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REVIEW ARTICLE

Prevalence, Clinical Features and Prognosis of Diastolic Heart Failure: An Epidemiologic Perspective

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Numerous reports suggest that about one-third of patients with congestive heart failure do not have any abnormality of left ventricular systolic function. These patients presumably have heart failure on the basis of ventricular diastolic dysfunction. Our objective was to develop a comprehensive overview of published reports of the prevalence, clinical features and prognosis of diastolic heart failure and to offer recommendations for future studies.

Thirty-one studies of patients with congestive heart failure with normal left ventricular systolic function were published in the time period from January 1970 through March 1995. These studies were identified with the use of computer-based searches in relevant data bases. Among patients with congestive heart failure, the prevalence of normal ventricular systolic performance in the published reports varies widely from 13% to 74%; the reported annual mortality rate also varies from 1.3% to 17.5%. The criteria for congestive heart failure, its chronicity and the age of the study sample affect the reported prevalence and prognosis of the disorder. The clinical signs and symptoms of diastolic heart failure are similar to those of patients with systolic heart failure, underscoring the need for evaluation of ventricular systolic function in patients with congestive heart failure. In the absence of any large-scale randomized clinical trial targeting these patients, the optimal treatment of diastolic heart failure is unclear.

We conclude that the heterogeneity in previous studies of diastolic heart failure hinders the comparison of published reports. There is a need to conduct prospective, community-based investigations to better characterize the incidence, prevalence and natural history of diastolic heart failure. Randomized clinical trials are needed to determine optimal treatment strategies.

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It is increasingly being recognized that the syndrome of congestive heart failure (CHF) may arise in the absence of any abnormality of left ventricular systolic function (1–9). Patients with abnormalities of ventricular diastolic filling may not be able to produce an adequate cardiac output at the usual ventricular filling pressures despite the presence of normal ventricular systolic function (1–11); in these patients, a compensatory elevation of ventricular filling pressures is necessary to maintain normal forward cardiac output. The elevated left atrial pressure is transmitted passively to the pulmonary vascular bed, resulting in pulmonary venous hypertension and its clinical manifestations. This syndrome has been termed diastolic heart failure (9).

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The pathophysiologic and etiologic mechanisms of the syndrome and its treatment have been extensively reviewed previously (1–12). In the present review we focus on the epidemiologic issues in evaluating the prevalence, clinical features and prognosis of diastolic heart failure. An overview based on published reports of the prevalence, clinical features and prognosis of diastolic heart failure is presented along with recommendations for future studies.

Thirty-one studies of CHF with normal left ventricular systolic function were published in the time period from January 1970 through March 1995 (13–43). These studies were identified with the use of computer-based searches in relevant data bases combined with other sources, such as references in the reports identified and in textbooks and published reports by experts in the field. The indexing terms *congestive heart failure, ejection fraction, ultrasound, radionuclide imaging* and *diastole* were used for study retrieval; a search was made in English and non-English published reports (with the constraint of "human" subjects). Studies were included in the present review if all patients had CHF; ventricular systolic function was evaluated with standardized techniques (echocardiography or radionuclide or contrast ventriculography); the issue of normal left ventricular systolic function in the presence of CHF was addressed; and the original data were published in a journal with peer review. Abstracts were excluded.

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Methods Utilized in Previous Studies

In this review, we summarize prior studies of diastolic heart failure with regard to study design, disease definition, imaging methods and study population characteristics (Table 1). We outline the methodologic problems encountered in defining the entities *CHF, normal systolic function* and *diastolic dysfunction*, the three essential components of a diagnosis of diastolic heart failure.

Study design and setting. Of the 31 studies (13–43) that described subjects with CHF who had normal left ventricular systolic function, 8 (26%) were case series, and the remaining 23 (74%) were clinical comparative studies that estimated the prevalence of normal ventricular systolic function in groups of patients with CHF (Table 1). Several of these studies were small and retrospective, and a majority were hospital based; only one study (40) was carried out in a community-based primary care setting.

A consideration of the study design and setting is important in the interpretation of the results of these studies. Hospital admission constitutes a more severe degree of illness; therefore, there is a referral bias in hospital-based studies. The results of hospital-based studies may be valid but are not generalizable to the outpatient with CHF. Hypotheses and disease associations emerging from case series and retrospective clinical studies must be recognized as being "data derived" (there being no a priori hypothesis) and must be tested and confirmed prospectively in studies designed to address specific issues (such as risk factors for diastolic heart failure) (44).

