Diastolic Dysfunction of The Left Ventricle  
A Review of the Physiology, Causes, Diagnosis, Treatment and Implications  
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ABSTRACT: Diastolic dysfunction of the left ventricle frequently occurs in people with left ventricular hypertrophy and coronary artery disease. It is a common cause of congestive heart failure, especially in the elderly. The mechanism of diastolic dysfunction; its causes, diagnosis and treatment, are reviewed. These are important factors to a Medical Director who must assess the results of non-invasive studies. Alerted by the possibility of diastolic dysfunction, the Medical Director can be more sensitive to other signs and symptoms that may represent early signs of congestive heart failure or ischemia.

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Introduction
The diagnosis of left ventricular dysfunction is encountered in attending physician statements more and more frequently today. The recent increased understanding of the physiology of diastolic function in the cardiac cycle accounts for this. What is diastolic dysfunction and what is its significance to the life insurance medical director? Most of the clinical knowledge of diastolic dysfunction has centered on its role in congestive heart failure (CHF). Indeed, diastolic dysfunction is thought to account for up to 40% of patients with CHF.

But in many people, diastolic dysfunction is often present without CHF. What is the significance of this situation? The following review will summarize diastolic function and dysfunction, including its causes, diagnosis and treatment. An understanding of this will allow the Medical Director to better evaluate such cases.

Diastolic Function
The presence of intra-cellular calcium is required to cause myocardial contraction. The influx of calcium into the cell is triggered by the action potential. This influx in turn triggers a rapid influx of calcium from the sarcoplasmic reticulum. The increased calcium allows for interaction with the actin and myosin causing contraction. This, of course, consumes energy. Myocardial relaxation is not the passive process it was thought to be for so many years, but is an active, energy consuming process. The iso-volumetric phase of relaxation (from the closure of the aortic valve to the opening of the A-V valve) is the time when the greatest portion of muscle relaxation takes place. At the cellular level, this involves pumping the intracytoplasmic calcium back into the sarcoplasmic reticulum storage sites and also out of the cell by a sarcolemmal pump and calcium-sodium exchange. The actin and myosin filaments then separate and the muscle relaxes. Other influences on the relaxation phase include the cardiac load, inotropic state of the heart, heart
rate and catecholamine levels which accelerate relaxation as well as contraction.\(^3,4\)

Normally, about 60-80% of ventricular filling occurs in the first third of the filling phase and is very dependent upon myocardial relaxation.\(^5\) The degree of relaxation may be so pronounced that blood is actually suctioned into the left ventricle from the left atrium.\(^6\) Later filling is dependent upon atrial contraction which itself depends on preload, atrial wall thickness, and catecholamines. As heart rate increases, diastole is shortened more significantly than systole and this rapidity of relaxation influences diastolic filling even more. Atrial contraction also becomes a more important influence on diastolic filling as it accounts for approximately 25% of ventricular filling. Additional factors also influence diastolic myocardial function; such as the geometry of the ventricle, (wall thickness; internal dimensions and shape), degree of fibrosis, connective tissue edema and age. Functional alterations of synchronization, muscle tone, heart rate, duration of diastole, coronary perfusion and drugs also influence diastolic relaxation and ventricular filling.\(^9,10,11\)

Diastolic Dysfunction as a Cause of Congestive Heart Failure
The conventional thinking is that congestive heart failure is due to a weakening of the heart’s systolic pumping action to a point where cardiac output cannot keep up with oxygen demand. The heart’s contractile ability is usually weakened with an ejection fraction of usually 35% or less. We think of this condition as getting progressively and relentlessly worse, leading ultimately to the individual’s death in a relatively short period of time, and treatment only delays the inevitable. Cardiac failure, that is systolic pump failure, has an annual mortality rate of 19-47%.\(^7\) However, numerous recent studies have shown that many people who present with signs and symptoms of congestive heart failure have normal systolic cardiac function with ejection fractions of over 45%.\(^9,\) Diastolic dysfunction occurs when relaxation time is slowed or when there is a reduction of ventricular compliance (increased stiffness). The slowing of diastolic relaxation causes a reduced early diastolic filling. This causes an increased dependence on late diastolic filling and atrial contraction. In addition, the ventricle is unable to fill properly at normal diastolic pressures. This leads to a decreased end-diastolic volume or elevated end-diastolic pressures, or both (Figure 1). The increased filling pressures leads to pulmonary congestion and congestive failure.\(^3,10\)

Causes of Diastolic Dysfunction
The most common causes of diastolic heart failure are related to or seen with the conditions found in Table 1.

