STATE-OF-THE-ART PAPER

Unlocking the Mysteries of Diastolic Function

Deciphering the Rosetta Stone 10 Years Later

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It has now been a quarter of a century since the first description by Kitabatake and his associates of the use of echo-Doppler to characterize the transmitral flow velocity curves in various disease states. A decade ago we described the role of echocardiography in the "Evaluation of Diastolic Filling of Left Ventricle in Health and Disease: Doppler Echocardiography Is the Clinician's Rosetta Stone." Over the ensuing decade, advances in echo-Doppler have helped to further decipher the morphologic and physiological expression of cardiovascular disease and unlock additional mysteries of diastology. The purpose of this review is to highlight the developments in echo-Doppler and refinements in our knowledge that have occurred over the past decade that enhance our understanding of diastology.   (J Am Coll Cardiol 2008;51:679–89) © 2008 by the American College of Cardiology Foundation

Echo-Doppler with its high spatial and unequaled temporal resolution has revolutionized our clinical access to cardiac physiology and pathophysiology. It has now been a quarter of a century since the first description by Kitabatake et al. (1) of the use of echo-Doppler to characterize the transmitral flow velocity curves in various disease states. A decade ago we described the role of echocardiography in the "Evaluation of Diastolic Filling of Left Ventricle in Health and Disease: Doppler Echocardiography Is the Clinician's Rosetta Stone" (2), the Rosetta Stone here being used as a metaphor to refer to anything that is a critical key to a process of decryption or translation of a difficult problem. The term "diastology" continues to refer to the science and art of characterizing left ventricular (LV) relaxation, filling dynamics, and their integration into clinical practice. The physiology of diastole remains valid as discussed a decade ago (2). However, over the ensuing decade, advances in echo-Doppler have helped to further decipher the morphologic and physiological expression of cardiovascular disease and unlock additional mysteries of diastology. The purpose of this review is to highlight the developments in echo-Doppler and refinements in our knowledge that have occurred over the past decade that enhance our understanding of diastology. Developments include:

1. Epidemiologic studies highlighting the prevalence and prognosis of those with diastolic dysfunction with and without clinical symptoms
2. The concept of "continuity disease" and "clustering"
3. Noninvasive measures of the acuity and chronicity of LV filling pressure elevation
4. Concepts of blood flow propagation within the LV
5. Stress testing, diastolic function response
6. The integration of echo-Doppler measures of diastolic function into a therapeutic treatment paradigm
7. Better understanding of the relationship of myocardial form with function and the ability to characterize measures of myocardial mechanics

Epidemiology

Over the past decade, there has been a steady rise in the prevalence of heart failure in those with a preserved LV ejection fraction (diastolic heart failure) (3). By the seventh decade of life, the incident cases of heart failure with a preserved LV ejection fraction approach, and by the eighth decade of life exceed, those of heart failure with reduced LV ejection fraction (4). The survival of patients with the clinical syndrome of heart failure is similar in those with persevered versus those with a reduced LV ejection fraction (5). The understanding of diastology has become even more germane to the practice of medicine as our understanding evolves of the profound adverse clinical consequences of clinically overt diastolic dysfunction and that the prevalence of asymptomatic diastolic dysfunction in the general community is not insignificant, a finding being noted in approx-

imately 25% to 30% of individuals ≥45 years of age (6,7). Note, diastolic dysfunction and diastolic heart failure are not interchangeable terms. Diastolic heart failure is used to describe clinically symptomatic individuals with the characteristic syndrome of heart failure in the setting of a normal ejection fraction, whereas diastolic dysfunction simply denotes an abnormality of diastolic function and does not characterize the clinical status of an individual.

"Continuity Disease"

The cardiovascular system is a continuous system of reservoir, pump, and vessels. An ailment in one part of the system will influence all contiguous components. An increase in vascular and ventricular stiffness is an integral component of aging (8–12). Vascular and ventricular stiffness appear to be a precipitant to impaired cardiac performance and clinical prognosis. Vascular stiffness histologically is associated with changes in vessel wall architecture and perivascular fibrosis (13). A change in the extracellular matrix of the myocardium, with the formation of excess collagen tissue and serologic evidence of an active fibrotic process, is a characteristic finding in those with diastolic dysfunction (14,15). At the cellular level, there is reduced phosphorylation of sarcomeric proteins (16) and at the proteomic level, an isoform change in important structural proteins such as titin, which functions to connect sarcomeres at their ends (Z-discs) and participates in cell signaling (15,17,18). The change in cardiovascular elastance is a marker for increased cardiac morbidity, and not surprisingly, it appears to be most prevalent in that segment of the community most likely to develop the clinical syndrome of heart failure independent of the underlying LV ejection fraction (11).

Effective arterial elastance (Ea) can be estimated as the ratio of end-systolic pressure/stroke volume (19). End-systolic pressure is estimated as $(0.9 \times$ systolic blood pressure) and stroke volume the product of the left ventricular outflow tract (LVOT) area and LVOT time velocity integral. During diastole, when the mitral valve is open, the left atrium (LA) is exposed to the loading pressure within the LV. Over time, exposure of the LA to increased filling pressure will result in its remodeling reflected in the measure of LA volume. A simple yet robust marker for the chronicity of change in Ea appears to be the LA size. In clinical practice, LA size expressed as volume indexed to body surface area is recommended (20,21). The biplane area-length or Simpson's methods are a practical means with which to measure LA volume (Fig. 1).