Disease definition and patient selection. *Criteria for diagnosis of CHF.* There is no single accepted definition for the diagnosis of CHF (45). Clinical criteria used for the diagnosis of CHF are heterogeneous both in clinical trials (46) and in office practice (47). Of the 31 studies included in this review, 7 (23%) did not explicitly state the criteria used for the diagnosis of CHF (18–20,30,40,42,43). Among the 24 studies that specified the criteria for congestive heart failure, the lack of uniformity of criteria is striking (Table 1). One study (22) utilized three sets of clinical criteria (48–50) to define CHF; there was significant variation in the number of subjects considered to have CHF (from 32% to 56%) and in the prevalence of normal systolic function (from 34% to 40% of subjects with CHF) when different sets of criteria were used. Thus, the heterogeneity of diagnostic criteria for CHF may contribute substantially to the significant variation in prevalence of diastolic heart failure among patients with CHF.

Severity of CHF. It has been suggested that any definition of CHF must be reproducible and must include subjects with both mild and overt disease (51). In practice, even when specified criteria for CHF are used, subjects are dichotomized into those with definite CHF and those without CHF. Because subjects with mild heart failure are less likely to meet the criteria for definite CHF, there is an inherent selection bias in favor of more severe cases of CHF being included in such studies (52). Although such a bias may be unavoidable, its presence needs to be acknowledged, especially when prognosis of diastolic heart failure is evaluated.

Source of patients with CHF within a medical facility and information regarding excluded subjects. Ideally, all consecutive subjects presenting to a medical facility with a diagnosis of heart failure must be included in a study designed to investigate the problem of diastolic heart failure. Only 9 studies of 31 included all consecutive patients with CHF presenting to the concerned medical facility (21,27,29,31–33,39,42,43). Clinicians do not order tests to estimate left ventricular function in all patients with CHF. Often such tests are ordered preferentially in the sicker patients (where a therapeutic decision may be based on the estimated ejection fraction) or in the relatively healthier subjects in whom the diagnosis of CHF itself is suspect.

Occasionally, an imaging test (for ventricular systolic function) may be ordered for a patient with CHF, but the result may be unsatisfactory and these patients excluded from the study. Information regarding the number of patients with CHF with unsatisfactory noninvasive studies is critical because such patients are often sicker than those with satisfactory studies (53). Nineteen studies did not provide details of patients with CHF with unsatisfactory noninvasive studies. In the 12 studies that did disclose this information, 16% to 42% of patients with CHF had inadequate or incomplete imaging studies.

Selection bias is also introduced when study patients are obtained from a particular diagnostic laboratory within a medical facility. For instance, patients with CHF obtained from the cardiac catheterization laboratory are more likely to have coronary disease as the etiologic factor. A sampling frame that uses patients with CHF undergoing radionuclide imaging may differ from another that utilizes such patients undergoing echocardiography. Radionuclide tests are often obtained in patients with pulmonary disease who have poor quality echocardiograms. Such patients are more likely to have dyspnea due to pulmonary disease and, therefore, are more likely to have intact left ventricular systolic function. Conversely, an echocardiogram is often obtained at the bedside of a patient too sick to be sent to the radionuclide laboratory or one with significant valvular heart disease.

Exclusion of other causes of dyspnea and provision of evidence of diastolic dysfunction. Because the signs and symptoms of CHF are nonspecific, it is essential to exclude an alternative explanation for the symptoms and, if feasible, provide evidence of elevated left ventricular filling pressures before accepting a diagnosis of CHF with normal systolic function. Only 3 studies of the 31 reviewed provided details regarding the exclusion of other causes of dyspnea (15,20,29). Significantly, in one study, 11 (16%) of 69 patients with suspected CHF had a pulmonary cause of dyspnea (20).

Presence of CHF with normal left ventricular systolic function is often treated as synonymous with the presence of "diastolic dysfunction," although this need not be the case. Only 6 (19%) of 31 studies assessed ventricular diastolic performance with imaging techniques to substantiate the presence of diastolic dysfunction in patients with CHF and normal

systolic function (20,25,31,34,39,41); ventricular diastolic filling indexes (estimated noninvasively) were abnormal in 20% to 62% of patients (20,25). This finding highlights the need to develop uniform criteria for diastolic dysfunction that must be satisfied before one can accept diastolic dysfunction as the pathophysiologic mechanism in a patient with CHF and normal ventricular systolic function.

