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LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND DIASTOLIC HEART FAILURE

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■ **Abstract** Thirty to fifty percent of patients presenting with signs and symptoms of heart failure have a normal left ventricular (LV) systolic ejection fraction. The clinical examination cannot distinguish these patients (diastolic heart failure) from those with a depressed ejection fraction (systolic heart failure), but echocardiography can. The management of diastolic heart failure has two major objectives. The first is to reverse the consequences of diastolic dysfunction (e.g., venous congestion), and the second is to eliminate or reduce the factors responsible for diastolic dysfunction (e.g., myocardial hypertrophy, fibrosis, and ischemia).

INTRODUCTION

Clinicians and physiologists have, in the past three decades, reexamined their concepts about the pathophysiology of heart failure. A major focus of this deliberation has been to clarify the important distinctions between left ventricular (LV) systolic dysfunction and diastolic dysfunction (Figure 1). Simply stated, systolic dysfunction can be considered a defect in the ability of the myofibrils to shorten against a load; the ventricle loses its ability to eject blood into a high-pressure aorta and the ejection fraction falls. The term diastolic dysfunction implies that the myofibrils do not rapidly or completely return to their resting length; the ventricle cannot accept blood at low pressures, and ventricular filling is slow or incomplete unless atrial pressure rises. Cardiac structure and function differ substantially in systolic and diastolic dysfunction, but the clinical consequences (i.e., the signs and symptoms of heart failure) are similar. A balanced view of the differences and similarities of these two conditions is essential to the process of diagnosing and treating patients with heart failure. In this review, we describe the clinical and pathophysiologic features of diastolic dysfunction and provide an approach to the diagnosis and treatment of patients with diastolic heart failure.

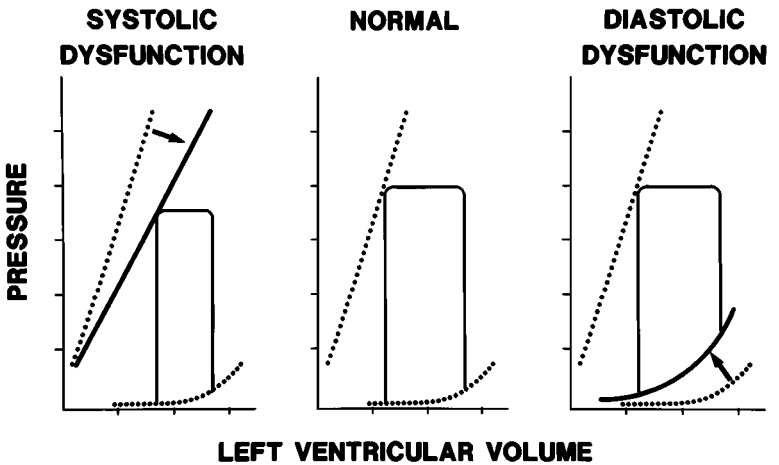

Figure 1 Diagram of left ventricular (LV) pressure-volume loops in systolic dysfunction and diastolic dysfunction. In systolic dysfunction, contractility is depressed, and the end-systolic pressure-volume line is displaced downward and to the right; there is diminished capacity to eject blood into a high-pressure aorta. In diastolic dysfunction, chamber stiffness is increased and the diastolic pressure-volume relation is displaced up and to the left; there is diminished capacity to fill at low diastolic pressures. The LV ejection fraction is low in systolic dysfunction and normal in diastolic dysfunction. (Adapted from Reference 40.)

Interest in the diastolic properties of the left ventricle, the nature of myocardial relaxation, and diastolic filling of the ventricles was stimulated by the early work of Henderson (1), Wiggers & Katz (2), and Meek (3)—and by the recognition that normal diastolic "function" is an important ingredient in the coordinated pump function of the heart. Over the past three decades, clinical investigators and basic scientists have studied the pathophysiology of diastole and have sought to understand the relationship between abnormalities in diastolic function and the clinical syndrome of heart failure.

During the 1970s, the study of diastole in humans was largely confined to the cardiac catheterization laboratory. Clinical investigators measured LV diastolic pressure and volume and described the mechanisms that underlie LV diastolic dysfunction. LV compliance or distensibility was decreased in patients with pressure overload hypertrophy, and it was suggested that such diastolic dysfunction limits the potential to utilize the Frank-Starling mechanism and thereby has a negative impact on LV systolic performance (4). Other investigators demonstrated the dramatic impact of ischemia on the diastolic properties of the ventricle (5, 6). The substantial increase in LV diastolic pressure seen during angina pectoris was largely a consequence of diminished diastolic distensibility or compliance of the ventricle. These and other studies, performed in the 1970s, examined the physical

properties of the fully relaxed ventricle and defined the determinants of passive chamber stiffness. The major determinants are the chamber volume, wall mass, and composition of the wall (7–9). They also examined dynamic factors that are intrinsic to the myocardium (i.e., the process of relaxation) as well as those extrinsic to the ventricle [i.e., the pericardium and the right ventricle (10, 11)]. Alterations in these factors, alone or in concert, could contribute to acute or chronic alterations in the diastolic properties of the ventricle, and that diastolic dysfunction could lead to heart failure (12, 13).

