Clinical Cardiology: New Frontiers

New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part II
Causal Mechanisms and Treatment

Michael R. Zile, MD; Dirk L. Brutsaert, MD

As described in Part I of this 2-part article, diastolic heart failure is common and causes significant alterations in prognosis. In Part II, experimental studies that have provided insight into the mechanisms that cause diastolic heart failure will be described. In addition, current treatment strategies and the design of future clinical trials of diastolic heart failure will be discussed. The development of truly effective therapy for diastolic heart failure depends on gaining a clear understanding of the basic mechanisms that alter diastolic function and the ability to efficiently target these mechanisms to correct these abnormalities in diastolic function.

Mechanisms That Cause Diastolic Dysfunction
Conceptually, the mechanisms that cause abnormalities in diastolic function that lead to the development of diastolic heart failure can be divided into factors intrinsic to the myocardium itself (myocardial) and factors that are extrinsic to the myocardium (extramyocardial; Table 1). Myocardial factors can be divided into structures and processes within the cardiac muscle cell (cardiomyocyte), within the extracellular matrix (ECM) that surrounds the cardiac muscle cell, and that activate the autocrine or paracrine production of neurohormones. Each of these mechanisms are active in the major pathological processes that result in diastolic dysfunction and heart failure. Myocardial and extramyocardial mechanisms, cellular and extracellular mechanisms, and neurohumoral activation each play a role in the development of diastolic heart failure caused by ischemia, pressure-overload hypertrophy, and restrictive and hypertrophic cardiomyopathy.

Cardiomyocyte
Diastolic dysfunction can be caused by mechanisms that are intrinsic to the cardiac muscle cells themselves. These include changes in calcium homeostasis caused by (1) abnormalities in the sarcoplasmic reticulum (SR) Ca$^{2+}$ reuptake caused by a decrease in SR Ca$^{2+}$ ATPase; and (3) changes in the phosphorylation state of the proteins that modify SR Ca$^{2+}$ ATPase function, such as phospholamban, calmodulin, and calstabin. Changes in any of these processes can result in increased cytosolic diastolic calcium concentration, prolongation in the calcium transient, and delayed and slowed diastolic decline in cytosolic calcium concentration. These changes have been shown to occur in cardiac disease and cause abnormalities in both active relaxation and passive stiffness.

The myofilament contractile proteins consist of thick-filament myosin and thin-filament actin proteins. Bound to actin are a complex of regulatory proteins that include troponin (Tn) T, C, and I. During relaxation, ATP hydrolysis is required for myosin detachment from actin, calcium dissociation from Tn-C, and active sequestration of calcium by the SR. Modification of any of these steps, the myofilament proteins involved in these steps, or the ATPase that catalyzes them can alter diastolic function.

Thus, relaxation is an energy-consuming process. Energetic factors necessary to maintain normal diastolic function include the requirement that the concentration of the products of ATP hydrolysis (ADP and inorganic phosphate [Pi]) must remain low and produce the appropriate relative ADP/ATP ratio. Diastolic dysfunction will occur if the absolute concentration of ADP or Pi increases or if the relative ratio of ADP/ATP rises. Abnormalities in these energetics factors may be caused by a limited ability to recycle ADP to ATP because of a decrease in phosphocreatine.

The cardiomyocyte cytoskeleton is composed of microtubules, intermediate filaments (desmin), microfilaments (actin), and endosarcomeric proteins (titin, nebulin, myomesin, and M-protein). Changes in some of these cytoskeletal proteins have been shown to alter diastolic function. Changes in titin isoforms have been shown to alter relaxation and viscoelastic stiffness. During contraction, potential energy is gained when titin is compressed, and during diastole, titin acts like viscoelastic springs, expends this stored potential energy, and provides a recoiling force to restore the myocardium to its resting length. In addition,
Changes in the structures within the ECM can also affect diastolic function. The myocardial ECM is composed of 3 important constituents: (1) fibrillar protein, such as collagen type I, collagen type III, and elastin; (2) proteoglycans; and (3) basement membrane proteins, such as collagen type IV, laminin, and fibronectin. It has been hypothesized that the most important component within the ECM that contributes to the development of diastolic heart failure is fibrillar collagen.\textsuperscript{11–15} The evidence that suggests that changes in ECM fibrillar collagen play an important role in the development of diastolic dysfunction and diastolic heart failure follows 3 lines. First, disease processes that alter diastolic function also alter ECM fibrillar collagen, particularly in terms of its amount, geometry, distribution, degree of cross-linking, and ratio of collagen type I versus collagen type III. Second, treatment of these disease processes, which is successful in correcting diastolic function, is associated with normalization of fibrillar collagen. Third, experiments in which a chronic alteration in collagen metabolism is accomplished result in an alteration of diastolic function.\textsuperscript{26–31} The role played by other fibrillar proteins, the basement membrane proteins, and the proteoglycans remains largely unexplored.

