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Diastolic dysfunction and heart failure: Causes and treatment options

■ ABSTRACT

Diastolic dysfunction is the underlying problem in one third of patients with heart failure, but it is still not well understood. Carefully excluding other causes of heart failure and recognizing indicators of diastolic dysfunction on invasive and noninvasive tests are important in establishing the diagnosis and in guiding therapy.

■ KEY POINTS

Left ventricular relaxation and stiffness and left atrial function are the most important factors acting together to maintain adequate cardiac output under normal filling pressure.

Echocardiography is the most important tool for the diagnosis of diastolic heart dysfunction. It is portable, safe, and excludes other causes of heart failure, such as valvular disease.

Diuretics can be used to reduce volume overload, but caution is advised, as aggressive diuresis decreases stroke volume more in diastolic dysfunction than in systolic dysfunction.

D IASTOLIC DYSFUNCTION—a condition in which higher-than-normal left ventricular (LV) filling pressures are needed to maintain a normal cardiac output—can cause symptoms ranging from impaired exercise tolerance to overt left-sided or right-sided heart failure. Although it causes fewer deaths than systolic dysfunction, it is now thought to be the underlying problem in at least one third of all patients with congestive heart failure.

This article describes factors that contribute to diastolic dysfunction, different diagnostic techniques used to identify it, and goals of pharmacotherapy.

■ SCOPE OF THE PROBLEM

Congestive heart failure is one of the most prevalent medical conditions, with 5-year mortality rates as high as 50% and health care expenditures of close to $10 billion annually in the United States alone.[1] The prevalence is projected to rise as the population ages.[2] Epidemiologic studies have shown that 30% to 50% of patients with confirmed congestive heart failure actually have adequate systolic function,[3] so that diastolic dysfunction is now believed to play an important role.

Furthermore, we now know that diastolic dysfunction plays an important role in the pathophysiology of the cardiomyopathies and valvular, hypertensive, and ischemic heart disease.[4]

Effect on survival
Although the prognosis for patients with congestive heart failure due to diastolic dysfunction is better than for those with systolic dysfunction, recent studies indicate that the survival rate is lower in persons with diastolic

TABLE 1

Factors associated with diastolic function

Afterload
Atrial function
Atrioventricular conduction
Heart rate
Intrathoracic pressure
Mitral valve function
Myocardial relaxation
Myocardial stiffness
Neurohormonal activation
Preload
Pericardial constraining effect
Right ventricular size and function

dysfunction than in those with normal diastolic function.[3]

■ PATHOPHYSIOLOGY

Diastole starts when the aortic valve closes and ends when the mitral valve closes and the left ventricle starts to contract. At a normal resting heart rate, diastole occupies about two thirds of the entire cardiac cycle, but as the heart rate increases, diastole shortens proportionally more than systole. This explains why preventing tachycardia is an important therapeutic goal.

Several factors interact to determine diastolic function—ie, to maintain adequate cardiac output under normal filling pressure (TABLE 1)[5]: the most important are LV relaxation and stiffness and left atrial function. Patients with diastolic dysfunction can have varying degrees of abnormality in these factors, resulting in symptoms ranging from subtle exercise intolerance to overt pulmonary congestion and edema.

Left ventricular relaxation

A normal ventricle relaxes forcefully, rapidly decreasing its cavity pressure during early diastole and suctioning blood from the left atrium across the mitral valve,[6] allowing the ventricle to fill with blood in the presence of normal or low left atrial pressure.

Symptoms can range from subtle exercise intolerance to overt pulmonary congestion

At the cellular level, relaxation is energy-dependent and requires adenosine triphosphate for the reuptake of calcium by the sarcoplasmic reticulum, thus allowing the release of the actin and myosin bridges. Since LV relaxation is energy-dependent, ischemia rapidly affects it.

Left ventricular diastolic stiffness

Once the LV pressure falls below the left atrial pressure, blood enters the left ventricle, rapidly increasing its volume. This increasing cavity volume causes the myocardial fibers to stretch. The muscle fibers resist stretching in a nonlinear fashion. Thus, the pressure required to stretch a muscle fiber increases geometrically.[7] The curvilinear relationship between filling pressure and volume is a measure of LV diastolic stiffness. It is influenced by myocardial fiber distensibility, elasticity of the connective tissue, cavity diameter, wall thickness, and the constraining effect of the pericardium. In a normal left ventricle, stiffness is low during diastole, and relatively large increases in volume cause relatively small increases in pressure.

