

Diastolic Dysfunction

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The clinical manifestation and relevance of diastolic dysfunction

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Congestive heart failure caused by abnormal diastolic function is far more common than previously recognized. The term diastolic dysfunction refers to the alteration in the complex processes whose interaction determines the resistance to filling of the left ventricle (LV) in patients with preserved LV systolic function, but with the signs and symptoms of congestive heart failure. The multifactorial nature of diastolic dysfunction and the possible coincidence with systolic dysfunction render the exact definition, accurate assessment, and differential diagnosis difficult. However, diastolic dysfunction and its clinical correlate, diastolic heart failure, have emerged over the last 10 years as a separate, yet still underestimated clinical entity. Today, characterization of diastolic dysfunction is based on well-defined cutoff values of indices of LV function. These indices, obtained during cardiac catheterization or preferably during noninvasive cardiac imaging, characterize abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness in different cardiac diseases. Since diastolic heart failure has a more benign prognosis and requires specific forms of treatment, its reliable diagnosis and differentiation from systolic impairment of LV function is of paramount importance. This review reflects clinically important pathophysiological mechanisms of diastolic dysfunction, the modern diagnostic armamentarium for the assessment of diastolic dysfunction, and the different treatment strategies for diastolic dysfunction in cardiac diseases in which diastolic heart failure frequently occurs.

Keywords: diastole; systole; heart failure; clinical symptoms; relaxation; resistance; distensibility

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CLINICAL SIGNIFICANCE OF DIASTOLIC DYSFUNCTION

Congestive heart failure, which is defined as the inability of the left ventricle (LV) to generate an adequate cardiac output at rest and during exercise while operating at normal LV filling pressures, is usually associated with impaired systolic (contractile) LV function. However, symptoms of congestive heart failure may occur in patients in the absence of any LV systolic dysfunction. In these patients, diastolic dysfunction is the principal cause of classic clinical symptoms like dyspnea and fatigue. The prevalence of diastolic dysfunction in the community is difficult to assess. However, diastolic heart failure, the final outcome of progressive diastolic dysfunction, accounts for approximately one third of all heart failure cases, especially in an elderly population.¹ Impairment of diastolic function precedes systolic dysfunction in the progression of most cardiac diseases. Several studies have reported that 30% to 40% of patients with clinical symptoms of congestive heart failure have normal systolic function and isolated diastolic dysfunction.^{2,3} Furthermore, even in the presence of overt systolic dysfunction, the clinical symptoms of heart failure are influenced primarily by the degree of diastolic dysfunction.^{4,5} A recently published report of the European Study Group on Diastolic Heart Failure proposes a definition of primary diastolic heart failure.⁶ In this definition, primary diastolic heart failure does not include diastolic LV dysfunction in the presence of systolic cardiac failure. This is important from a clinical point of view, since the natural history of isolated diastolic heart failure seems to be more benign than other forms of heart failure, with an annual mortality of 8% compared with 19% in congestive heart failure.^{1,2,7} Because of its increasing incidence in aging Western populations and of its different prognosis,⁸ specific treatment options for patients suffering from diastolic heart failure are currently being tested in large randomized trials. There is therefore now a

need to clarify the underlying mechanisms of normal diastolic function and diastolic dysfunction⁹ and to establish precise criteria for the diagnosis of diastolic heart failure.^{6,10}

MECHANISMS OF DIASTOLIC FUNCTION AND DYSFUNCTION

Diastole can be defined as the portion of the cardiac cycle that begins with isovolumic ventricular relaxation and ends with cessation of mitral inflow. The typical division of diastole into 4 phases is briefly described and illustrated in *Figure 1*.

Isovolumic relaxation

The relaxation phase is characterized by a fall in intraventricular pressure that begins at end-systole

and ends when LV pressure falls below left atrial pressure, the mitral valve opens, and rapid filling of the ventricles begins. During the fall in LV pressure, LV volume remains constant. The active process of myocardial relaxation actually begins in late systole and ends at mid-diastole, and is a major determinant of the rate of early LV filling.⁹ The active process of relaxation is energy-dependent, requiring high-energy phosphates for the uptake of intracellular calcium by the sarcoplasmic reticulum, which results in actin-myosin cross-bridge dissociation.

Rapid filling

With the opening of the mitral valve, left atrial pressure exceeds LV pressure and the blood that has accumulated in the left atrium during the previous systole flows rapidly into the LV, which is still actively relaxing.

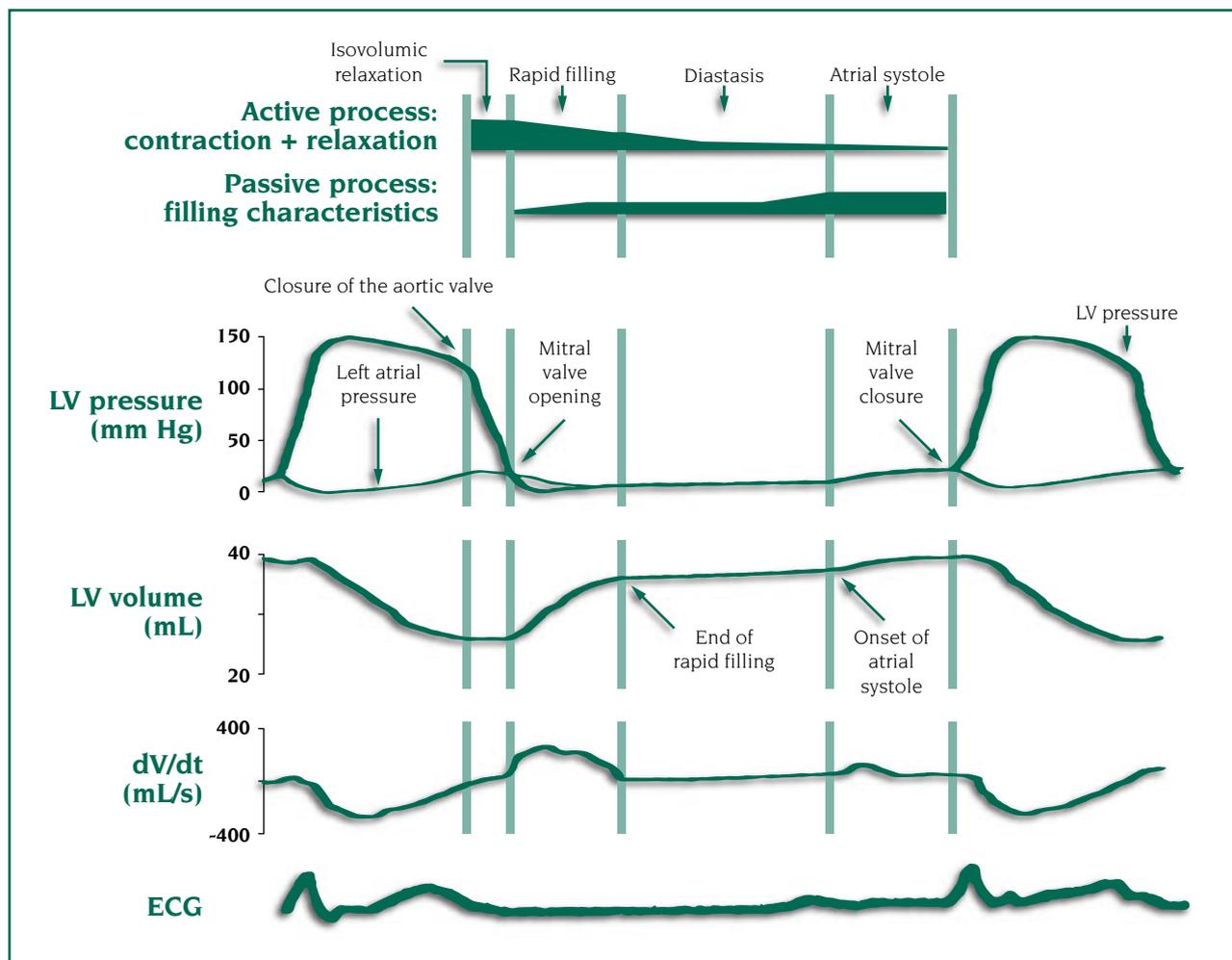


Figure 1. Pressure-volume relation. Schematic presentation of left ventricular (LV) pressure, indexed volume and its derivative, and the influence of determinants of LV diastolic performance on the 4 phases of diastole.



It is important to emphasize that LV pressure continues to decline in early diastole despite the rapid inflow of blood and that the rate of LV relaxation is the most important determinant of rapid ventricular filling.¹¹ Once relaxation is complete, the rapid filling phase is influenced by passive filling characteristics that are determined by the thickness of the ventricular wall, viscoelastic effects, and external structures such as the pericardium and the lungs.¹⁰ The slope of the pressure-volume relation that can be obtained after complete relaxation characterizes passive LV "stiffness," and subsequently increases with increasing volume.

A process that affects the determinants of passive filling leads to upward and leftward shifting of the pressure-volume relation, ie, increased LV pressures at a given volume. This can be distinguished from the solely upward shift in the pressure-volume relation observed with impaired relaxation, which primarily affects the early portion of the curve. In contrast, impairment of myocardial compliance affects the latter portion of the curve, resulting in the appearance of an upward and leftward shift. Finally, any elevation of left atrial pressure, which may occur in a variety of situations, enhances early diastolic filling.¹²

Diastasis

During this phase the pressures in the left atrium and LV have equilibrated and ventricular relaxation is complete. Filling is very slow during this part of diastole. Only that blood volume returning from the lungs flows through the left atrium into the LV, resulting in a gradual elevation in the LV pressure curve.

Atrial systole

During this phase, atrial contraction increases atrial pressure and produces a left atrial-to-LV pressure gradient that accelerates the blood flow into the LV cavity. This phase is mainly influenced by left atrial function, loading, and heart rate.

CLINICAL APPROACH TO THE DIAGNOSIS OF DIASTOLIC DYSFUNCTION

Diagnostic criteria that accurately characterize diastolic dysfunction in the clinical setting should be based on the underlying pathophysiological mechanisms of diastolic dysfunction. Moreover, they should be readily obtainable using state-of-the-art diagnostic tools and be applicable to different cardiac diseases with diastolic heart failure. Based on the proposal for the definition

of predominant diastolic heart failure by the European Study Group on Diastolic Heart Failure,⁶ three obligatory conditions must be simultaneously satisfied:

(i) presence of signs or symptoms of congestive heart failure; (ii) presence of normal or only mildly abnormal LV systolic function; and (iii) evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness.

Signs or symptoms frequently assessed in congestive heart failure

Congestive heart failure is characterized by a variety of signs or symptoms that include evidence of raised left atrial pressure, such as exertional dyspnea, orthopnea, gallop sound, lung crepitations, and pulmonary edema. The earliest event frequently observed in diastolic heart failure is exercise intolerance caused by exertional dyspnea related to pulmonary congestion.¹³ This form of exercise intolerance does not incorporate exercise-induced muscular fatigue, which results from impaired skeletal muscle metabolism and usually accompanies systolic heart failure.¹⁴ Objective evidence of reduced exercise tolerance in the clinical setting is provided by a progressive bicycle ergometric stress test showing a low peak exercise oxygen consumption ($<25 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Reduced exercise oxygen consumption is a highly reliable test in patients with suspected congestive heart failure, allowing for an objective classification of these patients in terms of functional impairment.⁷

Importance of preserved LV systolic function for the diagnosis of diastolic heart failure

Presence of normal or only mildly abnormal LV systolic function is a prerequisite for the diagnosis of diastolic heart failure. The demonstration of normal or only mildly abnormal LV systolic function allows a reliable differentiation of diastolic LV dysfunction from the frequent occurrence of diastolic LV dysfunction in patients with systolic LV dysfunction and congestive cardiomyopathy.^{15,16} A frequently used criterion for differentiating between diastolic LV dysfunction and a mixture of systolic and diastolic LV dysfunction is a threshold value for the baseline LV ejection fraction of 45%. As LV relaxation depends on end-systolic load and volume,^{17,18} this criterion needs to be implemented when the LV end-diastolic internal dimension index is normal or when the LV end-diastolic volume index is normal in order to exclude diastolic LV dysfunction secondary to high end-systolic load and volume.

Parameters of diastolic dysfunction and underlying mechanisms

The parameters of diastolic dysfunction include:

- (i) abnormal LV relaxation; (ii) abnormal filling;
- (iii) abnormal diastolic distensibility; and (iv) increased diastolic stiffness.

The underlying mechanisms of these heterogeneous parameters of diastolic dysfunction include: (i) slow

isovolumic LV relaxation; (ii) slow early LV filling; (iii) reduced LV diastolic distensibility; and (iv) increased LV chamber stiffness or increased myocardial muscle stiffness.

From the viewpoint of cardiac muscle physiology,¹⁹ LV diastole consists only of diastasis and the atrial contraction phase, and diastolic heart failure can therefore only be inferred from evidence of decreased LV diastolic distensibility or increased LV diastolic stiffness.²⁰

• SIGNS OR SYMPTOMS OF CONGESTIVE HEART FAILURE		• Exertional dyspnea (eventually objective evidence by reduced peak exercise oxygen consumption [$<25 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$]), orthopnea, gallop sounds, lung crepitations, pulmonary edema	
• AND NORMAL OR MILDLY REDUCED LV SYSTOLIC FUNCTION		• LVEF $\geq 45\%$ • and LVEDIDI $< 3.2 \text{ cm}\cdot\text{m}^{-2}$ or LVEDVI $< 102 \text{ mL}\cdot\text{m}^{-2}$	
• AND EVIDENCE OF ABNORMAL LV RELAXATION, FILLING, DIASTOLIC DISTENSIBILITY, AND DIASTOLIC STIFFNESS			
- slow isovolumic LV relaxation		• $\text{LVdP}/\text{dt}_{\text{min}} < 1100 \text{ mm Hg}\cdot\text{s}^{-1}$ • and/or $\text{IVRT}_{<30\text{y}} > 92 \text{ ms}$, $\text{IVRT}_{30-50\text{y}} > 100 \text{ ms}$, $\text{IVRT}_{>50\text{y}} > 105 \text{ ms}$ • and/or $\tau > 48 \text{ ms}$	
- and/or slow early LV filling		• $\text{PFR} < 160 \text{ mL}\cdot\text{s}^{-1}\cdot\text{m}^{-2}$ • and/or $\text{PFR}_{<30\text{y}} < 2.0 \text{ EDV}\cdot\text{s}^{-1}$, $\text{PFR}_{30-50\text{y}} < 1.8 \text{ EDV}\cdot\text{s}^{-1}$, $\text{PFR}_{>50\text{y}} < 1.6 \text{ EDV}\cdot\text{s}^{-1}$ • and/or $\text{E}/\text{A}_{<50\text{y}} < 1.0$ and $\text{DT}_{<50\text{y}} > 220 \text{ ms}$, $\text{E}/\text{A}_{>50\text{y}} < 0.5$ and $\text{DT}_{>50\text{y}} > 280 \text{ ms}$ • and/or $\text{S}/\text{D}_{<50\text{y}} > 1.5$, $\text{S}/\text{D}_{>50\text{y}} > 2.5$	
- and/or reduced LV diastolic distensibility		• $\text{LVEDP} > 16 \text{ mm Hg}$ or mean PCW $> 12 \text{ mm Hg}$ • and/or PVA flow $> 35 \text{ cm}\cdot\text{s}^{-1}$ • and/or $\text{PVAt} > \text{MVAt} + 30 \text{ ms}$ • and/or $\text{A}/\text{H} > 0.20$	
- and/or increased LV chamber or muscle stiffness		• $b > 0.27$ • and/or $b' > 16$	
A/H	ratio of atrial wave-to-total signal excursion on the apexcardiogram	LVEDVI	left ventricular end-diastolic volume index
b	constant of LV chamber stiffness	LVEF	left ventricular ejection fraction
b'	constant of muscle stiffness	MVAt	mitral atrial flow velocity duration
E/A	ratio of peak early-to-peak atrial Doppler flow velocity indexed for age groups	PCW	pulmonary capillary wedge pressure
EDV	end-diastolic volume	PFR	peak LV filling rate indexed for age groups
IVRT	isovolumic relaxation time indexed for age groups	PVA flow	pulmonary venous atrial flow velocity
LVdP/dt_{min}	peak negative left ventricular dP/dt	PVAt	pulmonary venous atrial flow velocity duration
LVEDIDI	left ventricular end-diastolic internal dimension index	S/D	ratio of pulmonary vein systolic and diastolic flow velocities indexed for age groups
LVEDP	left ventricular end-diastolic pressure	τ	time constant of LV pressure decay

Table 1. Diagnostic criteria for diastolic heart failure.

Adapted from ref 6: How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J. 1998;19:990-1003. Copyright © 1998, The European Society of Cardiology.



This theoretical approach is of limited value for clinical decision-making, as it usually requires invasive procedures (right and left heart catheterization) to establish the diagnosis of diastolic heart failure. However, LV relaxation and filling also affect LV diastolic distensibility (the position on a pressure-volume plot of the LV diastolic pressure-volume relation) in such a way that diagnostic evidence for diastolic heart failure can also be obtained from analysis of LV relaxation and filling,²¹ which can be performed more easily in clinical practice using modern noninvasive imaging techniques.