The regulatory control of collagen biosynthesis and degradation has at least 3 major determinants: transcriptional regulation by physical, neurohumoral, and growth factors; posttranslational regulation, including collagen cross-linking; and enzymatic degradation.\textsuperscript{17–19} Collagen synthesis is altered by load, including preload and afterload; neurohumoral activation, including the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system; and growth factors. Collagen degradation is under the control of proteolytic enzymes, which includes a family of zinc-dependent enzymes, the matrix metalloproteinases (MMPs).\textsuperscript{17–19} The balance between synthesis and degradation results in the total collagen present in a given pathological state at a specific time. Changes in either synthesis or degradation and their regulatory processes have been shown to alter diastolic function and lead to the development of diastolic heart failure.

### Neurohumoral and Cardiac Endothelial Activation

Both acutely and chronically, neurohumoral and cardiac endothelial activation and/or inhibition have been shown to alter diastolic function. Chronic activation of the RAAS has been shown to increase ECM fibrillar collagen and to be associated with increased stiffness. Inhibition of RAAS prevents or reverses this increase in fibrillar collagen and generally but not consistently reduces myocardial stiffness. In addition, acute activation or inhibition of neurohumoral and cardiac endothelial systems has been shown to alter relaxation and stiffness.\textsuperscript{32} These acute pharmacological interventions act in a time frame too short to alter the ECM; therefore, their effect on diastolic function must be caused by direct action on the cardiomyocyte to alter 1 or more cellular determinants of diastolic function. For example, acute treatment of patients with pressure overload with an ACE inhibitor, a direct NO donor, or an indirect endothelin-dependent NO donor caused left ventricular (LV) pressure decline and LV filling to be more rapid and complete and caused the LV pressure-versus-volume relationship to shift to the right.
Mechanism-targeted treatment

An investigation in relatively small groups of patients, clinical management of diastolic heart failure are based on clinical trials performed in patients with diastolic heart failure. Consequently, the guidelines for the treatment of diastolic heart failure are based on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on pathophysiological mechanisms. The treatment regimen outlined below and in Table 2 applies to those patients with symptomatic diastolic heart failure. Whether treatment of asymptomatic diastolic dysfunction confers any benefit has not been examined.

Treatment

General Approach
Unfortunately, there have been no randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic heart failure. Consequently, the guidelines for the management of diastolic heart failure are based on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on pathophysiological mechanisms. The treatment regimen outlined below and in Table 2 applies to those patients with symptomatic diastolic heart failure. Whether treatment of asymptomatic diastolic dysfunction confers any benefit has not been examined.

Treatment of diastolic heart failure can be framed in 3 steps. First, treatment should target symptom reduction, principally by decreasing pulmonary venous pressure at rest and during exertion. Both nonpharmacological and pharmacological approaches proposed but not proven to be effective in targeting symptoms are listed in Table 2. Second, treatment should target the pathological disease that caused the diastolic heart failure. For example, coronary artery disease, hypertensive heart disease, and aortic stenosis provide relatively specific therapeutic targets, such as lowering of blood pressure, induction of hypertrophy regression, performance of aortic valve replacement, and treatment of ischemia by increasing myocardial blood flow and reducing myocardial oxygen demand. Third, treatment should target the underlying mechanisms that are altered by the disease processes.

Symptom-Targeted Treatment

Decrease Diastolic Pressure
The initial step in treating patients presenting with diastolic heart failure is to reduce pulmonary congestion by decreasing LV volume, maintaining synchronous atrial contraction, and increasing the duration of diastole by reducing heart rate. By decreasing LV diastolic volumes, LV pressures “slide” down the curve of diastolic pressure-volume relationship toward a lower, less steep portion of this curve. LV diastolic pressures can be decreased by reducing total blood volume (eg, through fluid and sodium restriction or use of diuretics), decreasing central blood volume (nitrates), and blunting neurohumoral activation.