Left atrial function

Left atrial function is an important determinant of LV diastolic function. The left atrium acts as a reservoir of blood, as a conduit, and as an active pump at the end of diastole. According to the Frank-Starling mechanism, the left atrial volume and pressure determine the force of contraction. In younger, healthy patients, the left atrial contribution is minimal (< 20%); however, in patients with early diastolic dysfunction and impaired LV relaxation, the left atrium compensates, increasing its contractility and contributing up to 50% of the filling volume.

■ CONDITIONS THAT CAUSE DIASTOLIC DYSFUNCTION

A number of conditions are known to cause or contribute to diastolic dysfunction (TABLE 2).

Hypertensive cardiomyopathy and ischemic heart disease are the most common causes of diastolic dysfunction. Hypertensive cardiomyopathy is responsible for about one third of cases of heart failure requiring hospi-

talization.[8] Chronic arterial hypertension augments left ventricular systolic stress, inducing hypertrophy of the myocardial sarcomeres in parallel, thus increasing wall thickness.[9] Elevated angiotensin and insulin levels may also contribute to the development of cardiac hypertrophy.

Aging. The prevalence of diastolic dysfunction increases with age. The weight of the heart increases between 1 g and 1.5 g per year between the third and the ninth decade of life,[10] and myocyte hypertrophy and an increase in the connective tissue matrix, particularly in collagen type II, result in reduced relaxation and increased stiffness.[11] Yet despite these age-related abnormalities, most older people do not have symptoms of heart failure under normal circumstances. However, they often develop symptoms of heart failure if atrial fibrillation occurs.

Coronary artery disease affects left ventricular relaxation by limiting the availability of energy substrates. Acute ischemia impairs relaxation, and myocardial infarction increases stiffness due to interstitial fibrosis and scar formation.[12]

Restrictive cardiomyopathies. Diastolic dysfunction is common in patients with restrictive cardiomyopathies, disorders characterized by small left ventricular cavity size, abnormal relaxation, and increased stiffness.[13] Wall thickness is increased due to infiltration or fibrosis and not to myocyte hypertrophy. Therefore, the electrocardiographic QRS voltage is normal or low. Systolic function may also be impaired in patients with advanced disease. However, the ejection fraction is usually normal in patients with diastolic dysfunction.

Common causes of restrictive cardiomyopathy include primary and secondary amyloidosis, radiation treatment, glycogen storage disorders, and some types of muscular dystrophy.

Hypertrophic cardiomyopathy causes diastolic dysfunction via myocardial fiber disarray and a global or segmental increase in left ventricular wall thickness.[14] LV chamber stiffness is increased and relaxation is impaired by the asynchronous deactivation of muscle fibers caused by abnormal electrical conduction.[15]

> **TABLE 2**
>
> ## Cardiac conditions associated with diastolic dysfunction
>
> Cardiac tamponade
> Cardiomyopathies
>   Dilated
>   Hypertrophic
>   Restrictive
> Chemotherapeutic drug toxicity
> Congenital heart disease
> Constrictive pericarditis
> Hypertensive heart disease
> Ischemic heart disease
> Myocarditis
> Transplant rejection

Constrictive pericarditis can cause diastolic dysfunction via increased LV stiffness related to the constraining effects of a thickened and rigid pericardium. LV relaxation is normal in these patients, and symptoms of right heart failure predominate.[16] Subacute cardiac tamponade usually presents with signs and symptoms similar to those of constrictive pericarditis.

Dilated cardiomyopathy. Alterations in LV diastolic function are detected in most patients with dilated cardiomyopathy. LV filling abnormalities have been shown to have important independent prognostic implications in these patients.[17]

■ DIAGNOSTIC TESTS HELPFUL IN MEASURING DIASTOLIC DYSFUNCTION

The diagnosis of diastolic dysfunction in a patient with dyspnea and exercise intolerance requires careful analysis of the medical history, physical findings, and diagnostic test results.

Exclude pulmonary disease, other causes
The first step should be to exclude significant pulmonary parenchymal or vascular disease. Chest radiography and spirometry with measurement of carbon monoxide diffusing capacity should be obtained according to the clini-

First exclude significant pulmonary parenchymal or vascular disease

cal history. Metabolic stress testing may help to differentiate dyspnea from cardiac and pulmonary disease in different cases.