In the 1980s, clinicians reported what seemed to be a surprisingly high prevalence (approximately 30%) of a normal LV ejection fraction in patients with congestive heart failure (14–16). Recurrent pulmonary edema was reported in elderly patients with ischemic heart disease—despite a normal LV ejection fraction (17). A syndrome of hypertensive hypertrophic cardiomyopathy was described in elderly patients with dyspnea or chest pain (18). These patients had "abnormal diastolic function" in the presence of "excessive systolic emptying" (high normal ejection fraction), and it was suggested that treatment of such patients differed from that used in patients with a depressed LV ejection fraction. Others emphasized diastolic dysfunction in patients with hypertension (19) and the elderly (20). Thus, it became apparent that a significant number of patients with heart failure had a normal LV ejection fraction, and the terms diastolic dysfunction and diastolic heart failure emerged in the medical literature (21–24).

In the 1990s, the use of echocardiography and Doppler techniques to assess LV diastolic relaxation and filling grew at an exponential rate. The noninvasive nature and the widespread availability of these techniques contributed to this growth, and as a result, a prodigious volume of reports and clinical research on diastolic dysfunction was published. These studies provide considerable insight into the dynamics of LV relaxation and filling in health and disease (25–27). A most important contribution was the use of echocardiography to estimate LV filling pressure (28–31). These techniques also provide significant prognostic information. For example, the finding of echocardiographic evidence of diastolic dysfunction in an asymptomatic patient is a risk factor for the development of heart failure (32); the early identification of such patients provides a window of opportunity to prevent progression of what appears to be "preclinical heart disease" (33).

In recent years, our understanding of the epidemiology and clinical pathophysiology of diastolic dysfunction and heart failure has expanded (34–39). The prevalence of diastolic heart failure in the community is now known to be at least as high as that reported in previous studies of hospitalized patients; almost half of all patients with heart failure have diastolic heart failure. It is especially prevalent in elderly women. Clinicians now recognize that the manifestations of heart failure are similar in patients with systolic and diastolic heart failure—despite major differences in LV volume, mass, geometry, and function (37). Considerable progress in our understanding of the basic mechanisms underlying diastolic dysfunction is being made (38, 39), but to date, there have been no published double-blind

placebo-controlled randomized multicenter therapeutic trials in patients with diastolic heart failure.

TERMINOLOGY

Diastolic dysfunction refers to abnormal mechanical properties of the myocardium and includes abnormal LV diastolic distensibility, impaired filling, and slow or delayed relaxation—regardless of whether the ejection fraction is normal or depressed and whether the patient is asymptomatic or symptomatic. In this review, the term asymptomatic diastolic dysfunction is used to refer to an asymptomatic patient with a normal ejection fraction and an abnormal echo-Doppler pattern of LV filling; this is often seen, for example, in patients with hypertensive heart disease. If such a patient were to exhibit symptoms of effort intolerance and dyspnea, especially if there were evidence of venous congestion and edema, the term diastolic heart failure is used. This terminology parallels that used in asymptomatic and symptomatic patients with LV systolic dysfunction, and it facilitates the use of a pathophysiologic, diagnostic, and therapeutic framework that includes all patients with LV dysfunction—whether or not they have symptoms (40).

CAUSES OF DIASTOLIC DYSFUNCTION

The factors that influence and determine the LV diastolic pressure-volume relations are shown in Figure 2. The basic mechanisms that underly diastolic dysfunction may be intrinsic to the cardiomyocyte (e.g., abnormal calcium homeostasis), or they may be a consequence of abnormalities in the extracellular matrix (e.g., alterations in collagen). Neurohormonal and cardiac endothelial activity also modulate ventricular stiffness and relaxation (39). Clinically, the common causes of LV diastolic dysfunction are hypertrophy and ischemia, but several other conditions may cause heart failure in the presence of a normal LV ejection fraction (Table 1).

PATHOPHYSIOLOGY

The diastolic properties of the left ventricle are determined largely by the size or volume of the LV chamber, the thickness and physical properties of the ventricular wall, and the process of myocardial relaxation. Thus, a combination of increased myocardial mass and alterations in the extracellular collagen network may cause or contribute to an increase in passive elastic stiffness of the ventricle and a steep diastolic pressure-volume relation (Figure 1). Disorders of the active process of myocardial relaxation, acting alone or in concert with abnormal passive properties of the ventricle, can also stiffen the ventricle. As a result, LV compliance or distensibility is reduced, the dynamics of filling are altered, and the end-diastolic pressure is increased (9, 12, 13, 27, 38). Under these circumstances, a relatively

