WITH DHF IS SIMILAR TO THAT OF PATIENTS WITH SHF

In contrast, there are more recent studies (Table 1) that do not find differences in mortality in patients with CHF and reduced versus preserved systolic function. In a study of 94 patients (mean age 82 years) treated in a geriatric care unit, Taffet et al. (15) noted that there was no difference in survival between patients with CHF and preserved versus reduced systolic function. In their study, which included patients with incident and recurrent CHF episodes, the diagnosis of CHF was confirmed by using a modification of Framingham criteria. Similarly, in a study of consecutive CHF admissions to an academic medical center hospital, McDermott and co-workers (16) found that the cumulative probability of unadjusted survival at 27 months of follow-up was equal in patients with CHF and preserved versus reduced systolic function. All 192 patients (mean age 73 years) included in the McDermott et al. (16) study met the Framingham criteria for diagnosis of CHF, and patients with preserved systolic function were more frequently women. Among 41 patients age 75 to 86 years in the population-based Helsinki Aging Study, Kupari and colleagues (17) found no difference in survival between patients with CHF and intact versus depressed systolic function. Heart failure was diagnosed based on a number of clinical criteria. McAlister et al. (18) studied 566 patients evaluated in an outpatient CHF clinic; the diagnosis of CHF was made according to the Framingham criteria. The one- and three-year survival rates (systolic dysfunction vs. preserved systolic function) were similar. Patients with preserved systolic function were older, with a mean age of 69 years. Pernenkil et al. (19) reported on 501 patients (mean age 81 years) who were admitted to a university hospital with a diagnosis of CHF. The group with preserved ejection fraction had a more favorable three months' unadjusted mortality than patients with systolic dysfunction (13.5% vs. 23.2%), but unadjusted mortality from 3 to 12 months was similar in both groups (16.9% vs. 19.4%) (19). Patients with normal systolic function were older and more frequently women, compared to those with reduced systolic function. The diagnosis of heart failure in the Pernenkil et al. study was based on the presence of either definite radiographic evidence of pulmonary congestion or typical symptoms and signs of heart failure associated with a definite clinical improvement in response to diuretics.

In our study (Senni et al. [5]) of all patients with incident CHF (Framingham criteria) in Olmsted County, Minnesota, in 1991 (n = 216; mean age 77 years), 137 had assessment of ejection fraction within three weeks of diagnosis. Of these, 43% had an ejection fraction ≥50%. In our study, unadjusted survival was similar between patients with preserved and those with reduced systolic function (p =

Table 1. Studies Comparing Survival Among Patients With CHF and Preserved (DHF) or Reduced (SHF) Systolic Function

Study–Year of Publication	No. of Patients (% DHF)	Mean Age (yrs)	CHF Diagnosis	Mortality–SHF	Mortality–DHF	p Value SHF vs. DHF Mortality
Studies where mean age <65 yrs						
Warnowicz–1983 (22)	39 (41%)	DHF 63 ± 9 SHF 66 ± 11	Acute pulmonary edema	30% (9 mo)	25% (9 mo)	NS
Kinney–1989 (11)	91 (48%)	All 64 ± 10	2 major or 1 major + 1 minor§	Median survival = 11 mo	Median survival = 26 mo	0.01
Cohn–1990 (12)	623 (13%)	DHF 60 ± 7 SHF 58 ± 8	VO$_2$max <25/ml/kg/min	19% (annualized)	8% (annualized)	0.0001
Ghali–1992 (13)	78 (28%)	DHF 60 ± 11 SHF 59 ± 14	2 major or 1 major + 2 minor§	24% (1 yr) 46% (2 yr)	22% (1 yr) 26% (2 yr)	0.04
Studies where mean age >65 yrs						
Aronow–1990 (14)	166 (40%)	DHF 84 ± 6 SHF 81 ± 8	Rales + CXR vascular congestion	47% (1 yr) 71% (2 yr)	22% (1 yr) 38% (2 yr)	0.001
Taffet–1992 (15)	94 (43%)	DHF 82 ± na SHF 83 ± na	Framingham	≈24% (1 yr) ≈42% (2 yr)	≈24% (1 yr) ≈30% (2 yr)	NS NS
McDermott–1997 (16)	192 (46%)	DHF 73 ± na SHF 72 ± na	Framingham	35% (27 mo)	35% (27 mo)	NS (0.78)
Kupari–1997 (17)	41 (51%)	ALL ≈ 80	Other†	54% (4 yr)	43% (4 yr)	NS
Permenkil–1997 (19)	501 (34%)	DHF 81 ± 6 SHF 78 ± 6	Other‡	38% (1 yr) 19% (3–12 mo)	28% (1 yr) 17% (3–12 mo)	p = 0.045 p = NS
Senni–1998 (5)	137 (43%)	DHF 78 ± 12 SHF 74 ± 13	Framingham	24% (1 yr) 42% (3 yr)	24% (1 yr) 42% (3 yr)	NS (0.369)
McAlister–1999 (18)	566 (21%)	DHF 69 ± 14 SHF 65 ± 14	Framingham	17% (1 yr) 38% (3 yr)	12% (1 yr) 42% (3 yr)	NS (0.25)
Vasan–1999 (4)	73 (51%)	DHF 72 ± 9 SHF 74 ± 7	Framingham	64% (5 yr)	32% (5 yr)	p = 0.023 Adj*p = 0.13
Ansari–2001(abstr) (23)	376 (27%)	ALL 72 ± na	Framingham	20% (20 mo)	20% (20 mo)	NS