Slow isovolumic LV relaxation

The rate of isovolumic LV pressure decrease is intimately coupled to timing, myocardial loading,²² and segmental coordination.²³ Timing refers to the time interval from the Q wave on the ECG to the onset of LV relaxation.²⁰ Commonly used indices that are indicative of slow isovolumic LV relaxation are summarized in *Table I* according to the European Study Group on Diastolic Heart Failure.⁶

Slow early LV filling

Early peak LV filling rate (PFR) can be derived from LV contrast angiograms.²⁴ Early LV filling dynamics can also be analyzed on radionuclide LV angiograms.²⁵ A methodologically elegant approach to the analysis of global LV filling dynamics, such as appreciation of circumferential-longitudinal shear strain and torsional motion of the myocardium, has recently been achieved by magnetic resonance imaging in conjunction with myocardial tagging.²⁶

A noninvasive approach to early LV filling dynamics is provided by Doppler echocardiography.²⁷ Indices of early LV filling are peak early (E wave) Doppler flow velocity, E/A ratio (A = peak A wave Doppler flow velocity), deceleration time (DT) of E velocity, and the ratio of pulmonary vein systolic (S) and diastolic (D) flow velocities (S/D ratio). In general, slow LV pressure decay as a result of slow myocardial relaxation or of segmental incoordination related to coronary artery disease²⁸ or conduction disturbances, reduces the E/A ratio, prolongs DT, and increases the S/D ratio. Alterations of LV filling dynamics progressing from normal to slow relaxation, to pseudonormalization, and to restriction are paralleled by changes in left atrial function with augmented atrial reservoir function during the slow relaxation phase and augmented atrial conduit function during the restrictive phase.²⁹

Reduced LV diastolic distensibility

LV diastolic distensibility refers to the position on a

pressure-volume plot of the LV diastolic pressure-volume relation,³⁰ and a reduction in LV diastolic distensibility refers to an upward shift of the LV pressure-volume relation on the pressure-volume plot, irrespective of a simultaneous change in the slope. Therefore, evidence for diastolic LV dysfunction is provided by the demonstration of reduced LV diastolic distensibility. LV end-diastolic distensibility is reduced when LV end-diastolic pressure (>16 mm Hg) or mean pulmonary venous pressure (>12 mm Hg) are elevated in the presence of a normal LV end-diastolic volume index (<102 mL·m⁻²) or normal LV end-diastolic internal dimension index (<3.2 cm·m²).¹⁰ Similar diagnostic information on decreased LV end-diastolic distensibility can also be derived from a shortened Doppler mitral A wave deceleration time, from the Doppler pulmonary vein flow signal when it reveals reverse pulmonary venous A wave flow velocity, or from the pulmonary venous A wave duration when it exceeds mitral A wave duration.^{31,32}

Increased LV chamber or myocardial muscle stiffness

LV stiffness refers to a change in diastolic LV pressure relative to diastolic LV volume (dP/dV) and equals the slope of the diastolic pressure-volume relation: its inverse is LV diastolic compliance (dV/dP). Because the slope of the diastolic LV pressure-volume relation varies along the LV pressure-volume curve, LV stiffness is often compared at a common level of LV filling pressures. A relationship has been demonstrated between Doppler mitral inflow deceleration time and LV chamber stiffness.³³ Muscle stiffness is the slope of the myocardial stress-strain relationship and represents the resistance to stretch when the myocardium is subjected to stress. The mean value of the constant of muscle stiffness (b') observed in a control group and the mean value and upper range of the constant of chamber stiffness (b) in control subjects is presented in *Table I* according to the European Study Group on Diastolic Heart Failure.⁶

DIFFERENTIAL DIAGNOSIS OF DIASTOLIC HEART FAILURE WITH NORMAL SYSTOLIC LEFT VENTRICULAR FUNCTION

A systematic clinical approach to the evaluation of a patient presenting with clinical signs and symptoms of congestive heart failure, but normal systolic LV function on noninvasive testing,³⁴ usually by echocardiography, is shown in *Figure 2*. Since the signs and symptoms of congestive heart failure are nonspecific and can also be seen in noncardiac disorders

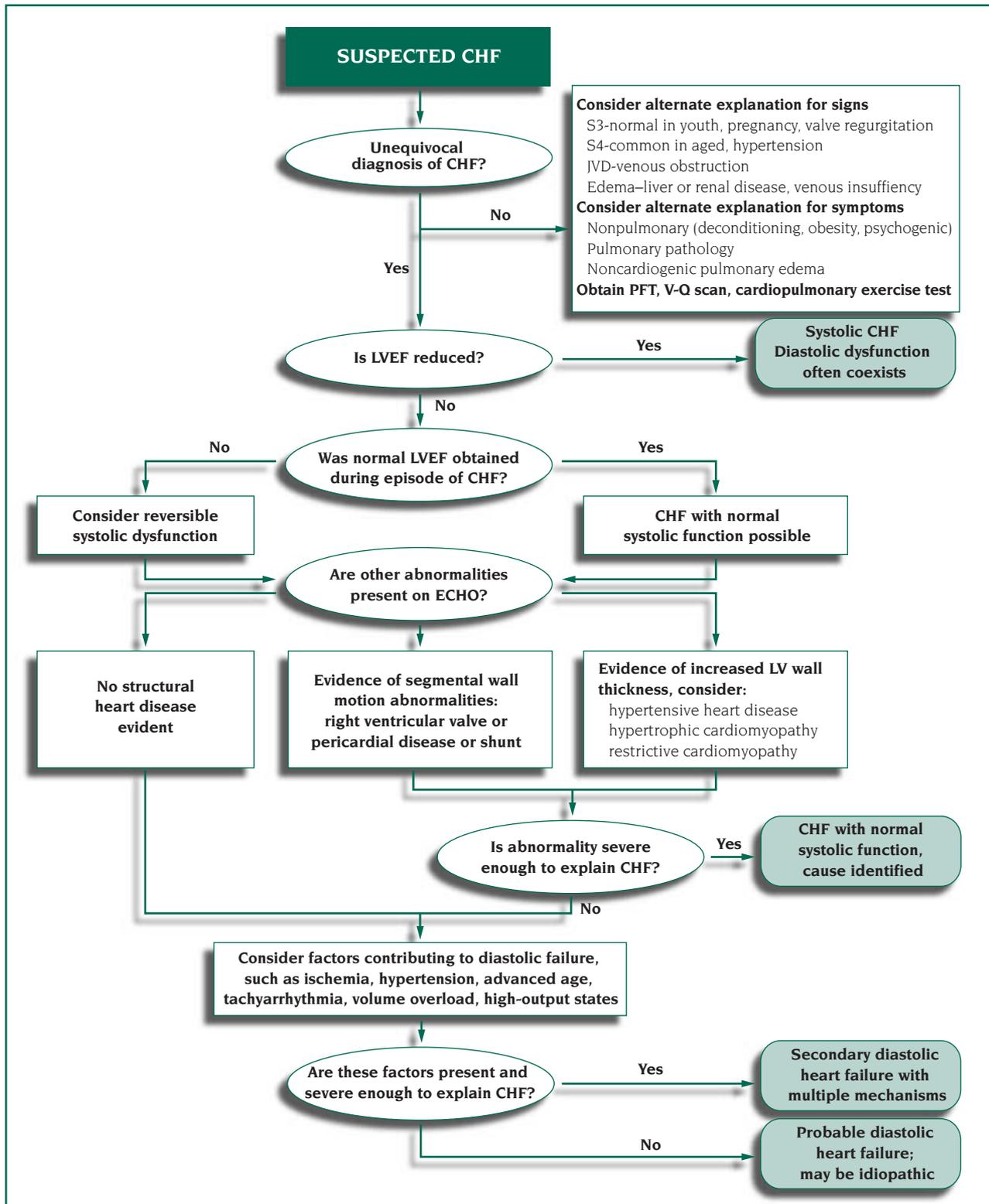


Figure 2. Evaluation strategy for a patient with suspected CHF due to diastolic dysfunction. Abbreviations: CHF: congestive heart failure; ECHO, echocardiogram; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; PFT, pulmonary function tests; V-Q, ventilation-perfusion scan. Adapted from ref 36: Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med. 1996;156:146-157. Copyright © 1996, American Medical Association.



(see Figure 2), the patient's clinical status must be critically evaluated before the diagnosis of diastolic heart failure with normal systolic function can be accepted. Table II summarizes some of the differential diagnoses that must be considered. Among the most common conditions that can mimic diastolic heart failure with normal systolic function are: (i) systolic LV

dysfunction with improvement at time of the evaluation; (ii) right heart failure; (iii) left atrial hypertension; and (iv) noncardiogenic pulmonary edema.

Moreover, restrictive cardiomyopathies and constrictive pericarditis can result in congestive heart failure with normal ventricular systolic function.

DIAGNOSIS	POSSIBLE CAUSE
Right heart failure diastolic (left ventricular dysfunction may be present)	<ul style="list-style-type: none"> • Pulmonary hypertension (primary or secondary; chronic thromboembolism, pneumoconiosis) • Pulmonic stenosis • Tricuspid valve disease • Right ventricular cardiomyopathy • Right ventricular infarction • Right atrial myxoma • Intracardiac shunts
Left atrial hypertension, normal left ventricular systolic and diastolic function	<ul style="list-style-type: none"> • Left ventricular inflow obstruction (mitral stenosis, left atrial myxoma, cor triatriatum) • Left atrial abnormalities (pulmonary venous obstruction, stiff left atrium) • Acute or chronic volume overload (valvular regurgitation, intracardiac shunts, chronic renal failure) • High-output heart failure (thyrotoxicosis, arteriovenous fistula, beriberi)
Noncardiogenic pulmonary edema	<ul style="list-style-type: none"> • Pericardial disease (constrictive pericarditis, pericardial effusion with tamponade)
Left ventricular diastolic dysfunction	<ul style="list-style-type: none"> • Ischemic heart disease • Left ventricular hypertrophy <ul style="list-style-type: none"> - Hypertension (essential, hypertensive hypertrophic, cardiomyopathy in elderly patients) - Hypertrophic cardiomyopathy - Left ventricular outflow tract obstructions (valvular and subvalvular aortic stenosis) • Restrictive cardiomyopathy <ul style="list-style-type: none"> - Infiltrative myocardial disease (amyloid, sarcoid, hemochromatosis, transplant rejection) - Endocardial disease (endocardial fibroelastosis, endomyocardial fibrosis) - Diabetes mellitus - Idiopathic • Aging • Obesity • Abbreviated left ventricular filling (sustained tachycardia, atrial fibrillation) • Idiopathic
Incorrect	
Systolic left ventricular dysfunction with improvement at time of evaluation	<ul style="list-style-type: none"> • Spontaneous improvement in left ventricular function • Severe hypertension with pulmonary edema • Acute ischemia-related pulmonary edema • Peripartum cardiomyopathy • Alcoholic cardiomyopathy with abstinence • Tachycardia-related cardiomyopathy • Other causes of reversible cardiomyopathy: selenium or carnitine deficiency, infections, drugs

Table II. Differential diagnosis of congestive heart failure with normal left ventricular systolic function.

Adapted from ref 36: Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med. 1996;156:146-157. Copyright © 1996, American Medical Association.

DIAGNOSTIC EVIDENCE OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN CARDIAC DISEASES

Coronary artery disease

The most common underlying cause of LV diastolic dysfunction is myocardial ischemia.³⁵ Diastolic dysfunction has been reported in up to 90% of patients with coronary artery disease. Transient and sustained ischemia causes profound alterations in LV diastolic function that may result in severe heart failure symptoms in patients who have otherwise well-preserved LV systolic function.³⁶

Evidence for abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness has been reported in the following manifestations of coronary artery disease: (i) at rest without previous myocardial infarction; (ii) at rest in the presence of previous myocardial infarction; and (iii) during acute ischemia (exercise, pacing, coronary occlusion).

Typical findings in patients with coronary artery disease and no detectable asynergy are a prolonged value of τ (53 ± 16 ms) and early LV filling assessed by radionuclide angiograms.³⁷ In a series of patients with single-vessel coronary artery disease and no evidence of prior myocardial infarction, two thirds of patients had a decreased peak filling rate and/or prolonged time to peak filling rate, both of which improved following angioplasty. These abnormalities could be ascribed to silent ischemia, altered myocardial mechanical loading because of reduced early diastolic coronary engorgement, or modified endothelial release of mediators because of lower endothelial shear stress. Chronic ischemic heart disease can cause diastolic dysfunction because of ventricular "remodeling," myocardial fibrosis, and scarring.³⁸ In this patient subset with previous infarction, τ was significantly longer than in controls (57 ± 13 ms vs 33 ± 8 ms). Moreover, frame-by-frame analysis of contrast LV angiograms revealed inward regional wall motion during isovolumic relaxation in the region of the affected coronary artery that resulted in marked prolongation (200 ms) of the isovolumic relaxation time on the M-mode echocardiogram, and early diastolic LV filling assessed by radionuclide angiograms is abnormal in the presence of previous myocardial infarction.

Systemic hypertension

Diastolic dysfunction is a common feature of systemic hypertension, where it may be related to LV hypertrophy or to an increase in the myocardial connective tissue matrix. A prolongation of the isovolumic relaxation

time and of τ has been observed in hypertensive LV hypertrophy.³⁹ This prolongation responds favorably to an acute intracoronary administration of angiotensin-converting enzyme inhibitors, and this response supports a key role of the cardiac renin-angiotensin system in diastolic LV dysfunction of hypertensive LV hypertrophy.⁴⁰ Indices of slow LV relaxation return towards normal values following antihypertensive therapy-induced regression of LV hypertrophy.⁴¹ Early LV filling is impaired, as evident from the reduced LV filling rate on radionuclide angiograms, depressed E/A ratio, and blunted E waves on the mitral Doppler inflow signal.⁴² This impairment of LV filling is related to LV mass index and leads to inadequate augmentation of LV end-diastolic volume during exercise to maintain systolic function.⁴³ Finally, LV diastolic distensibility and compliance are reduced in hypertensive LV hypertrophy.^{39,44}

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is another important cause of congestive heart failure with preserved ventricular systolic function, especially in the elderly. It may be genetic (familial, sporadic) or related to concomitant systemic hypertension, with the principal cause of impairment of cardiac function being abnormal diastolic function.

Indices of diastolic function have been shown to be abnormal in patients with hypertrophic cardiomyopathy, using several techniques.^{45,46} A prolongation of isovolumic relaxation time has been reported by numerous investigators using M-mode echocardiography and aortic valve closure sound, and a similar prolongation of τ was observed on microtip LV pressure recordings. M-mode echocardiographic and mitral inflow Doppler examinations of hypertrophic cardiomyopathy patients revealed reduced posterior wall thinning rates, prominent A waves, and prolonged deceleration times. Nuclear angiography showed asynchrony of regional lengthening leading to impairment of global filling. End-diastolic LV distensibility is clearly reduced in patients with hypertrophic cardiomyopathy, as evident from elevated end-diastolic pressures (22 ± 8 mm Hg) in the presence of small end-diastolic cavity volumes. In a substantial number of patients, the diastolic LV pressure-volume relation is often shifted upward and flattened, and the calculated constant of chamber stiffness underestimates the real stiffness due to a prolonged LV pressure decay into the filling phase.⁴⁷

Amyloidosis

Amyloidosis is the classic example of an infiltrative



restrictive cardiomyopathy that can be found with almost normal systolic, but impaired diastolic, LV function. In patients suffering from amyloidosis, end-diastolic LV internal dimension usually appears to be normal, but LV end-diastolic distensibility is reduced, as evident from elevated LV end-diastolic pressure in the presence of normal or mildly enlarged end-diastolic volume. When wall thickness is moderately increased (12-15 mm), the isovolumic relaxation time is prolonged and the Doppler inflow signal reveals a slow relaxation pattern.⁴⁸ For further increases in wall thickness, pseudonormalization of the Doppler inflow signals occurs. For a DT <150 ms the prognosis becomes worse for patients suffering from amyloidosis.⁴⁹

Diabetes

In patients with diabetes, mechanisms for diastolic heart failure include excessive myocardial fibrosis, interstitial accumulation of glycoproteins, slow sarcoplasmic reticulum calcium reuptake, or altered release from a dysfunctional coronary endothelium of mediators such as nitric oxide and endothelin.⁵⁰ Invasive studies have revealed a large increase in LV chamber stiffness, especially in the obese, which was related to plasma glucose and not to plasma insulin or LV mass, and which exceeded the increase in chamber stiffness observed in the same study in hypertensives.⁵¹ Noninvasive studies further confirmed a decrease in diastolic LV distensibility in children with type 1 diabetes, as evident from smaller end-diastolic cavity dimensions and an increased A wave on the mitral inflow signal, especially during a cold pressor test.⁵² A slow LV relaxation pattern through LV preload reduction unmasked by a reduced E/A ratio and prolonged deceleration time on the Doppler mitral inflow following administration of nitroglycerin was demonstrated in adults with uncomplicated type 1 diabetes.⁵³

Valvular heart disease

Valvular and subvalvular obstruction of the LV outflow tract can be associated with congestive heart failure due to diastolic LV dysfunction, with systolic function being preserved until late in the disease process.⁵⁴ In these patients, chronic structural intramyocardial abnormalities and impairment of myocardial relaxation represent a major cause of diastolic heart failure.⁵⁵ The enhanced susceptibility of hypertrophied myocardium to ischemia and the frequent elevation of right atrial pressure with concomitant engorgement of the coronary veins further contribute to the reduction in LV diastolic distensibility in valvular heart disease.⁵⁶ In aortic valve disease, 50% of patients with aortic stenosis and 90% of patients with aortic regurgitation

have signs of diastolic LV dysfunction in the presence of normal systolic function as evident from a prolongation of τ and an increase in myocardial stiffness.⁵⁷ In aortic stenosis, diastolic LV dysfunction is dependent on gender and age, being more common in male patients and in the elderly.⁵⁸

Cardiac allograft

Patients who have received a cardiac allograft typically show evidence of slow isovolumic relaxation and an increased diastolic LV chamber stiffness because of a steeper than normal diastolic LV pressure-volume relation.⁵⁹ These parameters of diastolic dysfunction, which have variously been attributed to donor-recipient heart size mismatch and repetitive episodes of rejection, contribute to the reduced exercise tolerance observed in allograft recipients.⁶⁰ During episodes of rejection, restrictive physiology of the allograft becomes more prominent, with a progressive abbreviation of isovolumic relaxation time. Even at the time of routine cardiac follow-up, some patients ($\approx 15\%$) show signs of persistent restrictive physiology with a sharp early diastolic dip on the LV pressure recording, a shorter isovolumic relaxation time, and a shorter deceleration time of mitral and tricuspid inflow. Importantly, these patients were found to have a significantly higher incidence of rejection.

