NOVEMBER 1999
Volume 3, Issue 3

Cardiology Rounds

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Diastolic heart failure: Diagnosis, mechanisms, and treatment

MICHAEL R. ZILE, MD

Congestive heart failure (CHF) may be caused by a primary abnormality in systolic function, diastolic function or both. Making this distinction is important because the prevalence, prognosis, and treatment of CHF is quite different depending on whether the basic mechanism causing CHF is systolic or diastolic dysfunction.[1,2] The purpose of this presentation is to define the syndrome of diastolic CHF, describe the methods used to make the clinical diagnosis, outline the current treatment of diastolic CHF, and identify the mechanisms causing diastolic CHF, especially as these mechanisms relate to the development of new treatment strategies.

Defining diastolic dysfunction

Diastolic dysfunction can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete; the ventricle is unable to accept an adequate volume of blood from the venous system, fill at low pressure, or maintain normal stroke volume. In its most severe form, diastolic dysfunction results in overt symptoms of congestive heart failure (diastolic CHF). In modest diastolic CHF, symptoms of dyspnea and fatigue occur only during stress or activity, such as exercise, when heart rate and/or end diastolic volume increase. In its mildest forms, diastolic dysfunction can be manifested as a slow or delayed pattern of relaxation and filling with little or no elevation in diastolic pressure and no cardiac symptoms. In diastolic CHF, the congestive symptoms that occur are a manifestation of increased pulmonary venous pressures. The myocardial relaxation impairment in diastolic dysfunction may also be accompanied by increased diastolic stiffness, or the diastolic stiffness may occur alone. When CHF is caused by an isolated abnormality in diastolic function, the ventricular chamber is not enlarged and the ejection fraction is normal.[1-8]

Prevalence

The prevalence of mild diastolic dysfunction with no clinical symptoms and moderate diastolic CHF limited to exercise-induced symptoms is not known. Overall, however, as many as one-third of patients presenting with overt congestive heart failure have a normal ejection fraction; these patients have clinically significant diastolic dysfunction and isolated diastolic CHF.[9-15] The incidence of diastolic CHF depends on age, gender and the particular population under consideration.[12] It is relatively uncommon in young and middle-aged patients, especially those preselected for clinical research or cared for at tertiary care centers. The prevalence of diastolic CHF increases with age, with an approximate incidence of 15-25% in patients less than sixty years old, 35-40% between age 60-70 years, and 50% in patients over 70 years of age.[13-15] In one study,the prevalence of diastolic CHF in patients residing in a nursing home exceeded 50%.[14]

BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Hospital of
HARVARD MEDICAL SCHOOL

Brigham and Women's Hospital
75 Francis Street
Boston,Massachusetts 02115
Fax:(617) 732-5291
Cardiovascular Division Website:www.heartdoc.org

The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Table 1: Diagnosis - Systolic vs diastolic CHF

	Normal EF (n=20) (%)	Abnormal EF (n=30) (%)
Symptoms		
DOE	85	96
PND	55	50
Orthopnea	60	73
Physical Exam		
JVD	35	46
Rales	72	70
PMI	50	60
S_3	45	65
S_4	45	66
Hepatomegaly	15	16
Edema	30	40
Chest X-Ray		
Cardiomegaly	90	96
PVH	75	80

Abbreviations: CHF = congestive heart failure, EF = ejection fraction, DOE = dyspnea on exertion, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, PMI = point of maximum impulse, PVH = pulmonary venous hypertension. This table was reprinted from the *American Journal of Medicine* 1983; 75: 750, with permission.

Prognosis

The prognosis of patients with diastolic CHF, although less ominous than patients with systolic CHF, is still poorer than for age-matched control patients.[12,16-18] The annual mortality for patients with isolated diastolic CHF approximates 5%. In comparison, the annual age-adjusted mortality for patients with systolic CHF approximates 10-15%. In patients with diastolic CHF, the prognosis is also affected by the clinical pathologic etiology causing the disease. When patients with coronary artery disease are excluded from analysis, but those with pressure overload LV hypertrophy are included, the annual mortality for isolated diastolic CHF approximates 2%.[17,18] In addition, morbidity from diastolic CHF is quite high, requiring frequent outpatient visits, hospital admissions, and significant health care expenditures. While the recent DIG trial suggests that the use of digitalis may improve symptom status and decrease hospital admissions,[60] treatment failures remain common, underscoring the need for further improvements in therapy.

