Evaluation and Management of Diastolic Heart Failure
Brad G. Angeja, MD; William Grossman, MD

Case presentation: A 73-year-old female smoker with a history of hypertension presents to the emergency room with dyspnea on exertion for 2 weeks, now progressing to shortness of breath at rest for 1 day. She has no angina, but has 2-pillow orthopnea and possible paroxysmal nocturnal dyspnea. On examination, blood pressure is 180/96 mm Hg, heart rate is 95 beats per minute and regular, and she is afebrile. Jugular venous pressure is 11 cm, and there are rales in the lower third of both lung fields. On cardiac auscultation there is an S4, but no S3 or murmur. On chest radiography, emphysematous changes are present, and there are patchy bilateral infiltrates consistent with pulmonary edema or pneumonia. Heart size is mildly increased. Is she suffering from congestive heart failure, and if so, why? What are the best management options acutely and after hospital discharge?

Overview
Congestive heart failure (CHF) is one of the most common reasons for hospital admission in the United States. The syndrome usually evokes images of an enlarged heart with reduced systolic function. However, perhaps 50% of patients with CHF have normal or only minimally impaired systolic dysfunction and are diagnosed with diastolic heart failure (D-CHF) by exclusion.1-4 Rather than define D-CHF by what it is not (that is, CHF without systolic dysfunction), we regard D-CHF as CHF due to increased resistance to diastolic filling of part or all of the heart. Causes of D-CHF so defined are listed in Table 1; this review will focus on the myocardial causes.5,6

Depending on the cohort studied and the exact definition, the prevalence of D-CHF increases with age and is higher in women than men. Hypertension and left ventricular hypertrophy (LVH) are common. Compared with classic systolic CHF (S-CHF), the prognosis is unclear, but long-term mortality may be similar, especially in older patients.7,8

Pathophysiology

Impaired Relaxation
Impaired diastolic filling is the first manifestation of active ischemia, and evidence in animals and humans confirms that demand ischemia results in an upward shift of the left ventricular diastolic pressure-volume relationship.9 Decreased levels or activity of the sarcoplasmic reticulum calcium ATP-ase pump (SERCA) can slow the removal of calcium from the cytosol. Increased levels or activity of phospholamban, the naturally occurring SERCA-inhibitory protein, can also impair relaxation. Increased cAMP, resulting from β-adrenergic stimulation or inhibition of cardiac phosphodies- terase, phosphorylates phospholamban to remove its inhibitory effect on SERCA. The net effect is an improvement in diastolic relaxation. Because the ability of SERCA to remove calcium from the cytosol in diastole is energy-dependent, it is not surprising that ischemia leads to impaired relaxation. Pathological LVH secondary to hypertension or aortic stenosis results in decreased SERCA and increased phospholamban, again leading to impaired relaxation. Similar changes are seen in the myocardium of patients with hypertrophic or dilated cardiomyopathy. Interestingly, levels of SERCA decrease with age, coincident with impaired diastolic function.10 In addition, hypothyroidism decreases SERCA and increases phospholamban, leading to impaired relaxation; the opposite effects occur with hyperthyroidism to accelerate relaxation. Animal experiments using gene transfer,11 captopril, and β-agonists have shown that increasing the action of SERCA (or decreasing the action of phospholamban) improves diastolic relaxation.

Increased Passive Stiffness
In addition to the active relaxation process, the left ventricle also has pas-
Diastolic filling of part or all of the heart.