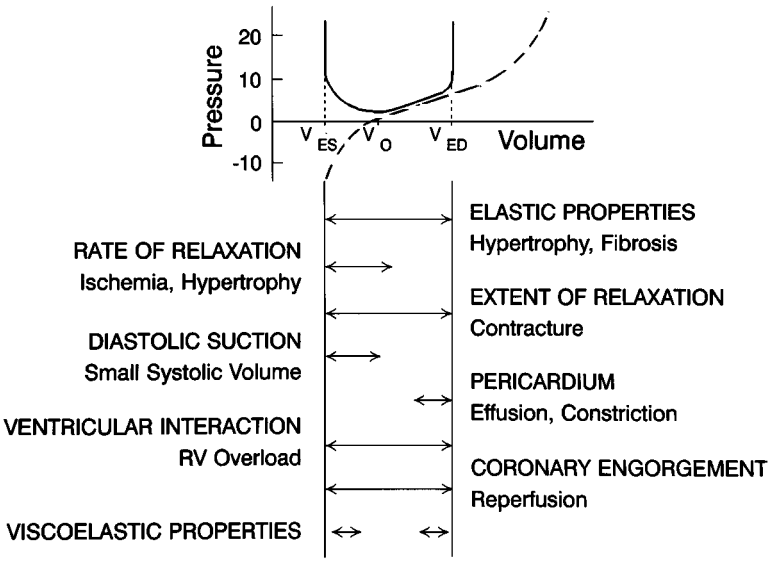

Figure 2 Diastolic pressure-volume relations (*upper panel*) and the factors that influence these relations. The effects of each of these factors depends on the time at which they occur; some factors exert their influence in early diastole (i.e., relaxation rate and diastolic suction), others in late diastole (i.e., pericardium), and still others throughout diastole (i.e., elastic properties). V_{ES} = end-systolic volume; V_o = equilibrium volume; V_{ED} = end-diastolic volume; RV = right ventricle. (Adapted from Reference 41).

small increase in central blood volume can produce a substantial increase in LV diastolic pressure and consequently pulmonary venous hypertension and pulmonary edema.

Several factors can promote fluid retention and precipitate overt heart failure in patients with heart disease. Common precipitants include uncontrolled hypertension, atrial fibrillation, noncompliance with or inappropriate discontinuation of heart failure medications, myocardial ischemia, anemia, renal insufficiency, administration of nonsteroidal anti-inflammatory drugs, and overindulgence in high-salt foods (42). The glitazones may have a similar effect (43). Patients with LV diastolic dysfunction are especially sensitive to these precipitants because of the steep LV diastolic pressure-volume relation, which results in large changes in LV diastolic pressure with only small changes in volume.

Thus, elevated LV diastolic and pulmonary venous pressures in patients with a normal ejection fraction (in the absence of valvular disease) are directly related to abnormalities in the diastolic properties of the ventricle (i.e., diastolic dysfunction). This is not to say that contractile function is entirely normal in patients with diastolic heart failure. Indeed, subtle abnormalities of contractile function are present in many if not most such patients; diastolic dysfunction, however, is the

TABLE 1 Causes of heart failure with a normal ejection fraction

Left ventricular diastolic dysfunction
Pressure-overload hypertrophy
hypertensive heart disease
aortic stenosis
Ischemic heart disease
acute myocardial ischemia
chronic coronary heart disease
Cardiomyopathy
hypertrophic
infiltrative
restrictive
Valvular heart disease
Acute aortic or mitral regurgitation
Mitral stenosis
Aortic stenosis
Pericardial disease
Constriction
Tamponade
Circulatory congestive states
Rapid fluid administration
Arterio-venous fistula
Severe anemia
Thyrotoxicosis

dominant feature. It should also be recognized that diastolic function is rarely normal in patients with heart failure and a low ejection fraction; however, in this case, systolic dysfunction is the dominant feature.

The differences and similarities between systolic and diastolic heart failure are summarized in Table 2. LV volume, geometry, and function differ substantially in these two conditions; at the microscopic level, significant differences in the cardiomyocyte and extracellular matrix are seen. Even brain natriuretic peptide (BNP) levels and survival differ. Despite these major differences, the clinical signs and symptoms of heart failure are present to a similar degree in patients with systolic and diastolic heart failure. Thus, the clinical history and physical examination do not provide information that allows a differentiation of systolic from diastolic heart failure.

Patients with diastolic heart failure, as well as those with diastolic dysfunction and little or no congestion, exhibit exercise intolerance for two principal reasons. First, elevated LV diastolic and pulmonary venous pressure causes a reduction in lung compliance, which increases the work of breathing and evokes the symptom of dyspnea. Second, a substantial number of patients who have LV hypertrophy, a

TABLE 2 Differences and similarities between systolic and diastolic heart failure

	Systolic heart failure	**Diastolic heart failure**
Signs and symptoms	present	present
BNP	↑↑	↑
Exercise testing		
Duration	↓	↓
Systolic BP	↑	↑↑
Pulse pressure	↑	↑↑
VO_2	↓↓	↓
LV remodeling		
End-diastolic volume	↑↑	N
End-systolic volume	↑↑	↓
Myocardial mass	↑ (eccentric LVH)	↑ (concentric LVH)
Relative wall thickness	↓	↑↑
Cardiomyocyte	↑ length	↑ diameter
EC matrix (collagen)	↓	↑↑
LV systolic function		
Ejection fraction	↓↓	N-↑
Stroke volume	N-↓	N-↓
Myocardial contractility	↓↓	↓
LV diastolic function		
Chamber stiffness	N-↓	↑↑
Myocardial stiffness	N-↑	↑
Relaxation time-constant	↑	↑
Filling dynamics	abnormal	abnormal
End-diastolic pressure	↑↑	↑↑
Preload reserve	exhausted	limited
Morbidity	↑↑	↑↑
Survival	↓↓	↓

Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure; VO_2, oxygen consumption; LV, left ventricular; LVH, LV hypertrophy; EC, extracellular.

high relative wall thickness, and a small end diastolic volume exhibit a low stroke volume and a depressed cardiac output (44); a ventricle with a normal ejection fraction cannot produce a normal stroke volume if the chamber size is small. Third, these hearts exhibit a limited ability to utilize the Frank-Starling mechanism during exercise (45, 46). Such limited preload reserve, especially if coupled with the chronotropic incompetence that is seen with advancing age, limits the cardiac output during exercise. This leads to lactate accumulation and structural as well as functional abnormalities of skeletal muscles; the result can be skeletal muscle fatigue (the legs and the accessory muscles of respiration). This latter mechanism helps to explain the poor relationship between exercise tolerance and changes

in LV diastolic pressure. Other mechanisms, including physical deconditioning, contribute to exercise intolerance.