The LA volume can be viewed as a morphologic expression of LV diastolic dysfunction. Left atrial volume is regarded as a "barometer" of the chronicity of diastolic dysfunction and to analogize, LA volume is to diastolic function and to all forms of heart disease as the HbA_{1c} is to diabetes. This simple measure of LA volume provides significant insight into an individual's risk for the development of adverse cardiovascular events including, myocardial infarction, stroke, atrial fibrillation, and heart failure (22–25). Left atrial volume is graded relative to risk, 28 to 33 ml/m^2 = mild; 34 to 39 ml/m^2 = moderate; and ≥40 ml/m^2 = high or severe (23). For the practicing cardiologist, LA volume, therefore, may be considered an excellent

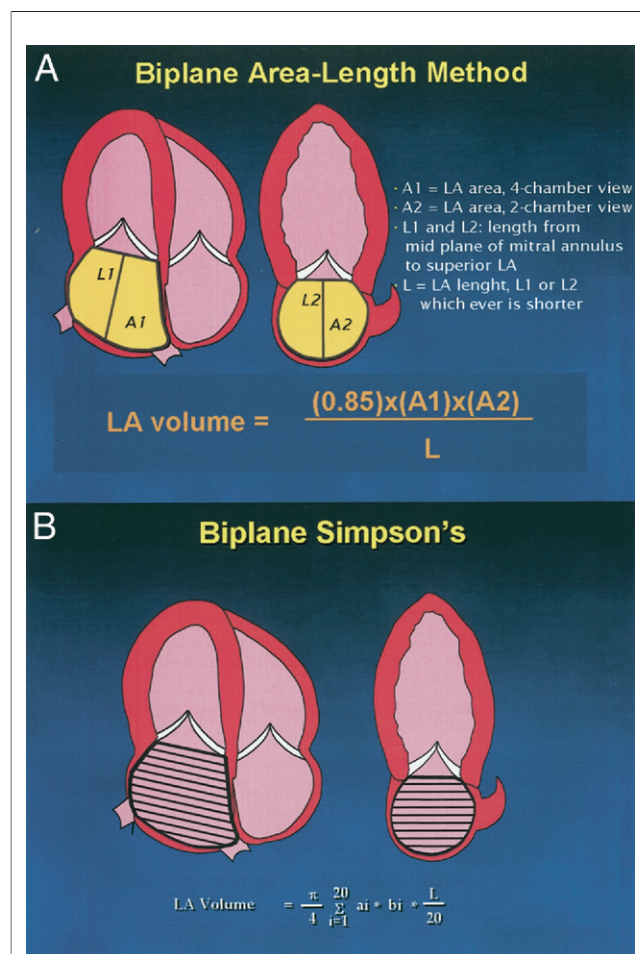**Figure 1**   **Biplane Methods With
Which to Calculate LA Volume**

(A) Biplane area length, A1 = left atrial (LA) area, 4-chamber view; A2 = LA area, 2-chamber view; L1 and L2: length from midplane of mitral annulus to superior LA, L = LA length, L1 or L2 whichever is shorter; **(B)** Biplane Simpson's where the volume of the LA is calculated as the sum of the volume of each individual disc.

biomarker of the chronicity of diastolic dysfunction and of cardiovascular disease risk (26).

Blood Flow and Myocardial Tissue Velocities

An enlarged LA reflects chronicity of LV filling pressure elevation while Doppler-derived LV filling dynamics, which reflect acuity, can vacillate moment to moment. An integrative evaluation of acuity and chronicity allows for clinical staging of diastolic dysfunction (Fig. 2). The strengths and weaknesses of various parameters used in the evaluation of LV filling pressure are outlined in Table 1 and discussed in the following text.

The mitral inflow velocity profile is used to initially characterize LV filling dynamics. The E velocity (E) represents the early mitral inflow velocity and is influenced by the relative pressures between the LA and LV, which, in turn, are dependent on multiple variables including LA pressure, LV compliance, and the rate of LV relaxation. The A velocity (A) represents the atrial contractile component of mitral filling and is primarily influenced by LV compliance and LA contractility. The deceleration time (DT) of the E velocity is the interval from peak E to a point of intersection of the deceleration of flow with the baseline and it correlates with time of pressure equalization between the LA and LV (Fig. 3). As the early LA and LV filling pressures either evolve toward or away from equivalence, so will the DT either shorten or lengthen respectively.

