

Diastolic Dysfunction

Gordon A. Ewy, MD

Diastolic dysfunction of the heart is characterized by normal left ventricular contractility and normal ejection fraction, however ventricular relaxation is impaired. In systolic dysfunction, ventricular contractility and ejection fraction are reduced, in addition to impaired relaxation. The prevalence of diastolic dysfunction is increased in the elderly, especially those who have had inadequately treated hypertension. Both diastolic and systolic dysfunction may result in similar clinical signs and symptoms. Therefore, echocardiography is needed to make the distinction. Left atrial (LA) enlargement, assessed by left atrial volume indexed to body surface area, appears to be the best measure to assess diastolic function. LA enlargement is likely when indexed LA volume is $\geq 34\text{--}40$ mL/m². B-type natriuretic protein appears to be useful for the diagnosis, assessment and prognosis of heart failure, but it does not distinguish between the two types of dysfunctions. Several drug treatments that have effects on the mechanism of diastolic dysfunction are under investigation.

Diastolic dysfunction is characterized by normal left ventricular contractility and normal ejection fraction. In diastolic dysfunction, the left ventricle contracts normally but doesn't relax well. Diastolic dysfunction is more prevalent with increasing age and is usually found in older people with high blood pressure. This is especially true if the hypertension has been inadequately treated.

In systolic dysfunction (volume overload), the left ventricle is dilated and does not contract well. The ventricular filling pressure can be normal or elevated. The left ventricle may not relax well leading to pulmonary congestion because high pressure is needed to fill the ventricle. Decreased systemic and renal perfusion lead to sodium and fluid retention, as well as other signs and symptoms of congestive heart failure.

Address: Professor and Chief of Cardiology, University of Arizona College of Medicine, 1501 N. Campbell Avenue, Room 6404, Tucson, AZ 85724; ph: 520-626-6332; fax: 520-626-6332; e-mail: gaewy@aol.com.

Correspondent: Gordon A. Ewy, MD.

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Heart failure is rarely purely systolic or diastolic. Usually both are present with one type of "dysfunction" predominating over the other. An exception is a condition called "stunning" of the heart, which occurs after blood supply is restored to the heart following an incident such as resuscitation from cardiac arrest or ventricular fibrillation. In stunning, there is equal systolic and diastolic dysfunction with reduced ejection fraction and increased filling pressures. Stunning, and the associated functional measures, often improves in 2–3 days.

The presenting symptoms and signs of diastolic and systolic heart failure are similar. Clinicians believe that a physical exam should be sufficient to determine which is present. The Table summarizes the prevalence of symptoms and signs in diastolic and systolic

Table. Clinical Diagnosis of Diastolic Heart Failure. Prevalence of Symptoms and Signs of Heart Failure in Diastolic and Systolic Heart Failure^{1,2}

Symptom or Sign	Diastolic	Systolic
LVEF	>50%	<50%
Dyspnea on exertion	85%	96%
Paroxysmal nocturnal dyspnea	55%	50%
Orthopnea	60%	73%
Jugular venous distention	35%	46%
Rales	72%	70%
Displaced LV apex	72%	70%
S3	45%	65%
S4	45%	66%
Edema	30%	40%
Cardiomegaly	90%	96%

heart failure. Since there is considerable overlap in symptoms and signs derived from history and examination, echocardiography is needed to distinguish between the two types of heart failure.

The major problem in any discussion of diastolic heart failure is that there is no simple definition. If a patient's ejection fraction is stated to be 50%, 30% or 10%, the degree of systolic dysfunction is understood. Currently, there is no simple definition of diastolic dysfunction that relies on a similar number. A definition that has been proposed states that diastolic heart failure is a clinical syndrome characterized by signs and symptoms of heart failure, normal systolic function (eg, preserved ejection fraction) and abnormal diastolic function. The question remains as to how to assess the presence of abnormal diastolic function.

Echocardiographers have created a science of looking at abnormal diastolic dysfunction calling it "diastology." This term refers to the characterization of left ventricular relaxation and filling dynamics and their integration into clinical practice. Simplistically, systole is thought to be the interval starting when the ventricle begins contracting up until aortic valve closure. Diastole was taught to be the interval between aortic valve closure, and when the ventricle begins its next contraction.