*In a multivariate model correcting for age and gender, the hazard ratio (95% confidence intervals) for death for "CHF with normal ejection fraction" was 0.59 (0.30–1.16), p = 0.13. The group with DHF was predominantly women. †Three of four criteria present: 1) shortness of breath on ordinary effort; 2) S$_3$ or heart rate >90 beats/min; 3) pulmonary venous congestion on chest radiograph or jugular venous distension or hepatomegally; and 4) cardiothoracic ratio 0.55 on chest radiograph. ‡Definite radiographic evidence of CHF or typical symptoms and signs of CHF in conjunction with definite clinical improvements in response to diuretic. §Major and minor criteria are similar to those specified the Framingham criteria.

Adj = adjusted; CHF = congestive heart failure; CXR = chest radiograph; DHF = diastolic heart failure; na = not available; NS = not significant (p value when available); SHF = systolic heart failure.

0.279) (5). Survival adjusted for age, gender, New York Heart Association functional class, and coronary artery disease (CAD) was still not significantly different in the two groups (relative risk = 0.80; p = 0.369).

We recently repeated a review of all patients with new-onset CHF and preserved systolic function in Olmsted County, Minnesota, during 1996 and 1997 (n = 83; mean age 77 years) (20,21). In a preliminary report, Chen et al. (21) indicate that the survival curves in this population-based study of patients with incident CHF and preserved systolic function are identical to those observed in the 1991 cohort. These data confirm our earlier findings regarding the poor outcome in patients with incident CHF and preserved systolic function in the community.

In a small study of 39 patients (mean age 63 years) who had myocardial infarction and acute pulmonary edema, Warnowicz and colleagues (22) found a similar nine-month mortality rate in patients with normal or reduced systolic function. In 73 patients (mean age 73 years) with a history of CHF who underwent echocardiography as a part of the Framingham study, Vasan et al. (4) found that mortality adjusted for age and gender was not significantly lower in patients with normal systolic function. In that study of prevalent CHF, *unadjusted* mortality was lower in patients with preserved systolic function. The mean time from CHF diagnosis to echocardiography was 2.8 years (range 0.1 to 15 years). Patients with normal systolic function were older and more frequently women, compared to those with systolic dysfunction. Recent preliminary data from Ansari et al. (23) in a large Veterans Administration (VA) cohort of elderly (mean age 72 years), primarily male patients with a diagnosis of CHF confirmed by Framingham criteria show identical survival curves (mean follow-up 20 months) for those with preserved and those with reduced systolic function.

WHY DO STUDIES DIFFER?

The factors responsible for the disparate findings regarding outcomes in CHF patients with preserved or reduced systolic function reported in these studies remain unclear. We note that most studies reporting a better prognosis for those with CHF and preserved systolic function were performed in younger cohorts of CHF patients (mean age <65 years). The Aronow et al. (14) study (mean age 84 years) is an exception and reported only on those patients with CHF and CAD, excluding 81 patients with CHF who did not have coronary disease. Those studies that did not show a survival difference between CHF and preserved versus reduced systolic function examined older populations (mean age >65 years; Table 1). It may be that the natural history of DHF in younger individuals is different from that observed in the elderly. As previously reported, the prevalence of DHF increases significantly with age. Indeed, heart failure secondary to diastolic dysfunction is primarily a disorder of advanced age. Thus, findings in elderly cohorts

may be more germane to the majority of patients with CHF and preserved systolic function.

Another factor that might play a role in the different prognoses reported in available studies is the choice of diagnostic criteria for CHF. In the early studies reporting relatively better outcomes in those with DHF, the criteria were more liberal and less specific compared to the Framingham criteria used in the later studies, which did not find survival differences (Table 1). Thus, it is possible that the group with preserved systolic function may have included patients with noncardiac symptoms, as has recently been reported by Caruana et al. (24) in patients with "suspected heart failure." Although the Framingham criteria are relatively insensitive for the detection of early manifestations of CHF, they have a high sensitivity and specificity for the detection of definite CHF (25). These findings underscore the need for standardized clinical criteria for CHF diagnosis. Difficulty establishing the clinical diagnosis often occurs when assessing elderly patients with co-morbidities and when the diagnosis of CHF is made by a noncardiologist, factors often present in patients with CHF and preserved systolic function.