Diastolic dysfunction is directly related to the reduction in early LV relaxation compromising the effective transfer of the blood from the atrial reservoir into the LV cavity. The reduction in LV relaxation may be characterized through the evaluation of mitral annular motion, generally with Doppler tissue imaging, which can resolve subtle changes in LV relaxation by identifying a low septal annular early diastolic mitral annular motion (e′) velocity (<10 cm/s). There are 2 fundamental causes of delayed LV relaxation and elevation of early LV filling pressure:
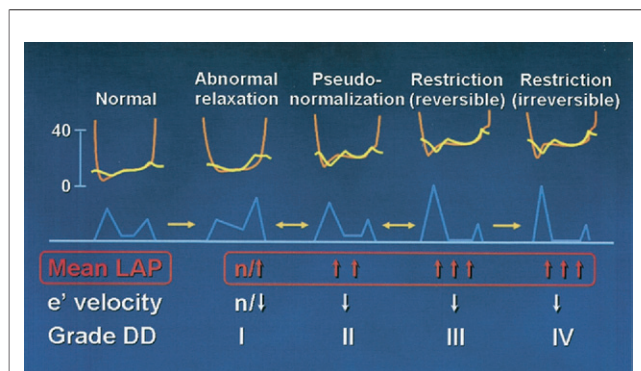

	Normal	Abnormal relaxation	Pseudo-normalization	Restriction (reversible)	Restriction (irreversible)
Mean LAP	n/↑	↑↑	↑↑↑	↑↑↑
e′ velocity	n/↓	↓	↓	↓
Grade DD	I	II	III	IV

Figure 2 **The Natural History of Diastolic Function and LV Filling**

DD = diastolic function; e′ = early diastolic mitral annular velocity; LAP = left atrial pressure; LV = left ventricular.

Table 1	Strengths and Weaknesses of the Parameters Used in the Evaluation of LV Filling Pressure	
	Strengths	**Weaknesses**
PW mitral inflow	1. Can be obtained in nearly all patients 2. Diagnostic and prognostic information	1. Highly pre-load dependent 2. Quantitative values influenced by PW sample volume placement 3. Problematic at high heart rates, atrial fibrillation, heart block, paced rhythms 4. Measurement of DT when there is a nonlinear velocity decline
DTI (e′)	1. Can be obtained in most patients 2. Early marker of diastolic dysfunction 3. Not influenced by changes in heart rate 4. Primarily load independent in disease states	1. Influenced by local changes in wall motion (infarction) 2. Possible influence by pericardial adhesions (note, possible strength too in helping to differentiate constriction from restriction)
PV flow	1. The relationship of PVAR to mitral A duration is the only marker specific for elevation in LVEDP 2. Complements PW mitral inflow and particularly helpful when there is E- and A-wave fusion to help classify diastolic filling	1. Can be difficult to obtain adequate signals 2. Influence by changes in rhythm (atrial fibrillation)
Mitral inflow propagation	1. Provides temporal, velocity, and spatial information	1. Observer reproducibility 2. Dependent on pre-load and cardiac chamber size
IVRT	1. Represents the earliest phase of diastole	1. Requires defining timing of 2 separate events AVC and MVO that may need slightly different imaging planes 2. Measurement reproducibility
LA volume	1. Provides morphologic and physiological evidence for chronic elevation in filling pressure 2. Severity scale based on clinical outcomes	1. Chronic volume overload (e.g., anemia, athletic heart, compensated valve disease) can result in an increase in LA volume yet a normal LV filling pressure

AVC = aortic valve closure; DT = mitral E-wave deceleration time; DTI = Doppler tissue imaging; e′ = septal annular early diastolic tissue velocity; IVRT = isovolumic relaxation time; LA = left atrial; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MVO = mitral valve opening; PV = pulmonary vein; PVAR = pulmonary vein A reversal duration; PW = pulsed wave.

1. The LV chamber is distorted (e.g., infarction, hypertrophy, cardiomyopathy, and dyssynergic wall motion), impairing the effective transfer of blood from the mitral orifice to the LV apex.
2. The LV ejection period is prolonged due to increased ventricular-arterial afterload.

Incomplete or delayed relaxation causes a delay in the transfer of blood from atria to ventricle. The pressures impeding forward flow are reflected backward (continuity disease) into the atria and pulmonary veins. Early in the
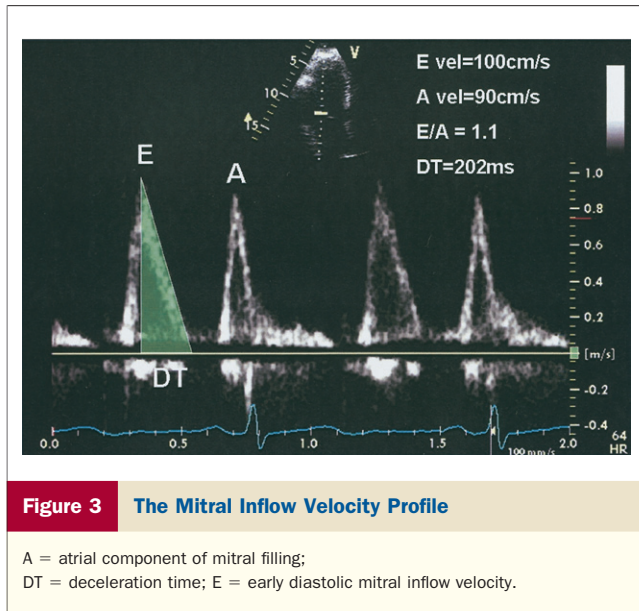
evolution of "diastolic dysfunction" the delay in emptying (DT >240 ms) is partially compensated by a more vigorous end-diastolic atria contraction, and, hence, the E/A ratio is reduced (<0.9, grade I diastolic dysfunction). With further increased impedance to atrial emptying, atrial pressure increases, and the relative difference between atria and ventricular pressure decreases (DT shortens). As a result, the E velocity and E/A ratio will now increase, and the mitral inflow velocity profile may appear normal (E/A = 0.9 to 1.5 and DT = 160 to 240, grade II diastolic dysfunction). However, the e′ velocity will remain reduced, identifying the underlying LV relaxation abnormality. A reduced e′ velocity, increased E/e′ ratio, and associated increased LA volume (>28 ml/m²) can, therefore, be readily used to discriminate an individual with normal versus grade II (pseudonormal) diastolic dysfunction (27,28). Similarly, individuals with grade III diastolic dysfunction, E/A >2, and DT <160 ms who are able to favorably influence their mitral inflow velocity profile with hemodynamic manipulation, often the Valsalva maneuver, declare themselves of less severe diastolic dysfunction than those with grade IV diastolic dysfunction who have an irreversible restrictive pattern and a very poor prognosis.