Relaxation actually starts in late systole. If relaxation is abnormal, it results in problems with ventricular filling and a variety of echocardiographic findings. These findings may be described as the following: prolonged deceleration times, slowed relaxation, pseudonormal pattern, delayed relaxation, restrictive pattern, and constrictive pattern. These echocardiogram report terms are as confusing to the average physician involved in patient care as they are to an insurance medical director.

Tsang et al from the Mayo Clinic developed a simple and useful index of diastolic dysfunction³ saying that, "left atrial volume is to diastolic dysfunction, as the ejection fraction is to systolic dysfunction." Upon careful consideration, this statement makes a lot of sense. With diastolic dysfunction, if the ventricle won't relax or if there is scarring, pressure has to increase. If the pressure in the ventricle has to increase in diastole when the mitral valve is open, the pressure in the ventricle and the atrium is the same. So with diastolic dysfunction, the atrium will have to enlarge. Tsang et al studied 140 adult patients, 70 men, mean age 58 ± 19 years (range 18–90), referred for standard echocardiograms for a variety of clinical indications but with no valvular heart disease or atrial arrhythmias. Standardizing left atrial (LA) volume to body surface area, these investigators found that indexed LA volume (mL/m^2) was strongly associated with the grade of diastolic dysfunction. From this, an echocardiographic grade of diastolic dysfunction was developed. Diastolic function was graded as normal, abnormal relaxation, pseudonormal or restrictive. The mean indexed LA volume for the subgroup of patients without detectable diastolic abnormalities ($n = 44$) was $22 \pm 5 \text{ mL}/\text{m}^2$, and there was a graded relation between indexed LA volume and severity of LV diastolic dysfunction (Figure), which could be expressed as a linear regression equation. Correspondingly, indexed LA volume $\geq 32 \text{ mL}/\text{m}^2$ was 100% specific (67% sensitive) for the detection of abnormal diastolic function. In multivariate regression, a cardiovascular risk score modified from the scoring method

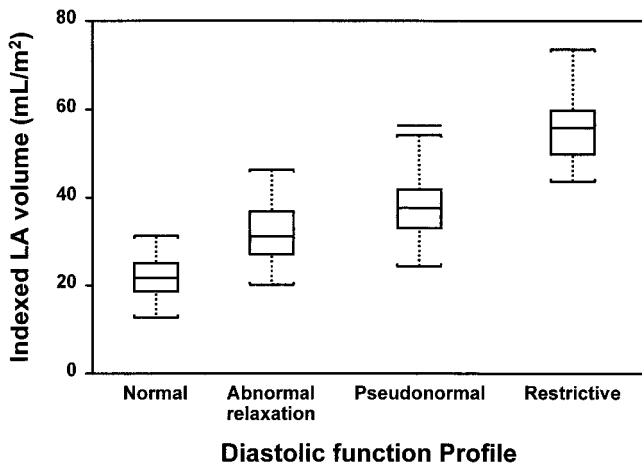


Figure. Relation between indexed LA volume and diastolic function grade. Reprinted from Tsang et al.³ Copyright 2002 with permission from Excerpta Medica, Inc.

of the Framingham Heart Study, history of vascular disease, congestive heart failure (CHF), transient ischemic attack (TIA) or stroke, and smoking history were independently related to the indexed LA volume. Unfortunately, there are no data as yet that relate indexed LA volume to mortality.

Because the left atrium has more of an egg shape than a round shape, indexed LA volume is a better measure than a single LA dimension, because volume calculation involves measures in 3 different planes. The measurement of LA volume is somewhat complicated, but with the newer, more sophisticated echo equipment, the LA image can be outlined, and the volume is calculated automatically. The normal LA volume is 22 ± 6 mL/m², which is all one needs to remember. If indexed LA volume is greater than one standard deviation (>28 mL/m²), there is mild LA enlargement. Greater than 2 standard deviations (>34 mL/m²) is moderate LA enlargement, and greater than 3 standard deviations (>40 mL/m²) is marked LA enlargement. In summary, normal is less than 28 mL/m², and LA enlargement is greater than 34–40 mL/m². These will probably be the values that are used to determine diastolic dysfunction, at least for the next few years.

Many current routine clinical echocardiographic exams are inadequate to measure diastolic dysfunction. A pseudonormal pattern

looks just like a normal pattern. Because there is a fairly high incidence of some ventricular stiffening, rapid deceleration times may be interpreted as mild diastolic dysfunction. The left atrial volume index currently reported is just atrial volume based on diameter. LA diameter must be included in the 3-plane volume formula and then corrected for body surface area. Hopefully, when left atrial volume corrected for body surface area is more widely reported, we will have a better handle on the assessment of diastolic dysfunction during routine echocardiographic assessment.