Diagnosing diastolic dysfunction

With few exceptions, diastolic CHF cannot be distinguished from systolic CHF on the basis of the history, physical examination, chest x-ray and ECG alone.[7] (Table 1) There are exceptions. Pulsus alternans, a PMI displaced into the axilla, or cor bovinum on chest x-ray indicate that CHF is caused by an abnormality in systolic function. More commonly, estimates of LV size and systolic function are needed in order to determine whether CHF is caused by systolic or diastolic dysfunction. These measurements can be made using echocardiography, radionuclide ventriculography, or contrast ventriculography. When a patient presents with dyspnea, pulmonary rales, and radiographic evidence of pulmonary venous hypertension, the detection of normal LV end diastolic volume and normal ejection fraction supports the diagnosis of isolated diastolic CHF. Conditions such as mitral stenosis and non-cardiogenic pulmonary edema must be ruled out. Thus, the diagnosis of diastolic CHF is functionally a diagnosis of exclusion in which patients have symptoms of CHF, but have no evidence of abnormal systolic function and have a preserved ejection fraction. This clinical approach can be supplemented by measuring indices of LV relaxation derived from the LV isovolumic relaxation and filling periods. However, acquisition of these data is not obligatory to establishing the diagnosis of diastolic CHF.

Filling dynamics can be assessed using echo-Doppler techniques of mitral valve inflow. The "E" wave represents early rapid filling and the "A" wave represents later ventricular filling produced by atrial contraction. Diastolic filling can be quantified by measuring the peak velocity, the area within the velocity vs time integral, and the rate of deceleration, as well as the "E" to "A" velocity ratio. When diastolic dysfunction is present, the "E" wave velocity is markedly reduced, "A" wave velocity is increased (reduced E/A ratio), velocity vs time integral is decreased, and deceleration time is prolonged.

These filling dynamics, like all of the proposed measurements of diastolic function, are influenced by changes in loading conditions, heterogeneity, and patient age.[1-8] Above the age of 60-65 years, a decreased E and an increased A wave may represent a normal pattern rather than the presence of diastolic dysfunction or disease.[19] When left atrial pressure is increased, a pseudonormalization of the pattern may occur masking the presence of diastolic dysfunction. Recent studies suggest that examination of the Doppler-derived pulmonary venous flow velocity and Doppler studies performed during a valsalva maneuver may provide information about coexistent loading conditions and enable the clinician to better interpret these Doppler-derived noninvasive indices of filling.[20,21] Pulmonary venous flow is divided into 3 periods:

1. forward flow during ventricular systole (S wave)
2. forward flow during early diastole (D wave)
3. reverse flow during atrial contraction (reverse A wave).

An increase in left atrial pressure may cause a decrease in the S wave, or an increase in the reverse A wave. In addition to examining pulmonary venous flow velocity, left atrial size and careful quantitation of other mitral inflow velocity-dependent measurements can be used to improve the assessment of LV diastolic function.

Pathological mechanisms

The pathological disease processes which cause diastolic heart failure include myocardial ischemia with or without epicardial coronary artery disease, pressure overload hypertro-

TABLE 2: Myocardial mechanisms of diastolic heart failure

A. MYOCARDIAL

1. Cardiomyocyte

a. Calcium homeostasis
- i) Channel function
- ii) Sarcoplasmic reticulum function, and
- iii) the proteins that modify it such as phospholamban, calmodulin, calsequestran

b. Myofilaments
- i) Troponin-C Ca^{++} Binding
- ii) Troponin-I phosphorylation
- iii) Myofilament Ca^{++} sensitivity

c. Energetics

d. Cytoskeleton
- i) Microtubules
- ii) Intermediate filaments (Desmin)
- iii) Microfilaments (Actin)
- iv) Endosarcomeric skeleton (Titin, nebulin)

2. Extracellular matrix
- a. Fibrillar collagen
- b. Other filamentous proteins
- c. Proteoaminoglycans
- d. MMP/TIMP

3. Neurohormones
- a. Renin-angiotensin-aldosterone
- b. Endothelin
- c. Nitric oxide
- d. Naturetic peptides

B. EXTRAMYOCARDIAL
1. Hemodynamic Load: preload, afterload
2. Heterogeneity
3. Systemic neurohormones
4. Pericardium

Abbreviations: MMP = Matrix metalloproteinase, TIMP = Tissue inhibitor of MMP, CA^{++} = Calcium

phy, genetic hypertrophy, infiltrative cardiomyopathies and constrictive pericarditis. Hypertrophy consequent to the physiological adaptation to pregnancy, hypertrophy which occurs in athletes, and volume overload hypertrophy do not cause abnormalities in diastolic function and do not cause the development of diastolic heart failure.

The basic mechanisms by which pressure overload hypertrophy and genetic hypertrophy cause diastolic CHF include extramyocardial factors and factors intrinsic to the myocardium, including changes both in the cardiac muscle cell, and in the extracellular matrix which surrounds the cardiomyocyte.[1-8,22-27] (Table 2). Intracellular processes such as changes in calcium homeostasis, contractile and non-contractile proteins, energetics and the cytoskeleton contribute to abnormalities in myocardial relaxation and stiffness. Changes in the extracellular matrix,particularly changes in fibrillar collagen, alter relaxation and stiffness. In addition to the cardiomyocyte and the extracellular matrix, local myocardial neuroendocrine activation can impair relaxation and increase stiffness. Activation of neurohormones such as the renin-angiotensin-aldosterone system may act directly to alter diastolic properties or may act indirectly by altering calcium homeostasis. Other neurohormones may act to enhance relaxation and reduce LV diastolic pressures. Finally, extramyocardial changes in loading conditions and changes in heterogeneity occur in hypertrophied ventricles and contribute to changes in relaxation and stiffness so that, even when the myocardium itself is normal, changes in these extramyocardial factors can cause abnormalities in diastolic function.