Imaging methodology. *Choice of imaging modality.* Fifteen studies (48%) utilized echocardiography, 12 (39%) radionuclide ventriculography, and 4 (13%) contrast ventriculography for assessing ventricular systolic function (Table 1). The potential biases arising from the selection of an imaging modality have been referred to earlier. Furthermore, disagreement in estimates of ventricular ejection fraction by these methods is well recognized (54). One study (21), which provided details of both radionuclide ventriculograms and echocardiograms, demonstrated disagreement between the results of the two investigations.

Variables for assessing systolic performance. Both echocardiographic and radionuclide studies utilized ejection phase indexes (ejection fraction or fractional shortening) for evaluating ventricular systolic performance (Table 1). Ejection phase indexes are not measures of myocardial contractility and are significantly influenced by changes in loading conditions. Thus, a low ejection fraction in a patient with severe aortic stenosis may not indicate contractile dysfunction; recovery of ejection fraction is frequent after aortic valve replacement (55). Conversely, a normal ejection fraction in the setting of severe mitral regurgitation may not indicate normal myocardial contractility; rather, it may simply reflect a lowered ventricular afterload (56). Fractional shortening is further limited by the fact that it assesses only the basal portion of the left ventricle and is likely to be erroneous in the presence of wall motion abnormalities or conduction system disease. Only one study (33) provided several indexes of ventricular contractility (including the relatively load-independent systolic blood pressure/end-systolic volume index). In that study, the prevalence of normal ventricular systolic function varied from 34% to 45% depending on the particular index selected to define ventricular contractile dysfunction.

Partition values for defining systolic dysfunction. Most studies dichotomized patients with CHF into those with normal and abnormal systolic function. Such a scheme (in which patients are dichotomized) ignores the frequent coexistence of systolic and diastolic mechanisms in the pathogenesis of CHF (3) and overlooks the fact that ejection phase indexes are continuous variables; normal values of these indexes may often blend into abnormal ones without a distinct threshold. The "cut points" of ejection phase indexes that were used for defining systolic dysfunction varied widely in these studies (Table 1), a factor that would influence the prevalence of the syndrome of CHF with "normal" systolic function. It has been suggested empirically (10) that an ejection fraction value of 0.40 be used for distinguishing patients with CHF with predominant systolic dysfunction from those with predominant diastolic dysfunction. There is no clear consensus in published reports regarding an optimal partition value for differentiating "predominant systolic" from "predominant diastolic" ventricular dysfunction.

Timing of study. It is essential to obtain an estimate of ventricular systolic function during the episode of cardiac decompensation because left ventricular function may improve with time (57). Important contributory mechanisms toward CHF (e.g., acute mitral regurgitation due to ischemic papillary muscle dysfunction) may be identified only during the actual episode of pulmonary edema. This is the distinction between "being in congestive heart failure" and meeting the criteria for CHF ("having had congestive heart failure"). Only eight studies (26%) provided information regarding the timing of the test used to assess left ventricular systolic function (Table 1).

Number of estimates of left ventricular systolic function. All studies reviewed included a one-time assessment of ventricular systolic function. Spontaneous variation of ventricular systolic function has been observed in patients with CHF. In one-third of patients with CHF, the ejection fraction may vary by more than five percentage points over a period of 12 weeks (58). When the index being measured has significant intraindividual variation over time, it is important to obtain more than one measurement of that index. In patients with an ejection fraction in the range 0.40 to 0.55, potential for misclassification may exist if only a single estimate ("snapshot") of left ventricular function is obtained.

Blinding of interpreter and reproducibility of measurements. Another major drawback of all but two studies (23,32) is the failure to provide specific information as to whether or not the assessment of ventricular function was performed with the observer "blinded" to all other clinical information regarding the patients.

The reported reproducibility of estimates of left ventricular ejection fraction by radionuclide ventriculography and echocardiography varies from 5 to 10 percentage points (54,59). The variability for estimation of ejection fraction with contrast ventriculography has been reported to be up to 15 percentage points (60). In this context, only one study (15) qualified its results with reports of reproducibility of estimating ejection fraction.

Study sample characteristics. *Age.* All studies recruited subjects in the sixth to ninth decades of age (Table 1). The age of the study subjects is of importance because some disorders such as hypertensive hypertrophic cardiomyopathy are seen more often in the elderly (18,61). Studies in elderly patients are likely to reflect a higher prevalence of CHF with normal systolic function. Age is also an important factor to consider in evaluating the prognosis of subjects with CHF because mortality related to CHF increases in a graded manner with advancing age (62–65).