BNP AND DIASTOLIC HEART FAILURE

Another measure that relates to prognostic significance of patients with heart failure is a protein called B-type natriuretic protein (BNP), which is produced by the left ventricle. Its name (B-type) is due to its original discovery in the brain tissue of swine, but in humans it is secreted by the left ventricle in response to stretch or pressure. BNP has a very short half-life, 14 ± 4 hours. BNP is used to assess patients who present in the emergency room with dyspnea. If measured BNP is <100 pg/mL, heart failure can most likely be excluded. If BNP is >100 pg/mL heart failure is likely. If BNP is >1000 pg/mL, severe heart failure is usually present. If BNP remains in the 500–700 pg/mL range (even with intense inpatient treatment), those individuals are likely to be readmitted soon after discharge and have a bad prognosis. Patients who are under age 65 years and who have persistently elevated BNP (>1000 pg/mL) may be candidates for heart transplantation or artificial heart devices.

There is also atrial natriuretic peptide (ANP), which is secreted by the atrium. However, measurement of this peptide has not been shown to be as helpful as BNP. More information about BNP in the assessment of both systolic and diastolic dysfunction will appear as research continues. Based on studies that are available now, BNP can be used acutely for diagnosis, as well as chronically

to monitor effectiveness of therapy and to assess prognosis.

PREVALENCE

As many as one third of individuals presenting with clinical heart failure have normal systolic function.⁴⁻⁹ The prevalence varies widely with the population studied. Prevalence is high in the elderly, particularly in patients who have inadequately treated hypertension. It is known that hypertension has been inadequately treated in the US population for some time. First, it was thought that diastolic blood pressure had more significance on the development of cardiovascular diseases, because in younger patients the diastolic pressure seems to increase. Then systolic blood pressure received more attention. For many years (perhaps decades), there was the misconception that normal blood pressure was 100 plus age. So for an 80 year old, a blood pressure of 180 was acceptable. More recently it has been learned that pulse pressure gives information on the stiffness of the arteries and has the greatest prognostic value. This suggests that an individual with blood pressure of 160/60 has a much worse prognosis than an individual with blood pressure of 160/110, which is thought provoking.

Many older people have inadequately treated hypertension, so they are at high risk for diastolic dysfunction. Renal clinic or dialysis patients have a high prevalence of diastolic function. On the other hand for patients in a coronary care unit or in a busy transplant evaluation service like the University of Arizona, the prevalence of diastolic dysfunction might be very low because these patients predominately are presenting for treatment of the consequences of systolic dysfunction. The incidence of diastolic dysfunction is age-related. Heart failure due to diastolic dysfunction rises dramatically with age.¹⁰⁻¹² The prevalence of diastolic heart failure is 15% in those less than age 50, 33% in those aged 50-70, and greater than 50% in those over age 70.¹³

Diastolic heart failure affects women and

the black population disproportionately.¹⁴ Women are affected more because they live longer than men and are more likely to get scarring and fibrosis of the ventricle. Blacks are more affected because they have a higher prevalence of hypertension. The estimated annual mortality due to diastolic dysfunction varies widely from 9%–28% depending on the patient series.^{7,16} In the Framingham Study, the mortality rate in patients with diastolic heart failure was 4 times that of patients without heart failure, but it was half that of patients with systolic heart failure.⁷

PROGNOSIS AND MORTALITY

In the V-HeFT trial, which Cohn et al conducted almost a decade and a half ago, various forms of heart failure treatment in middle-aged men were studied.¹⁶ They found that a few patients in that study had heart failure but normal systolic function—therefore diastolic function. In these patients, they found that the annual mortality of diastolic dysfunction (8%) was half the annual mortality of those with systolic dysfunction (19%).

The Olmstead County Project (Mayo Clinic) results question these differences, since they showed that both systolic and diastolic heart failure have similar prognosis, at least for the first 3–4 years of follow-up.⁶ Others have raised similar doubts.¹⁷ In a review of available studies from the interval 1983–2001, if the study population of patients with diastolic dysfunction was composed of elderly patients, predominantly women (characteristic of the majority of diastolic heart failure patients), then the natural history of diastolic heart failure may not be different from that observed in patients with CHF secondary to decreased systolic function.