Myocardial ischemia, particularly in the subendocardial region, is common when ventricular hypertrophy is present. Slow or delayed myocardial relaxation and perivascular fibrosis can adversely affect coronary blood flow and coronary blood flow reserve. This may contribute to the development of myocardial ischemia.[28,29] Therefore, myocardial ischemia may be part of a clinical syndrome of diastolic congestive heart failure even if there is no epicardial coronary disease.

Epicardial coronary artery disease, both in its acute manifestations of myocardial ischemia and in its chronic consequences of myocardial fibrosis, is frequently the underlying pathologic cause of diastolic heart failure.[17,18,30] Myocardial ischemia, caused either by an acute decrease in supply (coronary spasm but not coronary occlusion) or an increase in demand (exercise and tachycardia), results in impaired relaxation and an acute increase in myocardial stiffness.[30] An acute coronary occlusion actually can initially lower myocardial stiffness by the hydraulic effect.[28] Chronic coronary occlusions, however, result in myocardial fibrosis, remodeling, and diastolic heart failure. It is clear that the same basic mechanisms which cause diastolic dysfunction in the presence of pressure overload hypertrophy – whether myocardial, extramyocardial, cellular or extracellular, also underlie changes produced by coronary artery disease.

Treatment of diastolic CHF

The general principles used to guide the treatment of systolic CHF are based on randomized, double-blind, placebo-controlled, multicenter trials. Unfortunately, definitive randomized trials have not been performed in patients with diastolic CHF. Consequently,the guidelines for the management of diastolic CHF are based on clinical experience, clinical investigations in relatively small groups of patients, and on concepts based on the knowledge and understanding of the pathophysiology of the disease process.[1-6,31-33] The treatment regimen outlined below (Table 3) applies to those patients with diastolic CHF who have clear manifestations of congestion, either at rest or with exertion. Whether treatment of asymptomatic diastolic dysfunction confers any benefit has not yet been examined.

TABLE 3: General approach to treatment of diastolic heart failure

1. Symptom targeted treatment
- A. Decrease pulmonary venous pressure
  - i) Reduce left ventricular volume
  - ii) Maintain atrial contraction
  - iii) Reduce heart rate
- B. Improve exercise tolerance
- C. Use positive inotropic agents with caution

2. Disease targeted treatment
- A. Prevent/treat myocardial ischemia
- B. Prevent/regress ventricular hypertrophy

3. Mechanism targeted treatment
- A. Modify myocardial and extramyocardial mechanisms
- B. Modify intracellular and extracellular mechanisms

The general approach to the treatment of diastolic CHF can be framed in three steps. First, treatment should be targeted at reducing symptoms, principally those of increased pulmonary venous pressure. For example, treatment should include decreasing diastolic pressure by decreasing LV volume, maintaining atrial contraction and reducing heart rate. Second, treatment should be targeted at the pathology which causes the diastolic CHF. For example, coronary artery disease, hypertensive heart disease, and aortic stenosis provide relatively specific therapeutic targets: lowering blood pressure, induction of LVH regression, aortic valve replacement, and treatment of ischemia by increasing myocardial blood flow and reducing myocardial oxygen demand. Third, treatment should target the underlying mechanisms which are altered by the disease processes mentioned above.

With a number of notable exceptions, many of the drugs used to treat systolic heart failure are in fact the same as those used to treat diastolic heart failure. However, the rationale for their use,the pathophysiologic process which is being altered by the drug, and the dosing regimen may be entirely different depending on whether the patient has systolic or diastolic CHF. For example, beta-blockers are now recommended both for the treatment of systolic and diastolic CHF. In diastolic CHF, however, beta-blockers are used to decrease heart rate, increase diastolic duration and modify the hemodynamic response to exercise. In systolic CHF, beta-blockers are used – in the long run – to increase inotropic state and modify LV remodeling. Diuretics are another group of agents used in both the treatment of systolic and diastolic CHF. However, the doses of diuretics used to treat diastolic CHF are in general much smaller than the doses used in systolic CHF. Some drugs however, are used only to treat either systolic or diastolic CHF, but not both. Calcium channel blockers such as diltiazem, nifedipine and verapamil have no place in the treatment of systolic CHF. In contrast, each of these has been proposed as being potentially useful in the treatment of diastolic CHF.

Symptom targeted treatment: Decrease pulmonary venous pressure

The initial step in treating patients presenting with diastolic CHF is to reduce pulmonary congestion by decreasing pulmonary venous pressures. This can be accomplished by decreasing LV volume, maintaining synchronous atrial contraction, and increasing the duration of diastole by reducing heart rate.