Table 2. Diastolic Heart Failure: Treatment

<table>
<thead>
<tr>
<th>Symptom-targeted treatment</th>
<th>Decrease pulmonary venous pressure</th>
<th>Reduce LV volume</th>
<th>Maintain atrial contraction</th>
<th>Prevent tachycardia</th>
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<td>Nonpharmacological treatment</td>
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<td>Disease-targeted treatment</td>
<td>Prevent/treat myocardial ischemia</td>
<td>Prevent/regress ventricular hypertrophy</td>
<td>Modify myocardial and extramyocardial mechanisms</td>
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Decrease Diastolic Pressure

Decrease pulmonary venous pressure, maintain synchronous atrial contraction, and increase the duration of diastole by reducing heart rate. By decreasing LV diastolic volumes, LV pressures “slide” down the curve of diastolic pressure-volume relationship toward a lower, less steep portion of this curve. LV diastolic pressures can be decreased by reducing total blood volume (eg, through fluid and sodium restriction or use of diuretics), decreasing central blood volume (nitrates), and blunting neurohumoral activation. Treatment with diuretics and nitrates should be initiated at low doses to avoid hypotension and fatigue. Hypotension can be a significant problem, because these patients have a very steep diastolic pressure-volume curve such that a small change in diastolic volume causes a large change in pressure and cardiac output.

Both basic and clinical studies suggest that hypertension is associated with activation of neurohumoral systems such as the RAAS. One mechanism that causes fluid retention and an increase in central and systemic volume is activation of these neurohumoral systems. Therefore, treatment for diastolic heart failure might include agents such as ACE inhibitors, \(\beta\)-blockers, AT1 receptor antagonists, and aldosterone antagonists. In addition to promoting fluid retention, neurohumoral activation can have direct effects on cellular and extracellular mechanisms that contribute to the development of diastolic heart failure. Modulation of neurohumoral activation may also affect fibroblast activity, interstitial fibrosis, intracellular calcium handling, and myocardial stiffness.

Tachycardia is poorly tolerated in patients with diastolic heart failure for several reasons. First, rapid heart rates cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time, which can promote ischemic diastolic dysfunction even in the absence of epicardial coronary disease, especially in patients with LV hypertrophy. Second, a shortened diastole may cause incomplete relaxation between beats, resulting in an increase in diastolic pressure relative to volume. Third, hearts with diastolic dysfunction exhibit a flat or even negative relaxation velocity–versus–heart rate relationship, so that as heart rate increases, relaxation rate does not increase or may even decrease, which can then cause diastolic pressures to increase. \(\beta\)-Blockers and some calcium channel blockers can thus be used to prevent excessive tachycardia and produce a relative bradycardia. Although the optimal heart rate must be individualized, an initial goal might be a resting heart rate of ~60 to 70 bpm with a blunted exercise-induced increase in heart rate.

Improve Exercise Tolerance
Patients with diastolic heart failure have a marked limitation in exercise tolerance. There are a number of mechanisms decreasing stiffness. In addition, there is a cyclical release of NO in the heart that is most marked subendocardially and that peaks at the time of relaxation and filling. These brief bursts of NO release provide a beat-to-beat modulation of relaxation and stiffness.

Treat Intracellular and Extracellular Mechanisms

- Reduce stiffness
- Decrease pulmonary venous pressure
- Maintain atrial contraction
- Prevent tachycardia
- Improve exercise tolerance
- Use positive inotropic agents with caution
- Nonpharmacological treatment
  - Restrict sodium to prevent volume overload
  - Restrict fluid to prevent volume overload
  - Perform moderate aerobic exercise to improve cardiovascular conditioning, decrease heart rate, and maintain skeletal muscle function
- Pharmacological treatment
  - Diuretics, including loop diuretics, thiazides, spironolactone
  - Long-acting nitrates
  - \(\beta\)-Adrenergic blockers
  - Calcium channel blockers
  - Renin-angiotensin-aldosterone antagonists, including ACE inhibitors, \(\beta\) blockers, and aldosterone antagonists
- Disease-targeted treatment
  - Prevent/treat myocardial ischemia
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TABLE 3. Randomized Clinical Trials for Diastolic Heart Failure