Gender and race. Race and gender are other important determinants to be considered in evaluating the prevalence of diastolic heart failure and associated mortality trends. The prevalence of CHF is higher and prognosis worse in men (vs. women) (63,64) and in African-American patients (vs. white

Table 1. Clinical Studies of Patients With Congestive Heart Failure and Normal Left Ventricular Systolic Function

				Imaging Methodology			Study Sample Characteristics*					Total No. With CHF	No. (%) With Normal LV Systolic Function
Study (ref no.)	Design/Setting	Criteria for CHF	Selection Bias	Imaging Technique	Criteria for Normal LV Function	Time of Imaging	Mean Age (yr)	Gender (F/M)	HTN (%)	CAD (%)	Acute or Chronic CHF		
Case series													
Dodek et al. (13)	R/RH	Acute pulmonary edema	Cath lab	LVgram	Normal EF	After diuresis	58	NR	0	100 (incl. crit.)	Acute	6	2 (33)
Kunis et al. (14)	R/RH	Acute pulmonary edema	Cath/CABG	LVgram	NR	NR	80	3/1	NR	100 (incl. crit.)	Acute	4	4 (100)
Topol et al. (18)	R/RH	NR	HTN	Echo	Normal EF, NR	NR	73†	3/1†	100	NR	NR	9	9 (100)
Given et al. (19)	R/RH	NR	Severe HTN	Echo	EF ≥0.55	NR	65	1/7	100	0	NR	8	8 (100)
Quirko et al. (26)	P/RH	Clinical signs	HTN	Echo	LVID >5.5 cm or FS <0.30	NR	56†	1/1.5†	100	NR	NR	33	33 (100)
Kitzman et al. (35)	P/RH	Acute pulmonary edema	Cath lab	LVgram	EF >0.50	NR	65	1.3/1	57	0 (incl. crit.)	6 acute, 1 chronic	7	7 (100)
Judge et al. (36)	R/MC	≥2 symptoms	NYHA III/IV	LVgram	EF ≥0.45	NR	56†	1/1.2	45	67	Chronic	284	284 (100)
Brogan et al. (38)	R/RH	Elevated LVEDP	Cath lab	LVgram	EF ≥0.50	NR	55	3.8/1	83	4	Chronic	53‡	53 (100)
Clinical comparative studies													
Echeverria et al. (15)	P/RH	2 of 5 signs +	Echo referral	Echo	EF ≥0.50	NR	51	1.2/1	65	5	5 acute, 6 chronic, 9 both	50	20 (40)
Warnowicz et al. (16)	R/RH	Acute pulmonary edema	Acute MI survivors	RNV	EF >0.45	>10 d	63	1/2.2	NR	100 (incl. crit.)	Acute and with MI	39	16 (41)
Dougherty et al. (17)	P/RH	FHS	RNV referral	RNV	EF ≥0.45	24–72 h	63	1.1/1	65	53	NR	188	67 (36)
Soufer et al. (20)	P/RH	NR	RNV referral	RNV	EF ≥0.45	NR	68†	NR	29†	41†	25% acute, 75% chronic	74	31 (42)
Bier et al. (21)	P/RH	Acute pulmonary edema	—	Echo	2D echo	< 72 h	73†	1.5/1†	65	52	Acute	79	38 (48)