Reduce LV volume: By decreasing LV diastolic volumes, LV pressures slide down the curvilinear diastolic pressure/volume relationship toward a lower, less steep portion of this curve. As pressure throughout diastole falls, mean diastolic pressure, pulmonary capillary wedge, and pulmonary venous pressures fall. LV diastolic pressures can be decreased by decreasing total blood volume, decreasing central blood volume, and by blunting neuroendocrine activation. Total volume can be reduced by restricting fluids and sodium, and by using hemodialysis, hemofiltration, plasmaphoresis, and diuretics. Intravascular volume can be lowered by increasing venous capacitance using nitrates, nitroprusside, morphine, or rotating tourniquets. However, treatment with diuretics, nitrates, nitroprusside, or morphine should be initiated at low doses in order to avoid hypotension and fatigue. Hypotension can be a significant problem in the treatment of diastolic CHF because these patients have a very steep LV diastolic pressure/volume curve such that a small change in volume causes a large change in filling pressure and cardiac output. After the initial treatment of diastolic CHF has been completed, long-term treatment should include small to moderate doses of diuretics, moderate doses of a long-acting nitrate preparations, and significant restrictions in sodium intake. These agents effectively reduce the central blood volume, lower diastolic pressures, and thus alleviate the symptoms of the congestive state. Lower LV diastolic pressures may promote subendocardial blood flow. With the exception of their antihypertensive effects, diuretics do not affect the primary disease processes that led to diastolic CHF.

In a number of the pathological processes that cause diastolic CHF, both basic and clinical studies suggest that the process that results in hypertrophy is associated with activation of systemic and local cardiac neuroendocrine systems such as the renin-angiotensin-aldosterone system.[23,24] One mechanism causing fluid retention and the increases in central and systemic volume in patients with diastolic CHF is activation of these neuroendocrine systems. Therefore, treatment for diastolic CHF should include agents such as ACE inhibitors, AT_1 receptor antagonists, and aldosterone antagonists, which attenuate the fluid retention caused by neuroendocrine activation. In addition to promoting fluid retention, neuroendocrine activation can have direct effects on cellular and extracellular mechanisms that contribute to the development of diastolic

CHF. Modulation of neuroendocrine activation may also affect fibroblast activity, interstitial fibrosis, intracellular calcium handling, and myocardial stiffness.

The mechanisms that evoke activation of the neuroendocrine system remain incompletely understood in patients with diastolic CHF. A number of factors have been suggested. Myocardial ischemia, uncontrolled hypertension, and excessive dietary sodium may contribute to neuroendocrine activation. Limited distensibility of the atria may attenuate the secretion of atrial natriuretic factor and thereby reduce its diuretic effect.[34] Low systemic vascular resistance and/or low arterial pressure may contribute to an increase in RAAS activation and salt and water retention.[35] Elevated venous pressure may directly cause renal sodium retention.[36] The reduction in blood volume that follows the use of diuretics triggers an increase in sympathetic tone and further activation of the RAAS. Such neurohormonal activation can lead to vasoconstriction and a worsening of the congestive state. Some vasodilators, particularly nitrates and pure arteriolar vasodilators, evoke a similar response. By contrast, ACE inhibitors (and beta-blockers) blunt neurohormonal activation and decrease the salt and water retention that complicates the treatment of CHF.

Maintain synchronous atrial contraction: The second step in decreasing pulmonary venous pressures is to maintain atrial contraction. Maintaining atrial contraction is important both in preserving normal cardiac output and keeping LV diastolic pressure low. The mechanical basis underlying these facts were recently reviewed.[4] Atrial fibrillation is poorly tolerated in patients with diastolic CHF because it increases diastolic pressures, and leads to pulmonary edema and hypotension. Therefore, restoration of normal sinus rhythm should be a primary objective of therapy. If atrial arrhythmias persist or are recurrent and the patient cannot be maintained in normal sinus rhythm, LV diastolic pressures can be lowered by slowing the ventricular response rate and thereby increasing the duration of diastole. Patients who require a pacemaker should, when possible, receive sequential atrial-ventricular pacing.

Increase diastolic time period: The third strategy for maintaining low pulmonary venous pressures is to decrease heart rate thereby increasing the duration of diastole. Tachycardia is poorly tolerated in patients with diastolic CHF for several reasons. First, rapid heart rates cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time. This rapid rate can promote ischemic diastolic dysfunction even in the absence of epicardial coronary disease especially in patients with LV hypertrophy. Secondly, there may be incomplete relaxation between cardiac cycles resulting in an increase in diastolic pressure relative to volume. Thus, effective LV distensibility is reduced. Third, a rapid rate reduces diastolic filling time. Fourth,hearts with diastolic dysfunction exhibit a flat or even negative relaxation rate vs frequency relationship.[37-39] Thus, as heart rate increases, the relaxation rate is not augmented; in fact, it may become slower and incomplete, causing diastolic pressures, especially early in diastole, to increase. For these and other reasons, most clinicians use beta-blockers and calcium channel blockers to prevent excessive tachycardia and produce a relative bradycardia in patients with diastolic dysfunction. However, excessive bradycardia can result in decreased cardiac output despite an increase in LV filling.[37,40] Such considerations underscore the need for individualizing therapeutic interventions that affect heart rate. While the optimal heart rate must be individualized, an initial goal might be a resting heart rate of approximately 60 bpm with a blunted exercise-induced increase in heart rate.[41]

