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 sarcolemmal channels responsible for short- and long-term extrusion of calcium from the cytosol, such as the sodium calcium exchanger and the calcium pump; (2) abnormal sarcoplasmic reticulum calcium (SR Ca²⁺) reuptake caused by a decrease in SR Ca²⁺ ATPase; and (3) changes in the phosphorylation state of the proteins that modify SR Ca²⁺ ATPase function, such as phospholamban, calmodulin, and calasequestrin. 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 and tropomyosin (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, α-actinin, myomesin, and M-protein). Changes in some of these cytoskeletal proteins have been shown to alter diastolic function. Changes in titin isotypes 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,
Extracellular Matrix

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. 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. 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. 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). 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. These acute pharmacological interventions act in a time frame too short to alter the ECM; therefore, their effects 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

Disease-targeted treatment

Symptom-targeted treatment

Use exercise as a therapeutic tool ( eg, aerobic exercise to improve cardiovascular conditioning).

Decrease pulmonary venous pressure

Reduce LV volume

Maintain atrial contraction

Prevent tachycardia

Improve exercise tolerance

Use positive isotropic 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

β-Adrenergic blockers

Calcium channel blockers

Renin-angiotensin-aldosterone antagonists, including ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists

Disease-targeted treatment

Prevent/treat myocardial ischemia

Prevent/regress ventricular hypertrophy

Mechanism-targeted treatment

Modify myocardial and extramyocardial mechanisms

Modify intracellular and extracellular mechanisms

Table 2 applies to those patients with symptomatic diastolic heart failure. Whether treatment of asymptomatic diastolic dysfunction confers any benefit has not been examined.

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. β-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.

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.

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The abnormal relaxation velocity–versus–heart rate relationship that exists in patients with diastolic heart failure prevents augmentation of relaxation velocity as heart rate increases during exercise. As a result, during exercise, diastolic pressure increases, the stroke volume fails to rise, and patients experience dyspnea and fatigue. In patients with diastolic heart failure, there is frequently an exaggerated rise in blood pressure in response to exercise.41–44 The increased diastolic stiffness prevents the increase in LV end-diastolic volume that normally accompanies exercise.41–44

Positive inotropic agents are generally not used in the treatment of diastolic heart failure because they enhance SR function, promote more rapid and complete relaxation, increase splanchnic blood flow, increase venous capacitance, and facilitate diuresis.40–52 However, even short-term treatment with these agents may adversely affect energetics, induce ischemia, raise heart rate, and induce arrhythmias. Therefore, these agents should be used with caution, if they are used at all.

Results of the Digitalis Investigation Group trial53 suggested that patients with heart failure and a normal ejection fraction may have fewer symptoms and fewer hospitalizations 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-

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**TABLE 3. Randomized Clinical Trials for Diastolic Heart Failure**

<table>
<thead>
<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; V̇̇O2 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 Cilexett 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; V̇̇O2 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.
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 Reduction in Mortality and morbidity [CHARM] and Wake Forest). The third study targets intracellular calcium homeostasis using an agent that is proposed to improve SR calcium reuptake (MCC-135). With these 3 studies, and others that are currently under development, an effective treatment for diastolic heart failure will be more completely defined.

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