DIAGNOSIS

The clinical diagnosis of diastolic heart failure requires reliable evidence of heart failure in the presence of a normal or near-normal LV ejection fraction (greater than 40%–50%). It remains controversial whether measurements of diastolic function are necessary for the diagnosis of diastolic heart failure. Some insist that there must be hemodynamic (echocardiographic or catheterization) evidence of abnormal LV relaxation, filling, diastolic distensibility, or stiffness (47). Others do not accept echocardiographic data; rather, they require cardiac catheterization to document the presence of diastolic dysfunction before making a diagnosis of definite diastolic heart failure (48). Still others point out that virtually all patients with heart failure and a normal ejection fraction exhibit evidence of diastolic dysfunction, and they argue that echocardiographic or other documentation of diastolic dysfunction is merely confirmatory (49). Likewise, blood levels of BNP have been used to confirm the diagnosis of congestive heart failure (50), but further study will be required before BNP levels can be recommended as a method to differentiate systolic from diastolic heart failure (51).

Echocardiography is often used to assess the LV ejection fraction, but the method of choice depends on the availability of and institutional experience with other techniques such as radionuclide angiography and cineangiograpy. In addition to the ejection fraction, the echocardiogram provides other information on LV function, LV geometry and wall thickness, regional wall motion abnormalities, valvular disease, pericardial disease, and left atrial size. Echocardiography has proven to be most useful in the assessment of LV size and ejection fraction, but the use of Doppler-derived indices of diastolic function has had less impact on the management of individual patients with acute heart failure (52).

Recognizing these uncertainties, many if not most clinicians make the diagnosis of diastolic heart failure in patients with the signs and symptoms of heart failure in the presence of a normal LV ejection fraction, especially if there is evidence of LV hypertrophic remodeling (49). In the absence of hypertrophy, the diagnosis of probable diastolic heart failure may be more appropriate (48). After successful treatment, symptomatic patients who no longer exhibit evidence of congestion should carry the diagnosis of chronic diastolic heart failure.

MANAGEMENT

There are no large randomized placebo-controlled trials that provide evidence-based therapeutic strategies in patients with diastolic dysfunction or diastolic heart failure. The recommendations presented in this review are based on the results of small clinical studies, anecdotal experience, and an understanding of the

TABLE 3 Management of diastolic heart failure

Initial management
Treat the presenting syndrome
pulmonary edema/congestive state
systemic atrial hypertension
myocardial ischemia
atrial fibrillation/tachycardia
Clarify the diagnosis
history and physical examination
echocardiography
cardiac catheterization/angiography
biopsy
Long-term management
Consider mechanisms
promote regression of left ventricular hypertrophy
prevent/promote regression of fibrosis
modify cellular/extracellular mechanisms
Correct the pathophysiology
salt restriction and diuretics
block the renin-angiotensin-aldosterone system
maintain atrial contraction
prevent excessive tachycardia
treat hypertension
prevent myocardial ischemia

pathophysiology of diastole. In general, the management of diastolic heart failure has two objectives. The first is to reverse the consequences of diastolic dysfunction (e.g., venous congestion and exercise intolerance). The second is to eliminate or reduce the factors that are responsible for diastolic dysfunction (e.g., hypertrophy, fibrosis, ischemia). See Table 3.

ASYMPTOMATIC DIASTOLIC DYSFUNCTION

The prevalence of asymptomatic diastolic dysfunction is not known, but there is reason to believe that the condition is common—especially in people with hypertension or advanced age. The finding of diastolic dysfunction in an asymptomatic patient is a risk factor for the future development of congestive heart failure and the early identification of such patients provides a window of opportunity to prevent progression of what appears to be preclinical heart disease (32, 33, 40). There are no data that might support the use of treatment directed primarily at the diastolic dysfunction. Rather, the goal should be an aggressive management of hypertension and other potential causes of diastolic dysfunction.

ACUTE DIASTOLIC HEART FAILURE

The initial management of acute heart failure and pulmonary edema consists of measures that relieve pulmonary congestion while maintaining oxygenation, arterial pressure, and perfusion of vital organs. With few exceptions, the initial treatment of patients with diastolic heart failure is similar to that used in those with systolic heart failure. Treatment is frequently initiated prior to hospitalization, often in an ambulance, and later in a hospital emergency department.