Various other factors influence the natural history of CHF that were not controlled for in the observational studies reviewed here. Primary among these factors is the type of population studied, which varies widely in the reports analyzed in this review and includes hospitalized patients, patients referred to an imaging laboratory, residents of long-term care facilities, patients seen in a geriatric care center, patients participating in a multicenter study, patients seen in an outpatient CHF clinic, patients seen in the VA system and population-based studies. Studies also can vary as to whether the patients enrolled are presenting with a first-time or subsequent episode of CHF; this is often not specified. Studies vary as to whether ejection fraction was measured during the CHF episode or at a significantly later date. Findings from a recent study would suggest that if ejection fraction was found to be normal some days after presentation with acute pulmonary edema, it was usually normal during the pulmonary edema episode (26). In contrast, a significant number of patients who had normal ejection fraction months to years after a CHF episode had reduced ejection fraction during the CHF episode (27). Indeed, more patients with CHF and reduced systolic function may normalize their ejection fraction with standard therapy in the beta-blocker era. Thus, studies of *incident* CHF may have findings different from those that include patients with both incident and recurrent CHF.

As most studies characterizing the prognosis of patients with CHF and reduced versus preserved systolic function were observational, therapeutic management was not standardized, and this could influence survival in these retrospective studies. Indeed, recent retrospective cohort studies suggest that treatment with angiotensin-converting enzyme inhibition and beta-blockers may improve survival in patients with DHF (21,28). Although these studies do not

offer definitive proof that such agents are of benefit in patients with DHF, they do suggest that differences in treatment not controlled for in observational studies may influence findings regarding outcomes in different patient groups.

In addition, racial and socioeconomic differences may also exist in different studies and influence findings. A preliminary study from an inner-city urban hospital with a large percentage of African American patients reports that subjects with CHF and preserved systolic function were younger (mean age 60 years) than in most series, but outcomes in this population were not assessed (29).

CLINICAL IMPLICATIONS

This growing body of literature challenges the conventional belief regarding the natural history of DHF, particularly when there is a well-confirmed clinical diagnosis of CHF and when elderly cohorts are studied. Indeed, eight of the nine series in elderly cohorts with CHF report similar or marginally different mortality rates among those with preserved and reduced systolic function. Viewed in aggregate, these studies strongly suggest that, among the elderly, the clinical syndrome of CHF (when definitively characterized) carries a uniformly poor prognosis regardless of the level of systolic function. There are several important clinical implications of these data.

First, they should serve to heighten appreciation of the importance of the syndrome of DHF in the elderly and impress upon the physician the need for aggressive management both for improvement in survival and reduction of readmission and other morbidity associated with CHF. Rates of readmission usually parallel mortality statistics. Whereas some studies have suggested that readmission rates for DHF are lower than for those observed with CHF and reduced systolic function (5,16), preliminary findings from an inner-city hospitalized CHF population reports similar re-hospitalization rates for those with CHF and preserved or reduced systolic function (30). Although there is no proven treatment for DHF per se, most patients with DHF have hypertension and/or CAD, and aggressive therapy of these underlying conditions is available and proven to reduce CHF (31).

A second important implication of these studies relates to efforts to engender support for treatment trials in DHF. In order for these efforts to proceed, data regarding event rates and their relation to the type of population studied are crucial when designing the study size. These data would suggest that if the population enrolled is elderly, with well-defined and advanced CHF, event rates (and sample size) would be similar to those used in trials for CHF with reduced systolic function. However, should only younger patients or patients with milder CHF not satisfying Framingham criteria be enrolled, the event rates would be lower, and larger sample sizes would be required. Because trials in CHF and systolic dysfunction have traditionally

enrolled younger and more predominantly male populations, different enrollment strategies may be needed to study DHF. Data such as those summarized here, as well as enhanced efforts to standardize diagnoses (7,8), are needed if efforts to provide an evidence-based approach to this growing and important clinical syndrome are to succeed.

Conclusions. Although the natural history of DHF will probably continue to be debated, review of the available data confirms the seminal observations from the Framingham study, where the poor prognostic implications of the clinical diagnosis of CHF were established prior to widespread assessment of ejection fraction. We conclude that, at least among the elderly, the clinical diagnosis of CHF portends a grim prognosis that is independent of the level of measured ejection fraction.

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