Aging

Age-associated alterations in LV filling have been documented by several studies that used noninvasive indexes of ventricular function in normal aging subjects.⁶¹ However, the assessment of diastolic function in elderly subjects may be confounded by the increased prevalence of unrecognized myocardial ischemia and systemic hypertension as well as the many changes in cardiovascular physiology. These changes, which may affect diastolic filling indirectly, include increased LV mass and decreased arterial compliance. Although it is difficult to eliminate all confounding variables in clinical studies, a significant age-related reduction in diastolic filling was observed.⁶¹

TREATMENT STRATEGIES FOR DIASTOLIC DYSFUNCTION

No large controlled, randomized trials have targeted patients with diastolic dysfunction or diastolic heart failure. Most therapeutic recommendations for treating these patients are empirical and based on the results of small clinical studies.⁶² Treatment of diastolic dysfunction is difficult and, when developing treatment strategies, it must be remembered that symptomatic

ETIOLOGY	MECHANISM OF DIAGNOSTIC IMPAIRMENT	TREATMENT
<ul style="list-style-type: none"> • Coronary artery disease <ul style="list-style-type: none"> - Acute ischemia - Postinfarction scar or ventricular aneurysm 	<ul style="list-style-type: none"> • Impaired relaxation* (decreased inactivation due to diastolic cytosolic ionized calcium overload, nonuniform relaxation) • Increased chamber stiffness† (primarily due to increased myocardial stiffness); with near-complete coronary occlusion myocardial stiffness may decrease due to reduced coronary turgor • Pericardial restraint (in acute ischemic chamber dilatation) • Impaired relaxation (delayed inactivation, reduced contraction load, nonuniform relaxation, compensatory hypertrophy) • Increased chamber stiffness (increased myocardial stiffness, fibrosis) 	<ul style="list-style-type: none"> • Anti-ischemic agents; revascularization procedures if indicated • Drugs to prevent remodeling, such as converting enzyme inhibitors, treatment of residual ischemia
<ul style="list-style-type: none"> • Hypertension <ul style="list-style-type: none"> - Hypertensive urgency or emergency - Hypertensive heart disease 	<ul style="list-style-type: none"> • Impaired relaxation (elevated afterload) • Increased chamber stiffness (increased coronary turgor) • Impaired relaxation (altered contraction load, nonuniform relaxation due to fibrosis and regional variation in hypertrophy, diminished coronary reserve) • Increased chamber stiffness (altered geometry, increased myocardial stiffness) 	<ul style="list-style-type: none"> • Lower blood pressure • Hypertension treatment, left ventricular hypertrophy regression
<ul style="list-style-type: none"> • Hypertrophic cardiomyopathy 	<ul style="list-style-type: none"> • Impaired relaxation (increased contraction load in obstructive disease, reduced relaxation load, nonuniform relaxation due to fibrosis, cellular disarray and regional variation in hypertrophy, diminished coronary reserve) • Increased chamber stiffness (altered geometry, increased myocardial stiffness) 	<ul style="list-style-type: none"> • Negative inotropic drugs; dual chamber pacing and surgical myomectomy for refractory symptoms
<ul style="list-style-type: none"> • Restrictive or infiltrative cardiomyopathies 	<ul style="list-style-type: none"> • Impaired relaxation • Increased chamber stiffness (increased myocardial stiffness, fibrosis) 	<ul style="list-style-type: none"> • Treat any reversible factors‡ cardiac transplantation for end-stage cardiac failure; avoid digitalis and β-blockers in amyloidosis
<ul style="list-style-type: none"> • Valvular heart disease <ul style="list-style-type: none"> - Stenotic lesions (aortic and mitral stenosis) - Regurgitant lesions (aortic and mitral regurgitation) 	<ul style="list-style-type: none"> • Pressure overload (impaired relaxation, increased chamber stiffness due to concentric hypertrophy) • Volume overload (impaired relaxation, decreased chamber stiffness due to eccentric hypertrophy, which is offset by increased myocardial stiffness) • Pericardial restraint plays an important role in acute volume overload 	<ul style="list-style-type: none"> • Surgery, valvuloplasty, commissurotomy • Surgery, diuretics, and afterload reduction
<p>*Relaxation is normally under the triple control of inactivation (disengagement of myocardial crossbridges), load (contraction and relaxation loads), and nonuniformity of the process itself</p> <p>†Chamber stiffness is directly proportional to myocardial stiffness and inversely proportional to the ventricular volume-mass ratio</p> <p>‡Phlebotomy and iron chelation therapy for hemochromatosis, steroids for myocardial sarcoidosis</p>		
<p>GENERAL PRINCIPLES</p>		
<ul style="list-style-type: none"> • Reduce venous pressure; cautious use of diuretics and other preload-reducing agents • Treat precipitating factors; control of tachycardia; restore sinus rhythm and atrioventricular synchrony • Avoid positive inotropes in the absence of systolic dysfunction (an exception is the use of digoxin for control of ventricular rate in atrial fibrillation) • Identify and treat the underlying etiology 		

Table III. Treatment strategies of diastolic heart failure. Adapted from ref 36: Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med. 1996;156:146-157. Copyright © 1996, American Medical Association.



diastolic dysfunction is usually the result of convergence of a host of contributing factors and associated conditions. The treatment of diastolic dysfunction should focus not only on controlling symptoms, but also on resolving the underlying cause of the diastolic dysfunction and treating any factors that aggravate symptoms. *Table III* summarizes possible treatment strategies for diastolic heart failure adapted from a detailed review by Vasan et al.³⁶

Symptomatic treatment

Simple dietary measures, such as sodium (2 to 4 g/day) and fluid restriction (1 to 2 L/day), are extremely important and are the cornerstone of therapy. This is particularly important, as patients with diastolic dysfunction cannot tolerate large changes in intravascular volume (either increase or decrease) because of increased ventricular stiffness, and as many of these patients also suffer from some degree of renal dysfunction that further reduces their ability to excrete excessive volume loads. Among the therapeutic strategies in patients with diastolic dysfunction, maintenance of sinus rhythm is extremely important, and all efforts must be made to reestablish sinus rhythm if it is lost. This is important not only because sinus rhythm permits easier control of heart rate, but also because atrial systole in particular assures adequate ventricular filling in patients with abnormal relaxation.

Treatment of the underlying disease

Relief of myocardial ischemia with medication or by revascularization procedures has been shown to improve diastolic dysfunction in patients with coronary artery disease.⁶³ Treatment of hypertension is obviously important in order to reduce resistance to cardiac ejection, to allow regression of LV hypertrophy, and to reduce end-organ damage. However, care should be taken when reducing blood pressure in order to avoid hypotensive symptoms and worsening renal function, two side effects that are all too common, especially in older patients. Regression of LV hypertrophy can be obtained by multiple therapeutic regimens and should be a goal of therapy in these patients. Drugs such as angiotensin-converting enzyme inhibitors and perhaps calcium-entry blockers appear to lead to regression of both myocardial hypertrophy and fibrosis. Although it appears logical that regression of LV hypertrophy and improvement in diastolic function should improve symptoms and exercise tolerance in patients with diastolic dysfunction, at the current time there is no study that conclusively proves this.⁶⁴ Reduction of preload with venous dilators may be useful in some

patients. However, due to the reduced ability of these patients to respond to changes in ventricular filling pressures, great care must be taken when using these drugs. Particular care should be taken to avoid rapid and large changes in filling pressures. Procedures to relieve pericardial compression or limit cardiac infiltration should of course be attempted whenever possible in patients with pericardial or myocardial restrictive diseases.

THREE KEY QUESTIONS

Diastolic dysfunction, although still underestimated as a main contributor to congestive heart failure, has gained increasing conceptual and clinical importance in the past decade. However, the clinical assessment and differential diagnosis of diastolic dysfunction remain difficult, because diastolic dysfunction and diastolic heart failure are frequently the result of a convergence of factors such as advanced age, renal dysfunction, LV hypertrophy, and impaired myocardial perfusion. This leads Michael Shattock and Alison Cave to pose the question “**What are the cellular mechanisms of impaired myocardial relaxation and diastolic dysfunction?**” with regard to the broad range of disorders that promote the development of diastolic heart failure. Do these mechanisms differ from one disorder to the other, or are there common abnormalities present? What is the relationship between abnormalities of intracellular calcium metabolism⁶⁵ and changes in the extracellular collagen matrix, and how do these mechanisms affect early and late LV filling? Detailed knowledge about the pathophysiological mechanisms of diastolic dysfunction is essential in order to define reliable diagnostic criteria that should be readily obtainable by modern diagnostic tools and must be applicable to different cardiac diseases where diastolic dysfunction occurs. This topic is gone into in detail by Otto Hess, Christian Seiler, and Franz Eberli, who review the question: “**What is the best way to measure diastolic dysfunction?**” The correct diagnosis of diastolic dysfunction is of paramount importance in daily practice, because diastolic heart failure carries a more benign prognosis and requires specific forms of treatment, some of which are currently under investigation in large randomized clinical trials, as discussed by Luigi Tavazzi who addresses the question: “**What is the best treatment for diastolic dysfunction?**”

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Diastolic Dysfunction

Expert Answers to Three Key Questions

①

What are the cellular mechanisms of impaired myocardial relaxation and diastolic dysfunction?

M.J. Shattock, A.C. Cave

②

What is the best way to measure diastolic dysfunction?

O.M. Hess, C. Seiler, F.R. Eberli

③

What is the best treatment for diastolic dysfunction?

L. Tavazzi



What are the cellular mechanisms of impaired myocardial relaxation and diastolic dysfunction?

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Impaired myocardial relaxation is multifactorial and reflects a balance between the active processes responsible for calcium sequestration and removal from the cytosol, and physical factors responsible for load-dependent relaxation. In hypertrophy and heart failure, the slowing of the calcium transient (principally due to slowed sarcoplasmic reticulum calcium uptake) allows the slowed rate of calcium sequestration to dominate the rate of relaxation. This process is exacerbated at higher rates of stimulation where incomplete recovery of the calcium transient occurs between beats, and this in turn elevates end-diastolic pressure. The latter may be compounded by structural changes in the myocardium that increase stiffness. The profound neurohormonal and paracrine changes that accompany cardiac hypertrophy and failure also contribute to changes in calcium cycling, the responsiveness of the myofilaments to calcium, and ultimately to diastolic dysfunction.

Keywords: diastolic dysfunction; relaxation; calcium transient; SR Ca²⁺ ATPase; Na⁺/Ca²⁺ exchange; hypertrophy; heart failure

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This article must start by acknowledging the huge contribution made by Dirk Brutsaert and colleagues to the understanding of diastolic function and myocardial relaxation. In 1989, in an excellent review, Brutsaert and Sys comprehensively described the prevailing knowledge—anyone interested in this subject could do no better than to use this article as a keynote source.¹ In this short article, with its constraints on the number of citations, it would therefore be presumptuous of us to attempt to review the mechanics of diastolic dysfunction in their entirety. However, recent advances in molecular and cellular biology have revealed interesting new insights into the mechanisms responsible for calcium regulation in the normal and failing heart. In the present review, we will therefore concentrate on the processes responsible for relaxation and the subcellular basis of their impairment in the hypertrophied and failing heart. This decision to focus on the processes involved in relaxation (rather than those responsible for diastolic compliance) raises the questions of what we actually mean by *diastolic* dysfunction and what are the temporal limits of diastole?

DEFINITION OF DIASTOLIC DYSFUNCTION

For the heart to work effectively as a pump, it is self-evident that the

processes of relaxation and ventricular filling are as important as those of ventricular contraction and ejection. Many cardiologists and cardiac scientists have therefore chosen to label "contraction and ejection" as *systole* and "relaxation and the interbeat interval" as *diastole*. Thus, slowing of the process of relaxation by slow intracellular reuptake of calcium, for example, may lead to a rise in left ventricular end-diastolic pressure (LVEDP)—this would be termed *diastolic dysfunction*. Indeed, many articles have been written on the role of slowed recovery of the intracellular calcium transient in diastolic dysfunction (for review see references 2 to 4) However, as discussed at length by Brutsaert and Sys,¹ relaxation may be considered to be part of systole and hence such changes should be considered as *systolic* rather than *diastolic* in origin. It is therefore clear that we need to define at the outset what we mean by diastolic dysfunction and what are the temporal limits of diastole within the cardiac cycle.

Figure 1, redrawn from Brutsaert and Sys,¹ shows four of the many different subdivisions of the cardiac cycle that have been proposed over the last 100 years. Henderson,⁵ (scheme A), for example, divided the cardiac cycle into three phases: systole, diastole, and diastasis. Many clinicians, however, would consider diastole to commence on

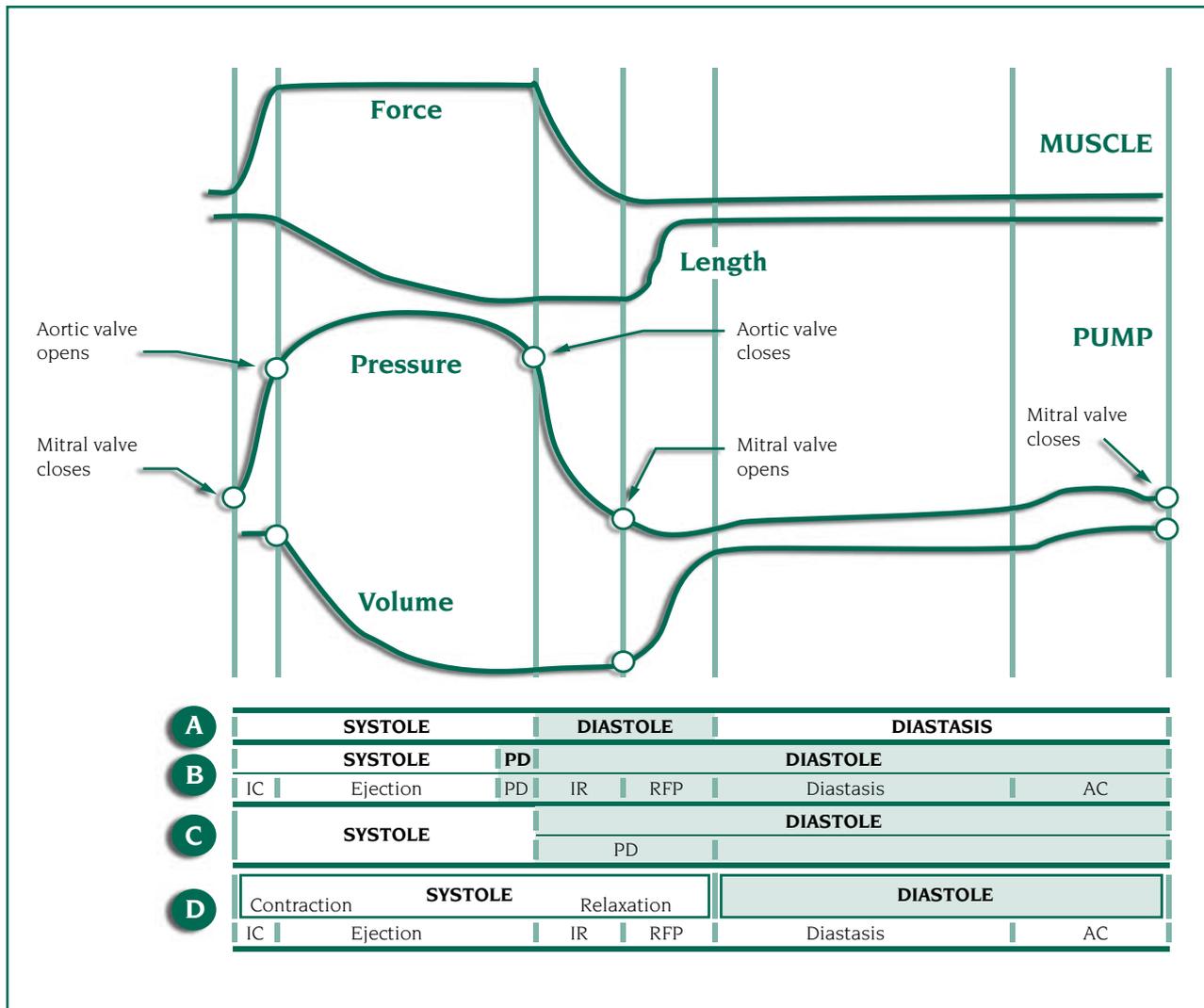


Figure 1. Subdivisions and phases of the cardiac contraction/relaxation cycle as variously defined. Force and length are estimated for an isolated cardiac muscle (top panel) and pressure and volume in the intact heart (lower panel). Systole and diastole are: (A) as defined by Henderson⁵; (B) according to Wiggers,⁶ with separate phases; (C) according to widely recognized clinical definition; and (D) as proposed by Brutsaert and Sys.¹ AC, atrial contraction; IC, isovolumic contraction; IR, isovolumic relaxation; PD, protodiastole; RFP, rapid filling phase.

Redrawn from ref 1: Brutsaert DL, Sys SU. Relaxation and diastole of the heart. *Physiol Rev.* 1989;69:1228-1315. Copyright © 1989, American Physiological Society.

the closing of the aortic valve and continue through to the closing of the mitral valve (scheme C). Brutsaert and Sys,¹ however, favor scheme D, where diastole starts only at the termination of relaxation (when fiber length and ventricular volume return to their resting state), and then continues until the start the next contractile cycle and the reinitiation of active force development. In this scheme, relaxation

forms part of systole.^{1,5,6} However, defects in both systolic relaxation and genuine diastolic dysfunction lead to impaired pump performance and what is regarded (erroneously or not) as "diastolic" dysfunction. Therefore, for the purposes of this review, we will consider the cellular bases of both changes in the relaxation process and in diastolic compliance, and how they may act together to compromise pump function.