Prehospital Management

Airway management and the administration of oxygen should be the first consideration. A face mask is generally used, but there is evidence that continuous positive airway pressure can improve lung mechanics, lessen the work of breathing, and reduce the need for intubation (53). Morphine reduces anxiety and has vasodilator properties, but its use can increase the need for mechanical ventilation. A second goal should be to reduce the pulmonary venous pressure. This can be achieved safely and effectively with sublingual or intravenous nitroglycerin (10–50 μg/min depending on clinical response). The use of nitroglycerine avoids electrolyte disturbances that can be seen when intravenous diuretics are administered as the initial treatment. Indeed, when treatments with nitrates, furosemide, and morphine are compared, optimal clinical outcomes are seen with nitrates (54). Moreover, the effects of nitrates are rapidly reversible in the event of hypotension. Rotating tourniquets also can effect a rapidly reversible reduction in central venous pressures. If the prehospitalization period is expected to be prolonged, the intravenous administration of nitroprusside (0.1–10 μg/kg/min) may be necessary in patients with severe hypertension, but there are no clear indications for angiotensin-converting enzyme (ACE) inhibitors or beta-adrenergic agonists during the prehospitalization period.

Initial Hospital Treatment

On admission to the emergency department, the diagnosis of heart failure should be confirmed and associated, or complicating problems should be considered (e.g., pneumonia, myocardial infarction, pulmonary embolism, dissection of the aorta). At the same time, treatment should be initiated.

OXYGEN In most patients, arterial hypoxemia can be reversed by oxygen administration with a Venturi mask. If this is not effective, continuous positive airway pressure can be used (vide supra). Endotracheal intubation may be required if arterial oxygenation cannot be maintained or if there is progressive hypercapnia.

MORPHINE This agent (administered intravenously in a dose of 3–5 mg over several minutes) diminishes the patient's distress and reduces the work of breathing. Morphine achieves its beneficial hemodynamic effects by acting as a vasodilator

and thereby pooling blood in the splanenic circulation. Special caution is necessary if the pulmonary edema is associated with hypotension, stroke, or independent pulmonary disease—especially in patients with hypercapnia.

PRELOAD REDUCTION A decrease in left atrial and pulmonary venous pressure is obviously desirable in patients with acute pulmonary edema. In patients with LV systolic dysfunction and acute exacerbation of chronic heart failure (most of whom have an expanded central blood volume), a substantial reduction in pulmonary venous pressure can be achieved without a significant drop in arterial pressure. However, patients with diastolic heart failure often develop a dramatic decrease in arterial pressure when attempts are made to reduce preload. This occurs as a consequence of a steep LV diastolic pressure-volume relation; even a small reduction in diastolic volume can result in relatively large reduction in LV diastolic pressure and systemic arterial pressure. Therefore, if there is reason to believe that diastolic heart failure is present, the initial attempts at preload reduction should be conservative.

Diuretics are effective and commonly used in the initial treatment. Furosamide is administered intravenously at an initial dose of 40–80 mg; subsequent doses depend on the response to the initial dose. Intravenous nitroglycerine (10–50 μg/min) is also used to reduce preload. It has the advantage of being anti-ischemic and does not result in electrolyte abnormalities. Nesiritide (0.015–0.06 μg/kg/min) produces a dose-dependent decrease in pulmonary capillary wedge pressure and systemic vascular resistance, and an increase in cardiac output in patients with systolic heart failure (55). There is little published experience in patients with diastolic heart failure.

AFTERLOAD REDUCTION Many, if not most, patients with acute pulmonary edema and diastolic heart failure are hypertensive (56). Although nitroglycerine or nesiritide are both effective in reducing blood pressure and relieving pulmonary edema, nitroprusside is the vasodilator of choice when a substantial reduction in pressure is required. It is administered by intravenous infusion a dose of 0.1–10 μg/kg/min; the dose is adjusted to obtain the desired hemodynamic effects. Nitroprusside is used only in situations requiring short-term reductions in blood pressure; early arrangements should be made to substitute other antihypertensive agents. Beta-adrenergic receptor blockers may be used alone or in combination with nitroprusside.

CHRONIC DIASTOLIC HEART FAILURE

Any attempt to develop a long-term therapeutic plan must be based on a careful consideration of the cause of the diastolic dysfunction and its potential response to treatment. For example, verapamil can be effective in symptomatic patients who have hypertrophic cardiomyopathy (57), but it is contraindicated in patients who have cardiac amyloidosis (58). Coronary artery disease, hypertensive heart disease,

chronic constrictive pericarditis, and aortic stenosis provide relatively specific therapeutic targets, but the problem is often less specific. For example, the complex mechanisms that underlie heart failure in elderly patients with hypertensive hypertrophic cardiomyopathy tend to preclude simple therapeutic interventions (59). In general, emphasis is placed on control of arterial hypertension, management of the congestive state, maintenance of normal sinus rhythm, and prevention of myocardial ischemia. It is particularly important to avoid the known "precipitants" of heart failure (see "Pathophysiology," above).

Specific Therapeutic Targets

VENOUS CONGESTION The renin-angiotensin-aldosterone system is activated in patients who have chronic heart failure, but the mechanisms that evoke its activation remain unclear in patients who have LV diastolic dysfunction. In some, myocardial ischemia, uncontrolled hypertension, and excessive dietary sodium may promote the development of congestion, whereas in others, low systemic vascular resistance or low arterial pressure may contribute to salt and water retention (60). Elevated venous pressure can directly cause renal sodium retention (61). Despite a limited understanding of the pathogenesis of salt and water retention in patients with diastolic dysfunction, diuretics remain the mainstay of therapy for venous congestion. After the initial treatment (vide supra), salt restriction is necessary, and long-term administration of a diuretic is usually required. It should be recognized that diuretics have the potential to reduce cardiac output, especially in patients with small LV chambers. With the exception of their antihypertensive effects, diuretics do not alter the primary disease processes that lead to diastolic dysfunction.