If there is a suspicion of chronic pulmonary embolism, a ventilation-perfusion scan or high-resolution contrast computed tomography should be obtained.

Significant anemia, thyrotoxicosis, mitral and aortic valvular disease, and congenital heart defects may all present with dyspnea and heart failure and must be excluded. Coronary artery disease may present with symptoms of heart failure, the result of intermittent dysfunction induced by myocardial ischemia.

Outmoded tests

Cardiac catheterization can establish the diagnosis of heart failure, but it is rarely required today for this purpose. It can estimate LV relaxation from the rate of intracavitary pressure decay during isovolumic relaxation—ie, the interval between aortic valve closure and mitral opening. LV stiffness is determined by simultaneous assessment of LV volume and LV pressure. Unfortunately, serial assessment of these measurements is often necessary in patients with suspected diastolic dysfunction, and being an invasive procedure, cardiac catheterization is not practical.

Radionuclide ventriculography can assess the peak filling rate, the time to peak filling rate, and the early-to-late filling ratio. Radionuclide methods, however, have been largely replaced by echocardiographic methods, which do not involve radiation exposure.

Echocardiographic techniques

Echocardiography is the most important tool for the diagnosis of diastolic heart dysfunction.[18] It is portable and safe. It excludes other causes of heart failure (eg, valvular disease). Measurements obtained via different echocardiographic techniques—ie, two-dimensional structural data and Doppler flow velocities—may be combined to enhance the evaluation.

Two-dimensional echocardiography. Significant diastolic dysfunction is unlikely in the presence of a structurally normal heart. Two-dimensional echocardiography evaluates global and regional LV and right ventricular
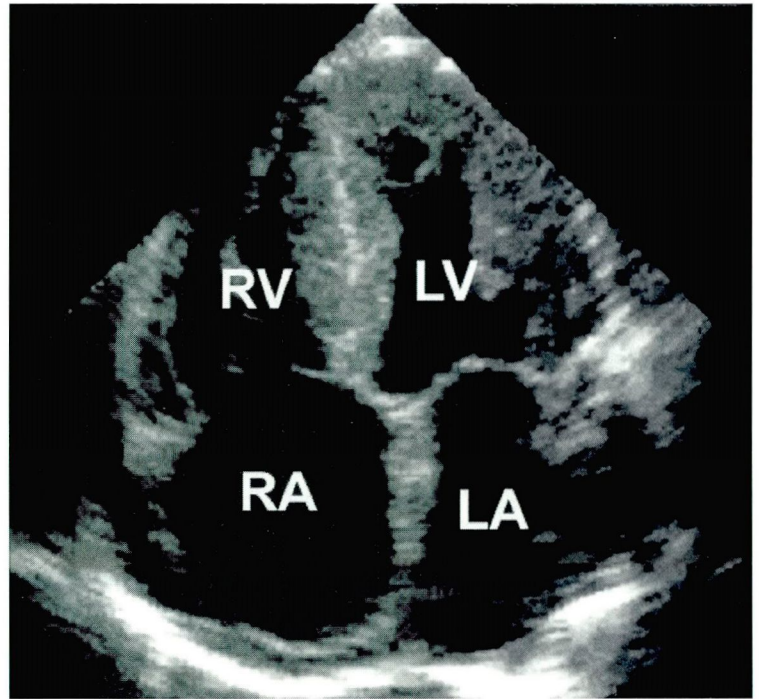
FIGURE 1. Two-dimensional echocardiogram in a patient with pure diastolic dysfunction. The left ventricle (LV) demonstrates small cavity size and increased wall thickness. The left atrium (LA) and right atrium (RA) are enlarged.
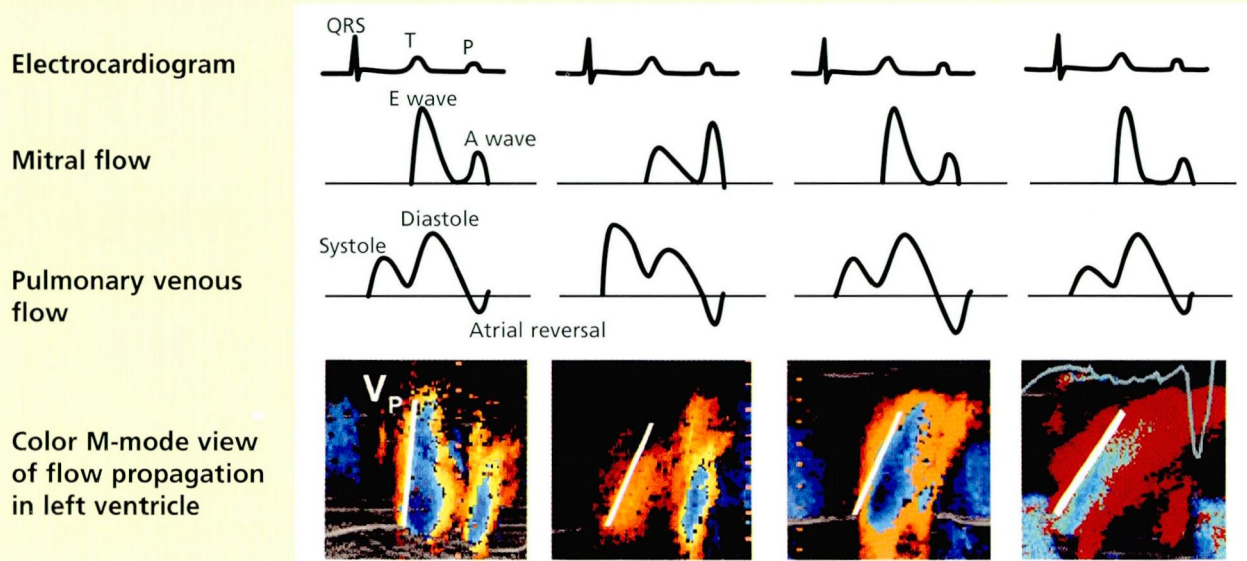
systolic function, mass, atrial size, and pericardial thickness (**FIGURE 1**). It helps exclude valvular heart disease and other causes of heart failure. It also identifies left atrial enlargement, caval and hepatic dilation, and increased LV mass.