Insights into LV diastolic function can be deciphered through the evaluation not only of the relationship of the amplitude of E to e′ but also through the evaluation of the relationship of the timing of the onset of E to the onset of e′. Normally mitral inflow is initiated with rapid LV relaxation and "suction" of blood into the LV. When this occurs, the onset of e′ will be slightly before or simultaneous with the onset of E. If, however, LA pressure is elevated and LV relaxation reduced, E velocity onset may precede the onset of e′. These timing relationships have been correlated with LV filling pressure (29,30) (Fig. 4).

A limitation of the use of the e′ velocity is the fact that acquisition is generally from a single site, the mitral annulus,

and values obtained assume that they reflect global LV relaxation. Although much less practical, the average e′ velocity from multiple sites enhances the test characteristics of the E/e′ ratio to predict LV filling pressures (31). The use of 2-dimensional speckle tracking technologies allows for the characterization of global parameters of myocardial motion. A measure of global diastolic strain rate during the isovolumic relaxation phase of the cardiac cycle (SRivr) directly measures a global myocardial relaxation parameter less influenced by annular and valvular pathology. The relationship of the mitral E-wave velocity to SRivr appears to provide enhanced discriminatory power with which to detect an elevation in mean pulmonary capillary wedge pressure when compared with the E/e′ ratio (Fig. 5) (32).
Pulmonary vein flow. The ability to evaluate myocardial motion with high temporal resolution (Doppler tissue imaging) and thus detect the underlying LV relaxation abnormality (low e′) present with little exception in those with diastolic dysfunction has minimized, but not relegated obsolete, the utility of the evaluation of pulmonary vein flow in the assessment of LV filling pressure. Over the past decade, insights into the physiology of the pulmonary vein Doppler velocity profile has evolved (33). The parameters measured and insights into diastolic function gained from their interpretation, however, remain as discussed a decade ago (2). It is worthy of note that if the mitral inflow velocity
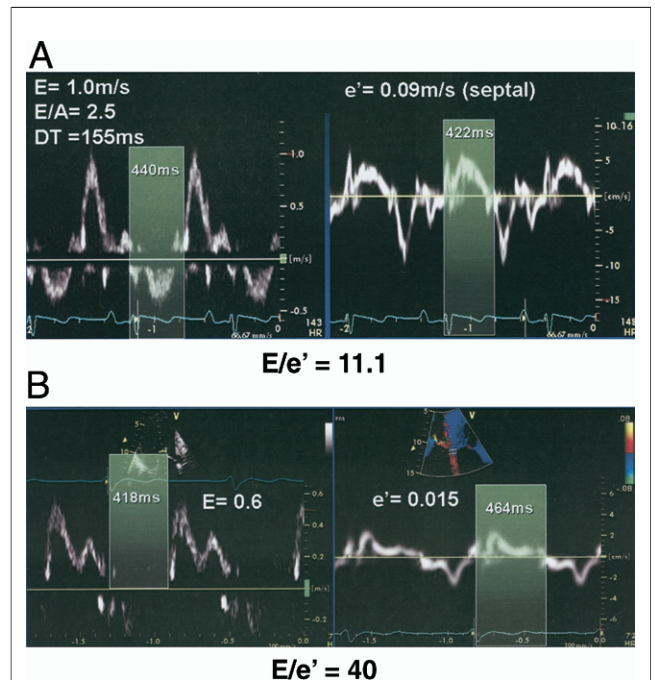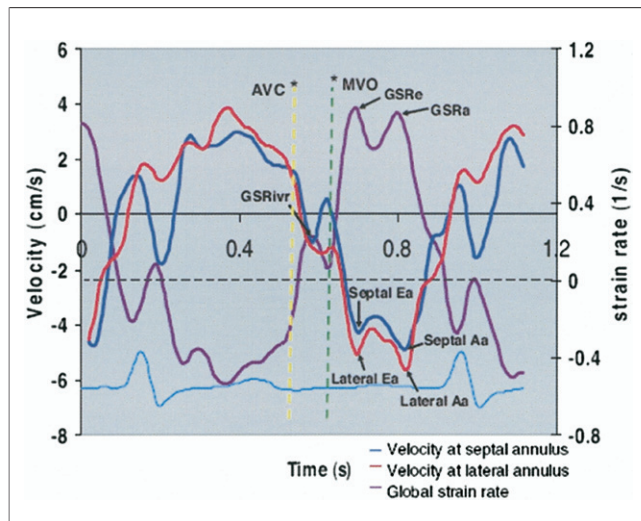
Figure 5   Global Strain Rate Profile