Thiazide diuretics (HCTZ 25–50 mg p.o. QD) can suffice for management of mild heart failure, but the side effects of carbohydrate intolerance and hyperuricemia can be undesirable. Loop diuretics such as furosemide (40–240 mg p.o. QD) are more potent than the thiazide diuretics, especially when the glomerular filtration rate is reduced. The combination of furosemide and a thiazide diuretic can be especially useful when edema is refractory to either agent alone. For patients who develop hypokalemia, the potassium-sparing diuretic spironolactone may be added. Spironolactone also has the potential to retard the fibrosis that contributes to abnormal chamber stiffness.

The reduction in blood volume produced by diuretics may trigger an increase in sympathetic tone and renin-angiotensin activation, which can lead to vasoconstriction and worsening of the pathophysiology. Some vasodilators, particularly nitrates and pure arteriolar vasodilators, evoke a similar response. ACE inhibitors (and beta-blockers) blunt the neurohormonal activation and decrease the salt and water retention that complicates the treatment of heart failure. In addition, the ACE inhibitors may also have salutary effects on the active and passive properties of the left ventricle. If hypotension does not limit their use, ACE inhibitors (e.g., Lisinopril 10–40 mg p.o. QD) can at the very least provide useful adjunctive therapy in

patients with diastolic dysfunction, particularly those with evidence of a chronic congestive state.

ATRIAL ARRHYTHMIAS Rapid atrial fibrillation in patients with LV diastolic dysfunction is usually accompanied by a substantial increase in ventricular diastolic and atrial pressures, leading to pulmonary edema and hypotension. Overt decompensation occurs because of inadequate time for complete ventricular relaxation and also because of the loss of atrial mechanical function and its contribution to ventricular filling. An attempt to restore and maintain sinus rhythm is mandatory. Direct current cardioversion may be necessary on an emergency basis. In less urgent situations, electrical or chemical cardioversion can be performed after rate control with beta-blockers, calcium channel blockers, or digitalis.

RATE CONTROL Tachycardia is poorly tolerated in most cardiac disorders. Atrial tachyarrhythmias, and even sinus tachycardia, have a negative impact on diastolic function for several reasons. A rapid heart rate causes an increase in myocardial oxygen demand and a decrease in coronary perfusion time, which can promote ischemic diastolic dysfunction even in the absence of coronary artery disease. In addition, tachycardia does not allow sufficient time for relaxation, and as a result there is incomplete relaxation between beats, which causes an increase in diastolic pressure relative to volume. Tachycardia also reduces the LV diastolic filling time and the coronary perfusion time. Accordingly, most clinicians use beta-blockers or calcium channel blockers to prevent excessive tachycardia and produce a relative bradycardia in patients who have diastolic dysfunction. It should be recognized, however, that bradycardia can result in a fall in cardiac output despite some potential for improved filling pressures. Such considerations underscore the need for individualizing therapeutic interventions that affect heart rate; an initial goal might be a resting rate of approximately 65–70 bpm with a blunted exercise-induced increase in heart rate (and a blunted increase in blood pressure during exercise).

Although the optimal heart rate for hypertrophic or failing hearts is not known, it is likely that such hearts would function most efficiently at relatively slow rates. This has several potentially beneficial effects that are largely related to the salutary effects on myocardial energetics and the prolonged diastolic interval that allows complete relaxation between beats. Furthermore, hypertrophied and failing hearts exhibit a flat or even negative force-frequency relationship, and in contrast to normal hearts, function may improve as the rate is slowed (62, 63).

MYOCARDIAL ISCHEMIA An extensive clinical and experimental literature documents the deleterious effect of ischemia on diastolic function of the left ventricle. A transient increase in LV stiffness and diastolic pressure develops during myocardial ischemia caused by coronary spasm, exercise, rapid atrial pacing, angioplasty balloon inflation, and spontaneous angina (64). Ischemia can be treated with nitrates, beta-blockers, and calcium channel blockers, percutaneous coronary intervention,

or coronary artery bypass surgery. When the signs of ischemic diastolic dysfunction are prominent, bypass surgery is appropriate (65); yet even after successful surgery there may be recurrent episodes of heart failure (66).

HYPERTENSION AND HYPERTROPHY Several factors contribute to the diastolic dysfunction seen in hypertensive heart disease (67). First, the abnormal loading conditions imposed by arterial hypertension reduce LV relaxation and filling rates. Second, concentrically hypertrophied hearts exhibit increased passive stiffness (caused by a low LV volume-mass ratio and fibrosis of the myocardium) and impaired relaxation that is independent of hemodynamic loads. Third, limited coronary vascular reserve can be responsible for myocardial ischemia, even in the absence of epicardial coronary disease. Each of these factors should be considered in the treatment of patients with hypertensive heart disease and diastolic dysfunction. Abnormalities of diastolic function can be detected in asymptomatic hypertensive patients with or without measurable hypertrophy (68). Adequate control of the arterial pressure in these patients with preclinical heart disease should favorably alter loading conditions in the short term, while, in the long-term, promoting regression of hypertrophy.