Doppler echocardiography measures blood flow velocities across the mitral and tricuspid valves, in the pulmonary and hepatic veins, and within the LV cavity.

With the onset of LV filling, the early atrioventricular pressure gradient accelerates the blood across the mitral valve, generating the early Doppler filling wave (the E wave). As blood enters the left ventricle, LV pressure increases and left atrial pressure decreases until the gradient disappears or reverses, causing a deceleration of the early Doppler filling wave. After a period of diastasis, the left atrium contracts, accelerating flow across the mitral valve (the A wave).

We have found that a shorter deceleration of the E wave may be associated with increased LV stiffness.[19] Furthermore, a short

	Normal diastolic function	Mild diastolic dysfunction	Pseudonormal stage	Restrictive-filling stage
Left ventricular relaxtion	Normal	↓	↓↓	↓↓↓
Left ventricular stiffness	Normal	↑	↑↑	↑↑↑
Left atrial contractility	Normal	↑	Normal	↓
Preload	Normal	Normal	↑	↑↑
Electrocardiogram				
Mitral flow				
Pulmonary venous flow				
Color M-mode view of flow propagation in left ventricle				

FIGURE 2. Doppler echocardiography shows how left ventricular (LV) relaxation, LV stiffness, and left atrial contractility are altered in patients with mild diastolic dysfunction (ie, impaired relaxation) and advanced diastolic dysfunction ("pseudonormal" stage and restrictive-filling stage). With the electrocardiogram as a reference, the mitral flow measurement shows, from left to right, first a decrease in early filling (E) velocity due to decreased LV relaxation with a compensatory increase in atrial contraction (A) velocity, followed by an increase in E due to elevated filling pressures (pseudonormalization), and finally, a short E deceleration time due to increased LV stiffness. Pulmonary venous flow velocity measurements demonstrate changes in systolic and diastolic flow that also reflect the opposing effects of alterations in LV relaxation and preload. The atrial reversal magnitude and duration increase with increasing LV stiffness but may decrease when atrial systolic dysfunction occurs. Color M-mode shows LV blood flow in both space and time. Decreasing LV relaxation increases the time that the column of blood takes to reach the apex (Vp, white line).

E deceleration time in patients with restrictive[20] and dilated cardiomyopathy[21] has been associated with reduced survival.