Global strain rate (SR) signal (**purple**, right axis), and mitral velocity (**left axis**) tracings by color tissue Doppler from the septal (**blue**) and lateral side (**red**) of the mitral annulus from the same cardiac cycle. Note the SR signal during the isovolumic relaxation phase of the cardiac cycle (*) and the corresponding velocity tracings from the mitral annulus recording during the same interval. Aa = late diastolic velocity; AVC = aortic valve closure; Ea = mitral annulus early diastolic velocity; GSRa = global strain rate during late left ventricular filling; GSRe = global strain rate during early left ventricular filling; GSRivr = global strain rate during the isovolumic relaxation phase of the cardiac cycle period; MVO = mitral valve opening. Reprinted, with permission, from Wang et al. (32).

profile indicates a predominant relaxation abnormality with a low E/e′ ratio (normal mean LA pressure), a pulmonary vein flow duration greater than mitral inflow duration at atrial contraction may indicate an earlier stage of reduced LV compliance as well as increased LV end-diastolic pressure.

Isovolumic relaxation time (IVRT). The IVRT is the time interval between aortic valve closure and mitral valve opening. The transducer is placed in the apical position with either a pulsed or continuous wave Doppler sample placed between the aortic and mitral valves. A normal IVRT is approximately 70 to 90 ms. The IVRT will lengthen with impaired LV relaxation and shorten when LV compliance is decreased and LV filling pressures are increased. Note the IVRT will vary with heart rate and ventricular function, and, thus, absolute values cannot always be interpreted to dichotomize normal versus abnormal LV filling pressure. Isovolumic relaxation time may be very helpful in following clinical response to various treatment strategies.

Mitral inflow propagation velocity (Vp). Important in the mechanics of LV diastole are regional differences in myocardial relaxation. Normally there is a wave of relaxation originating at the apex and moving toward the base. This results in a base-to-apex pressure gradient allowing blood to literally be sucked into the LV. With LV diastolic dysfunction and the associated relaxation abnormality, the regional differences in relaxation are less pronounced and the intra-

ventricular pressure gradient responsible for normal LV filling reduced or even absent.

Color M-mode of the mitral inflow obtained by placing the M-mode cursor in the direction of the mitral inflow jet seen on the color Doppler map can be used to evaluate LV relaxation (34–36). This display will provide temporal, spatial, and velocity information. There have been various methods described with which to calculate the Vp from LV base (annulus) to apex. A practical approach is to measure the slope of the line of the first aliasing velocity from the mitral valve plane to approximately 4 cm distal into the LV (normal >50 cm/s) (Fig. 6). Like e′, Vp characterizes LV relaxation, and not surprising, therefore, the ratio of E/Vp can be used to estimate LV filling pressure, with an E/Vp >1.5 suggestive of a pulmonary capillary wedge pressure of >15 mm Hg (37,38). Caution in the interpretation of this ratio is recommended in the setting of LV hypertrophy and a small LV cavity size where Vp may be high and this ratio may not, therefore, accurately reflect LV filling pressure. In our clinical practice, we perform only a qualitative interpretation of the color M-mode mitral inflow velocity only providing an estimate of the velocity, temporal, and spatial distribution of LV filling.

Practical Approach

Although there are other echocardiographic parameters that may be used to characterize diastology, the parameters discussed in the preceding text represent those that are commonly used in daily practice. The measure of LA volume is the cornerstone to evaluation for its ability to provide insight into the chronicity of elevation of LV filling pressure and to characterize global cardiovascular risk.

Initial observations of 2-dimensional echocardiographic features often provide diagnostic clues as to the status of diastolic function. Patients with diastolic dysfunction qual-
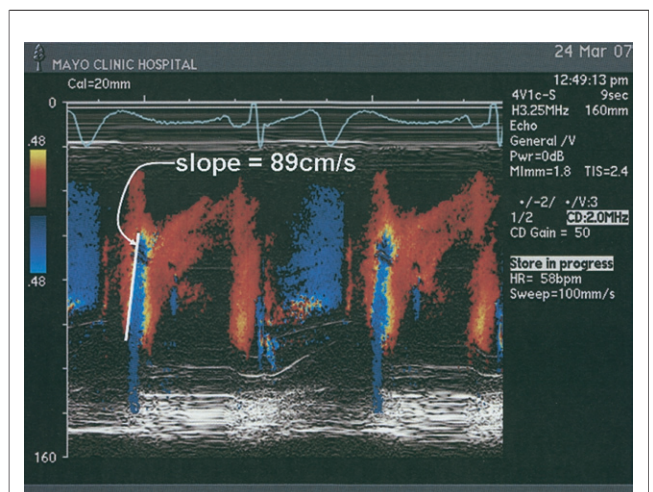