Although the short-term treatment of elevated systemic arterial pressure tends to augment diastolic function, the effect of load reduction is difficult to demonstrate during long-term therapy; indeed there is considerable variation in the effects of different antihypertensive agents on myocardial relaxation. For example, despite an equivalent reduction in arterial pressure, nifedipine augments LV filling rate and other relaxation indices, but propranolol does not (69). Some studies of patients who have hypertensive heart disease indicate that diastolic dysfunction improves as LV hypertrophy regresses (70, 71). Other studies have confirmed improved diastolic function, prolonged exercise duration, and better heart failure scores in verapamil-treated patients who have hypertensive heart disease and clinically significant LV diastolic dysfunction, but these clinical benefits were not closely related to changes in blood pressure or heart rate (72). Differences in the effects of treatment on diastolic function probably depend on the amount of hypertrophy regression, the alterations in LV loading conditions, the direct myocardial effect of the antihypertensive agent, and possibly changes in coronary reserve.

Progressive interstitial fibrosis accompanies the hypertrophic response to systemic arterial hypertension; fibrosis can also be prominent in the hypertrophy seen with aortic stenosis and hypertrophic cardiomyopathy. This abnormal accumulation of fibrillar collagen is a result of enhanced collagen synthesis (and/or decreased degredation) by cardiac fibroblasts that is related in part to the activity of the renin-angiotensin-aldosterone system. The important functional consequences of progressive interstitial and perivascular fibrosis include increased myocardial stiffness and impaired coronary flow reserve. In experimental studies, ACE inhibitors or spironolactone appears to protect against this exaggerated fibrous tissue response (73). Thus, the imperative to treat arterial hypertension may include prevention of the deleterious effects of angiotensin II and aldosterone. Angiotensin-converting

enzyme inhibitors are widely used, effective antihypertensive agents that can produce regression of LV hypertrophy, and a salutary effect on cardiac fibrosis may constitute an unexpected bonus. As a preventive or treatment strategy this has not yet been tested in humans with diastolic dysfunction.

HYPERTROPHIC CARDIOMYOPATHY AND RELAXATION Although hypertrophic cardiomyopathy is a unique entity, diastolic dysfunction is an important component of its pathophysiology. The diastolic dysfunction is caused by increased passive stiffness of the ventricle, (due to a low LV volume-mass ratio, fibrosis, and fiber disarray) and abnormal myocardial relaxation (due to abnormal calcium metabolism, altered loading conditions, and nonuniformity) (74).

As a result of depressed calcium sequestration by the sarcoplasmic reticulum and perhaps an increase in membrane calcium channels, myocardial calcium overload contributes to a slow or delayed myocardial relaxation (a slow and prolonged dissociation of actin-myosin), which leads to increased diastolic tension (75). Such prolonged relaxation can persist throughout the entire diastolic interval, especially in the presence of tachycardia. Assuming that the alterations in passive stiffness are relatively fixed and irreversible (which may not be true), medical therapy has generally been directed toward the relaxation abnormalities.

The calcium channel blockers verapamil, diltiazem, and nifedipine can improve many of the abnormal indices of relaxation and provide symptomatic relief (75), but these agents do not directly benefit myocardial calcium homeostatis. Verapamil, the most widely used calcium channel blocker in hypertrophic cardiomyopathy, has a beneficial effect on angina and dyspnea; it also improves exercise capacity (57). Therapy is initiated at 120–240 mg/day and gradually increased to 360–480 mg/day; the optimal dose is determined by the symptomatic response of the patient. Unfortunately, the vasodilating effects of calcium channel blockers can lead unpredictably to intensification of an outflow obstruction or hypotension even in the absence of obstruction.

Although beta-blockers can impair ventricular relaxation, they are commonly used in patients who have hypertrophic cardiomyopathy. Angina, dyspnea, and presyncopal symptoms tend to improve during treatment. Angina seems to respond more favorably than dyspnea. Thus, treatment with metoprolol may be initiated at 25–50 mg. twice a day; the dose is then gradually increased to 100–200 mg depending on the clinical response. Some patients require higher doses to achieve a beneficial effect on exercise capacity and symptoms (76).

When symptoms prove refractory to medical therapy, alcohol ablation of the interventricular septum, surgical procedures such as myotomy-myectomy, mitral valve replacement, or atrioventricular sequential pacemakers may favorably influence the diastolic properties of the left ventricle and produce symptomatic relief in selected patients with hypertrophic obstructive cardiomyopathy.

EXERCISE INTOLERANCE Patients who have a history of diastolic heart failure (even those who have diastolic dysfunction and little or no congestion) often exhibit

substantial exercise intolerance (vide supra). Given the limited understanding of the precise factors responsible for dyspnea and fatigue (77, 78), it has been difficult to develop a standard treatment plan for patients with LV diastolic dysfunction. Certainly, hypertension, myocardial ischemia, and clinically apparent congestion must be treated, but caution must be exercised to avoid even mild volume depletion that can contribute to a reduced cardiac output. A most important (and largely ignored) treatment is directed against the deconditioning that is prominent in many patients with diastolic heart failure. Cardiac rehabilitation programs can be very helpful in this regard (79).

