

Evaluation and Management of Diastolic Heart Failure

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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 dys-

function 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 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.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-

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(*Circulation*. 2003;107:659-663.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000053948.10914.49

TABLE 1. Causes of Diastolic Congestive Heart Failure

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

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.¹² 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.

Endocardial and Pericardial Disorders

Endocardial fibroelastosis, mitral stenosis, and pericardial constriction or tamponade cause increased resistance

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.¹³ 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,¹⁴ 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.¹⁵

Neurohormonal Regulation

An upregulated renin-angiotensin system contributes to D-CHF not only through development of hypertension but also via impaired myocardial relaxation.^{16–18} 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.¹⁹ Abnormal diastolic function correlates with reduced heart rate variability, suggesting autonomic imbalance.²⁰

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.²¹ 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 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.²² 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.²³ 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

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

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

Echocardiographically, normal diastolic function is characterized by predominantly early diastolic mitral flow (E wave exceeds A wave velocity). With impaired relaxation, atrial contraction contributes relatively more to ventricular filling (A wave > E wave velocity, with prolonged deceleration of the E wave, usually >240 milliseconds). This state is common with increasing 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 deceleration, first in a pseudonormal 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 pseudonormal or restrictive mitral inflow 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 isolated D-CHF as well, distinguishing D-CHF from chronic obstructive lung disease and identifying pseudonormal and restrictive echocardiographic filling patterns with sensitivity and specificity of about 85%, using an upper

limit of 62 pg/mL.²⁵ The simplest definition of D-CHF may be an elevated BNP with normal systolic function. Because BNP increases during exercise 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 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.² 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.²⁷ For patients in atrial fibrillation, restoration of normal sinus rhythm and an organized atrial contraction 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 animal studies.^{16,17} Short-term treatment with losartan may be associated with increased exercise time, perhaps via afterload reduction.²⁹ 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 hypertension and LVH shown by ECG, losartan reduced cardiovascular complications compared with atenolol.³⁰ Of note, losartan has been associated with greater regression of biopsy-proven myocardial fibrosis and reduced LV chamber stiffness.³¹ 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.³² 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 im-

prove 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.

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