Symptom targeted treatment: Improve exercise tolerance

Patients with diastolic CHF have a marked limitation in exercise tolerance. There are a number of mechanisms responsible for this limitation. Exercise in a normal patient is accompanied by an increase in myocardial relaxation rate, an increase in the rate of LV pressure decline, a decrease in LV minimum pressure,an increase in the early left ventricle to left atrium transmitral pressure gradient which results in an increased filling rate. In addition,there is an increase in LV end diastolic volume allowing the ventricle to utilize the Frank-Starling mechanism to augment stroke volume and ejection fraction. In patients with diastolic CHF, the ability to use the Frank-Starling mechanism is limited despite the increased filling pressures because increased diastolic stiffness prevents the increase in LV end diastolic volume which normally accompanies exercise in the normal, more distensible ventricle.[42-45] As a result, the ejection fraction and stroke volume fail to rise and patients experience dyspnea and fatigue. Frequently in patients with diastolic CHF, there is an exaggerated rise in blood pressure and heart rate in response to exercise. The exaggerated increase in blood pressure boosts LV load which in turn impairs both LV emptying as well as myocardial relaxation and filling.[27] In addition, the abnormal relaxation rate vs frequency relationship which exists in patients with diastolic CHF prevents augmentation of relaxation rate as heart rate increases during exercise.[37-39] These changes in load and heart rate result in an increase in diastolic filling pressures. Chronic elevations of intraventricular diastolic pressures cause a reduction in lung compliance, increase the work of breathing, and evoke the symptom of dyspnea. Increased LV diastolic pressure during exercise may also limit subendocardial blood flow during a period of increased myocardial oxygen demand, further worsening diastolic function. An inadequate cardiac output during exercise contributes to anaerobic metabolism in skeletal muscles and lactate accumulation, and consequently fatigue of the legs and the accessory muscles of respiration.

Calcium blockers, beta-blockers and AT_1 antagonists may have a salutary effect on symptoms in some patients with dias-

tolic CHF. However, the benefits of these agents on exercise tolerance are not necessarily accompanied by improved LV diastolic function or increased relaxation rate. Nonetheless, a number of small clinical trials have shown that the use of these agents results in both short-term and long-term improvement in exercise capacity in patients with diastolic CHF.[29,46]

Symptom targeted treatment: Use positive inotropic drugs with caution

Positive inotropic agents are generally not used in the treatment of patients with isolated diastolic CHF because the LV ejection fraction is preserved and there appears to be little potential for benefit.Moreover, positive inotropic agents have the potential to worsen the pathophysiologic processes of diastolic CHF. In contrast to long-term use, positive inotropic drugs may be beneficial in the short-term treatment of pulmonary edema associated with diastolic CHF. Positive inotropes such as beta-adrenergic agonists and phosphodiesterase inhibitors can enhance SR function, promote more rapid and complete relaxation, increase splancnic blood flow, increase venous capacitance, and facilitate diuresis.[40,47-49] However, even short-term treatment with these agents may adversely affect energetics, induce ischemia, raise heart rate, and produce arrhythmias.[40] Therefore, these agents should be used with caution, if at all.

Digitalis, by inhibiting the sodium-potassium-ATPase pump, augments intracellular calcium and thereby augments the contractile state. In this way, digitalis produces an increase in systolic energy demands while adding to a relative calcium overload in diastole. These effects may not be clinically apparent under many circumstances, but during hemodynamic stress or ischemia, digitalis may promote or contribute to diastolic dysfunction.[47] Therefore, until recently and with the exception of patients with chronic atrial fibrillation (to slow ventricular rate), digitalis was not recommended in the treatment of diastolic CHF. However,results of the DIG trial suggest that even patients with a normal ejection fraction may have fewer symptoms and fewer hospitalizations if they are treated with digitalis. This salutary effect is not likely to result from digitalis'effect on inotropy, but rather its ability to blunt neuroendocrine activation[60].

Disease targeted treatment: Prevent/treat pathologic cause

The second step in the treatment of diastolic CHF is to treat the underlying clinical disease. In pressure overload hypertrophy, treatment should be aimed at normalizing load, preventing and/or reducing LV hypertrophy, correcting abnormalities in intracellular processes, and modifying the extracellular matrix response.[50] These steps will alter the mechanisms by which hypertensive heart disease and aortic stenosis cause diastolic CHF.

A number of antihypertensive pharmacologic agents are useful in preventing the development of LVH and in stimulating LVH regression. In so doing, these agents prevent or treat the development of diastolic CHF. However, the effect of these pharmacologic agents on the mechanisms that cause diastolic CHF may not be uniform. For example, beta-blockers and calcium channel blockers both directly reduce relaxation rate by their actions on intracellular processes. However, they normalize loading conditions, decrease heart rate, prevent ischemia, and can cause the regression of hypertrophy. The effect on these mechanisms is – indirectly – to speed relaxation and increase filling. Taken together, the aggregate effect of these drugs may result in symptomatic improvement in patients with diastolic heart failure. However,it is an oversimplification to suggest that beta-blockers and calcium channel blockers alone speed relaxation via a direct effect on the cardiac muscle cell.