NORMAL MECHANISMS RESPONSIBLE FOR RELAXATION

Calcium removal from the cytosol

In unloaded myocytes, the principal factor responsible for myocardial relaxation is the removal of calcium from the myoplasm.⁷ The mechanisms responsible for cytosolic



calcium removal and the recovery of the calcium transient are shown in *Figure 2*. Bers has shown that the fractional contributions of the various cellular mechanisms responsible for calcium sequestration or removal are similar whether calcium is measured directly or the recovery of tension or unloaded relengthening are used as surrogates.⁷ This close correlation between relaxation and the recovery of the calcium transient suggests that, under these conditions, calcium removal is the principal determinant of relaxation. Under steady-state conditions there is a competition principally between the sarcoplasmic reticulum Ca^{2+} ATPase and the surface membrane $\text{Na}^+/\text{Ca}^{2+}$ exchanger for cytosolic calcium with the sarcolemmal Ca^{2+} ATPase and the mitochondrial uniporter (the "slow pathways") being relatively unimportant. The relative

roles of these calcium transporting mechanisms, however, vary between species and tissues, and—importantly from the perspective of this article—are altered by various pathological conditions. Bers and colleagues⁷⁻¹⁰ have estimated the fractional contribution of each of these calcium transporters to the recovery of the calcium transient in a number of species and these are summarized in *Table I (next page)*.^{8,9,11,12}

Role of the myofilaments

As described above, in unloaded myocytes, the principal factor determining the rate of relaxation is the rate of removal of calcium from the myoplasm.⁷ In isometrically contracting muscle or in the intact heart, however, other factors may influence relaxation, including: (i) the Ca^{2+} -

independent rate of dissociation of cross-bridges; (ii) the afterload applied to the muscle; and (iii) the elastic properties of the tissue.

In isometric contraction, both the calcium transient and the removal of calcium from troponin C occur more rapidly than the decline in tension.¹³ Peterson et al have shown that the removal of calcium from troponin C does not appear to limit the rate of relaxation, and suggest that other factors may play a role.¹³ One such factor may be the Ca^{2+} -independent rate of cross-bridge detachment. However, whatever the rate-determining step is, it appears to be only marginally slower than the removal of calcium from troponin C, as a slight slowing of the rate of calcium decline (with ryanodine, for example) causes the calcium recovery to become rate-limiting.

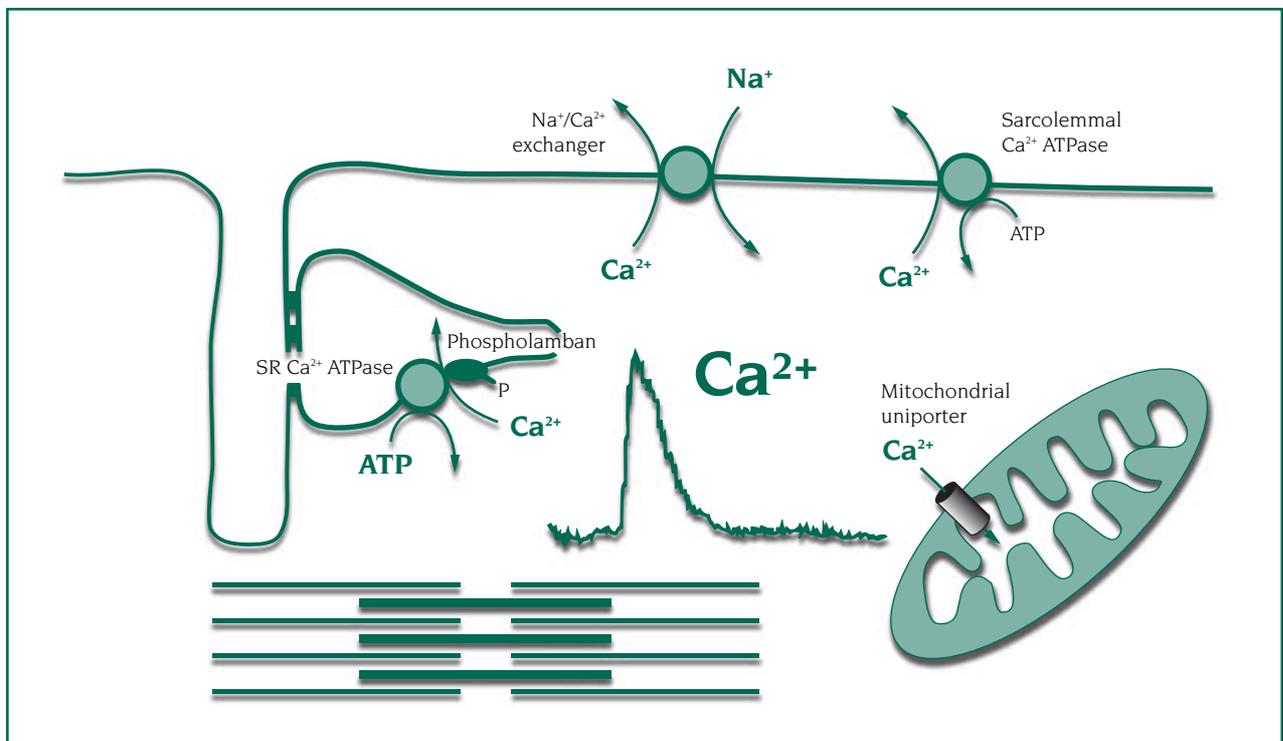


Figure 2. Principal mechanisms responsible for cytosolic calcium removal in the mammalian myocardium. In most species, sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchange and sarcoplasmic reticulum (SR) Ca^{2+} ATPase compete for cytosolic calcium and are the major pathways responsible for the recovery of the calcium transient. The mitochondrial uniporter and the sarcolemmal Ca^{2+} ATPase (the slow mechanisms) contribute little to the recovery of the transient, but may play a longer-term modulatory role in regulating cellular calcium. Estimates of the relative contributions of each of these processes to relaxation are given in *Table I*.

	Sarcoplasmic reticulum Ca ²⁺ ATPase	Na ⁺ /Ca ²⁺ exchanger	Mitochondria + sarcolemmal Ca ²⁺ ATPase	Other mechanisms?	Reference #
Rat	92%	7%	1%	-	9
Rabbit	70%	28%	2%	-	9
Ferret	64%	29%	4%	≈3%	8
Guinea pig	64%	36%	-	-	11
Human (normal)	70%	25%	5%	-	*
Human (heart failure)	≈50%	≈50%	-	-	12

Table I. Estimates of the contributions of the various calcium transporting mechanisms to the recovery of the intracellular calcium transient and relaxation in ventricular muscle from various species. The numbers for rat, rabbit, and ferret are taken from the work of Bers and colleagues.^{8,9,11,12} The numbers for the failing human heart are estimated from the relative contributions of each system to the calcium transient (which, under steady-state conditions, should approximate to the contribution of each system to relaxation) and from a personal communication from Bers 1999*. NB: the ferret, appears to have an additional transporting mechanism to those shown in Figure 2 (which has yet to be identified), which contributes to relaxation and extrudes calcium across the sarcolemmal membrane

Role of afterload

Afterload is one of the primary determinants of the rate of relaxation in vivo. Brutsaert and Sys¹ have defined relaxation as being either *load-dependent* or *inactivation-dependent*, according to the influence of afterload. As discussed above, in unloaded myocytes, it appears that the inactivation of the myofilaments, subsequent to the decline in the calcium transient and calcium binding to troponin C, is the principal rate-determining step. However, in isometric or loaded contractions, calcium is removed from the myoplasm (and troponin C) faster than the rate of relaxation, and other load-dependent factors subsequently determine the rate of relaxation. Thus, in species where the sarcoplasmic reticulum is functionally efficient (ie, cat, rat, etc; see *Table I*), relaxation is dominated by load-dependent processes, while in species or tissues where the sarcoplasmic reticulum is deficient or absent (ie, in frog ventricle or the failing human heart), the calcium removal processes are sufficiently slow to dominate relaxation. In

load-dependent muscles (such as cat ventricle), relaxation can be accelerated by imposing a load late during relaxation.¹ Thus, at higher afterloads, relaxation is accelerated, and this feature of cardiac muscle may aid ventricular filling during the latter part of relaxation when myoplasmic calcium is low.

Since there is a delicate equilibrium between inactivation-dependent and afterload-dependent processes in determining the rate of relaxation, it follows that perturbation of either system can have profound effects. For example, a slight slowing of calcium uptake processes in mammalian ventricular muscle can switch relaxation from being primarily load-dependent to being primarily inactivation-dependent.¹ During cardiac hypertrophy and failure, progressive changes occurring in both of these processes can thus profoundly influence relaxation.

GENERAL MECHANISMS OF IMPAIRED RELAXATION AND DIASTOLIC DYSFUNCTION

Impaired relaxation and diastolic

dysfunction have been observed in, and may contribute to, a wide range of pathologies, including hypertrophy, early and late heart failure, ischemia, reperfusion, hibernation, cardiomyopathy, and hypertension. Although the consequences for efficient pump function may be similar, the underlying mechanisms may differ between these different conditions. In this article, we will concentrate on what is known of the cellular mechanisms responsible for the changes in relaxation—and hence diastolic function—that occur in cardiac hypertrophy and failure.

Relaxation is dependent on four principal factors: (i) the rate of recovery of the calcium transient; (ii) the rate of dissociation of calcium from the myofilaments and cross-bridge detachment; (iii) the elastic restoring forces both within the muscle cell and the myocardial tissue; and (iv) the prevailing afterload. The relative contribution of each of these factors varies in normal cardiac muscle according to experimental conditions, and in vivo all of these factors are influenced by the processes of hypertrophy and failure.



CELLULAR BASIS OF PROLONGED SYSTOLIC CONTRACTION AND ABNORMAL RELAXATION

Calcium regulation in the hypertrophied and failing heart

In hypertrophy and failure, the majority of studies indicate that the calcium transient is prolonged. Much of the seminal work in this area comes from the laboratory of James Morgan in Boston. *Figure 3* shows calcium transients from failing human myocardium, with a decrease in the peak systolic calcium level and a slowed recovery of the calcium transient. The failing human myocardium is also characterized by a negative rather than a positive force-frequency staircase,^{2,12} a frequency-dependent decrease in peak systolic calcium, and a rise in end-diastolic calcium and tension.

As discussed above, the recovery of the calcium transient reflects competition between the sarcoplasmic reticulum Ca^{2+} ATPase and the sarcolemmal $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger (see *Figure 2*). It is now widely, but not invariably,^{14,15} accepted that reductions in sarcoplasmic reticulum Ca^{2+} ATPase protein level or function are the principal factors underlying the slowed recovery of the calcium transient in heart failure.¹⁶⁻¹⁹ The role of the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger in the prolongation of the calcium transient in hypertrophy and failure is somewhat less clear. Some studies report an increase in $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger protein levels and suggest that this may compensate for the decrease in sarcoplasmic reticulum calcium uptake.¹⁸⁻²⁰ Other studies in heart failure, however, report that functional calcium extrusion through the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger may be unaffected²¹ or may even be reversed such

that there is a stimulation of calcium *influx* via this pathway.²² A recent study by Hasenfuss et al has attempted to clarify this by measuring $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger, sarcoplasmic reticulum Ca^{2+} ATPase and the force-frequency relationship in muscles from various subgroups of failing and nonfailing human hearts.¹⁸ In this study, diastolic dysfunction with increasing stimulation rate was associated with a decrease in sarcoplasmic reticulum Ca^{2+} ATPase level and unchanged $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger expression. However, in some muscles, both diastolic function and sarcoplasmic reticulum Ca^{2+} ATPase levels were preserved and $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger protein levels were markedly increased. Thus, there is a spectrum of changes in calcium regulation in heart failure with changes in diastolic dysfunction principally associated with deficiencies in cytosolic calcium

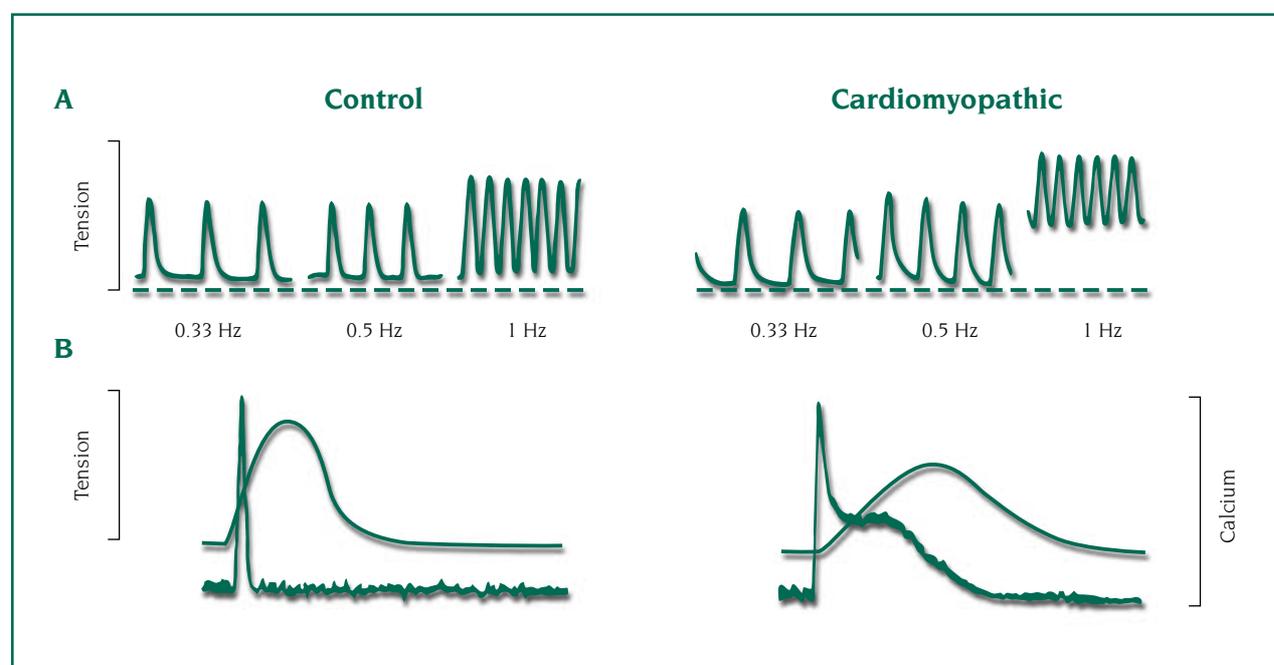


Figure 3. Intracellular calcium and tension recordings from control and failing human myocardium at various stimulation rates. Panel A shows the characteristic reversal of the force-frequency staircase in the failing myocardium (developed force declines with increasing frequency) with diastolic dysfunction apparent at higher pacing rates. Panel B shows the characteristic failure-induced depression of isometric contraction, the slowing of relaxation, and the marked prolongation of the calcium transient.

Redrawn from ref 2: Perreault CL, Williams CP, Morgan JP. Cytoplasmic calcium modulation and systolic versus diastolic dysfunction in myocardial hypertrophy and failure. *Circulation*. 1993;87:VII31-VII37. Copyright © 1993, American Heart Association.

sequestration by the sarcoplasmic reticulum Ca^{2+} ATPase.

Role of the myofilaments

The time-course of contraction and relaxation can be modified by changes in the sensitivity of the myofibers to activator calcium. In rats, for example, an hypertrophy-induced shift in myosin isoform from V_1 to V_3 prolongs contraction and relaxation. In the human heart, however, where the V_3 isoform predominates, the general consensus is that myofilament isoform expression and myofilament sensitivity are unaffected by hypertrophy and failure. Wolff et al,²³ however, have reported an *increase* in calcium sensitivity of myofilaments from failing human hearts, which could be reversed by treatment with protein kinase A. They suggest that this may reflect a reduction of adrenergically-mediated phosphorylation of myofibrillar regulatory proteins in heart failure. This hypothesis is supported by a study by Bodor et al,²⁴ who have reported a decrease in phosphorylated cardiac troponin I in failing human hearts—a change that would increase myofilament sensitivity.²⁵ Both Wolff et al²³ and Bodor et al²⁴ speculate that this reported increase in myofilament sensitivity to calcium may partially compensate for the decrease in the systolic calcium transient in the failing heart. However, a increase in myofilament calcium sensitivity in the face of elevated diastolic calcium would contribute to diastolic dysfunction.

PARACARINE MODULATION OF RELAXATION AND DIASTOLIC FUNCTION

Locally produced factors, particularly from the endothelium, have been shown to modulate cardiac contrac-

tility. Limited by the confines of this review, we have restricted discussion of the paracrine modulation of diastolic function to the effects of nitric oxide, angiotensin II, and bradykinin on myocardial relaxation. Since the production and release of these factors is known to be modulated by the processes of hypertrophy and heart failure, it is clear that changes in local regulation may influence relaxation and diastolic function.

Nitric oxide

The role of nitric oxide (NO) in the regulation of vascular tone is well known. More recently, however, it has become clear that NO has direct effects on the cardiac myocyte that selectively enhance relaxation, independently of any increase in coronary flow.²⁶ Furthermore, there is increasing evidence that alterations in NO synthesis are of pathophysiological importance in heart failure. Several studies have now demonstrated both reduced gene expression for endothelial NO synthase²⁷ and reduced NO release²⁸ in heart failure in both humans and animals. However, a reduction in endothelial gene expression is not limited to NO in heart failure, suggesting that regulation of several endothelial genes may be disturbed in the etiology of this disease.²⁷

In isolated ejecting guinea-pig hearts, the exogenous NO donor sodium nitroprusside induced premature and faster early left ventricular (LV) pressure decline without affecting end-diastolic pressure, peak LV pressure, or $\text{dP}/\text{dt}_{\text{max}}$.²⁶ These changes occurred at constant filling pressure, afterload, and heart rate. Similarly, global intracoronary infusion of sodium nitroprusside in humans results in an earlier onset of LV isovolumic relaxation, increased LV diastolic distensibility, and a signif-

icant reduction in LV peak and end-diastolic pressures.²⁹ In isolated single rat ventricular myocytes, the cGMP analog 8-bromo-cGMP induced similar changes in relaxation without any effect on the cytosolic calcium transient or action potential.³⁰ These results suggest that cGMP, and thus NO, enhance relaxation by a reduction in the myofilament sensitivity to calcium. In heart failure, where NO production may be compromised, the contribution of such changes to relaxation and diastolic dysfunction have yet to be characterized.