Marantz et al. (22)	P/RH	FHS, Duke, Boston	RNV referral	RNV	EF≥0.50	NR	64†	1/1.8†	53	NR	NR	191, 228, 132	76 (40), 85 (35), 45 (34)
Wong et al. (23)	R/CBH	2 of 3 clinical signs	Echo referral	Echo	Normal wall motion	NS	70	1.1/1	65	48	NR	99	29 (29)
Kinney et al. (24)	R/RH	≥2 signs or symptoms	Echo referral	Echo	FS >0.17	NR	64	1/44	NR	NR	NR	91	44 (48)
Aguirre et al. (25)	P/RH	≥2 signs of CHF	Echo referral	Echo	EF ≥0.55	NR	73	1.8/1	67	27	35% acute, 65% chronic	151	51 (34)
Aronow et al. (27)	P/RH	Any 2 clinical signs	—	Echo	EF ≥0.50	NR	84	3.5/1	53	100	NR	166	68 (41)
Cohn et al. (28)	R/MC	CTR >0.55 or LVID >2.7 cm/m^2 or EF <0.45	RNV referral	RNV	EF ≥0.45	NR	59	Men only	53	26	Chronic	623	83 (13.3)
Duch et al. (29)	P/RH	Boston criteria	NYHA III/IV	Echo	EF ≥0.55	NR	72	1.5/1†	17	17	NR	100	36 (36)
Bareiss et al. (30)	R/RH	Clinical signs	RNV referral	RNV	EF ≥0.45	NR	66	1/1.8	65	NR	75% acute, 25% chronic	152	40 (26)
Stone et al. (31)	P/RH	Acute pulmonary edema	—	RNV	EF ≥0.48	< 12 h	76†	1.5/1†	70†	100 (incl. crit.)	Acute	40	11 (27)
Ghali et al. (32)	P/RH	FHS	—	Echo	FS ≥0.24	NR	60	1.3/1	64	13	Acute and chronic	82	23 (28)
Cocchi et al. (33)	P/RH	Boston criteria	Geriatric clinic	Echo	EF ≥0.50	NR	74	2.1/1	57	45	Chronic	118	53 (45)
Cregler et al. (34)	R/RH	FHS	Only men	RNV	EF ≥0.45	NR	63	Men only	56	41	NS	372	89 (23)
Taffet et al. (37)	R/RH	FHS	Geriatric clinic	RNV	EF ≥0.45	NR	82	Men only	60	65	NR	94	40 (43)
Takarada et al. (39)	P/H	FHS	—	Echo	FS ≥0.30	<24 h	66†	1/1.5†	58	NR	NR	172	41 (24)
Wheeldon et al. (40)	P/CBH	Diuretic intake for "CHF"	Echo referral	Echo	FS ≥0.25,	NR	72†	1.6/1†	0	NR	Chronic	78	36 (59)
Iriarte et al. (41)	R/RH	Pulmonary edema	HTN	RNV	EF ≥0.5	>9 d	65	1.3/1	75	NR	Acute and chronic	301	90 (29)
Madsen et al. (42)	P/CBH	NR	—	RNV	EF ≥0.53	14.5 mo	66†	1/2.5†	11†	66†	Chronic	186	27 (14)
Francis et al. (43)	P/RH	Diuretic intake for "CHF"	Echo referral	Echo	FS ≥0.25	NR	73†	1.2/1†	24†	62†	NR	119	88 (74)

*For patients with normal ventricular systolic function, unless otherwise indicated. †For entire group of patients with congestive heart failure (CHF). ‡Number of patients with elevated left ventricular end-diastolic pressure (LVEDP). Unless otherwise indicated, data presented are number, percent or number (%) of patients. Boston = Boston University criteria for congestive heart failure (50); CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; Cath = catheterization; CBH = community-based hospital; CTR = radiologic cardiothoracic ratio; d = days; Duke = Duke University criteria for congestive heart failure (49); Echo = echocardiography; EF = ejection fraction; F = female; FHS = Framingham Heart Study criteria for congestive heart failure (48); FS = fractional shortening; HTN = hypertension; incl. crit. = inclusion criteria; lab = laboratory; LV = left ventricular; LVgram = left ventricular angiocardiogram; LVID = left ventricular internal dimension at end-diastole; M = male; MC = multicenter study; MI = myocardial infarction; NR = not reported; NYHA = New York Heart Association classification of dyspnea; P = prospective; R = retrospective; ref = reference; RH = referral hospital; RNV = radionuclide ventriculography; — = none.

patients) (66–68). In this context, 3 studies (28,34,37) included only men, and 28 included both male and female patients. Only seven studies (17,23–25,29,32,41) provided information regarding the racial origin of the subjects enrolled: four studies focused on African-American (32), Asian (23) and Spanish (29,41) patients, and three other studies (17,24,25) had a mixed sample of both white and African-American subjects. These differences in characteristics of the study population may account for some of the heterogeneity in the results of various studies of diastolic heart failure.

Acute versus chronic CHF and duration of CHF. The distinction of acute from chronic CHF is of importance in studying the prognosis of these patients. Patients with chronic, persistent CHF are likely to have fewer reversible features and consequently may have a worse prognosis than those in whom an acute episode resolves (e.g., CHF related to acute ischemia or severe hypertension). Only 17 studies (55%) provided information regarding the acuteness of CHF in study patients (Table 1).