Left ventricular hypertrophy (LVH) is the most common cause of diastolic dysfunction.\(^9,10,11\) Sustained hypertension and significant aortic stenosis lead to cardiac hypertrophy. The hypertrophied heart experiences an impairment of relaxation which leads to prolonged relaxation time and a ventricle that becomes stiff (decreased compliance). This is due in part to a defect in the calcium/actin-myosin complex leading to a build up of calcium.\(^15\) The prolonged relaxation time causes a reduction in the rapid filling phase, incomplete filling and a shift in the ventricular pressure-volume relationship. This causes an increase in atrial pressure, in order to improve late filling, to preserve cardiac output. However, the myocardial hypertrophy associated with athletic training does not interfere with diastolic function.\(^3\) Approximately 60% of patients with diastolic heart failure have systemic hypertension.\(^13\)

 Coronary artery disease is the second major cause of diastolic dysfunction. During a transient episode of myocardial ischemia, such as during an attack of angina pectoris, there is a partial loss in the energy required for calcium to be pumped out of the cytoplasm into the sarcoplasmic reticulum, causing impairment
of the dissociation of the actin and myosin filaments. This causes an increase in left ventricular (LV) chamber stiffness, a slowing of relaxation and a shift in the diastolic pressure-volume curve with a rise in atrial filling pressure. The slowing of relaxation further compromises coronary artery filling, aggravating the situation. These changes revert to normal with the resolution of the ischemia. In this regard, dyspnea with effort, in the absence of pulmonary disease, may be an anginal equivalent and should not be discounted as being "out of shape". The changes in the myocardium, seen during transient ischemia, are non-uniform and heterogeneous in distribution.

Acute ischemia due to increased demand, as in angina pectoris, affects systolic function only slightly, but diastolic function is affected earlier in the ischemia process. However, in ischemia due to the cessation of coronary blood flow, systolic dysfunction overshadows diastolic dysfunction. In a state of chronic myocardial ischemia, or postinfarction, the heterogeneous pattern is altered further by the areas of fibrosis and scarring and by the accompanied compensatory hypertrophy in areas of normal myocardium. These changes are more likely to be permanent.

Aging causes a progressive decrease in diastolic function, while resting systolic function is usually preserved. There is an increase in interstitial collagen content, which results in an increased left ventricular stiffness. There is also a reduction in calcium removal further interfering with the actin-myosin disassociation. In this regard, the normal myocardial changes of aging make an elderly person more susceptible to the effects of myocardial ischemia, hypertension and hypertrophy.

Primary hypertrophic cardiomyopathies may be concentric or asymmetric. An autosomal dominant inheritance pattern is seen in at least 50% of people. It is associated with abnormalities in the contractile proteins which leads to prolonged iso-volumetric relaxation times, stiff ventricles, and abnormal diastolic filling.

In patients with mitral regurgitation and mitral stenosis, the problem is associated with high atrial pressures and, in the case of mitral stenosis, reduced LV filling due to the mechanical inability of the atrium to empty.

Constrictive pericarditis mechanically restricts filling. Infiltrative myopathies cause stiff ventricles with slow relaxation.

**Diagnosis of Diastolic Dysfunction**

Most patients who have diastolic dysfunction are seen without congestive heart failure. Patients with hypertension and/or left ventricular hypertrophy will have some degree of diastolic dysfunction, especially in the elderly. This can be assessed on echocardiography as abnormal diastolic filling with a low or reversed E/A ratio. Thallium stress testing may reveal an abnormally increased lung:heart ratio in an otherwise normal test. Cardiac catheterization studies will reveal abnormal filling pressures and a high end diastolic pressure. The left ventricular systolic function (ejection fraction) will be normal or nearly normal. This may be the only manifestation of ischemia in a person with CAD.