Angiotensin II, ACE, and bradykinin

It is now recognized that a locally active renin-angiotensin system is present in the human heart, which is involved in various disease states characterized by diastolic dysfunction, such as hypertrophy and heart failure. In rats, cardiac angiotensin-converting enzyme (ACE) content has been shown to be twofold higher in hypertrophied hearts compared with their appropriate controls.³¹ Furthermore, the intracardiac angiotensin I to II conversion rate was four times higher in hypertrophied hearts.³¹ Angiotensin II is a direct positive inotrope that has been reported to delay relaxation particularly in diseased hearts.³² In hypertrophied rat heart, exogenous angiotensin II markedly increased end-diastolic pressure with an accompanying increase in expression of ACE mRNA.³³ Chronic treatment with ACE inhibitors reduces mortality and has beneficial effects on ventricular remodeling and diastolic function in heart failure and following acute myocardial infarction.^{34,35}

The beneficial effects of an ACE inhibitor in heart failure, however,



can, at least in part, be attributed to an increase in bradykinin levels and the subsequent increase in the release of NO and other arachidonic acid metabolites, such as prostacyclin. Indeed, the bradykinin receptor antagonist HOE 140 blocked angiotensin II-induced incorporation of [³H]phenylalanine (an in vitro marker of hypertrophy) in adult rat myocytes cocultured with endothelial cells.³⁶ This beneficial effect was abolished by inhibition of NO synthase. Similarly, prevention of cardiac hypertrophy by bradykinin is abolished by NO synthase inhibition.³⁷

DIASTOLIC DYSFUNCTION AND COMPLIANCE

The bulk of this article has focused on the mechanisms responsible for impaired relaxation as mediators of diastolic dysfunction. However, after systolic relaxation is complete and during genuine diastasis, diastolic compliance may also be influenced by a wide range of factors that may have a profound influence on diastolic filling. Within the limits of this brief review it not possible to detail all of these processes, and readers are referred to the literature cited below and to reviews by Brutsaert and Sys¹ and Lorrell.³⁸ Factors that directly influence compliance during diastasis may include changes in resting free calcium,³⁹ myofilament calcium sensitivity,³⁹ rigor bond formation,⁴⁰ subcellular architecture,⁴¹ fibrosis,^{42,43} collagen deposition,^{44,45} ventricular remodeling,⁴⁵ pericardial constraint,³⁸ nonuniformity of muscle activation,¹ intracellular pH,^{39,40} coronary turgor pressure,^{46,47} edema⁴⁶ and cross-talk from right ventricular overload.⁴⁸

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What is the best way to measure diastolic dysfunction?

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Diastolic dysfunction is defined by symptoms of heart failure in the presence of normal systolic pump function. Its assessment is difficult in the clinical setting, and must rely on noninvasive and invasive techniques to detect changes in relaxation, filling, and distensibility. One of the most commonly used diagnostic techniques is Doppler echocardiography, which distinguishes diastolic dysfunction from abnormal transmitral flow patterns, altered pulmonary venous flow, and unrelated changes in tissue imaging parameters (diastolic abnormalities). As it may fail to take into account pseudonormalization of flow signals and changes in loading conditions that can mask diastolic dysfunction, cardiac catheterization is often necessary for a reliable quantitation of relaxation disturbances (time constant of pressure decay), changes in filling pressure (increase in minimal diastolic and end-diastolic pressure), and diastolic distensibility (pressure-volume and stress-strain data).

Keywords: diastolic dysfunction; heart failure; Doppler echocardiography; magnetic resonance imaging; cardiac catheterization

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The syndrome of heart failure is defined as the inability of the left ventricle (LV) to generate an adequate cardiac output at rest and during exercise, while operating at normal LV filling pressure. Typically, this syndrome is associated with impaired LV systolic function. However, as many as 30% to 40% of all patients with typical symptoms of heart failure have a normal or slightly reduced ejection fraction. Diastolic dysfunction is the principal cause of the classic symptoms of exertional dyspnea and fatigue. The most common causes of diastolic dysfunction are LV hypertrophy secondary to hypertension, valvular heart disease, post-myocardial infarction, and hypertrophic and restrictive cardiomyopathy. Clinical diagnosis of diastolic dysfunction is often difficult, due to the fact that most function parameters are normal and altered diastolic filling parameters may be compensated or even normalized by effective compensatory mechanisms. The question: "What is the best way to measure diastolic dysfunction?" is often difficult to answer and a definite conclusion frequently requires the recourse to invasive hemodynamic monitoring.

DEFINITIONS

According to the classic definition, diastole starts when the mitral valve opens and the blood enters the left ventricle, and it ends with the onset of systolic contraction when the mitral valve closes.^{1,2} The clinical

definition of diastole includes isovolumic relaxation as well, and hence, diastole commences at end-ejection, when the aortic valve closes.^{3,4}

Systolic dysfunction can be defined as a decreased ejection or an inability to generate pressure of one or both ventricles. Diastolic dysfunction can be defined as an impaired relaxation or filling of one or both ventricles. Clinically, diastolic dysfunction is defined by the triad:

- Presence of signs or symptoms of congestive heart failure;
- Presence of normal or only mildly depressed LV systolic function;
- Evidence of increased diastolic filling pressure.

Signs or symptoms of congestive heart failure include evidence of raised left atrial pressure with exertional dyspnea, orthopnea, gallop sounds, lung crepitations, pulmonary edema. Signs of raised right atrial filling pressure include distended neck veins, hepatomegaly, ascites, pretibial edema, and gallop sound (4th heart sound). Exertional dyspnea and a reduced peak maximal oxygen consumption (<20 mL/kg/min) are the earliest signs of diastolic heart failure.

The diagnosis of diastolic heart failure requires the presence of a normal or only slightly decreased LV systolic function (isolated diastolic dysfunction). Because of the frequent concomitant occurrence

of systolic and diastolic dysfunction, eg, in patients with end-stage heart failure, the diagnosis of diastolic dysfunction is complicated and usually refers to patients with isolated forms of diastolic dysfunction.

The presence of an increased diastolic filling pressure can be demonstrated best by direct intracavitary pressure measurements,⁵ but there are a few indirect (noninvasive) parameters that allow assessment of filling pressures, eg, the difference between the diastolic cuff blood pressure and the end-diastolic velocity of an aortic or mitral regurgitant Doppler spectrum.

NONINVASIVE ASSESSMENT OF DIASTOLIC FUNCTION

The noninvasive assessment of LV diastolic function has been one of the major advantages of Doppler echocardiography in the past few years.⁶⁻¹² The techniques used include: (i) transmitral Doppler echocardiography with relaxation and filling parameters; (ii) pulmonary venous Doppler echocardiography; and (iii) Doppler tissue imaging.

These different techniques and methods have been used alone or in combination to assess LV diastolic function, but most of them are heart rate-, preload- and afterload-dependent, and may vary over time and according to patient. Noninvasive assessment of LV pressure and myocardial distensibility is not yet possible with these techniques. Nevertheless, these measurements yield important information on diastolic function. Parameters such as the isovolumic relaxation time (IVRT) and the ratio of early-to-late transmitral Doppler spectrum may allow differentiation between relaxation disturbances and changes in the passive elastic properties of the myocardium.

Transmitral Doppler echocardiography

The transmitral flow pattern has been widely used to assess diastolic function on the basis of the early (E-wave) and late (A-wave) diastolic inflow pattern. The transmitral velocity pattern is easy to acquire and rapidly categorizes patients into normal filling patterns (E>A), delayed relaxation patterns (E<A), and restrictive filling patterns (E>>A).⁶ E-wave acceleration is directly related to left atrial pressure and inversely related to the relaxation time constant. E-wave deceleration is directly related to mitral valve area and inversely related to ventricular distensibility, ie, the stiffer the ventricle, the more rapid the deceleration^{6,7} (Figure 1).

Color Doppler transmitral flow allows study of the inflow dynamics across the mitral valve. The speed of flow propagation is enhanced with rapid relaxation and ventricular suction, but is delayed in ventricular ischemia or LV hypertrophy, indicating diastolic dysfunction.⁸

Pulmonary venous Doppler echocardiography

The pulmonary venous flow pattern⁹ provides important information on

ventricular diastolic function (Figure 2). Systolic (S-wave) and diastolic (D-wave) pulmonary venous flow typically change during normal aging, with S<D in youth becoming S>D, reflecting delayed relaxation in later life, then reverting to S<D as a restrictive pattern develops. One of the key problems of the pulmonary venous flow pattern is to distinguish the truly normal from the pseudonormal transmitral filling pattern. In the pseudonormal setting, the small, reversed A-wave is increased and prolonged because the atrium is contracting against an increased ventricular stiffness, resulting in an elevated pulmonary venous A-wave. However, the wide variability in normal values¹⁰ renders the interpretation of pulmonary venous flow data difficult.

Doppler tissue imaging

Doppler tissue imaging yields important information on intramyocardial velocities, providing unique insight into ventricular mechanics during systole and diastole, as well as isovolumic contraction and relaxation.¹¹

Doppler-derived relaxation and filling parameters have been used to estimate relaxation and filling disturbances. The most commonly used parameter is isovolumic

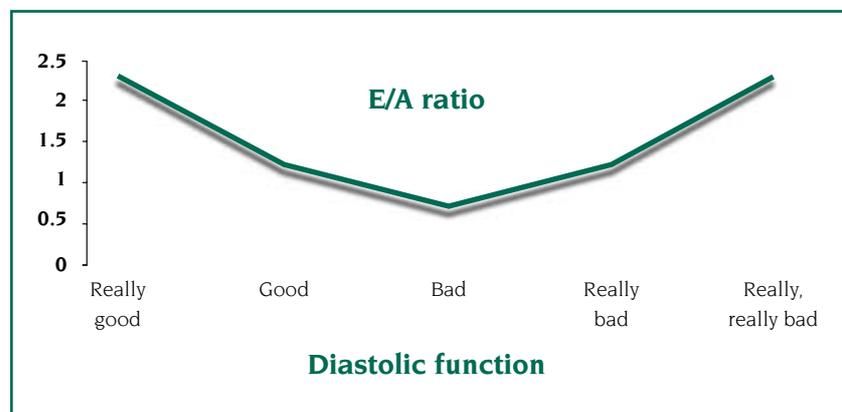


Figure 1. U-shaped relationship between E/A-wave ratio and the severity of diastolic dysfunction (based on data from ref 7).

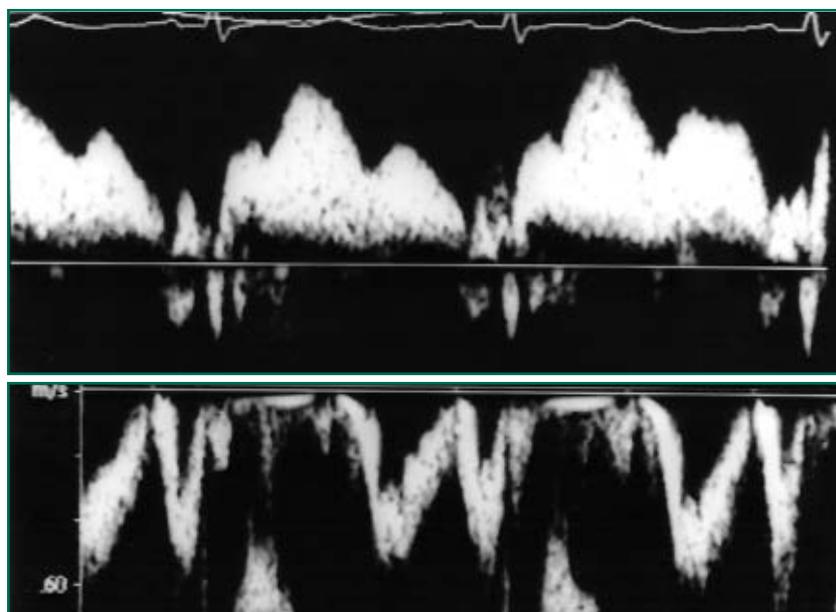


Figure 2. Pulmonary venous flow (top) and transmitral flow signal (bottom) in a normal subject. Systolic and diastolic venous flow is followed by a short inverse A-wave, whereas transmitral inflow shows an early E-wave and a late diastolic A-wave.

relaxation time, which is, however, preload- and afterload-dependent. In the patient with diastolic dysfunction, a short isovolumic relaxation time interval reflects an elevated left atrial pressure rather than an improved relaxation rate.¹²

Through an integrated use of these Doppler techniques it is possible today to obtain a precise picture of ventricular diastolic function in most patients with heart failure.

Other noninvasive techniques

There are several new techniques that may be useful for the diagnosis of diastolic dysfunction, such as magnetic resonance imaging. LV contraction and relaxation can be assessed by means of standard imaging sequences, but newer techniques such as myocardial tagging allow the labeling of specific myocardial regions. From these tags, the rotational and translational motion of the left ventricle—which is characterized by a systolic wring-

ing motion followed by a rapid diastolic untwisting—can be determined. This untwisting motion is directly related to relaxation and may be used as a measure of the rate and completeness of relaxation as well as an estimate of early diastolic filling parameters.¹³

INVASIVE ASSESSMENT OF DIASTOLIC FUNCTION

Cardiac catheterization with simultaneous pressure and volume measurements is and still represents the gold standard for assessing LV diastolic function. Prerequisites are high-fidelity pressure recordings with simultaneous angiography or echocardiography or the use of the conductance technique. From these data, the rate of LV relaxation, early and late diastolic filling, and passive elastic properties can be estimated.^{1,5}

Indexes of isovolumic LV relaxation

The most commonly used parameter

is the time constant of isovolumic pressure decay (τ ; ms), which has been shown to be exponential under most circumstances, but may deviate from a true monoexponential decay during aortic regurgitation or myocardial ischemia. Originally, a logarithmic pressure-time relation was used, based on the assumption that the asymptote of the pressure decline was zero. However, it has been recently shown that, in the transiently nonfilling ventricle, LV pressure declines to negative values. Most authors today therefore use a logarithmic pressure-time relationship with asymptote:

$$P = Ae^{-\alpha t} + P_b$$

where P = pressure, A = pressure at peak negative dP/dt , e = base of natural logarithms, α = slope of the pressure-time relationship, t = time, and P_b = pressure asymptote.

The time constant τ is calculated as:

$$\tau = -1/\alpha$$

In controls, τ averages 48 ms, with a range from 40 to 60 ms.¹

Relaxation is assumed to be complete at 3.5 times the time constant τ after aortic valve closure.⁵

Indexes of LV diastolic filling

LV diastolic filling has been obtained from frame-by-frame analyses of LV angiograms using instantaneous filling rates. This approach has been found to be time-consuming and less accurate than Doppler echocardiography. However, filling parameters calculated from the conductance technique have been very useful, as is the case with the first derivative of LV volume versus time.

Indexes of passive diastolic function

For practical purposes, it is important to distinguish between ventric-

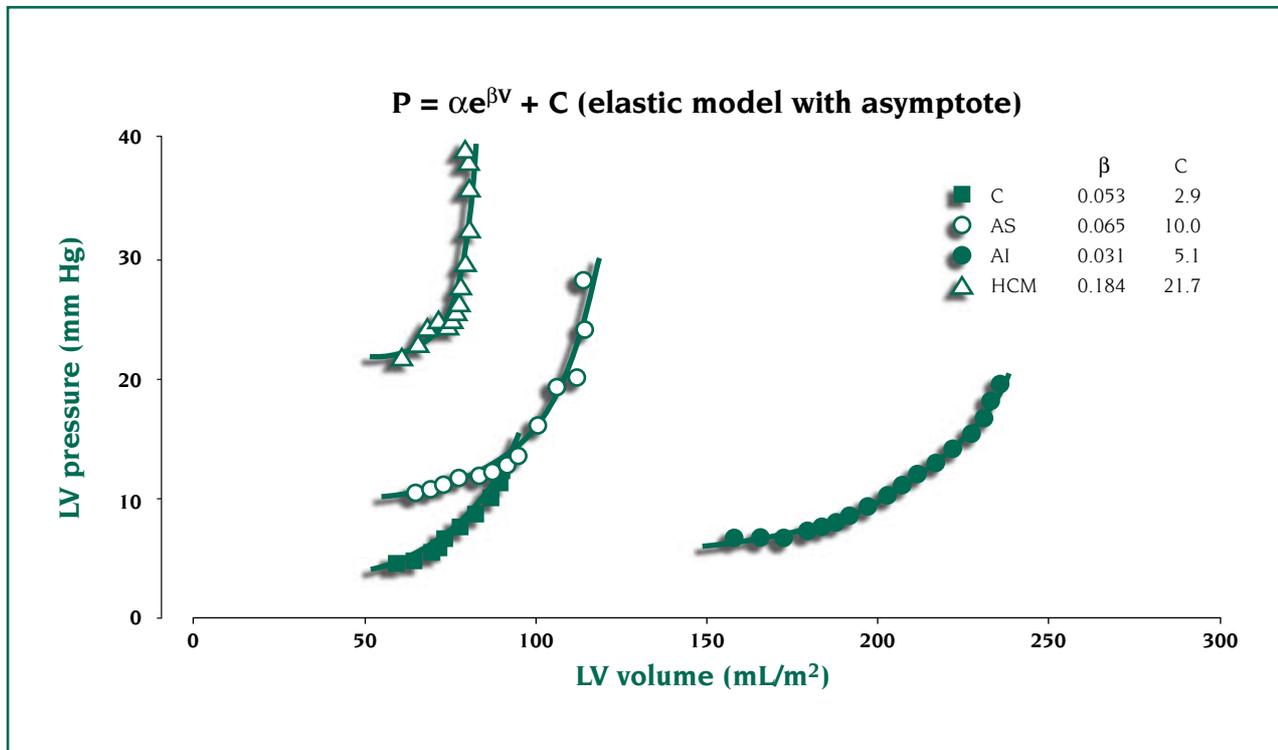


Figure 3. Left ventricular (LV) pressure-volume relationship in a control subject (C) and a patient with aortic stenosis (AS), aortic regurgitation (AI), or hypertrophic cardiomyopathy (HCM). There is a large upward shift in the HCM and a mild shift in the AS patient due to diastolic dysfunction.

ular (= chamber stiffness) and myocardial properties (= muscle stiffness). Ventricular passive diastolic function is directly related to the symptoms of the patients, whereas myocardial properties reflect the functional status of the heart muscle itself and may or may not be influenced by the organ as a whole. Calculation of chamber stiffness is performed by plotting LV diastolic filling pressure against LV diastolic volume from minimal diastolic pressure to end-diastolic pressure,^{14,15} including or excluding the rapid early diastolic filling phase and atrial contraction. The most commonly used equation for assessing chamber stiffness is:

$$P = \alpha e^{\beta V} + C$$

where P = pressure, α = intercept, e = natural logarithm base, β = slope of the pressure-volume relationship (chamber stiffness

constant), V = volume, and C = pressure asymptote. Mathematic evaluation is carried out using a non-linear curve-fitting procedure.^{14,15} Normal values average 0.05 mL⁻¹ ranging between 0.01 and 0.09 mL⁻¹ (Figure 3).