Among patients with chronic CHF, it is important to obtain information regarding the duration of symptoms; failure to consider disease duration can lead to a "lead time bias" (69). Patients who are diagnosed at an early stage of disease are likely to live longer than those with the same disease process identified at a more advanced stage. Such information was not available in any of the studies reviewed.

Principal Findings in Published Reports

Prevalence. The prevalence of diastolic heart failure in the community is unknown. Among patients with CHF, the prevalence of normal ventricular systolic performance in published reports varies widely from 13% to 74% in clinical studies (Table 1). Despite the wide variation in reported prevalence, it is remarkable that a majority of studies report values ~40%. These patients are presumed to have diastolic heart failure. The criteria used for defining CHF affect the reported prevalence of diastolic heart failure (22). A study (43) that identified patients with CHF on the basis of diuretic intake for a diagnosis of CHF (without specifying the criteria for CHF) estimated a prevalence of normal ventricular systolic function of 74%. In view of the high (50%) false positive diagnosis of CHF in primary care (52), it is conceivable that some estimates of the prevalence of CHF with normal ventricular systolic function were inflated by the inclusion of patients without CHF. In addition, a careful perusal of Table 1 reveals that chronicity of CHF and the age of the study sample affect the reported prevalence of the disorder. Studies that included patients with acute and chronic CHF yielded intermediate prevalence estimates (25% to 40%) of normal ventricular systolic function (Table 1). In studies restricted to middle-aged patients with chronic CHF, the prevalence of normal ventricular systolic performance has been <15% (28,42). Four studies that evaluated elderly patients with CHF reported a high prevalence (41% to 45%) of normal systolic function (23,27,33,37).

Age-related trends in the prevalence of normal ventricular systolic function among patients with CHF were specifically examined in only two studies. The prevalence of normal ventricular systolic function was significantly lower in patients with CHF <65 years old than those >65 years old (6% vs. 34% and 12% vs. 30%) (23,39).

Clinical features. *Symptoms and signs.* Eleven of 31 studies provided details regarding the physical signs observed in patients with CHF and normal systolic function (15,17, 18,20, 23,25,27,32,33,39,41). Both third and fourth heart sounds were frequently present. Distension of jugular veins was observed in <50% of patients. Five studies (18,23,25,27,39) commented on the presence of atrial arrhythmias; atrial fibrillation was seen in 0% to 75% of patients. The prevalence of coronary disease varied from 5% to 67% in various studies. Between 11% and 83% of subjects were reported to be hypertensive (Table 1).

Predictors of normal left ventricular systolic function in presence of CHF. Twelve studies provided information regarding the clinical predictors of normal systolic function in the presence of CHF by comparing characteristics of this group with those of patients with CHF and systolic dysfunction. The findings, shown in Table 2, reveal considerable disagreement among the studies. Clinical features (age, gender, hypertension, alcohol intake or smoking status) and physical examination (jugular venous distension, a third heart sound) failed to discriminate consistently between subjects with intact systolic function and those with systolic dysfunction.

Prognosis. The reported annual mortality rate of patients with CHF and intact left ventricular systolic function has varied widely from 1.3% to 17.5% (Table 3) (16,24,27,28,36–38,70,71). The influences of etiology and subject selection (factors such as age or gender) on mortality could in part account for these disparate results. None of the studies provided age-adjusted mortality rates. The three studies reporting the highest annual mortality rates may have been skewed by the choice of an unusually low partition value for abnormal ventricular systolic function in one study (24) and a very high mean age of subjects in the other two (27,37). The impact of the presence or absence of coronary artery disease on the survival of subjects with CHF and intact systolic function is also controversial, with one study reporting no impact (70) and another reporting a negative impact (36). The lowest reported annual mortality rate (1.3%) was in a study (38) that included subjects with isolated diastolic dysfunction (by excluding the presence of coronary disease); the mean age of patients in this study was also the lowest. Studies of patients with a mean age of 55 to 71 years (with a prevalence of coronary disease ranging from 14% to 67%) reported an annual mortality rate of 3% to 9%. It is clear that the reported mortality rate of patients with diastolic heart failure is considerably lower than that of patients with systolic heart failure (with an annual mortality rate of 15% to 20%) (10).