Figure 6   Mitral Inflow Propagation Velocity

bpm = beats/min; HR = heart rate.

itatively may have increased LV wall thickness, an increase in LA size, and reduced mitral annular motion. The more quantitative assessment of diastolic function and the "acuity" measure of LV filling pressure then generally begins by characterizing the mitral inflow velocity profile as either normal (E/A ratio 0.9 to 1.5, DT 160 to 240 ms), restrictive (E/A ratio typically >2, DT <160 ms), or delayed relaxation (E/A ratio <0.9, DT >240 ms). A dilemma exists when the mitral inflow velocity profile is characterized as normal and the integration of the measures of mitral inflow with measures of tissue and other blood flow velocities help to decipher normal from abnormal diastolic function (Table 2). The E/SRivr is an intellectually intriguing parameter that with further validation may become standard in the evaluation of LV filling pressures.

Although particular reference is made to the septal mitral annular e′ velocity, the lateral mitral annular e′ velocity may also be useful. It must be noted, however, that the lateral e′ velocity generally exceeds the septal e′ velocity, and, thus, in our practice a lower E/e′ cutoff (12 vs. 15) is used to dichotomize normal from elevated filling pressures when the lateral e′ velocity is used. The E/e′ ratio derived from the septal e′ is preferred (28).

When the mitral inflow velocity profile is characterized as restrictive, it too is important to integrate these findings with measures of mitral annular motion as discussed in the preceding text. With rapid relaxation (health), the LV is able to "suck" blood into itself at high velocities and the E/A ratio may exceed 2. Here, however, the rapid relaxation is clearly denoted by a robust annular e′ velocity and low E/e′ ratio. One important clinical caveat is constrictive pericarditis, where the e′ velocity may be normal and the E/e′ ratio low despite an increase in LV filling pressure ("annulus paradoxus") (39). A low e′ and increase in E/e′ ratio

confirms a reduction in LV diastolic function and an increase in LV filling pressure.

A non–E-wave dominant mitral inflow velocity profile essentially excludes demonstrable increases in LV filling pressure. However, here too a measure of LA volume and e′ is important, as there is a subset of individuals with a mitral inflow velocity profile characterizing a relaxation abnormality (grade I) diastolic dysfunction who have an increased LA volume and/or an increased septal E/e′ ratio (>15, e.g., E = 80 cm/s, A = 110 cm/s, e′ = 4 cm/s, E/e′ = 20). We designate these individuals as having grade Ia diastolic dysfunction (mild elevation in LV filling pressure).

Diastolic Stress Test

A patient reporting symptoms of dyspnea in the setting of a normal pulmonary evaluation, a negative contemporary stress test, and normal resting diastolic function often presents a clinical enigma. Analogous to those with reactive airways disease, diastolic dysfunction my not be identified without provocation, "diastolic stress test." The mitral annular e′ velocity is not significantly altered by changes in cardiac cycle length. Any change in e′ velocity noted secondary to a change in cardiac cycle length is directly related to the transmitral pressure gradient as thus concordant changes in the mitral E-wave velocity are noted (40). The E/e′ ratio is a representation of mean LA pressure and can be measured during an echocardiographic stress test (41,42). Mean LA pressure with exercise remains within normal limits in healthy individuals. Therefore, a measure of the E/e′ ratio during aerobic stress may be useful for distinguishing patients with cardiac disease and help to solve the clinical enigma (41–44).

| Table 2 | Determination of Diastolic Function Grade |

	Normal	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Severe (Grade 4)
PW-mitral inflow					
DT (ms)*	160–240	>240	160–240	<160	<130
E/A*	0.9–1.5	<0.9	0.9–1.5	>2.0	>2.5
Modifiers DTI*					
e′ (cm/s)	≥10	<10	<8	<5	<5
E/e′ (septal)	1–14	≥15	≥15	≥20	≥25
LAVI* (ml/m²)	22 ± 6	>28	>28	>35	>40
Valsalva	Negative	Positive	Positive	Positive	Negative
PVAR and mitral A duration	<30 ms	≥ or <30 ms (depending on LVEDP)	>30 ms	>30 ms	>30 ms
PV flow	PVs2 ≥ PVd (PVs2 can be < PVd in young persons)	PVs2 ≫ PVd	PVs2 < PVd	PVs2 ≪ PVd	PVs2 ≪ PVd
IRVT (ms)	70–90	>90	<90	<70	<70
Mitral inflow propagation					
Vp (cm/s)	≥50	<50	<50	<50	<50
E/Vp	≤1.5	>1.5	>1.5	>1.5	>1.5

*Most important.

E/A = the ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; LAVI = left atrial volume index; PVd = pulmonary vein diastolic forward flow velocity; PVs2 = pulmonary vein second systolic forward flow velocity; Valsalva positive = E/A ratio to decrease by ≥0.5 and increase in A velocity; Vp = mitral inflow propagation velocity; other abbreviations as in Table 1.