**Microvascular Flow, Myocardial Turgor**

Once LVH has occurred and(3,3),(995,997) diastolic pressure begins to rise, myocardial ischemia may play a role in worsening D-CHF, even without significant coronary stenoses. Extravascular compression caused by high LV diastolic pressure acts mainly on capillaries and small resistance coronary vessels, perhaps disrupting autoregulation and the ability to vasodilate. Indeed, the presence of LVH in hypertensive patients has been associated with impaired coronary flow reserve as compared with patients without LVH. Replacement of stenotic aortic valves has been associated with LVH regression and coincident improvement in coronary flow reserve. Thus, some combination of LVH and high diastolic ventricular pressure may impair microvascular function and cause silent ischemia, thereby worsening D-CHF. Myocardial turgor, resulting from engorgement of the microvasculature with blood, can cause an increase in diastolic stiffness. Clinically, this most likely occurs in association with right heart failure, as increased right atrial pressure leads to coronary venous engorgement.

**Neurohormonal Regulation**

An upregulated renin-angiotensin system contributes to D-CHF not only through development of hypertension but also via impaired myocardial relaxation. Both angiotensin II and endothelin contribute to LVH. In a rat model, the transition to D-CHF in hypertrophied hearts was also associated with “overdrive” of gene expression of endothelin and B-type natriuretic peptide. Abnormal diastolic function correlates with reduced heart rate variability, suggesting autonomic imbalance.

**Diagnosis**

The diagnosis of D-CHF is usually a clinical one: the presence of symptoms and signs of heart failure in the setting of increased ventricular filling pressure, with normal systolic function. Ideally, there should also be objective evidence of diastolic dysfunction by echocardiography or cardiac catheterization. Because the specific lower limit of ejection fraction or other criteria is arbitrary, the distinction between D-CHF and S-CHF is often blurred. A complicating fact is that diastolic dysfunction frequently accompanies systolic dysfunction. In addition, D-CHF is even more difficult to identify in the compensated state. Unlike S-CHF, in which a persistently decreased ejection fraction is evident, all but a few subtle baseline abnormalities may disappear with volume and blood pressure control and relief of ischemia in patients with D-CHF.

**Diabetic Testing**

The diagnostic standard for D-CHF is cardiac catheterization, which demonstrates increased ventricular diastolic pressure with preserved systolic function and normal ventricular volumes. The pressures in cardiac chambers proximal to the affected ventricle are also elevated; eg, increased left atrial and pulmonary capillary wedge pressures in patients with left ventricular diastolic dysfunction. If micromanometer catheters are used, peak negative dp/dt and τ (time constant of LV relaxation) are 2 useful parameters of impaired LV diastolic relaxation.

A more practical alternative is echocardiography, which can at least exclude S-CHF. Although echocardiography may not always be available in the acute setting, measurements of ejection fraction made several days after admission correlate with acute measurements in patients with acute pulmonary edema and hypertension. Doppler techniques can measure intracardiac blood flow and thereby infer pressures. The diastolic filling of cardiac chambers is complex, and multiple parameters have been studied. The most familiar of these are the mitral inflow velocities, the E and A waves that correspond to early flow during LV relaxation and the subse-
TABLE 2. Current and Potential Treatments for Diastolic Congestive Heart Failure

<table>
<thead>
<tr>
<th>Pathophysiological Basis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relieve volume overload</td>
<td>Diuretic</td>
</tr>
<tr>
<td></td>
<td>Fluid and sodium restriction</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
</tr>
<tr>
<td>Decrease heart rate, prolong diastolic filling time</td>
<td>β-adrenergic blockade</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockade (verapamil or diltiazem)</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmic agents</td>
</tr>
<tr>
<td></td>
<td>Cardioversion</td>
</tr>
<tr>
<td>Restore atrial contraction (atrial fibrillation)</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td></td>
<td>Angiotensin receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Investigational agents</td>
</tr>
<tr>
<td>Renin-angiotensin axis blockade</td>
<td>Additional agents if needed</td>
</tr>
<tr>
<td>Aldosterone blockade</td>
<td>Medical therapy</td>
</tr>
<tr>
<td>Control hypertension</td>
<td>Revascularization</td>
</tr>
<tr>
<td>Relieve ischemia</td>
<td></td>
</tr>
</tbody>
</table>