Because abnormal diastolic function can be detected in asymptomatic hypertensive patients with or without increased LV mass,[51] it could be argued that early treatment directed at normalizing diastolic function might be desirable. There are, however, no data to support such an early treatment of diastolic dysfunction. Treatment of asymptomatic patients should be directed primarily at preventing the known complications of hypertension and secondarily at preventing hypertrophy and fibrosis.

The short-term treatment of elevated systemic arterial pressure, especially in severely hypertensive patients, improves LV diastolic function.[53] Such a salutary effect on load reduction is more difficult to demonstrate during long-term therapy. Indeed, there is considerable variation in the effects of different antihypertensive agents on myocardial relaxation.[50] For example, despite an equivalent decrease in arterial pressure, nifedipine augments LV filling rate and other relaxation indices, but propranolol does not.[54] Some studies of patients with hypertensive heart disease indicate that diastolic dysfunction improves as LV hypertrophy regresses[55-57] Still others show an improved diastolic function, prolonged exercise duration, and better heart failure scores in verapamil-treated patients with hypertensive heart disease and diastolic CHF.[33] Differences in the effects of treatment on diastolic dysfunction probably depend on the amount of hypertrophy regression, changes in ventricular loading conditions, direct myocardial effect of the antihypertensive agent, and possibly the changes in coronary reserve. Despite these differences it is now generally agreed that early treatment of hypertension can prevent the development of LV hypertrophy; treatment of hypertension results in regression of LV hypertrophy and normalization of diastolic function.

In coronary artery disease, treatment should be aimed at decreasing myocardial oxygen consumption (demand) and increasing myocardial blood flow (supply). Nitrates, calcium channel blockers and beta-blockers have all been shown to improve diastolic function. Likewise, both catheter-based and surgery-based methods of revascularization have been shown improve diastolic function.[30,58]

Mechanism-targeted treatment

Future directions: Conceptually, an ideal therapeutic agent should augment myocardial relaxation without promoting calcium overload. It should reduce heart rate, blunt neuroendocrine activation, prevent and regress fibrosis and hypertrophy and avoid an increase in myocardial oxygen consumption. A combination of agents that block calcium influx (like verapamil), augment calcium uptake by the sarcoplasmic reticulum (like beta-agonists),decrease heart rate (like zatebradine)[59] and blunt neuroendocrine and sympathetic activation might achieve this goal.Unfortunately,no such agent exists for the treatment of diastolic CHF. Therefore, drug development targeted at correcting the mechanisms that cause diastolic CHF is necessary. In addition, randomized, double-blind, placebo-controlled trials of existing agents – singly or in combination – must be performed. In the meantime, long-term therapy must rely on nonspecific treatment to reduce pulmonary venous pressures, including diuretics, nitrates, and agents which reduce heart rate. In addition, treatment should include specific treatment of the underlying pathologic mechanisms.

Diastolic CHF, now recognized as an important component of the overall burden of heart failure – especially in the elderly – has not yet received appropriate investigative attention. Renewed emphasis on diagnostic studies and therapeutic trials are sorely needed in this common but poorly understood and inadequately treated condition.

References:

1. Gaasch WH,Schick EC,Zile MR. Management of left ventricular diastolic dysfunction. In:Smith TW (ed). *Cardiovascular Therapeutics. A Companion to Braunwald's Heart Disease*, Philadelphia: W. B. Saunders Company, 1996;237-242.
2. Lorell BH. Significance of diastolic dysfunction of the heart. *Ann Rev Med* 1991;42,411-436.
3. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. *Ann Intern Med* 1992;117:502-510.
4. Zile MR. Diastolic dysfunction and heart failure in hypertrophied hearts. *CHF* 1998;4:32-42.
5. Brutsaert DL,Sys SU, Gillebert TC. Diastolic failure:pathophysiology and therapeutic implications. *J Am Coll Cardiol* 1993;22:318-325.
6. Gaasch WH,Blaustein AS, LeWinter MM. Heart failure and clinical disorders of left ventricular diastolic dysfunction. In:Gaasch WH,LeWinter MM eds. *Left Ventricular Diastolic Dysfunction and Heart Failure*, Philadelphia: Lea & Febiger,1994:245.
7. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA* 1994;271:1276-1280.
8. Gilbert J,Glantz S. Determinants of left ventricular filling and of the diastolic pressure-volume relation. *Circ Res* 1989;64:827-852.
9. Echeverria HH, Bilisker MS, Myerburg RJ,Kessler KM. Congestive heart failure:echocardiographic insights. *Am J Med* 1983;75-750-755.
10. Dougherty AH,Naccarelli GV,Grey EL,et al. Congestive heart failure with normal systolic function. *Am J Cardiol* 1984;54:778-782.
11. Soufer R, Wohlgelemter D,Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. *Am J Cardiol* 1985;55:1032-1036.
12. Cohn JN, Johnson G, and the Veterans Administration Cooperative Study Group. Heart failure with normal ejection fraction: the V-HeFT study. *Circulation* 1980;81(suppl III):48-53.
13. Luchi RJ, Snow E,Luchi JM,et al. Left ventricular function in hospitalized geriatric patients. *J Am Geriatr Soc* 1982;30:700-705.
14. Forman DE,Coletta D,Kenny D,et al. Clinical issues related to discontinuing digoxin therapy in elderly nursing home patients. *Arch Intern Med* 1991;151:2194-2198.
15. Wong WF,Gold S, Fukuyama O, Blanchette PL. Diastolic dysfunction in elderly patients with congestive heart failure. *Am J Cardiol* 1989;63:1526-1528.
16. Setaro JF, Soufer R,Remetz MS, et al. Long-term outcome in patients with congestive heart failure and intact systolic left ventricular performance. *Am J Cardiol* 1992;69:1212-1216.
17. Judge KW,Pawitan Y, Caldwell J, et al. Congestive heart failure in patients with preserved left ventricular systolic function: analysis of the CASS registry. *J Am Coll Cardiol* 1991; 18:377-382.
18. Brogen WC,Hillis LD, Flores ED, et al. The natural history of isolated left ventricular diastolic dysfunction. *Am J Med* 1992;92:627-630.
19. Warren SE,Cohn LH, Schoen FJ,et al. Advanced diastolic heart failure in familial hypertrophic cardiomyopathy managed with cardiac transplantation. *J Appl Cardiol* 1988;3:415-419.
20. Rakowski H,Appleton C,Chan KL,et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography:from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. *J Am Soc Echocardiogr* 1996,9:736-760.
21. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;21:1687-1696.
22. Apstein CS, Morgan JP. Cellular mechanisms underlying left ventricular diastolic dysfunction. In: Gaasch WH,LeWinter MM eds. *Left Ventricular Diastolic Dysfunction and Heart Failure*, Philadelphia: Lea & Febiger, 1994:3.
23. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;83: 1849-1865.
24. Weber KT, Sun Y, Guarda E. Structural remodeling in hypertensive heart disease and the role of hormones. *Hypertension* 1994;23:869-877.
25. Zile MR,Richardson K,Cowles MK, et al. Constitutive properties of adult mammalian cardiac muscle cells. *Circulation.* 1998;98:567- 579.
26. Tian R, Nascimben L, Ingwall JS, Lorell BH. Failure to maintain a low ADP concentration impairs diastolic function in hypertrophied rat hearts. *Circulation* 1997;96:1313-1319.
27. Zile MR, Nishimura RA, Gaasch WH. Hemodynamic loads and left ventricular diastolic function: factors affecting the indices of isovolumetric and auxotonic relaxation. In: Gaasch WH,LeWinter MM eds. *Left Ventricular Diastolic Dysfunction and Heart Failure*, Philadelphia: Lea & Febiger, 1994:219.
28. Watanabe J, Levine MJ, Bellotto F, et al. Left ventricular diastolic chamber stiffness and intramyocardial coronary capacitance in isolated dog hearts. *Circulation* 1993;88:2929-2940.
29. Udelson JE, Bonow RO, O'Gara PT, et al. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. *Circulation* 1989; 79:1052-1060.
30. Paulus WJ, Bronzwaer JGF, de Bruyne B, Grossman W. Different effects of "supply" and "demand" ischemia on left ventricular diastolic function in humans. In: Gaasch WH,LeWinter MM eds. *Left Ventricular Diastolic Dysfunction and Heart Failure*, Philadelphia:Lea & Febiger,1994:286.
31. Topol EJ,Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *N Engl J Med* 1985;312;277-283.
32. Bonow RO, Dilsizian V, Rosing DR,et al. Verapamil-induced improvement in left ventricular filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short and long term results. *Circulation* 1985;72:853-863.
33. Setaro JF, Zaret BL, Schulman DS,et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990; 66;981-986.

34. Anand IS, Ferrari R,Kalra GS, et al. Pathogenesis of edema in constrictive pericarditis: studies of body water and sodium,renal function, hemodynamics, and plasma hormones before and after pericardiectomy. *Circulation* 1991;83:1880-1887.

35. Anand IS, Chandrashekhar Y, Ferrari R, et al. Pathogenesis of congestive state in chronic obstructive pulmonary disease: studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. *Circulation* 1992;86:12-21.

36. Firth JD, Raine AEG, Ledingham JGG. Raised venous pressure: a direct cause of renal sodium retention in oedema. *Lancet* 1988;1:1033-1035.

37. Liu CP, Ting CT, Lawrence W, et al. Diminished contractile response to increased heart rate in intact human left ventricular hypertrophy: systolic versus diastolic determinants. *Circulation* 1993;88:1893-1906.

38. Mulieri LA, Hasenfuss G, Leavitt B, et al. Altered myocardial force-frequency relation in human heart failure. *Circulation* 1992;85:1743-1750.