Although calcium channel blockers and beta blockers improve symptoms in some patients with LV diastolic dysfunction, the benefit on exercise capacity is not always paralleled by improved measures of LV diastolic function. For example, in symptomatic patients who have hypertrophic cardiomyopathy, a placebo-controlled double-blind comparison of the effects of verapamil and propranolol on exercise tolerance indicated that both agents produced an increase in exercise duration; however, relaxation rate increased with verapamil and decreased with propranolol (80). The observation that such verapamil effects persist in the long-term (57) and that it is effective in patients who have other causes of diastolic dysfunction (72) makes this agent a treatment of choice for exercise intolerance. Beta-blockers are an acceptable alternative, despite a direct depressant effect on myocardial relaxation.

ACE inhibitors or angiotensin II–receptor-blocking agents also have the potential to improve exercise tolerance in patients who have diastolic dysfunction. For example, treatment with losartan is associated with an increase in exercise capacity and improved quality of life in patients who have hypertensive cardiovascular disease and documented diastolic dysfunction (81). These responses are similar to those observed in patients treated with verapamil (72). The salutory effects of losartin and verapamil are at least in part related to their antihypertensive effect.

Positive Inotropic Drugs

Most patients with heart failure caused by LV systolic dysfunction benefit from treatment with positive inotropic agents. Such therapy is generally not used in the long-term treatment of patients with diastolic heart failure because the LV ejection fraction is preserved and there appears to be little potential for a beneficial effect. Moreover, positive inotropic agents have the potential to worsen the pathophysiologic processes that cause diastolic dysfunction. Digitalis, by inhibiting the sodium-potassium adenosine triphosphatase pump, augments intracellular calcium through a sodium-calcium exchange mechanism and enhances the contractile state. By doing so, digitalis produces an increase in systolic energy demands while adding to a diastolic calcium overload. These effects may not be clinically apparent in many circumstances, but during hemodynamic stress or ischemia, digitalis may promote diastolic dysfunction (82). Data from the Digitalis Investigators

TABLE 4 Ongoing clinical trials in patients with diastolic heart failure. The CHARM-Preserved Trial data indicate that treatment with candesartin reduces hospitalization rates in patients with diastolic heart failure (87)

	CHARM	MCC-135	PEP-CHF	Seniors	Hong Kong	I-Preserve
Entrance criteria						
Signs and symptoms of HF	Yes	Yes	Yes	Yes	Yes	Yes
NYHA functional class	II–IV	II–III	II–IV	II–IV	II–IV	II–IV
Prior hospitalization	Yes	Yes	Yes	Yes	No	Yes
Ejection fraction (%)	>40	>40	>40	>35	>45	>45
Enrollment						
Total	6500	500	1000	2000	1000	3600
Diastolic heart failure	2500	230	1000	1000	1000	3600
Treatment						
Study drug(s)	Candesartin	MCC-135	Perindapril	Nebivolol	Diuretic alone Diuretic+Ramiprel Diuretic+Irbesartan	Irbesartan
Duration (months)	24	6	12	18	12	24
Endpoints & measurements						
Death	X	X	X	X	X	X
Hospitalization	X	X	X	X	X	X
Echocardiography	X	X	X	X	X	X
Cardiac MRI		X				
Exercise tolerance		X	X	X	X	
Exercise VO_2		X				
Brain natriuretic peptide		X	X			X
Completion of study (year)	2003	2003	2004	2004	2004	2006

Abbreviations: HF, heart failure; NYHA, New York Heart Association; MRI, magnetic resonance imaging; VO_2, oxygen consumption.

Group study, however, suggest that digitalis might have a beneficial effect, despite a normal LV ejection fraction, on some clinical outcome measures, such as heart failure hospitalizations (83). However, there appears to be a corresponding increase in endpoints related to myocardial ischemia and arrhythmias. Recognizing conflicting opinions on this issue, most clinicians do not use digitalis in patients with diastolic heart failure.

Beta-adrenergic agonists, by increasing intracellular cyclic adenosine monophosphate, enhance calcium sequestration by the sarcoplasmic reticulum and thereby promote a more rapid and complete myocardial relaxation between beats (84). Beta-agonists can also increase venous capacitance, which leads to a reduction in ventricular filling pressures. Phosphodiesterase inhibitors can produce similar salutary effects on myocardial relaxation and venous capacitance (85). Unfortunately, all cyclic adenosine monophosphate-dependent agents promote calcium influx into the cell and augment myocardial energy demands. Thus, dopamine, amrinone, and similar agents are used only in the short-term management of acute diastolic heart failure.

ONGOING CLINICAL TRIALS

There are at least six ongoing large randomized placebo-controlled therapeutic trials in patients with diastolic heart failure (see Table 4). All six require that the patients exhibit signs and symptoms of heart failure, a recent hospitalization for heart failure, and no more than a mild reduction in the ejection fraction. Three of them include subgroups with low ejection fractions. Four are directed at inhibition or blocking the renin-angiotensin system; one uses a beta-adrenergic blocker; and one is directed at calcium homeostatis. These studies will make available a variety of information (especially echocardiographic and exercise data) that should better characterize the syndrome of diastolic heart failure and hopefully provide direction for management and treatment (86).

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