In the trial by the Digoxin Investigators Group, digoxin had similar reductions in hospitalization for CHF patients with and without systolic dysfunction; perhaps rate-slowing is the mechanism by which this benefit occurred. In contrast to the many clinical trials in S-CHF, there are few studies on therapy for D-CHF. Our approach to therapy of D-CHF depends on modification of the pathophysiology and is summarized in Table 2. One treatment that has obvious empirical benefit for symptom relief is volume reduction with diuretics, or with dialysis in the patient with renal failure. In addition, if the hallmark of D-CHF is impaired diastolic LV filling, then allowing the maximum time for filling to occur might be expected to relieve symptoms. Thus, rate-slowing agents are commonly used. Calcium-channel blockers and β-blockers have been shown to improve some exercise parameters and, in small studies or subgroup analyses, to reduce mortality.

In contrast to the many clinical trials in S-CHF, there are few studies on therapy for D-CHF. Our approach to therapy of D-CHF depends on modification of the pathophysiology and is summarized in Table 2. One treatment that has obvious empirical benefit for symptom relief is volume reduction with diuretics, or with dialysis in the patient with renal failure. In addition, if the hallmark of D-CHF is impaired diastolic LV filling, then allowing the maximum time for filling to occur might be expected to relieve symptoms. Thus, rate-slowing agents are commonly used. Calcium-channel blockers and β-blockers have been shown to improve some exercise parameters and, in small studies or subgroup analyses, to reduce mortality.

In the trial by the Digoxin Investigators Group, digoxin had similar reductions in hospitalization for CHF patients with and without systolic dysfunction; perhaps rate-slowing is the mechanism by which this benefit occurred. For patients in atrial fibrillation, restoration of normal sinus rhythm and an organized atrial contraction may improve diastolic filling.

As noted above, angiotensin II has deleterious effects on relaxation itself, and blockade of the renin-angiotensin system improves diastolic distensibility of the ventricle in both human and animal studies. Short-term treatment with losartan may be associated with increased exercise time, perhaps via afterload reduction. In addition, when LVH is a major component of D-CHF, agents associated with LVH regression might have particular benefit. The Losartan Intervention For Endpoint reduc-
tion in hypertension (LIFE) study has shown that among patients with hyper-
tension and LVH shown by ECG, losar-
tan reduced cardiovascular complica-
tions compared with atenolol. Of note,
losartan has been associated with greater
regression of biopsy-proven myocardial
fibrosis and reduced LV chamber stiff-
ness. Currently there are several mul-
ticenter, placebo-controlled, randomized
trials evaluating angiotensin-converting
enzyme inhibitors, angiotensin-receptor
blockers, and β-blockers in patients with
D-CHF.2

Investigational Agents
Aldosterone seems to be important in the
development of fibrosis, both in the
remodeling of S-CHF and in the devel-
opment of LVH. In the Randomized ALDactone (spironolactone) Evaluation
Study for congestive heart failure (RALES), which focused on patients
with S-CHF, placebo-treated patients with the highest serum levels of mark-
ers of collagen turnover had the worst
prognosis, and such patients had the
greatest response to spironolactone.32
Whether similar results might be ob-
served in patients with D-CHF is not
known, but the idea is attractive on
pathophysiological grounds.

Associated Risk Factors
In the Framingham cohort and other
databases, hypertension is the stron-
gest risk factor for CHF, and the de-
velopment of LVH is the likely segue
to D-CHF in particular. Therefore, ag-
gressive treatment to normalize blood
pressure in these individuals is essen-
tial. On the basis of what we know
about the pathophysiology of D-CHF,
treatment of hypertension in these pa-
tients should focus on blockade of the
renin-angiotensin axis, use of diuretics
(especially aldosterone antagonists),
and β-blockers. Finally, with the same
intensity as for systolic dysfunction,
the diagnosis of D-CHF should prompt
a thorough workup for coronary artery
disease. Ischemic episodes can cause
D-CHF through impaired relaxation,
which can result in flash pulmonary
edema. Revascularization and medical
therapy reduce symptoms and may im-
prove survival in patients with coro-
nary artery disease, and patients should
be treated according to existing Amer-
ican College of Cardiology/American
Heart Association guidelines.33