Calculation of LV myocardial stiffness is achieved by plotting instantaneous LV wall stress against LV mid-wall strain. The most commonly used equation for assessing myocardial stiffness is:

$$S = \alpha e^{\beta E} + C$$

where S = wall stress, α = intercept, e = natural logarithm base, β = slope of the stress-strain relationship (muscle stiffness constant), E = strain, and C = stress asymptote. Mathematical evaluation is carried out using a nonlinear curve-fitting procedure. Normal values average 12, ranging between 5 and 20.^{1,5}

CLINICAL IMPLICATIONS OF DIASTOLIC DYSFUNCTION

Diastolic dysfunction may be present for several years before any symptoms occur, and may thus represent the first phase of heart failure before systolic dysfunction prevails. Therefore, it is of great importance to detect diastolic dysfunction in due time and start treatment before systolic dysfunction with irreversible structural changes occurs.

Noninvasive techniques such as Doppler and tissue Doppler echocardiography are the most important tools to achieve this goal, but a precise diagnosis still requires invasive techniques in order to measure diastolic filling pressures, the time constant of relaxation, and chamber and muscle stiffness constants.



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What is the best treatment for diastolic dysfunction?

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Though numerous reports suggest that about one third of patients with congestive heart failure (CHF) have preserved left ventricular systolic function, in the absence of any large-scale clinical trial targeting these patients, the optimal treatment of diastolic heart failure remains unknown. Patients with CHF attributable to diastolic dysfunction form an extremely heterogeneous group and, in the majority of cases, once pericardial disease and restrictive and hypertrophic cardiomyopathies have been excluded, no specific disease sustaining diastolic dysfunction can be evidenced. Accordingly, the management of such patients consists of general measures such as vigorous blood pressure control, relief of myocardial ischemia, maintenance of sinus rhythm, and prevention of an elevated heart rate. This article discusses the scarce published experience of the use of drugs and cardiac electrical stimulation in heart failure with diastolic dysfunction.

Keywords: congestive heart failure; diastolic heart failure; heart failure with preserved systolic function; ventricular diastolic dysfunction; heart failure treatment; treatment of ventricular diastolic dysfunction

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Though numerous reports suggest that about one third of patients with congestive heart failure (CHF) have preserved left ventricular (LV) systolic function, in the absence of any large-scale clinical trial targeting these patients the optimal treatment of diastolic heart failure remains

unknown. In a recent review of the published reports on this subject, Vasan et al¹ noted that only 1 of the 30 studies reviewed (the Veterans Administration Heart Failure Trial [V-HeFT I]²) provided details on the selection of a specific therapeutic regimen and treatment-based outcome. This is hardly surprising

- **Inaccurate diagnosis of CHF** (eg, COPD)
 - **Inaccurate measurement of LVEF**
 - **LV systolic function overestimated by LVEF** (eg, mitral regurgitation)
 - **Episodic LV systolic dysfunction with improvement at time of evaluation** (eg, severe hypertension, ischemia, tachycardia, volume overload, peripartum cardiomyopathy, alcoholic cardiomyopathy with abstinence, infections, drugs, spontaneous variability of ventricular function)
 - **Obstruction to LV inflow** (mitral stenosis, left atrial myxoma)
 - **Diastolic dysfunction**
 - Abnormalities of LV relaxation*
 - Ischemia
 - Hypertrophy (eg, hypertension, HOCM, aortic stenosis)
 - Cardiomyopathies
 - High-output states (eg, infections, anemia, thyrotoxicosis, beri beri, arteriovenous shunt, tachyarrhythmia)
 - Overload (eg, hypertension, volume overload from ESRD, aortic stenosis, HOCM)
 - Aging
- Altered passive elastic properties**
- Hypertrophy
 - Aging
 - Altered collagen composition
 - Diabetes mellitus
 - Fibrosis
 - Infiltrative myocardial disease (eg, amyloidosis, sarcoidosis)
 - Storage myocardial disease (eg, hemochromatosis)
 - Endomyocardial disease (eg, endomyocardial fibrosis, radiation, anthracycline)
 - Pericardial disease (eg, pericardial constriction or tamponade)

Table 1. Causes of CHF with preserved systolic function. Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HOCM, hypertrophic obstructive cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction.

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given the possible causes of CHF with preserved systolic function (Table I). Indeed, patients with CHF with preserved systolic function form an extremely heterogeneous group, and the therapeutic approach can differ substantially according to the cause of the disease.

Moreover, virtually all randomized clinical intervention trials on CHF had, as inclusion criteria, a depressed ejection fraction (EF) and/or LV dilatation (in an attempt to include correctly diagnosed patients). This precluded the proper testing of any drug in diastolic CHF.

A FEW CAVEATS BEFORE INSTITUTING THERAPY

A preliminary step before planning the treatment of a patient with so-called diastolic CHF is to consider etiology and whether systolic function is actually preserved.³ Usually, the diagnosis of diastolic CHF is based on the presence of symptoms and signs of CHF associated with a preserved left ventricular ejection fraction (LVEF) (usually $\geq 45\%$) and not on documented LV diastolic dysfunction. This is misleading and exposes several potential biases leading to incorrect diagnosis. These are mainly related to either inaccurate or unrepresentative measurements of ejection fraction. Several causes of transient LV systolic dysfunction are common in acute cardiac decompensation: uncontrolled hypertension, myocardial ischemia, rapid atrial fibrillation, and alcohol abuse can reversibly depress left ventricular function and cause CHF, which may appear to have preserved systolic function if ventricular function is determined after functional recovery. Another possible source of confusion is mitral regurgitation. In this case, an accurate measurement of the ejection fraction can yield values in the normal range, but systolic myocardial function

can be severely impaired. None of these patients have CHF with preserved systolic function.

THERAPY-ORIENTED PATHOPHYSIOLOGY

A discussion of the pathophysiology of diastolic dysfunction is beyond the scope of this article and has been reviewed in detail elsewhere.⁴⁻⁷ Briefly, the pathophysiological derangements that can produce clinically manifest diastolic abnormalities are of two general categories: alterations of myocardial relaxation and reduced LV compliance. The reduction in myocardial relaxation is related to a slow restoration of systolic Ca^{2+} levels after the massive release of Ca^{2+} ions by sarcoplasmic reticulum that occurs during systole. The process is energy-dependent and rapidly becomes impaired during myocardial ischemia and other energy-deficient states. The decrease in ventricular compliance (or increase in passive stiffness) can be due to increased muscle mass and/or alterations in the interstitial elements of the ventricle, including fibrosis, or altered collagen composition. Acutely, these alterations can occur in isolation; chronically, progressive alterations of diastolic function are usually seen, represented diagrammatically in Figure 1.⁸ Hypertension, diabetes, infiltrative diseases such as amyloidosis and sarcoidosis, and overload diseases such as hemochromatosis can induce marked alterations in ventricular compliance. Pericardial disease decreases myocardial compliance by acting as an extramyocardial constraint.

GENERAL THERAPEUTIC APPROACH

In the majority of patients with diastolic CHF, once pericardial disease and restrictive and hypertrophic

cardiomyopathies have been excluded, no specific disease sustaining diastolic dysfunction can be evidenced. Most are elderly, and aging has been associated with abnormalities of both myocardial relaxation and compliance. The majority have a history of hypertension, which is frequently associated with left ventricular hypertrophy (LVH). Many patients have coronary artery disease. Diabetes and some degree of renal dysfunction are frequently present. In the long term, morbidity and mortality seem to be better in patients with diastolic CHF than in patients with systolic CHF.

In the absence of any specific treatment, the management of patients with diastolic CHF consists of general measures. Firstly, vigorous blood pressure control is important in order to reduce resistance to cardiac ejection and promote regression of CHF. Maintenance of sinus rhythm is also important, because an adequate ventricular filling period can be critical in these patients, and sinus rhythm permits easier control of heart rate. Moreover, atrial systole is essential in assuring adequate ventricular filling in patients with abnormal diastolic ventricular function. Relief of myocardial ischemia with medication or by revascularization procedures has been shown to improve diastolic dysfunction in patients with coronary artery disease.^{9,10}

Drug therapy

As mentioned above, no prospective controlled trials of specific therapies in diastolic CHF are available. The only controlled randomized study including patients with preserved systolic ventricular function was VHeFT I.² A small subset of 83 patients with EF $>45\%$ were followed up for 2 to 3 years on average, and the mortality rate in

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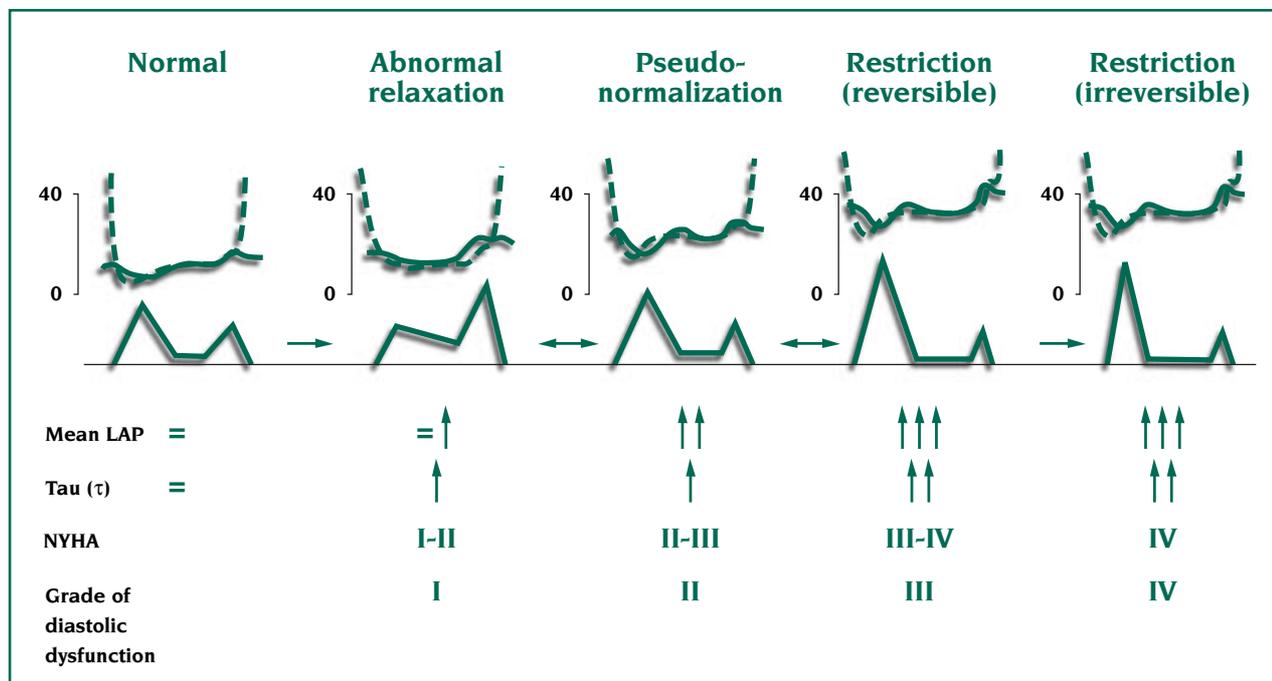


Figure 1. Proposed grading system for diastolic dysfunction based on the progression of the disease pattern in patients with cardiac disease. Below the high-fidelity left atrial and left ventricular pressure curves is a schematic representation of the mitral flow velocity curve. Below this is the mean left atrial pressure (LAP), time constant of relaxation (Tau τ), and New York Heart Association (NYHA) class associated with the various mitral flow velocity curves. The natural progression is from a normal pattern, to an abnormal relaxation pattern, to a pseudonormalization pattern, to a reversible restriction pattern, and finally to an irreversible restriction pattern.

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the intervention group treated with an isosorbide dinitrate-hydralazine combination, was lower (5.3%) than that of the placebo group (9.0%). However, the difference failed to reach statistical significance. Moreover, it cannot be said whether this apparent benefit was related to the nitrate component, hydralazine, or their combination.

Diuretics

Loop diuretics relieve symptoms of pulmonary congestion and peripheral edema in diastolic as well as systolic CHF. In the former, however, there are more risks associated with the use of these drugs than in the latter. Due to the steep LV diastolic pressure-volume relationship, ventricular function is particularly sensitive to ventricular volume changes; small volume increments

can easily result in pulmonary edema, but increased diuresis may produce a marked fall in end-diastolic pressure and hence compromise stroke volume and cardiac output. Moreover, prolonged use of diuretics leads to activation of the renin-angiotensin-aldosterone system, which can have adverse consequences on the progression of CHF.

Calcium antagonists

These drugs act by slowing heart rate (verapamil) thereby prolonging filling time, and by improving myocardial relaxation as a consequence of a reduction in intracellular calcium in myocardium, with calcium overload due to altered sarcoplasmic reticulum function. Additional benefits may be an improved subendocardial flow supply-demand ratio, resulting from prolongation of

diastole and coronary dilatation, and regression of ventricular hypertrophy in hypertensive patients. In spite of these theoretical advantages, a significant proportion of patients with CHF do not improve on calcium-antagonist drug therapy and may even deteriorate. The only placebo-controlled study available evaluated verapamil in 20 subjects, and showed hardly more than a small improvement in exercise capacity.¹¹

ACE inhibitors

As for other classes of drugs, there are good pathophysiological reasons to expect benefits from angiotensin-converting enzyme (ACE) inhibition, but little clinical evidence. Angiotensin II delays cardiomyocyte relaxation¹² and produces an upward shift of the diastolic pressure-volume relationship.¹³



Moreover, cardiac fibroblasts increase production of collagen with increasing concentrations of angiotensin II and aldosterone.¹⁴ In animal studies, increased tissue ACE gene expression has been evidenced in hypertrophied myocardial tissue,¹⁵ and, in humans with CHF, the renin-angiotensin-aldosterone system is overactivated. In a recent meta-analysis, ACE inhibitors appeared to be effective in reducing LVH in patients with arterial hypertension, and this beneficial activity seemed to be greater with this class of drugs than with other drugs evaluated in clinical trials.¹⁶ In a small unblinded study, some benefit was reported from the administration of enalapril to a group of elderly postinfarction patients with CHF and preserved ventricular systolic function.¹⁷ In another observational study among 350 patients with CHF and preserved ($\geq 40\%$) LVEF, ACE inhibition therapy was associated with a trend toward a lower risk of death and delayed time to hospital readmission, but not absolute rates of hospitalization.¹⁸

On this background of major deficiency in our knowledge of how to treat diastolic CHF, and a lack of information on treatment for CHF in the elderly in general, a trial has been undertaken, the PEP-CHF trial, aimed at assessing the potential benefit of the ACE-inhibitor perindopril in treating elderly people with CHF (over the age of 70 years), but without major LV systolic dysfunction. The choice of this drug was based on its sustained blood pressure-lowering effect (over the whole 24-hour period), the extensive experience of its use in elderly hypertensive patients, with little risk of first-dose hypotension, and its well-documented effect on cardiovascular remodeling. The PEP-CHF trial is due to report in the year 2001.¹⁹

β -Blockers

Given the remarkable reduction in mortality and morbidity recently reported in patients with CHF and systolic ventricular dysfunction treated with various β -blockers,^{20,21} this strategy has also become very attractive with regard to treatment of diastolic CHF. Few data are available, however. All the trials testing β -blockers in CHF had impaired systolic ventricular function as an entry criterion. β -Blockers improve systolic ventricular function by counteracting several mechanisms activated by chronic adrenergic hyperactivity in the failing heart (β -receptor down-regulation, alterations in signal transduction, decrease in α -myosin chains, etc), but it is still unclear what effect they have on diastolic ventricular dysfunction. In principle, β -blockade is of no use in diastolic dysfunction due to altered relaxation, since calcium reuptake from the sarcoplasmic reticulum should be favored by (normal) adrenergic activation. However, β -blockers could be useful by reducing heart rate, thus prolonging diastolic filling time and relieving myocardial ischemia when present. Prolonged use of β -blockers leads to a reduction in LV volumes in patients with a dilated left ventricle and CHF^{20,21} and regression of LVH in patients with arterial hypertension.¹⁶

In the only randomized study performed in patients over 62 years of age with CHF and LVEF $\geq 40\%$ treated with diuretics plus ACE inhibitors, propranolol appeared to decrease mortality and improve left ventricular systolic function.²²

Digitalis

The only available trial designed to include a sizeable subgroup of patients with CHF and preserved systolic function was the Digitalis

Investigators Group (DIG) trial. In this trial, 988 patients with CHF and EF $>45\%$ were enrolled. The main results of the trial were a reduction in mortality and hospitalization for CHF in patients treated with digoxin, and neutral effects on total mortality.²³ The findings in patients with CHF and systolic ventricular dysfunction were similar to those observed in the subgroup of patients with preserved systolic function. The reduction in the combined end point of mortality and hospitalization due to CHF was 18% for EF $>45\%$, and 20% for EF between 25% and 45%.²⁴ All-cause mortality in patients with EF $>45\%$ was not increased, and there were, if anything, fewer arrhythmic events attributable to digoxin than in patients with more severe LV systolic dysfunction.²⁴

Is there any reason to expect digitalis to be beneficial in patients with diastolic CHF? Massie and Abdalla recently reviewed this topic,²⁴ and did not see any mechanism whereby digitalis could improve ventricular relaxation. Some experimental data suggest that digitalis may affect the ventricular remodeling process by both hemodynamic and nonhemodynamic mechanisms. It has been recognized that digitalis glycosides can sensitize sinoaortic and cardiopulmonary baroreceptors, which are characteristically down-regulated in patients with CHF. The ultimate effect is a decrease in sympathetic nervous system activity, which is abnormally elevated in CHF.²⁵⁻²⁷ Indeed, digoxin, unlike other agents with positive inotropic effects, reduces circulating levels of norepinephrine and plasma renin activity and brings about potentially favorable changes in heart rate variability. Although most of these data have been collected in patients with systolic dysfunction, digoxin also appears to reduce sympathetic nervous system activity in patients

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with relatively preserved LV function. Patients with hypertension, and specifically those with LVH, also have impaired baroreceptor sensitivity. In these patients, responsiveness can be restored by a digitalis glycoside infusion.²⁸ In spite of this growing body of data, as Massie and Abdalla emphasize,²⁴ the limited information available on the effect of digoxin in patients with CHF and preserved LV systolic function does not warrant its routine use in this setting.