<table>
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<tr>
<th>Trial</th>
<th>Inclusion</th>
<th>End Points</th>
<th>Duration</th>
<th>Drug</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>CHF; EF&gt;40%</td>
<td>Mortality; hospitalization</td>
<td>3 y</td>
<td>Candesartan; placebo</td>
<td>AstraZeneca LP</td>
</tr>
<tr>
<td>Wake Forest</td>
<td>Hypertension; EF&gt;50%</td>
<td>Exercise tolerance; V̇O₂ max</td>
<td>6 mo</td>
<td>Losartan; hydrochlorothiazide</td>
<td>Merck</td>
</tr>
<tr>
<td>MCC-135</td>
<td>CHF; EF&gt;40%</td>
<td>Exercise tolerance; remodeling</td>
<td>6 mo</td>
<td>MCC-135; placebo</td>
<td>Mitsubishi-Tokyo</td>
</tr>
</tbody>
</table>

CHARM indicates Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; EF, ejection fraction; Wake Forest, the effect of losartan versus hydrochlorothiazide on exercise tolerance in patients with exercise-induced hypertension and asymptomatic diastolic dysfunction; V̇O₂ max, maximum oxygen consumption; and MCC-135, a phase II, double-blind, randomized, placebo-controlled, dose-comparative study of the efficacy, tolerability, and safety of MCC-135 in subjects with chronic heart failure, New York Heart Association class II/III.

Results of the Digitalis Investigation Group trial53 suggested that patients with heart failure and a normal ejection fraction may have fewer symptoms and fewer hospitalization days if they are treated with digitalis. However, a detailed analysis of these data in patients with a preserved ejection fraction has not been published, and a beneficial effect has not been proved. Digitalis may produce 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.53 Therefore, the utility of digitalis in the treatment of diastolic heart failure remains unclear.

Differences Between Pharmacological Treatment of Systolic and Diastolic Heart Failure

With a number of notable exceptions, many of the drugs used to treat diastolic heart failure are in fact the same as those used to treat systolic heart failure. However, the rationale for their use, the pathophysiological process that is being altered by the drug, and the dosing regimen may be entirely different depending on whether the patient has systolic or diastolic heart failure. For example, β-blockers are now recommended for the treatment of both systolic and diastolic heart failure. In diastolic heart failure, however, β-blockers are used to decrease heart rate, increase the duration of diastole, and modify the hemodynamic response to exercise. In systolic heart failure, β-blockers are used chronically to increase inotropic state and modify LV remodeling. In systolic heart failure, β-blockers must be titrated slowly and carefully over an extended time period. This is generally not necessary in diastolic heart failure. Diuretics are used in the treatment of both systolic and diastolic heart failure. However, the doses of diuretics used to treat diastolic heart failure are generally smaller than the doses used in systolic heart failure. Some drugs are used only to treat either systolic or diastolic heart failure but not both. For example, calcium channel blockers such as diltiazem, nifedipine, and verapamil have no place in the treatment of systolic heart failure. By contrast, each of these has been proposed as being useful in the treatment of diastolic heart failure.

Mechanism-Targeted Treatment (Future Directions)

Conceptually, an ideal therapeutic agent should target the underlying mechanisms that cause diastolic heart failure. Therefore, a therapeutic agent might improve calcium ho-
meostasis and energetics, blunt neurohumoral activation, or prevent and regress fibrosis. Fortunately, some pharmaceutical agents that fit these design characteristics are already in existence, and many more are under development. Unfortunately, randomized, double-blind, placebo-controlled, multicenter trials that examine the efficacy of these agents used either singly or in combination have been slow to develop. Difficulties that have prevented these kinds of studies have included a lack of recognition of the importance of diastolic heart failure, an inability to define a homogeneous study population, a lack of agreement on the definition and diagnostic criteria for diastolic heart failure, and a perception that there would be a marginal return on investment for funding these kinds of studies. There is now, however, reason for a great deal of optimism. Diastolic heart failure is now recognized as an important problem, guidelines for diagnosis have been developed, and the pharmaceutical industry has supported (and it is hoped that in the near future, government agencies will support) randomized, double-blind, placebo-controlled, multicenter trials. Three such trials are now under way (Table 3). Two of these trials target neurohumoral activation in the RAAS by inhibiting the angiotensin II receptor (Candesartan cilexetil in Heart failure Assessment of fibrosis and renin-angiotensin-aldosterone system. Circulation. 1991;83: 1849–1865). Two of these trials target neurohumoral activation in the RAAS by inhibiting the angiotensin II receptor (Candesartan cilexetil in Heart failure Assessment of fibrosis and renin-angiotensin-aldosterone system. Circulation. 1991;83: 1849–1865).

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