Table 3	Common Etiologies of Diastolic Heart Failure
Etiology of Diastolic Heart Failure	Management
Systemic hypertension	Adequate control and monitoring of blood pressure
Ischemic heart disease	Relieve ischemic (acute or chronic)
Diabetic heart disease	Good blood sugar control
Obesity/metabolic syndrome	Reduce weight, lipid management
Sleep-disordered breathing	CPAP
Valvular heart disease	Early intervention
Constrictive pericarditis	Pericardiectomy
Restrictive cardiomyopathy	Symptomatic treatment, cardiac transplant
Hypertrophic cardiomyopathy	Pharmacotherapy, relieve outflow obstruction
Infiltrative disorders (e.g., amyloid)	(e.g., stem cell transplant)/disease-specific treatment
Storage disease (e.g., hemochromatosis)	(e.g., phlebotomies)/disease-specific treatment

CPAP = continuous positive airway pressure.

Treatment

In clinical medicine there are essentially only 2 therapeutic targets: to improve symptoms and, hence, quality of life, and to enhance survival, quantity of life. In those with the clinical syndrome of heart failure, it must be emphasized that heart failure is not a diagnosis but rather a constellation of signs and symptoms representing a final common pathway of a heterogeneous group of diseases (45). In those presenting with the clinical syndrome of heart failure, one must initiate a meticulous search for the underlying etiology and precipitant causes. As such, the treatment strategy must be first and foremost directed toward the identification and correction of the underlying precipitating and pathogenic mechanism(s) (Table 3). This highlights the need to individualize the therapeutic approach.

Nondisease-specific (general) therapeutic approach. General, nondisease-specific therapies are then used to help better control symptoms. These therapies may too be tailored to an outcome of a more favorable diastolic function grade (Fig. 2). In the normal heart, as heart rate increases there is an increase in contractility and faster relaxation. In myocardial disease, there is a slower LV pressure decline and incomplete pressure restitution, and thus higher LV diastolic pressure and reduced coronary flow reserve. For individuals with grade I and II diastolic dysfunction, the duration of diastole is critical, and beta-blockers or rate-slowing calcium-channel blockers often provide a favorable symptomatic response allowing more time for ailing diastole to do its work either at rest and/or to truncate an exercise-induced increase in heart rate. In contrast, in patients with grade III or IV diastolic dysfunction, LV filling may be complete by mid-diastole. Such patients have a fixed stroke volume, and empirically slowing the heart rate into the 50s and 60s may result in a further reduction in cardiac output and a worsening of the clinical symptom complex. Therefore, in these patients, the initiation of beta-blocker therapy

should be monitored closely and initiated with small doses with small increments.

Diuretics have a salutary effect on symptoms by reducing intravascular volume and steering the LV to a more favorable position on its end-diastolic pressure volume relation and reducing pericardial restraint (Fig. 7). Therapies that result simply in a change in position on the LV end-diastolic pressure volume curve without imparting a right and downward curve shift are likely analogous to treating a fever with acetaminophen; they improve the symptom but do not influence the underlying root cause and, hence, have no impact on long-term survival. Those able to respond favorably to hemodynamic manipulation do, however, appear to have a better prognosis (46–48) as they likely represent those with less severe disease. Intriguing are therapies that may favorably influence the underlying final common pathway, the increase in vascular and ventricular stiffness.

Treating the final common pathway, vascular-ventricular stiffness. The presence of diastolic dysfunction regardless of symptom status portends significant risk for future adverse cardiovascular outcomes, and the absence of patient voiced complaints does not support the absence of therapeutic intervention. In those with clinically occult diastolic dysfunction, the initial therapeutic approach is identical to that recommended for those with symptoms: identify and treat the underlying etiology and precipitant cause(s). For example, the treatment of hypertension in those with clinically occult diastolic dysfunction results in an objective improvement in diastolic function (49). Neurohormonal modulation of the renin-angiotensin-aldosterone system is currently the only therapy with a salutary effect on some of the pathophysiological mechanisms responsible for the increase in vascular and ventricular stiffness (50,51).
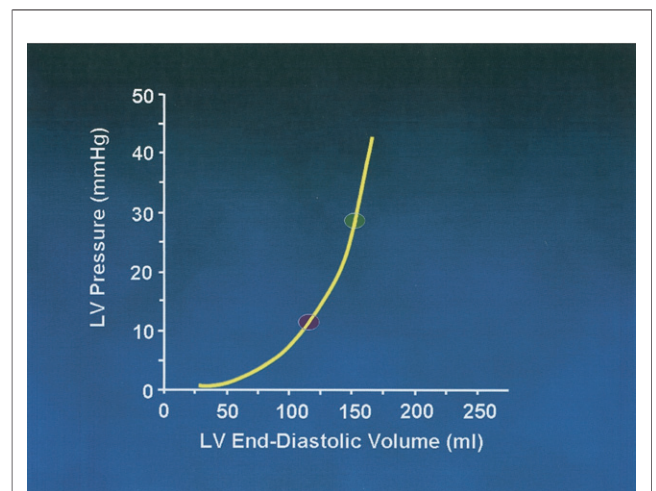

Figure 7	The LVEDP Volume Relationship

Purple = more favorable position; **Green** = less favorable position.
LV = left ventricular; LVEDP = left ventricular end-diastolic pressure.