**Atrioventricular,
interventricular,
and intraventricular
resynchronization**

One of the goals of pharmacological therapy in patients with diastolic CHF is to prolong the ventricular filling time. However, in patients with a restrictive ventricular filling pattern, where most of the filling of the left ventricle occurs in early diastole, any measure that would only prolong diastolic filling would not be beneficial, and the result would be a decrease in cardiac output caused by a decrease in heart rate. Other patients in whom ventricular filling is compromised are those with a prolonged atrioventricular (AV) conduction time. An early atrial contraction shortens diastolic filling, and as LV pressure increases above left atrial pressure at mid-diastole, diastolic mitral regurgitation may occur, further reducing the preload of the left ventricle. Such AV dyssynchrony is frequently associated with the presence of wide QRS complexes and major left intraventricular conduction disturbances, making both LV systolic and diastolic function less effective.

In these patients, the first nonpharmacological therapeutic attempt was dual chamber AV pacing with short AV delay. After initial enthusi-

astic experiences, a number of studies of permanent dual chamber pacing (DDD) showed contrasting and even unfavorable results. It can now be concluded that conventional DDD pacing with a short AV delay provides variable, but on average nonsignificant, benefits in patients with chronic cardiomyopathy.²⁹ However, in patients with a 12-lead surface ECG showing a long PR interval and prolonged QRS interval (usually with electrocardiographic morphology of left bundle-branch block with left axis deviation), with a transmitral Doppler flow pattern characterized by a short LV filling time and end-diastolic mitral regurgitation, and a relevant functional (systolic) mitral regurgitation, electrical stimulation of the heart, aimed at resynchronizing the phases of the heart cycle by optimizing the sequential interaction between the heart chambers, can be beneficial. Triple chamber pacing is required to provide both optimized AV sequence and simultaneous biventricular pacing. This is aimed at resynchronizing either AV or interventricular and intraventricular mechanical activity. In some patients with a long interatrial conduction time, especially in association with recurrent and/or drug-refractory atrial tachyarrhythmias, biatrial pacing (four-chamber pacemaker) seems to achieve both better mechanical interaction between the atria and the ventricles and prevention of recurrence of atrial arrhythmias.²⁹ In patients with atrial fibrillation, radiofrequency catheter ablation may be required before implantation to ensure permanent ventricular pacing.

Controlled studies are needed to evaluate the clinical value of the new pacing techniques, the optimal pacing configuration, and to define the selection criteria of the patients. However, at present, multisite pacing appears capable of providing

remarkable and sustained (at least for some months) hemodynamic improvement in selected patients with both systolic and diastolic ventricular dysfunction and advanced CHF.

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Diastolic Dysfunction

Summaries of Ten Seminal Papers

①

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B. Pinamonti and others. *J Am Coll Cardiol.* 1993

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Highlights of the years by Dr P.B. Garlick
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The natural history of isolated left ventricular diastolic dysfunction

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Am J Med. 1992;92:627-630

Isolated left ventricular (LV) diastolic dysfunction was defined in this paper by the following criteria: (i) an elevated LV end-diastolic pressure with normal LV end-diastolic and end-systolic volumes; (ii) a normal LV ejection fraction; and (iii) no coronary artery or valvular disease. Importantly, no Doppler echo criteria for an impaired LV filling rate were part of the inclusion criteria, nor was any measure of LV passive stiffness made; however, an elevated end-diastolic pressure with a normal end-diastolic volume implies an increase in passive stiffness, at least at the end-diastolic volume point. When these criteria were applied to 3100 patients undergoing combined right and left heart catheterization, over a 10-year period, only 97 fit this diagnosis of isolated LV diastolic dysfunction. Fifty-one of these patients were subsequently followed for an average of 68 months.

The results indicate that isolated LV diastolic dysfunction, characterized solely by an increase in LV end-diastolic pressure, is associated with a low cardiac mortality risk. Over an average follow-up period of 5.8 years, only 2 patients were lost to follow-up. Although 7 patients died, the cause of death was cardiovascular in only 1, and 1 was of unknown etiology. If the unknown etiology and 2 patients lost to follow-up are presumed to have died of cardiovascular causes, the incidence of cardiac death among these patients was, at most, 7.6%, yielding an annual mortality of only 1.3%. During the same period, there was a 6.9% annual incidence of the onset of symptoms of congestive heart failure (CHF), a 3% annual incidence of hospitalization with new or recurrent CHF, and a 4.2% annual incidence of hospitalization for recurrent chest pain. Thus, isolated LV diastolic dysfunction is not associated with substantial mortality, but with an increased cardiovascular morbidity in terms of CHF and chest pain.

The patient selection criteria were unusual. Only 3% of patients undergoing cardiac catheterization fit the inclusion criteria. Most studies report an approximately 30% or greater prevalence of primary diastolic dysfunction

and a higher prevalence of diastolic dysfunction combined with systolic dysfunction.

The patient cohort selected for this study probably represents the mildest form of the diastolic dysfunction syndrome. At entry, only 8% of patients had a history of CHF symptoms and only 16% had evidence of LV hypertrophy. A patient cohort with a higher incidence of CHF and LV hypertrophy—features that are present in many patients with isolated LV diastolic dysfunction—would probably have a worse prognosis than the cohort reported in this article.

1992

32-year-old Linford Christie becomes
the oldest winner of the 100 meters title
at the Barcelona Olympics;
Mohamed Boudiaf, President of Algeria,
is assassinated;
and US film director Hal Roach dies, aged 100



Evaluation of left ventricular diastolic function from the pattern of left ventricular filling

W.C. Little, J.G. Warner Jr, K.M. Rankin, D.W. Kitzman, C.P. Cheng

Clin Cardiol. 1998;21:5-9

Reviewed in this article are the left ventricular (LV) Doppler echocardiographic filling patterns and underlying physiologic mechanisms in normal hearts and those with diastolic dysfunction. Doppler echocardiography measures the transmitral flow velocity (which reflects the transmitral pressure gradient, ie, the driving force for LV filling), but does not directly measure LV filling volume. Nonetheless, abnormal diastolic function can be inferred from the Doppler filling pattern.

Normally, most LV filling occurs rapidly and early in diastole. A rapid fall in LV pressure, due to myocardial relaxation and elastic recoil of the compressed and twisted LV, reduces LV pressure to less than left atrial (LA) pressure. This produces a transmitral pressure gradient and results in rapid early diastolic filling (Doppler E wave). The rate and extent of myocardial relaxation and the LA pressure level are the two major factors that determine the pressure gradient and LV filling rate. Normally, more than two thirds of the stroke volume enters the LV during early diastole. The time required for deceleration of early diastolic flow is predominantly determined by LV chamber stiffness—the stiffer the LV, the more rapid the LV pressure rise during filling, with consequent elimination of the transmitral pressure gradient, shortening the deceleration time, and production of a narrower E wave.

Atrial contraction augments late diastolic filling. Since most LV filling occurs early in diastole, normally, this atrial contribution is unnecessary; however if early diastolic filling is impaired it is more important. The relative contribution of early (E wave) and late (atrial or A wave) filling is expressed as the E/A ratio, and is normally >1.

LV diastolic dysfunction is classified into three filling patterns of progressively worse dysfunction: impaired relaxation, "pseudonormalization," and "restricted." In the mildest form, impaired relaxation, the peak rate and amount of early filling are reduced, and the relative

importance of atrial filling is increased, resulting in a "reversed" E/A ratio; the A wave is taller than the E wave and the LV deceleration time is usually prolonged (broad E wave).

The "pseudonormalized" pattern, indicating moderate diastolic dysfunction, is due to an increase in LA pressure, which compensates for the slowed LV relaxation and restores the normal early diastolic transmitral pressure gradient. Therefore, the E wave is larger than the A wave, but the time for E wave deceleration is shortened, reflecting a greater severity of LV stiffness, and producing a narrower E wave.

The "restricted" filling pattern indicates severe diastolic dysfunction. Due to a marked increase in LA pressure and LV stiffness, the E wave is much larger than the A wave, with a very short E wave deceleration time, resulting in a tall narrow E wave.

A pulmonary venous flow pattern with increased retrograde flow from the LA into the pulmonary veins during atrial systole (AR wave) indicates increased LV end-diastolic stiffness.

1998

Microsoft's Bill Gates is hit by a flying custard pie
on a trip to Belgium;
Israeli transsexual Dana International wins
the Eurovision Song Contest;
and Japanese film director Akira Kurosawa dies,
aged 88

Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure

R.S. Vasan, E.J. Benjamin, D. Levy

Arch Intern Med. 1996;156:146-157

This article reviews the diagnosis and treatment of congestive heart failure (CHF), emphasizing the importance of diastolic heart failure or diastolic dysfunction. "Diastolic heart failure" is defined as patients with elevated left ventricular (LV) and left atrial (LA) filling pressures in the presence of normal systolic function. This definition is similar to "primary diastolic dysfunction" used by other authors and excludes the diastolic dysfunction that results from systolic dysfunction and chronic increases in LV volume. Echocardiography is appropriately given a central role in the algorithm for assessing the patient with signs and symptoms of heart failure. The authors look at the problems of an incorrect diagnosis, assessment of reversible systolic function, and the potential roles of the right ventricle, ventricular interaction and pericardial restraint in impairing LV filling; they also consider other conditions that elevate LA pressure without intrinsic LV disease, such as mitral stenosis and LV volume overload lesions.

Transient or sustained acute ischemia can cause profound alterations in LV diastolic dysfunction, resulting in severe CHF symptoms in patients who have otherwise well-preserved LV systolic function. Chronic ischemic heart disease can cause diastolic dysfunction because of ventricular remodeling and myocardial fibrosis and scarring. Therefore, coronary artery disease (CAD) must be considered in patients with CHF and normal ventricular systolic function. Ischemia-induced LV diastolic dysfunction with concomitant CHF signs and symptoms may be confused with angina or the "angina equivalent" syndrome. Therefore, exercise stress testing is recommended in the workup of patients with CHF symptoms, particularly if systolic function is normal.

Other common causes of LV diastolic dysfunction include systemic hypertension, especially in the presence of LVH, valvular and subvalvular LV outflow tract obstruction, and hypertrophic cardiomyopathy. Ventricular diastolic function declines with age because of an increase in ventricular stiffness. Elderly patients with subclinical diastolic

dysfunction are predisposed to develop overt CHF, often with normal systolic function, in the setting of ischemia, sustained tachycardia, atrial fibrillation, anemia, elevated blood pressure, or volume overload. Moderate-to-severe obesity has also been associated with CHF and abnormalities of LV filling.

Because no clinical feature or physical examination finding reliably distinguishes patients with CHF with intact LV systolic function from those with systolic dysfunction, the authors recommend routine assessment of LV ejection fraction by echocardiography when CHF is suspected. The transmitral flow patterns of "impaired relaxation," "pseudonormalization," and "restrictive" indicate progressive impairment of LV diastolic function. The pulmonary venous flow pattern also provides important information. All LV filling indices, whether assessed by echocardiography or radionuclide imaging, are indirect measures of diastolic function because they are age-dependent, sensitive to changes in posture, sympathetic tone, heart rate, PR interval, loading conditions, and the position of a sample volume on echo. Thus, ventricular filling pattern indices can change without any true change in LV diastolic properties.

Astonishingly, no randomized controlled clinical trials have targeted patients with diastolic heart failure despite its high prevalence, especially among older patients. The current therapeutic approach, reviewed in this article, is therefore empirical. Randomized controlled clinical trials are therefore needed to evaluate the efficacy of the various agents proposed.

1996

The election of Emil Constantinescu ends
communist rule in Romania;
18-year-old David Dicks becomes the youngest
nonstop circumnavigator of the world;
and pop superstar Michael Jackson weds
for the second time



Relaxation-systolic pressure relation. A load-independent assessment of left ventricular contractility

T.C. Gillebert, A.F. Leite-Moreira, S.G. De Hert

Circulation. 1997;95:745-752

Gillebert et al set out here to review the influence of loading conditions on the decrease in left ventricular pressure (LVP) during late systole and early diastole. The relationship between the height of LV systolic pressure and the rate of fall of pressure is called "contraction-relaxation coupling." This load regulation of LVP fall has to be distinguished from neurohumoral regulation, from effects induced by arterial reflected waves, and from long-term load effects on contractility.

The first step in this analysis is a consideration of the acute load effects of LVP fall. This is assessed by brief variations of afterload to avoid neurohumoral effects and is accomplished by transient partial or complete cross-clamping of the ascending aorta in experimental models. Moderate LVP elevation (5 - 20 mm Hg) had a highly variable effect on tau (τ , time constant of pressure decay). With experimental or clinical congestive heart failure, τ has an increased load-dependence.

The underlying explanation of how load and contractility interact in regulating the load-dependence of LVP fall (τ) depends on the concept of "relative load." Relative load is defined as the ratio of baseline systolic LVP in an ejecting state to isovolumetric LVP in the cross-clamped state, and is expressed as a percentage. A low relative load (<70%) is associated with normal systolic function, whereas a high relative load (>80%) is indicative of overt cardiac dysfunction. The concept of relative load is useful in explaining why the normal heart responds to a moderate elevation of systolic LVP with a delayed onset and faster rate of LVP fall, whereas a similar intervention in the failing heart induces premature onset and slowing of LVP fall.

Relative load also proves to be a useful concept in understanding and treating the diastolic dysfunction that is induced or facilitated by excessive load. In the setting of heart failure, both the slower LV pressure fall and impaired diastolic filling might be attributed, at least partly, to impaired contractility and excessive systolic load,

rather than to primary alterations of diastolic function. This idea introduces the concept of "afterload" reserve. Afterload reserve is the capacity of the ventricle to respond to afterload elevation with a limited increase in systolic volume and no slowing of LVP fall. The failing ventricle with limited or absent afterload reserve demonstrates a markedly slow relaxation in contrast to the normal ventricle.

This concept is further expanded by suggesting that clinical assessment of contraction-relaxation coupling and relative load might provide valuable information on contractile function. This relationship can be defined in patients simply with a high-fidelity LV pressure catheter and does not require measurements of LV dimension or volume. The response to loading conditions can be obtained by administration of nitroprusside, caval occlusion, phenylephrine infusion, partial aortic occlusion, or passive elevation of the legs.

This review article elegantly summarizes a very complex area of cardiac function: contraction-relaxation coupling in the intact ventricle and in isolated muscle.

1997

Tinky-Winky, Dispsy, Laa-laa,
and Po make their television debut;
Woody Allen weds Soon-Yi Previn in Venice;
and "Dolly," the cloned sheep,
is created in Edinburgh

Diastolic dysfunction in congestive heart failure

W. Grossman

N Engl J Med. 1991;325:1557-1564

Grossman, in his comprehensive review of diastolic dysfunction, summarizes the pathophysiological features of this syndrome. Diastolic heart failure (diastolic dysfunction) is defined as an increased resistance to filling of one or both cardiac ventricles. This broad definition includes mitral or tricuspid stenosis, constrictive pericarditis, restrictive cardiomyopathies, ischemic heart disease, hypertrophic heart disease, volume-overload lesions, and dilated cardiomyopathy. The resistance to ventricular filling may result from structural abnormalities (valve stenosis, pericardial fibrosis, myocardial hypertrophy and fibrosis, myocardial infiltration with amyloid or iron deposition), or impaired myocardial (myocyte) relaxation. These factors are not mutually exclusive. Myocardial hypertrophy can increase passive diastolic stiffness due to increased muscle mass and collagen content, but hypertrophied myocardium also exhibits impaired myocardial relaxation, especially in the presence of ischemia.

The important distinction is made between "heart failure" and "congestive heart failure," although these terms are often interchangeable. The congestive manifestations of heart failure, such as pulmonary or peripheral edema, distended neck veins, and dyspnea, usually indicate elevated right or left ventricular filling pressure and result from diastolic dysfunction with or without concomitant systolic dysfunction. Approximately 40% of patients with congestive heart failure have normal systolic function and thus have primary diastolic heart failure or diastolic dysfunction.

Diastolic dysfunction is common in the presence of global ventricular hypertrophy, resulting from pressure or volume overload, and with the regional hypertrophy that occurs during ventricular remodeling after myocardial infarction. Myocardium hypertrophied secondary to pressure overload exhibits an increased susceptibility to ischemia-induced diastolic dysfunction. Patients with hypertrophic cardiomyopathy may have striking diastolic dysfunction.

The process of myocardial relaxation is controlled by energy-dependent cellular mechanisms (sarcolemmal and

sarcolemmal calcium pumps) that restore cytosolic calcium to its normal low concentration during diastole. The decreased ATP availability during ischemia impairs calcium removal and may contribute importantly to impaired relaxation. Hypertrophied left ventricular (LV) myocardium results in a marked increase in the message for angiotensin-converting enzyme (ACE); the increased synthesis of angiotensin II appears to be related to its increased diastolic dysfunction. Abnormalities of cell calcium regulation and a deficient production of cyclic AMP may also contribute to diastolic dysfunction. The cellular mechanisms that result in ischemic diastolic dysfunction depend in part on whether "supply" or "demand" ischemia is present.

Clinically, diastolic dysfunction plays a contributory role in most patients with congestive heart failure, and a dominant role in some. Diastolic dysfunction may be due to structural or mechanical factors, but an increasing body of evidence indicates that biochemical alterations in the myocyte can be of great importance. The immediate metabolic consequences of ischemia or hypoxia, such as an increase in diastolic intracellular calcium concentrations or a decrease in ATP levels, may cause acute diastolic dysfunction, whereas altered gene expression of critical ion pumps, or regulatory or contractile proteins may make a more chronic contribution to diastolic dysfunction. The discovery that the ACE level is increased in hypertrophied myocardium and is associated with marked diastolic dysfunction raises the possibility that ACE inhibitors may be clinically useful in this syndrome.