Patients with CHF on the basis of valvular heart disease (aortic stenosis or regurgitation) and who have normal left ventricular systolic function constitute a separate subgroup with a very high annual mortality rate (in excess of 25%) if the

Table 2. Clinical Predictors for Presence of Normal Left Ventricular Systolic Function in Patients With Congestive Heart Failure: Summary of Clinical Studies

Study (ref no.)	Factors Predicting Normal LV Function	Factors Not Predictive
Warnowicz et al. (16)	None	Age, gender, HTN
Dougherty et al. (17)	HTN	Age, gender, diabetes mellitus, smoking status, alcohol intake, S_3, S_4, JVD, ECG LVH
Bier et al. (21)	Admission blood pressure >160/100 mm Hg, paroxysmal nocturnal dyspnea, pedal edema	Gender, HTN, CAD
Wong et al. (23)	Old age, female gender, atrial fibrillation, echo LVH	HTN, diabetes mellitus, CAD, smoking status, alcohol intake
Kinney et al. (24)	None	Age, gender, HTN, S_3, jugular venous distension, paroxysmal nocturnal dyspnea, CAD, alcohol intake, lung disease
Aguirre et al. (25)	Old age, echocardiographic LVH and normal wall motion, absence of history of CAD or paroxysmal nocturnal dyspnea and absence of S_3	Gender, HTN, S_4, jugular venous distension, exertional dyspnea, orthopnea
Aronow et al. (27)	Age > 80 yr, absence of S_3	Gender, HTN, atrial fibrillation
Bareiss et al. (30)	Age, acute onset, female gender, HTN, absence of jugular venous distension or cardiac enlargement	S_3, S_4
Stone et al. (31)	None	Mitral regurgitation
Ghali et al. (32)	Female gender, obesity, absence of jugular venous distension, diastolic blood pressure >105 mm Hg	Age, HTN, CAD, alcohol intake, smoking status, S_3, edema, cardiac enlargement, echocardiographic LVH
Cocchi et al. (33)	None	Age, gender, HTN, CAD, jugular venous distension, S_3
Taffet et al. (37)	None	Age, HTN, CAD, diabetes mellitus, alcohol intake
Takarada et al. (39)	Age > 65 yr	Gender, HTN, atrial fibrillation

ECG = electrocardiographic; LVH = left ventricular hypertrophy; S_3 and S_4 = third and fourth heart sounds, respectively; other abbreviations as in Table 1.

valve disease is not corrected surgically (72,73). Further studies are required to identify the prognosis of patients with diastolic heart failure of different etiologies.

Treatment. Only 1 of the 30 studies reviewed provided details regarding the selection of a specific therapeutic regimen and treatment-based differences in patient outcome (28). In that study, a trend toward a prolongation of life with the use of hydralazine and isosorbide dinitrate was observed (vs. placebo), but the sample size was too small to achieve statistical significance. A beneficial effect of enalapril was reported in a randomized trial (74) conducted in a small group of elderly patients with prior myocardial infarction and diastolic heart failure, but that study was limited by the nonblinded assessment of end points. A third randomized, placebo-controlled, crossover trial (75) utilizing verapamil reported a benefit, but the study was limited by the small sample size of 20 patients. In view of the paucity of clinical trials targeting patients with diastolic heart failure, the optimal treatment of diastolic heart failure remains unknown and empiric.

Future Directions

Diagnosis of diastolic heart failure. There is a lack of consensus among clinicians regarding what constitutes diastolic dysfunction (as measured by noninvasive means). The development of consensus criteria for diastolic heart failure would be an important step toward obtaining a reasonable estimate of the burden of diastolic heart failure in the community because its prevalence and prognosis remain largely unknown despite the profusion of published reports on the subject. There is also a need to develop simple diagnostic tools for diastolic heart failure that have reasonable accuracy combined with ease of usage for clinical and epidemiologic studies. Currently used Doppler echocardiographic indexes of diastolic function derived from the study of ventricular filling dynamics are limited by their load dependence and by "the lack of validation of most of the variables by comparison to appropriate independent standards" (76). Better assessment of ventricular systolic and diastolic function with load-independent indexes should enable the formulation of criteria that permit a distinction among systolic, diastolic and combined (systolic and diastolic) mechanisms of cardiac failure. The role of newer methods of evaluating ventricular systolic (77,78) and diastolic (79–85) function remains to be determined. Furthermore, any diagnostic test must be interpreted with the observer blinded to clinical information and with the evaluation of test reproducibility (interobserver and intraobserver).

