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. 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.

**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. 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 phosphodiesterase, 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. 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, 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-
to diastolic filling of part or all of the heart.

**Microvascular Flow, Myocardial Turgor**

Once LVH has occurred and LV 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.

**Endocardial and Pericardial Disorders**

Endocardial fibroelastosis, mitral stenosis, and pericardial constriction or tamponade cause increased resistance to diastolic filling. Extrinsic compression by tumor can cause diastolic filling.

**TABLE 1. Causes of Diastolic Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial</td>
<td>Impaired relaxation</td>
</tr>
<tr>
<td></td>
<td>Epicardial or microvascular ischemia</td>
</tr>
<tr>
<td></td>
<td>Myocyte hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathies</td>
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<tr>
<td></td>
<td>Aging</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Increased passive stiffness</td>
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<tr>
<td></td>
<td>Diffuse fibrosis</td>
</tr>
<tr>
<td></td>
<td>Post-infarct scarring</td>
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<tr>
<td></td>
<td>Myocyte hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Infiltrative (eg, amyloidosis, hemochromatosis, Fabry’s disease)</td>
</tr>
<tr>
<td>Endocardial</td>
<td>Fibroelastosis</td>
</tr>
<tr>
<td></td>
<td>Mitral or tricuspid stenosis</td>
</tr>
<tr>
<td>Epicardial / Pericardial</td>
<td>Pericardial constriction</td>
</tr>
<tr>
<td></td>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Coronary microcirculation</td>
<td>Venous engorgement</td>
</tr>
<tr>
<td>Capillary compression</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Volume overload of the contralateral ventricle</td>
</tr>
<tr>
<td></td>
<td>Extrinsic compression by tumor</td>
</tr>
</tbody>
</table>

sive compliance and becomes stiffer with age. This seems to be due in part to diffuse fibrosis, as revealed by pathological studies and also by measuring serum markers of collagen turnover. Procollagen type I C-terminal propeptide is released during the synthesis of collagen type I, and serum concentrations seem to be increased in cardiac fibrosis. Passive stiffness is also increased in patients with focal scar or aneurysm after myocardial infarction. Myocyte hypertrophy can increase passive as well as active stiffness. Infiltrative cardiomyopathies such as amyloidosis increase passive myocardial stiffness and impair diastolic function in a similar fashion.

**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.

**Diagnostic 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 \( \tau \) (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-
waves of pulmonary vein flow, during
pulmonary vein flow in older patients
than twice the A wave velocity). Both
(high E wave velocity, usually more
tion, first in a pseudonormal pattern
ominant but with rapid decelera-
t to filling, the E wave again becomes
atrial contraction contributes little
to atrial contraction (atrial fibrillation)
Renin-angiotensin axis blockade
Aldosterone blockade
Control hypertension
Relieve ischemia

TABLE 2. Current and Potential Treatments for Diastolic Congestive Heart Failure

<table>
<thead>
<tr>
<th>Pathophysiological Basis</th>
<th>Therapy</th>
</tr>
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<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</td>
<td>β-adrenergic blockade</td>
</tr>
<tr>
<td>filling time</td>
<td>Calcium channel blockade (verapamil or diltiazem)</td>
</tr>
<tr>
<td></td>
<td>Consider digoxin</td>
</tr>
<tr>
<td>Restore atrial contraction (atrial</td>
<td>Antiarrhythmic agents</td>
</tr>
<tr>
<td>fibrillation)</td>
<td>Cardioversion</td>
</tr>
<tr>
<td>Renin-angiotensin axis blockade</td>
<td>Angiotensin-converting enzyme inhibitors</td>
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<tr>
<td></td>
<td>Angiotensin receptor antagonists</td>
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<tr>
<td></td>
<td>Spironolactone</td>
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<td></td>
<td>Investigational agents</td>
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<td></td>
<td>Additional agents if needed</td>
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<tr>
<td></td>
<td>Medical therapy</td>
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<td></td>
<td>Revascularization</td>
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</tbody>
</table>

quent contribution from atrial con-
traction. Pulmonary vein flow is also mea-
sured in 2 phases, systolic and
diastolic. Newer modalities that are not
as well validated include color
M-mode of the mitral flow propaga-
tion wave and Doppler tissue imaging
(diastolic velocities of the myocardial
tissue itself).