On the other hand in younger individuals, the prognosis of diastolic failure may be better than in secondary heart failure.¹⁷ In the elderly, the prognosis of heart failure secondary to diastolic dysfunction may well be similar to that of systolic failure. The difference in the two may be related to “presbycardia,” which will be discussed in more detail.

Looking at diastolic heart failure alone, an age effect is seen with both mortality and morbidity. The 5-year mortality rate for patients under age 50 is 15%. For patients aged 50–70, it is 33%, and for patients over age 70, 5-year mortality is 50%. For morbidity, as assessed by 1-year incidence of hospital admission for CHF, the rate is 25%, 50%, and 50% for ages <50, 50–70, and >70, respectively.¹³

RISK FACTORS

The chief risk factors for diastolic heart failure are advanced age, hypertension, diabetes, left ventricular hypertrophy, and coronary artery disease. The mechanical factors which lead to cardiac muscle thickening or scarring includes hypertrophy, fibrosis (collagen), presbycardia, pericardial disease or restraint, coronary turgor, and infiltration of the myocardium. Functional factors that contribute to the development of diastolic dysfunction are tachycardia and arrhythmias, ischemia, delayed relaxation, altered relaxation patterns, and calcium overload (stone heart).

When considering hypertrophy as a mechanism, if a normal left ventricular (LV) wall is 1 cm thick, then in an individual with severe left ventricular hypertrophy with a 2 cm thick LV wall, the ventricle contracts well but has difficulty relaxing.

One of the major mechanisms contributing to diastolic dysfunction, particularly with aging, is fibrosis. In the ventricular myocardium, myocytes occupy two thirds of the volume, and only account for one third of the cells. On the other hand, the myocardial interstitium, which serves to hold actin, myosin, and other contractile elements together, occupies one third of the volume, but accounts for two thirds of the cells. Myocytes are made up a series of sarcomeres, bound together into myofibrils by a collagen weave similar to tendons. If there is a lot of scarring, these can be seen as little “ropes” that won’t let the ventricle relax well. Since there is a lot of muscle, there is no problem with contraction, so systolic function is adequate, but impaired relaxation in diastole leads to isolated

diastolic dysfunction. Microscopically, these fibrous “ropes” can be seen as complex coils during contraction, becoming straight and parallel during relaxation limiting this phase.

Fibrosis, or scarring, is just a matter of increased collagen in the heart. The normal collagen content is about 3%–5%, and more than that result in scarring. Special histologic stains can demonstrate excess fibrous tissue. Fibrous tissue accumulation in the myocardium is the major determinate of abnormal ventricular stiffness.^{18–20}

Presbycardia is the “old heart.” Adult cardiac myocytes are terminally differentiated.²¹ These cells begin as multipotent cells, but once associated with the heart in embryologic development, they differentiate into heart cells and remain so. Therefore, they are regarded as “terminally differentiated.” One mechanism of aging is that cell loss occurs via apoptosis, “programmed” cell death and by necrosis. When heart cells are lost, “new” heart cells are not regenerated. Compensatory hypertrophy develops, therefore old hearts are hypertrophied hearts. Presbycardia is the loss of myocardial cells. If a heart attack occurs in a 40 year old, almost all of those patients will survive. If a heart attack occurs in an 80 year old, they are less likely to survive because half of the heart cells have already been lost, and those that remain are hypertrophied.

Therefore, presbycardia is a hypertrophied heart and a stiffer heart. With aging alone, hypertrophy and fibrosis develop even in the absence of hypertension. Half of the US population over the age of 65 has hypertension. The combination of age and hypertension on the development of diastolic heart failure is dramatic. Prognosis in diastolic dysfunction does appear to be related to etiology. Unfortunately, detailed data that would establish conclusive associations is not yet available.

TREATMENT

A number of drugs that can decrease cardiac scar tissue and collagen content are being developed. It has been thought that a scar

was unmodifiable, but there are active building and destructive processes within a scar. The rate and relative balance of these processes determine whether scar extent and size remains stable, increases or decreases. There are some data to suggest that the angiotensin converting enzyme (ACE) inhibitors, the angiotensin receptor blockers (ARB), and aldosterone blockers (eg, Aldactone) will affect the amount of scar tissue present. Further study of these possible actions is anticipated.

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