1991

Michael Stich and Steffi Graf produce
a German "double" at Wimbledon;
the "Birmingham Six" are freed after 16 years
of wrongful imprisonment;
and US jazz musician Miles Davis dies, aged 65



How to diagnose diastolic heart failure

European Study Group on Diastolic Heart Failure

Eur Heart J. 1998;19:990-1003

This report of the European Study Group on Diastolic Heart Failure proposes guidelines for the diagnosis of diastolic heart failure using well-defined cutoff values of indices of left ventricular (LV) function obtainable during cardiac catheterization or during noninvasive cardiac imaging, and summarizes existing evidence of abnormal LV relaxation, filling, and diastolic distensibility and stiffness in different cardiac diseases frequently characterized by diastolic heart failure. The report deals exclusively with primary diastolic dysfunction and does not include diastolic LV dysfunction in the presence of systolic cardiac failure. An update and outline of exact diagnostic criteria is warranted because of the increasing number of patients presenting with diastolic heart failure and because different treatment modalities are currently being tested in large randomized trials.

A diagnosis of primary diastolic dysfunction requires three conditions to be simultaneously satisfied: (i) presence of signs or symptoms of congestive heart failure; (ii) presence of normal or only mildly abnormal LV systolic function; (iii) evidence of abnormal LV relaxation, abnormal LV filling, diastolic distensibility, or diastolic stiffness. A normal or mildly decreased systolic function was defined as an LV ejection fraction of at least 45%. The paper then defines all the parameters of abnormal LV relaxation, filling, and diastolic distensibility and stiffness with invasive methods, echocardiography, nuclear medicine, and even such questionable methods as the apex cardiogram. Referring to all available evidence, normal values are defined for parameters of LV relaxation (peak negative LV dP/dt , isovolumic relaxation time [IVRT], the time constant of LV pressure decay τ), and for parameters of slow early LV filling (early peak LV filling rate [PFR], early Doppler flow velocity [E wave], the ratio of E-wave to early A wave [Doppler flow velocity E/A ratio], deceleration time of E velocity [DT], and the ratio of pulmonary vein systolic and diastolic flow velocities [S/D ratio]). One difficulty of assessing LV diastolic dysfunction is the load dependence of many of the parameters, particularly the indices derived from Doppler-echocardiographic measurements. This aspect is discussed in detail, and the contribution of changes in

left atrial function and filling on the alterations of LV filling dynamics, progressing from normal to slow relaxation, to pseudonormalization, and to restriction are outlined. This discussion is an expression of the difficulties in assessing or quantifying diastolic dysfunction by noninvasive methods. It highlights the fact that both a combination of multiple abnormal parameters and the clinical presentation together are necessary to diagnose diastolic dysfunction. The report does not qualify the different parameters, nor does it specifically identify the most robust, ie, the least load-dependent factors. It hints that the time constant of pressure decay τ is the most reliable invasive measurement. As for reliable echocardiographic parameters, there is now newer evidence available that suggests that an abnormal S/D ratio of pulmonary vein flow velocity is the least load-dependent parameter.

At the European Society of Cardiology Meeting in 1999 in Barcelona, Yusuf, and others, argued that so far no evidence was available that diastolic dysfunction existed, or that it had any clinical relevance. The value of this thorough report of the European Study Group on Diastolic Heart Failure summarizing all the evidence of diastolic heart failure and unifying the measurements and definitions of diastolic dysfunction therefore cannot be overestimated. In particular, the final chapter describing the evidence of diastolic dysfunction in coronary artery disease, hypertrophic cardiomyopathy, cardiac amyloidosis, hypertensive heart disease, diabetes, and cardiac transplantation clearly emphasizes the considerable morbidity that is associated with diastolic heart failure.

1998

John Paul II becomes the first Pope to visit Cuba;
Brazilian striker Ronaldo is voted Footballer
of the Year for the second time in succession;
and the low budget "The Full Monty" is screened
to become an instant success

Diastolic failure: pathophysiology and therapeutic implications

D.L. Brutsaert, S.U. Sys, T.C. Gillebert

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J Am Coll Cardiol. 1993;22:318-325

D iastole and diastolic failure are defined, in this classic review, from a physiologic point of view, and a description is given of the pathophysiology of pressure- or volume-overloaded hearts. It introduces the concept of a physiologic, compensatory prolonged contraction and of a pathophysiological, impaired (incomplete or slowed) relaxation. It then describes the pathophysiological transition from compensated prolonged compensation to diastolic and combined systolic and diastolic failure. Finally, therapeutic approaches to diastolic failure during the different phases of the disease are discussed.

From the viewpoint of cardiac muscle physiology, of which these authors are the very experts, systole consists of one cycle of contraction-relaxation. The decrease in left ventricular (LV) pressure and the increase in ventricular volume during early rapid filling are part and parcel of this cycle and therefore are considered part of systole. According to Brutsaert et al, the term diastole should be restricted to the phase during the cardiac cycle that separates two such consecutive contraction-relaxation transients, that is, to the diastasis and atrial contraction phase. Accordingly, diastolic failure is defined as a condition resulting from an increased resistance to filling of one or both ventricles, leading to symptoms of congestion due to an inappropriate upward shift of the diastolic pressure-volume relation.

The problem with this puristic, physiologic approach to diastolic failure is its limited clinical applicability. Assessing diastolic failure only by pressure-volume analysis would require invasive examination of all patients. Even the authors of this review, as members of the European Study Group on Diastolic Heart Failure, acknowledged in their report that, because LV relaxation and filling affect LV diastolic distensibility, diagnostic evidence for diastolic heart failure can also be obtained from analysis of LV relaxation and filling. Nevertheless, the authors of this review put forward an important concept for diagnostic and therapeutic considerations of diastolic failure. A prolonged systolic contraction (or a delayed or retarded relaxation) should be distinguished from an impaired systolic relax-

ation. An upward shift of the pressure-volume relation during true diastole is not observed in conditions of compensatory prolonged contraction, except during tachycardia. Hence, this condition is regarded as a compensatory mechanism to pressure or volume overload. By contrast, impaired systolic relaxation extends into true diastole and results in an upward shift of the pressure-volume relation. Accordingly, impaired systolic relaxation is considered deleterious and is observed in ischemia and the advanced phase of hypertrophy. The causes for this decompensation may result from: (i) impaired activation-inactivation (eg, calcium homeostasis); (ii) excessive changes in load; or (iii) inappropriate nonuniformities of load and activation-inactivation in time and space. Impaired systolic relaxation may further advance to additional systolic failure. The heart then loses its ability to prolong systolic contraction, systolic contraction is instead decreased, and the onset of relaxation is induced prematurely, which further complicates the already existing clinical picture of diastolic failure.

This review therefore describes the mechanical transition from compensatory prolonged systolic contraction, to impaired systolic relaxation, to diastolic, and eventually systolic, failure, as observed in disease states such as pressure-overload or volume-overload hypertrophy. It suggests that compensatory systolic prolongation precedes impaired relaxation. Impaired relaxation, of course, is the first pathological event usually recognized in diastolic failure.

The last part of the review deals with the therapeutic approaches to diastolic failure. It emphasizes the need for a good understanding of the pathophysiological mechanisms to introduce effective therapy.

1993

"Farewell my Concubine" wins the Palme d'Or
at the Cannes Film Festival;
King Kong celebrates his 60th birthday;
and football legend Bobby Moore dies, aged 51



Left ventricular hypertrophy and impaired diastolic filling in essential hypertension. Diastolic mechanisms for systolic dysfunction during exercise

A. Cuocolo, F.L. Sax, J.E. Brush, B.J. Maron, S.L. Bacharach, R.O. Bonow

Circulation. 1990;81:978-986

In many patients with essential hypertension, in the absence of coronary artery disease, left ventricular (LV) systolic function is normal at rest, but may respond abnormally during exercise. This paper tested the hypothesis that impaired LV filling might be partly responsible for the reduced systolic functional reserve of patients with hypertension during exercise.

The study population consisted of 41 subjects with mild or moderate hypertension and no coronary artery disease. Patients underwent supine bicycle exercise and radionuclide angiography at rest and during maximal exercise. In addition, echocardiographic studies were performed for assessment of wall thickness and LV muscle mass. Patients were divided into group 1, with an increase in ejection fraction of 5% or more during exercise, or into group 2, in which ejection fraction increased less than 5% or decreased with exercise. Group 1 had a normal LV filling at rest. In contrast, group 2 had an impaired LV diastolic filling, as evidenced by a reduced peak filling rate and a prolonged time to peak filling. However, the observation of impaired diastolic filling at rest in patients with a diminished exercise ejection fraction response was not dependent on this arbitrarily chosen threshold value; a continuum was observed between the ejection fraction response to exercise and resting measures of diastolic filling. For the entire study population a correlation existed between the magnitude of change of ejection fraction during exercise and both peak filling rate and time to peak filling rate. Furthermore, there was a significant linear relation between LV mass index and both peak filling rate and time to peak filling rate.

Therefore, the hypothesis that impaired diastolic filling could cause diminished ejection reserve during exercise in patients with hypertension was confirmed. In patients with decreased ejection fraction reserve during exercise, systolic wall stress at rest was normal, and in fact, lower than in the patients in whom ejection fraction increased. Thus, an inappropriately increased afterload was not the cause of the decreased systolic reserve in these patients. Patients with decreased ejection reserve during exercise showed no signs of beginning decompensation.

The cause for the diastolic dysfunction most likely was the more extensive LV hypertrophy in these patients. The mechanisms for diastolic dysfunction in LV hypertrophy could include both abnormalities in calcium homeostasis and increased muscle stiffness secondary to increased interstitial fibrosis. Exercise-induced tachycardia amplifies these abnormalities and results in incomplete ventricular filling. However, changes in calcium homeostasis are less likely to play a major role because catecholamines are increased with exercise, and thus calcium handling proteins are phosphorylated to a greater extent; in addition, excitation-contraction is more homogeneous during exercise. In this regard, a study of patients with hypertrophic cardiomyopathy by Udelson JE et al (*Circulation.* 1990;82:1174-1182) showed that isoproterenol increased heart rate and LV pressure and improved relaxation despite a concomitant induction of ischemia. Since coronary flow reserve is decreased in patients with hypertension, subendocardial ischemia could contribute to diastolic dysfunction in these patients with reduced ejection fraction reserve during exercise. However, when all patients that had symptoms of exertional chest pain were excluded, results were comparable to those of the entire group. Similarly, age and gender did not seem to affect the results.

This study strongly supports the concept that exercise-induced systolic dysfunction in hypertensive patients with LV hypertrophy arises predominantly from diastolic mechanisms. A similar mechanism is likely the cause for exercise-induced decrease of ejection fraction in patients with LV hypertrophy secondary to other etiologies.

1990

Rupert Bear celebrates his 70th birthday;
Oliver Stone wins the Best Director Oscar
for "Born on the 4th July";
and US Hollywood star Ava Gardner dies, aged 69

Nonuniform course of left ventricular pressure fall and its regulation by load and contractile state

A.F. Leite-Moreira, T.C. Gillebert

Circulation. 1994;90:2481-2491

This article reports the results of experiments examining the effect of changes in load on the course of left ventricular (LV) pressure fall. The nonuniform course of pressure fall relates to the fact that LV pressure falls during three phases of the contraction-relaxation cycle. The first initial fall occurs during the ejection phase while the aortic valve is still open and the LV volume decreases rapidly. The second phase resembles the closest to an isovolumetric relaxation from the closure of the aortic valve to the opening of the mitral valve, and the time course of pressure decay is close to monoexponential. In the third phase, the fall in pressure is accompanied by an increase in LV volume after mitral valve opening.

These three phases of pressure decay are affected differently by changes in load. For example, maximal negative dP/dt becomes more negative with increasing LV systolic pressure, indicative of faster initial fall in LV pressure, but the time constant of relaxation τ increases, reflecting a slower course of subsequent LV pressure fall.

Since relaxation, like contraction, is dependent on a complex interplay between preload, afterload, and contractility, testing of the influence of load alone on pressure decay is difficult—but this paper set out to do just that. To avoid an influence of contractility or preload, load changes were induced by acutely closing the aorta by a balloon in an open-chest canine experimental model, and the beat-to-beat changes were analyzed.

In a first series of experiments, the aorta was totally occluded at three different time points. Early occlusion, ie, before aortic valve opening, resulted in isovolumetric nonejecting beats. Mid-ejection occlusions were performed at 55% to 60% of LV ejection duration. Late occlusions were performed between 88% and 92% of LV ejection duration. Early occlusion resulted in an increased extent and slower course of pressure fall, with a decrease in maximal negative dP/dt and an increase in the time constant of LV pressure decay, τ . In mid-occlusions, the maximal negative dP/dt change was variable, but τ increased. Late occlusion

led to an accelerated pressure fall with an increase in maximal negative dP/dt and a decrease in τ . Of note, terminal LV pressure fall remained unaffected by all these interventions.

In a second protocol, the effects of a graded early occlusion ranging from 2 mm Hg to peak isovolumetric LV pressure were examined. Interestingly, at matched 12 mm Hg elevations of LV pressure relaxation as a mean did not change, but in an individual animal such a change resulted in a reproducible acceleration or deceleration of pressure fall. The changes in τ were moderately correlated with commonly used indexes of contractility (peak + dP/dt , $r=-0.78$; regional fractional shortening, $r=-0.63$), suggesting that load-induced changes in relaxation are dependent on the contractile state. Furthermore, the afterload level might influence the course of the pressure fall. Indeed, changes in τ were closely correlated with the systolic LV pressure of the test beat, expressed as a percentage of peak isovolumetric LV pressure obtained with total aortic occlusion. An afterload increase up to 82.5% of peak isovolumetric pressure accelerated, and an increase beyond this load level decelerated, pressure fall. The cutoff remained at that level when in an individual heart the contractile state was changed by IV calcium chloride or β -blockers.

This paper showed very conclusively that the relaxation response to afterload of the intact left ventricle was identical to that of a load-dependent isolated cardiac muscle. It further emphasized the influence of the working conditions (ie, proximity to maximal isovolumetric pressure) and contractile state for the response to load changes in an individual heart.

1994

Nelson Mandela is elected as the first black
President of South Africa;
the Nobel Prize for literature is won
by Japan's Kenzaburo Oe;
and 27-year-old rock star Kurt Cobain commits suicide



Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. Heart Muscle Disease Study Group

B. Pinamonti, A. Di Lenarda, G. Sinagra, F. Camerini

J Am Coll Cardiol. 1993;22:808-815

In systolic heart failure, symptoms of pulmonary congestion and dyspnea on exertion are signs of concomitant diastolic failure. In fact, delayed left ventricular (LV) pressure decay affecting the diastolic pressure-volume relationship is often the first manifestation of impaired systolic function. In the eighties, Hatle, Appleton, and Popp were the first to systematically evaluate the use of Doppler-echocardiography flow patterns for the assessment of diastolic dysfunction. Mitral valve inflow patterns were found to be reproducible Doppler echocardiographic indices of diastolic failure. A slowed LV pressure decay reduced the E wave-to-A wave flow velocity ratio and prolonged the deceleration time of the E wave velocity at normal filling pressure. However, that group also found a wide variation of flow patterns with progressive diastolic failure: a pseudonormalization of the pathological mitral inflow and an eventual restrictive pattern with an increased E/A ratio and a shortened deceleration time of the E wave velocity. The restrictive pattern was observed in more symptomatic patients with increased filling pressures.

The objectives of the study by Pinamonti et al were to evaluate the frequency of the restrictive filling pattern in dilated cardiomyopathy, its clinical and hemodynamic correlations, and the prognostic implications. Clinical evaluation, invasive hemodynamic studies, and Doppler-echocardiographic studies were conducted in 79 consecutive patients with dilated cardiomyopathy. Patients with dilated cardiomyopathy were separated into two groups on the basis of Doppler echocardiographic mitral inflow pattern: group 1 with restrictive filling pattern had an E deceleration time <115 ms, group 2 had an E deceleration time of >115 ms. The cutoff point of 115 ms was arbitrarily chosen to correspond to the mean value \pm SD from normal control subjects (177 ± 31 ms).

Of the patients with dilated cardiomyopathy, 46% showed a restrictive pattern of mitral inflow. These patients were significantly younger, were more symptomatic, and had more dilated and more severely dysfunctional left and right ventricles, a larger atrium, and higher left- and right-sided filling pressures. The Doppler mitral inflow pattern in this

group showed a higher E wave peak velocity, lower A wave peak velocity, and a higher E/A ratio. At multivariate analysis, a restrictive filling pattern, ie, the shortened E deceleration time, was the most powerful independent prognostic indicator of poor outcome. In this series, all 14 patients who died or underwent heart transplantation had a restrictive LV filling pattern with an extremely short E wave deceleration time (<80 ms). The authors concluded that a restrictive filling pattern is frequent in dilated cardiomyopathy and is associated with more severe disease and poor outcome.

The progression from impaired relaxation to pseudonormalization to restrictive pattern is not confined to dilated cardiomyopathy. In fact, amyloidosis is the classic example where after an initial abnormal filling pattern, indicative of relaxation abnormalities, disease progression results in an increase in LV filling pressures. Increased filling pressures in turn increase the transmitral pressure gradient, resulting in an increased E wave and a short deceleration time as a consequence of a quick equalization of pressures in the left atrium and left ventricle.

The load dependence of the mitral inflow patterns is responsible for the limitations of the Doppler-echocardiographic flow patterns in evaluating diastolic dysfunction. After the publication of this important paper, several other methods and parameters were evaluated. It seems that the flow pattern in the pulmonary veins is less sensitive to load changes and therefore should be used preferentially over mitral flow patterns to assess diastolic dysfunction in heart failure. Furthermore, color-Doppler assessment of mitral-to-apical flow propagation now allows the assessment of the slowed flow propagation that is characteristic of poor LV systolic function.

1993

Cuba celebrates the 40th anniversary
of its revolution;
the 51-day siege in Waco, Texas, ends in an inferno;
and US actress Lillian Gish dies, aged 90

Diastolic Dysfunction

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