Echocardiographically, normal dia-
stolic function is characterized by pre-
dominantly early diastolic mitral flow
(E wave exceeds A wave velocity).
With impaired relaxation, atrial con-
traction contributes relatively more to
ventricular filling (A wave > E wave
velocity, with prolonged deceleration
of the E wave, usually >240 milli-
seconds). This state is common with in-
creasing age and may identify patients
at risk for D-CHF. When ventricular
diastolic pressure increases to the point
that atrial contraction contributes little
to filling, the E wave again becomes
predominant but with rapid decceler-
ation, first in a pseudornormal pattern
and ultimately in a restrictive pattern
(high E wave velocity, usually more
than twice the A wave velocity). Both
of these filling patterns are reliably
associated with diastolic-dominant
pulmonary vein flow in older patients
(over 50 years of age). There are 2
waves of pulmonary vein flow, during
systole and diastole, analogous to the x
and y descents of the jugular veins.
Elevated left atrial pressure impairs
atrial filling during descent of the base
in ventricular systole, and pulmonary
vein flow occurs predominantly during
diastole when the mitral valve is open.
This pattern can be seen with either
S-CHF or D-CHF. Echocardiography
during the acute presentation of our
patient might be expected to show a
pseudo normal or restrictive mitral in-
flow pattern with diastolic-dominant
pulmonary vein flow.

Newer Methods
A major limitation in diagnosing
D-CHF is the clinical assessment of
CHF itself. Our patient’s history of
smoking and her chest x-ray findings
are consistent with pulmonary disease,
which could also account for her
symptoms and masquerade as CHF.
What if her BNP level were 689
pg/mL (normal <80)? BNP has been
proposed as a tool to distinguish CHF
from other causes of acute dyspnea.24
This test seems to have utility in iso-
lated D-CHF as well, distinguishing
D-CHF from chronic obstructive lung
disease and identifying pseudonormal
and restrictive echocardiographic fill-
ing patterns with sensitivity and spec-
ificity of about 85%, using an upper
limit of 62 pg/mL.25 The simplest def-
nition of D-CHF may be an elevated
BNP with normal systolic function.
Because BNP increases during exer-
cise along with LV filling pressure in
CHF patients, exercise measurement
of BNP might even be a provocative
test to identify chronic D-CHF.26

Treatment
Modification of Pathophysiology
In contrast to the many clinical trials in
S-CHF, there are few studies on ther-
apy for D-CHF. Our approach to ther-
apy of D-CHF depends on modifica-
tion 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 symp-
toms. Thus, rate-slowing agents are
commonly used. Calcium-channel
blockers and β-blockers have been
shown to improve some exercise pa-
rameters and, in small studies or sub-
group analyses, to reduce mortality.2
In the trial by the Digoxin Investigators
Group, digoxin had similar reduc-
tions in hospitalization for CHF pa-
tients with and without systolic
dysfunction; perhaps rate-slowing is
the mechanism by which this benefit
occurred.27 For patients in atrial fibril-
ratio, restoration of normal sinus
rhythm and an organized atrial con-
traction may improve diastolic
filling.28

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 ani-
mal studies.16,17 Short-term treatment
with losartan may be associated with
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tion in hypertension (LIFE) study has shown that among patients with hypertension and LVH shown by ECG, losartan reduced cardiovascular complications compared with atenolol. Of note, losartan has been associated with greater regression of biopsy-proven myocardial fibrosis and reduced LV chamber stiffness. Currently there are several multicenter, 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 development 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 markers of collagen turnover had the worst prognosis, and such patients had the greatest response to spironolactone. Whether similar results might be observed 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 strongest risk factor for CHF, and the development of LVH is the likely segue to D-CHF in particular. Therefore, aggressive treatment to normalize blood pressure in these individuals is essential. On the basis of what we know about the pathophysiology of D-CHF, treatment of hypertension in these patients 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 improve survival in patients with coronary artery disease, and patients should be treated according to existing American College of Cardiology/American Heart Association guidelines.33

Conclusions
Although clinical and echocardiographic criteria are still imperfect, a clinical presentation of CHF in a patient 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-angiotensin system and aldosterone are particularly attractive, on the basis of pathophysiological studies.

References


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