39. Gwathmey JK, Warren SE,Briggs M,et al. Diastolic dysfunction in hypertrophic cardiomyopathy:effect on active force generation during systole. *J Clin Invest* 1991;87:1023-1031.

40. Udelson JE,Cannon RO, Bacharach SL, et al. Beta adrenergic stimulation with isoproterenol enhances left ventricular diastolic performance in hypertrophic cardiomyopathy despite potentiation of myocardial ischemia:comparison to rapid atrial pacing. *Circulation* 1989;79:371-382.

41. Levine HJ. Optimum heart rate of large failing hearts. *Am J Cardiol* 1988; 61:633-636.

42. Cuocolo A, Sax FL, Brush JE, et al. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension: diastolic mechanisms for systolic dysfunction during exercise. *Circulation* 1990;81:978-986.

43. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am CollCardiol* 1991;17:1065-1072.

44. Packer M. Abnormalities of diastolic function as a potential cause of exercise intolerance in chronic heart failure. *Circulation* 1990;81(suppl III):78-86.

45. Chikamori T,Counihan PJ,Doi YL, et al. Mechanisms of exercise limitation in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1992;19:507-512.

46. Udelson JE, Bonow RO. Left ventricular diastolic function and calcium channel blockers in hypertrophic cardiomyopathy. In Gaasch WH, Le Winter MM (eds):Left Ventricular Diastolic Dysfunction and Heart Failure, p 465. Philadelphia:Lea & Febiger,1994.

47. Lorell BH, Isoyama S, Grice WN,et al. Effects of ouabain and isoproterenol on left ventricular diastolic function during low-flow ischemia in isolated, blood-perfused rabbit hearts. *Circ Res* 1988;63:457-467.

48. Lang RM, Carroll JD, Nakamura S, et al. Role of adrenoceptors and dopamine receptors in modulating left ventricular diastolic function. *Circ Res* 1988;63:126-134.

49. Monrad ES, McKay R,Baim DS, et al. Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone. *Circulation* 1984;70:1030-1037.

50. Hoit BD,Walsh RA. Diastolic function in hypertensive heart disease. In: Gaasch WH,LeWinter MM eds. *Left Ventricular Diastolic Dysfunction and Heart Failure*, Philadelphia:Lea & Febiger,1994:354.

51. Inouye I,Massie B, Loge D,et al. Abnormal left ventricular filling: an early finding in mild to moderate systemic hypertension. *Am J Cardiol* 1984; 53:120-126.

53. Given BD, Lee TH, Stone PH, et al. Nifedipine in severely hypertensive patients with congestive heart failure and preserved ventricular function. *Arch Intern Med* 1985;145:281-285.

54. Zusman RM. Nifedipine but not propranolol improves left ventricular systolic and diastolic function in patients with hypertension. *Am J Cardiol* 1989;64:51F-61F.

55. Smith VE, White WB, Meeran MK, Karimeddini MK. Improved left ventricular filling accompanies reduced left ventricular mass during therapy of essential hypertension. *J Am Coll Cardiol* 1986;8:1449-1454.

56. Schulman SP,Weiss JL, Becker LC, et al. The effects of antihypertensive therapy on left ventricular mass in elderly patients. *N Engl J Med* 1990; 322:1350-1356.

57. Betocchi S, Chiariello M. Effects of antihypertensive therapy on diastolic dysfunction in left ventricular hypertrophy. *J Cardiovasc Pharmacol* 1992; 19:S1116-S1121.

58. Kunis R, Greenberg H, Yeoh CG, et al. Coronary revascularization for recurrent pulmonary edema in elderly patients with ischemic heart disease and preserved ventricular function. *N Engl J Med* 1985;313:1207-1210.

59. Breall JA, Watanabe J, Grossman W. Effect of zatebradine on contractility, relaxation, and coronary blood flow. *J Am Coll Cardiol* 1993;21:471-477.

60. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336:525-533.

Michael R. Zile, M.D., F.A.C.C.

Dr. Zile received his undergraduate degree from Knox College and his medical degree from Rush University. He completed his internal medicine training at Rush Presbyterian-St. Lukes Medical College in Chicago and his clinical cardiology fellowship at Tufts-New England Medical Center in Boston. Dr. Zile is currently Professor of Medicine at the Medical University of South Carolina, the Director of the Medical Intensive Care Unit at the Ralph H. Johnson Department of Veterans Affairs Medical Center, and a member of the Gazes Cardiac Research Institute. Dr. Zile's research interests include: identifying the basic myocardial, cellular, extracellular, and molecular mechanisms causing diastolic heart failure, developing new treatment strategies to treat diastolic heart failure, and defining the transsarcolemmal and intracellular signal transduction mechanisms which modulate myocardial, extracellular matrix and cardiomyocyte growth. His laboratory is supported by grants from the National Heart, Lung and Blood Institute, the American Heart Association, the Department of Veterans Affairs, and the Medical University of South Carolina.

Brigham and Women's Hospital,
Cardiovascular Division website:
www.heartdoc.org