Exercise testing employing perfusion imaging, radionuclide angiography or echocardiography, further offers significant information with respect to etiology and physiology of diastolic dysfunction. To get more sophisticated measurements of relaxation times, filling pressures and filling times, invasive studies need to be done. However, we do not need such sophisticated studies to make a diagnosis of CHF due to diastolic dysfunction. With the results of a well done history and physical, echocardiogram, and imaging stress test, a strong presumptive diagnosis can be made.
Generally speaking, the diagnosis of CHF due to diastolic dysfunction can be made in a person with dyspnea, who has a heart with normal or small LV chamber size, an ejection fraction over 40% and the presence of pulmonary venous hypertension. A history of significant hypertension, aortic stenosis, primary hypertrophic cardiomyopathy, mitral valve disease, or CAD is usually the background cause. This is especially true in the elderly when pulmonary congestion accompanies CAD, hypertension, or LVH. The echocardiogram can be of great help in further analyzing cardiac function, as well as cardiac anatomy. Left ventricular wall thickness, LV chamber size and ejection fraction are readily measured and it can also give evidence of infiltrative disease, constrictive pericarditis, mitral or aortic valve disease. Doppler echocardiography can also help provide evidence of abnormal filling dynamics, as can radionuclide angiography. The clinician is initially surprised that a “normally functioning heart” can be in failure and may even dismiss it in his APS. He may say something to the effect that since the applicant had “normal cardiac function”, the dyspnea is non-cardiac. We should be alert to these types of statements.

Treatment
The treatment of diastolic dysfunction involves regimens that aim to improve relaxation times, improve diastolic filling and reduce filling pressures. Digitalis generally has no place in the treatment of CHF due to diastolic dysfunction, as its action on intracellular calcium may further adversely affect diastolic function.

In hypertensives, therapy is directed primarily at reducing blood pressure, thereby attempting to relieve LVH and improve diastolic filling. Beta blockers, some calcium-channel blockers, and diuretics seem to be the drug of choice in the treatment of diastolic dysfunction. In theory, beta blockers may be detrimental because they do block the catecholamine enhancement of relaxation. However, they are used primarily to reduce blood pressure and to slow the heart rate, which allows for a more complete atrial emptying. The calcium-channel blockers, verapamil and diltiazem, in addition to the above, also may cause coronary artery dilation, and a reduction of the excess intracellular calcium, improving relaxation. Diuretics help in reducing pre-load, but care must be taken not to reduce volume too much as these people, especially the elderly, are very fluid sensitive and vigorous diuresis can result in symptomatic hypotension. Arterial vasodilators may be equally hazardous especially in the elderly with diastolic dysfunction as they too may lead to hypotension.

The renin-angiotension system has adverse effects on diastolic function and may actually stimulate myocardial fibrosis. Therefore, ACE inhibitors may be an excellent choice of medication for improving diastolic function, by reduction in BP and LVH, as well as the possibility of limiting myocardial fibrosis.

Atrial fibrillation can be devastating in people with diastolic dysfunction due to the loss of atrial contraction which accounts for about 25% of ventricular fillings. There are also reduced relaxation and filling times associated with a rapid atrial fibrillation. Once again, Beta blockers and Ca blockers like verapamil can be quite useful in slowing the heart rate.

Conclusion
The insurance Medical Director must assess the results of non-invasive studies in light of both the causes and the effects of diastolic dysfunction and not dismiss a cases as normal simply because the ejection fraction is normal. Alerted by the possibility of diastolic dysfunction, we can be more sensitive to other signs and symptoms that may represent early signs of CHF or perhaps ischemia. We can also more readily appreciate the significance of exercise-induced dyspnea as a sign of myocardial ischemia, and the increased
significance of atrial fibrillation or poorly controlled blood pressure. The rate of progression from diastolic dysfunction to CHF is unknown, but it can be assumed that those with diastolic dysfunction are at increased risk of developing overt failure.

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Table 1
Causes of Diastolic Dysfunction

1. Cardiac hypertrophy with sustained pressure overload as seen in patients with hypertension, aortic stenosis, or hypertrophic cardiomyopathies.

2. Myocardial ischemia as seen during an anginal attack in patients with coronary artery disease.

3. Advanced age.

4. Mitral stenosis and regurgitation.

5. Constrictive pericarditis.

6. Infiltrative restrictive cardiomyopathy (such as hemochromatosis or amyloidosis).

References
Fig. 1. Curves representing the relationship between left ventricular diastolic pressure and volume in the normal heart compared with the hypertrophic heart. The shift of the curve upward and to the left shows how a small increase in volume markedly increases filling pressure.