Doppler flow velocity measurement of the left and right upper pulmonary veins provides information about the systolic, diastolic, and atrial reversal phases of pulmonary venous flow. This information can complement transmitral Doppler flow velocity measurements, since the atrial reversal phase of pulmonary venous flow appears to be strongly related to left atrial contractility,[21,22] and the magnitude and duration of atrial reversal flow is directly related to LV end-diastolic stiffness.[23]

TABLE 3

Stages of diastolic dysfunction

	NORMAL DIASTOLIC FUNCTION	MILD DIASTOLIC DYSFUNCTION	ADVANCED DIASTOLIC DYSFUNCTION	
		DELAYED RELAXATION	PSEUDONORMAL FILLING	RESTRICTIVE FILLING
Early-to-atrial LV filling ratio (cm/sec)	> 1	< 1	1–2	> 2
Early LV filling deceleration time (msec)	< 220	> 220	150–200	< 150
Isovolumic relaxation time (ms)	< 100	> 100	60–100	< 60
Systolic-to-diastolic pulmonary venous flow ratio	≥ 1*	≥ 1	< 1	< 1
Pulmonary venous peak atrial contraction reversed velocity (cm/sec)	< 35	< 35	≥ 35	≥ 25
Flow propagation velocity on color M-mode echocardiography (cm/sec)	> 45†	< 45	< 45	< 45
Peak early diastolic myocardial velocity (cm/sec)	> 8‡	< 8	< 8	< 8

*Less than 1 in young patients
†Greater than 55 cm/sec in young patients
‡Greater than 10 cm/sec in young patients

ADAPTED FROM GARCIA ET AL. NEW DOPPLER ECHOCARDIOGRAPHIC APPLICATIONS FOR THE STUDY OF DIASTOLIC FUNCTION. J AM COLL CARDIOL 1998; 32:865–875.

If chronic pulmonary embolism is suspected, obtain a V/Q or CT scan

Color M-mode Doppler echocardiography measures the spatiotemporal distribution of blood flow velocities within the left ventricle. The velocity at which flow propagates within the ventricle is indicated by the slope of the color wave-front (FIGURE 2). Because it contains both spatial and temporal information, it quantitatively estimates intraventricular pressure gradients, which are implicated in the generation of LV suction and relaxation.[6] Color M-mode Doppler ventricular flow propagation is reduced in ventricles with delayed relaxation[24] (FIGURE 2). Combined indices of color M-mode and pulsed Doppler filling can be used to estimate LV filling pressures in patients in the intensive care unit.[25]

Tissue Doppler echocardiography displays the velocities of the myocardium during contraction and relaxation. Clinical studies show an inverse relationship between tissue Doppler echocardiographic diastolic myocardial velocities and LV relaxation.[24] These velocities are useful in differentiating restrictive cardiomyopathy from constrictive pericarditis,[26] which are often difficult to distinguish in the clinical setting using two-dimensional and standard Doppler echocardiography alone.

Diuretics reduce stroke volume more in diastolic than in systolic dysfunction
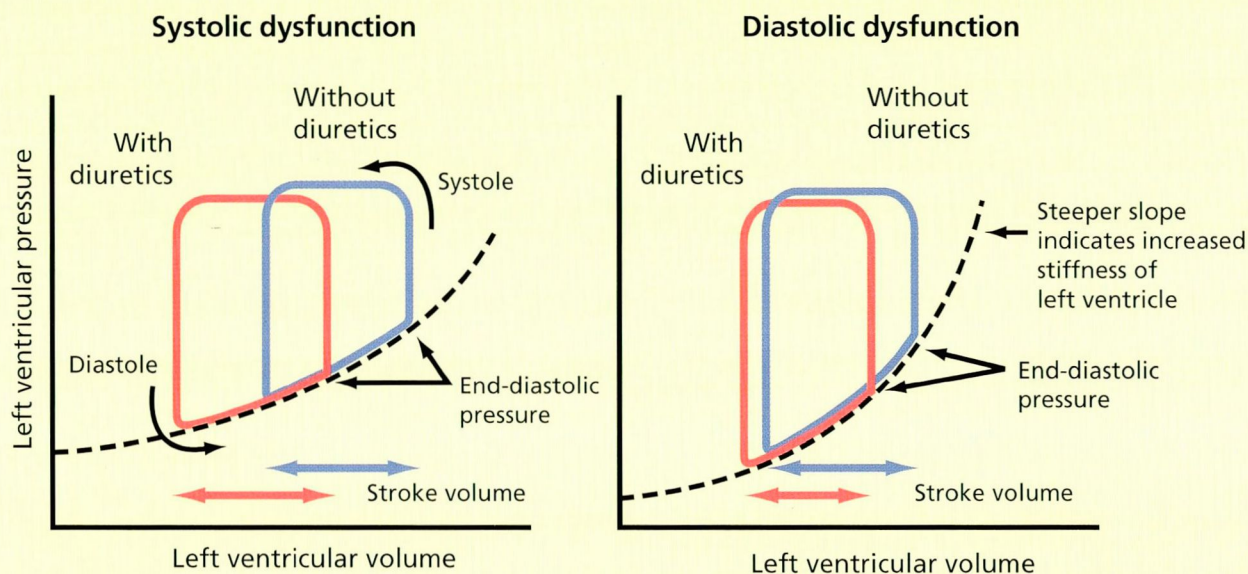
FIGURE 3. Pressure-volume loops demonstrate the shift in the pressure-volume relationship with the use of diuretics in patients with systolic vs diastolic dysfunction. For the same reduction in left ventricular end-diastolic pressure, the stroke volume decreases more in the patient with diastolic dysfunction due to the higher stiffness (steeper slope of dotted line).