Conclusions
Although clinical and echocardi-
ographic criteria are still imperfect, a
clinical presentation of CHF in a pa-
tient with preserved systolic function
likely represents D-CHF. Incorporation
of serum BNP measurement in practice may increase the accuracy of
the diagnosis. Until further evidence is
available from randomized therapeutic
trials, clinicians should focus on a few
general principles in the treatment of
D-CHF: reduce volume overload, slow
the heart rate, control hypertension,
and relieve myocardial ischemia. Agents that block the renin-angioten-
sin system and aldosterone are particu-
larly attractive, on the basis of patho-
physiological studies.

References
1. Grossman W. Defining diastolic dys-
astolic heart failure: neglected or misdi-
agnosed? J Am Coll Cardiol. 2002;39:
138–141.
Congestive heart failure in subjects with
normal versus reduced left ventricular
ejection fraction: prevalence and mortality in
a population-based cohort. J Am Coll
Importance of heart failure with preserved
systolic function in patients > or =65 years
of age. CHS Research Group Cardiovascular
Health Study. Am J Cardiol. 2001;87:
413–419.
5. Zile MR, Brutsaert DL. New concepts in
diastolic dysfunction and diastolic heart
failure: part I. Circulation. 2002;105:
1387–93.
6. Zile MR, Brutsaert DL. New concepts in
diastolic dysfunction and diastolic heart
failure: part II. Circulation. 2002;105:
1503–1508.
7. Senni M, Redfield MM. Heart failure with
preserved systolic function: a different
natural history? J Am Coll Cardiol. 2001;38:
1277–1282.
elderly persons: influence of left ventricular
systolic function. The Cardiovascular Health
Simultaneous assessment of left ventricular
systolic and diastolic dysfunction during
pacing-induced ischemia. Circulation. 1985;
with age in senescent human myocardium.
Improvement in survival and cardiac metabolism
after gene transfer of sarcoplasmic reticulum
Ca(2+)-ATPase in a rat model of heart failure.
chemical assessment of myocardial fibrosis
in hypertensive heart disease. Hypertension.
2001;38:1222–1226.
ventricular diastolic chamber stiffness and
intramyocardial coronary capacitance in
isolated dog hearts. Circulation. 1993;88:
2929–2940.
14. Stern S. Angina pectoris without chest pain:
clinical implications of silent ischemia. Cir-
Effects of coronary venous pressure on left
ventricular diastolic distensibility. Circ Res.
Intracardiac angiotensin-converting enzyme
expression improves diastolic function in
patients with left ventricular hypertrophy due
to aortic stenosis. Circulation. 1994;90:
2761–2771.
Distribution and functional significance of
cardiac angiotensin converting enzyme
in hypertrophied rat hearts. Circulation. 1993;
87:1328–1339.
18. Flesch M, Schiffer F, Zolk O, et al. Angio-
tensin receptor antagonism and angiotensin
converting enzyme inhibition improve dia-
stolic dysfunction and Ca(2+)-ATPase
expression in the sarcoplasmic reticulum in
hypertensive cardiomyopathy. J Hypertens.
Local neurohumoral regulation in the transi-
tion to isolated diastolic heart failure in
hypertensive heart disease: absence of AT1
receptor downregulation and ‘overdrive’ of
the endothelin system. Cardiovasc Res.
Influence of gender and family history of
hypertension on autonomic control of heart
rate, diastolic function and brain natriuretic
21. Vasan RS, Levy D. Defining diastolic heart
failure: a call for standardized diagnostic
The pathogenesis of acute pulmonary edema
2001;344:17–22.
23. Vitarelli A, Gheorghiade M. Diastolic heart
failure: standard Doppler approach and