Incidence, prevalence and prognosis. The incidence and prevalence of diastolic heart failure can be assessed in prospective community-based cohort studies that utilize uniform criteria for the condition. Such studies can help in the identification of risk factors for diastolic heart failure. All consecutive patients with heart failure must be included, and care taken to ensure adequate representation of minority populations. Studies investigating the prognosis of diastolic heart failure must utilize a sample of patients at a similar point in the course of disease. Morbidity and mortality data in such studies must be adjusted for age, relevant prognostic variables (e.g.,

Table 3. Mortality Rate and Its Determinants in Patients With Congestive Heart Failure and Normal Left Ventricular Systolic Function

Study (ref no.)	No. of Pts	Follow-Up Duration (yr)	Mean Age of Pts (yr)	CAD (% of pts)	Cumulative Mortality Rate (%)		Average Annual Mortality Rate (%)	Mechanism of Death	Predictors of Mortality
					1 yr	4 yr			
Warnowicz et al. (16)	16	0.75	63	100	25	NR	NR	All cardiac (MI 75%, sudden cardiac death 25%)	NR
Kinney et al. (24)	44	4	64	NR	35	70	17.5	Majority cardiac	NR
Aronow et al. (27)	68	4	84	100	22	56	14	92% cardiac	Age, HTN
Cohn et al. (28)	83	5.7	59	26	8	27*	8	84% cardiac (sudden cardiac death 75%, pump failure 25%)	Ventricular tachycardia on Holter
Judge et al. (36)	284	6	56	67	5*	12*	3	NR	Wall motion score, no. of diseased vessels, age, HTN, lung disease, diabetes mellitus, LVEDP, other vascular disease
Taffet et al. (37)	40	3	82	65	25*	45* (at 3 yr)	15	45% cardiac (sudden cardiac death 20%, pump failure 73%)	Age, recurrent admissions
Brogan et al. (38)	53	5.6	55	0	3	5	1.3	44% cardiac	NR
Setaro et al. (70)	52	7	71	52	20*	40*	6.5	90% cardiac (mostly pump failure)	CAD not predictive
Ghali et al. (71)	22	4	60	14	22	36	9	75% cardiac (pump failure 84%, sudden cardiac death 16%)	HTN

*Data obtained by interpolation of Kaplan-Meier survival curves. Pts = patients; other abbreviations as in Table 1.

etiology, gender, race and acuteness of heart failure) and treatment.

Treatment and prevention. There is a need for randomized clinical trials to determine the appropriate treatment for patients with established diastolic heart failure. Such trials must utilize objective, clinically relevant outcome criteria that must be specified a priori. The assessment of outcomes must be "blinded," and the results adjusted for extraneous prognostic variables (besides treatment).

Prevention of diastolic heart failure is feasible with vigorous efforts to prevent and control important underlying conditions, such as hypertension, coronary disease, diabetes mellitus and obesity. The elderly and African-Americans are two segments of the U.S. population that are at high risk for developing diastolic heart failure. There is a need to develop safe and cost-effective methods for screening high risk patients for the early detection of CHF (and predisposing conditions such as left ventricular hypertrophy) with a view to preventing the morbidity and mortality associated with diastolic heart failure. Specific approaches aimed at reversing the molecular events that mediate cardiac hypertrophy (e.g., drug therapy for regressing left ventricular hypertrophy or gene therapy for familial hypertrophic cardiomyopathy) need to be investigated in view of recent evidence that regression of cardiac hypertrophy is associated with improved cardiovascular outcome (86).

Conclusions

The syndrome of diastolic heart failure is common in clinical practice. The signs and symptoms of the disorder are quite similar to those of patients with CHF with left ventricular systolic dysfunction. However, the prognosis of these patients is different from that of subjects with systolic heart failure, underscoring the need for evaluation of ventricular systolic function in patients with CHF.

Previous studies of diastolic heart failure differ considerably with regard to patient selection criteria, diagnostic criteria for CHF, quantitative methods for assessment of ventricular systolic function and duration of follow-up. Such heterogeneity in prior studies makes the comparison of published reports regarding the prevalence of this disorder and its natural history difficult. There is a need to evaluate these patients prospectively in community-based studies (with uniform criteria for the presence of CHF, normal systolic function and diastolic dysfunction) to better characterize the disorder and its natural history. There is

also a need for randomized clinical trials to determine the optimal treatment for patients with established diastolic heart failure.

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