Echocardiographic overview of diastolic dysfunction

Combining color M-mode and tissue Doppler measurements with the Canadian Consensus on Diastolic Dysfunction criteria[24,27] provides an overview of diastolic dysfunction (TABLE 3):

• Normal diastolic function is characterized by rapid LV relaxation, low stiffness, and normal filling pressures; the atrial contribution to left ventricular filling is minimal

• Early diastolic dysfunction is characterized by a slow LV relaxation rate but relatively normal filling pressures; patients are asymptomatic or may have mild dyspnea during exercise; and the atrial contribution to LV filling is increased, frequently more than 30% of the stroke volume

• Advanced diastolic dysfunction is characterized by an increase in LV filling pressure to maintain cardiac output; the atrial contribution diminishes due to the elevated stiffness of the left ventricle and atrial mechanical failure.

Advanced diastolic dysfunction can be separated into a "pseudonormal" stage and a restrictive-filling stage, characterized by higher left ventricular stiffness and filling pressures. FIGURE 2 summarizes the alterations in LV relaxation, LV stiffness, left atrial function, and the diagnostic Doppler echocardiographic findings seen in patients with normal and varying degrees of diastolic dysfunction.

■ TREATMENT OF DIASTOLIC DYSFUNCTION

Treatment of diastolic dysfunction has the following goals:

• Resolve or control the underlying condition (eg, myocardial ischemia, hypertensive heart disease, restrictive cardiomyopathy)

• Slow the heart rate to lengthen the duration of diastole

• Maintain atrial rhythm

• Avoid excessive use of diuretics.

To date, no large randomized trial has been conducted to determine the effect of specific pharmacologic agents for the management of diastolic heart failure. However, evi-

dence supports that most treatments for systolic heart failure also improve diastolic dysfunction.

Use diuretics with caution to reduce volume overload

Diuretics are useful in patients with diastolic dysfunction who have evidence of volume overload. However, aggressive diuresis can significantly decrease cardiac output and prerenal azotemia, due to the steep pressure volume relationship characteristic of the "stiff" left ventricle (FIGURE 3).

Afterload reduction

Afterload reduction with **calcium channel blockers** and **angiotensin-converting enzyme (ACE) inhibitors** in patients with hypertension can substantially reduce LV mass in the long term and improve LV filling.

Verapamil has been reported to improve LV relaxation and symptoms in some familial forms of hypertrophic cardiomyopathy.[28] However, calcium channel blockers can cause a deterioration of diastolic function in nonhypertensive patients, particularly if systolic dysfunction is also present.[29]

ACE inhibitors have been shown to improve LV relaxation and stiffness in patients with diastolic dysfunction regardless of ejection fraction in both acute and chronic models.[30] In a recent study,[31] we demonstrated that treatment of hypertension with an ACE inhibitor (perindopril) resulted in a reduction of LV mass and left atrial size, and an improvement of filling parameters, associated with a reduction in atrial natriuretic hormonal levels, an indirect marker of left atrial pressure.[31] Recent studies have also shown beneficial results of long-term therapy with angiotensin I inhibitors.[32]

Increasing the diastolic filling time

Preventing tachycardia is important in order to increase diastolic filling time. Treatment with beta-blockers has been shown to be effective.[33] This effect seems paradoxical, because catecholamines enhance left ventricular relaxation. Since the atrial contribution is important in patients with early diastolic dysfunction, maintenance of sinus rhythm is important.

> Most agents for systolic heart failure also improve diastolic dysfunction

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