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin I receptor antagonists (ARBs), and aldosterone receptor antagonists (ARAs), independent of their hemodynamic effects, mediate potentially favorable effects of reduced smooth muscle cell growth, prevention of collagen deposition, reduced growth factor expression, and regression of myocardial fibrosis (52–56). The finding of an enlarged LA in the absence of a definitive underlying precipitating cause (e.g., mitral regurgitation or a high output state) is a call to arms, and our approach beyond therapeutic lifestyle intervention is to initiate ACEI or ARB therapy currently targeting a blood pressure of 110/75 mm Hg. Of interest, ACEI therapy may result in favorable remodeling of the LA independent of their influence on blood pressure (57).

In those with the clinical syndrome of heart failure and a preserved LV ejection fraction, an *evidence*-based approach to treatment is lacking; however, there is information supporting a clinical *judgment*-based approach to management. The CHARM-Preserved (Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction) trial, a prospective outcome trial evaluating a treatment strategy (candesartan) solely for individuals with heart failure and a normal ejection fraction, included a heterogeneous etiologic classification of heart failure (58). The findings, however, were promising, showing a significant reduction in hospitalization for heart failure and a strong trend toward significance in the primary outcome of death or hospital admission for heart failure. The PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) study evaluated individuals ≥70 years of age with a clinical diagnosis of heart failure and a preserved LV ejection fraction. Here too the findings were promising, showing an improvement in symptoms and exercise capacity along with fewer hospitalizations in those in the active treatment group noted in the first year of follow-up (59). We await the results of the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial, where inclusion defined a more discriminate patient population (60).

Statins similarly have touted favorable pleiotropic effects too on diastolic function, and the art of medicine suggests that a low threshold for the use of statins may be appropriate (61,62). Beta-blockers as discussed in the preceding text are often helpful in the symptomatic management of patients with diastolic heart failure. However, several clinical trials, again including individuals with heterogeneous pathophysiological mechanisms for heart failure, have shown that primarily those with too low an LV ejection fraction may derive a survival advantage with beta-blocker therapy (63,64). The SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) trial suggests that the elderly with heart failure can tolerate beta-blocker therapy and derive a favorable clinical benefit (reduction is composite of death or cardiovascular hospitalization) particularly if target doses are achieved (65). This trial did include patients with preserved LV ejection fractions (approximately one-third), but the mean LV ejection fraction for each group was approximately 35%. Other trials have suggested that the use of beta-blockers in those with heart failure and a preserved LV ejection provides mortality benefit (66).

Endothelin influences myocardial inotropic and lusitropic function, and intellectually intriguing is the potential role of an endothelin receptor antagonist in the management of patients with heart failure (67,68). However, when evaluated in an etiologically heterogeneous group of heart failure patients, endothelin receptor blockers when added to standard therapy did not improve outcome, currently casting doubt on the use of endothelin receptor blockers for the management of heart failure (69–71). Further pathophysiological insight into disease inception may influence novel therapeutic strategies targeting the vasculature, with end points encoded somewhere in the cardiovascular structural and functional continuum. For example, it has recently been proposed that endothelial cells may, in fact, transition into mesenchymal cells and thus contribute fibroblasts to the process of cardiac fibrosis (72). In a mouse model of pressure overload and chronic allograft rejection, recombinant human bone morphogenic protein-7 could preserve the endothelial phenotype and retard the progression of fibrosis (72). In addition, preliminary small animal studies suggest that phosphodiesterase-5A inhibition with oral sildenafil may suppress chamber and myocyte hypertrophy, remodeling, and fibrosis by deactivating various hypertrophy signaling pathways (73,74). Additional preliminary and novel strategies directed at influencing the final common pathway of disease hold promise (75). Definitive comments on the impact of beta-blockers, ACEIs, ARBs, ARAs, statins, and other pharmacologic therapies in those with heart failure and a preserved LV ejection fraction are pending prospective randomized clinical trials. Until then, such individualized treatments encompass clinical judgment-based therapeutic strategies.

Where Are We Going?

Although it is practical to classify cardiac dysfunction as either systolic or diastolic, such a classification is based on physiological principles destitute of virtue as each component of the cardiac cycle is functionally dependent on the other. Different than 2-dimensional echocardiography, where crude parameters of cardiac performance such as ejection fraction are used, Doppler echocardiography is able to detect and quantitatively display minor amplitude and temporal subtleties that may occur in ventricular mechanical function. Traditionally, parameters of diastolic function have been derived from Doppler and those of systolic function from 2-dimensional variables. This may create the illusion that individuals have "isolated diastolic dysfunction." The interrogation of cardiac function with derived parameters of deformation such as strain and strain rate

confirm the illusion despite frequent pronouncement. Measures of global parameters of myocardial motion using advanced speckle tracking algorithms may allow for enhanced prediction models of LV filling pressure.

The contemporary belief is that the macro architecture of LV myofiber geometry is chiral with the subendocardial layer composed in the form of a right-handed helix gradually evolving into a left-handed helical fiber orientation in the subepicardial layer. As such, LV fiber orientation is a function of transmural location, with the fiber direction being predominantly longitudinal in the endocardial and epicardial surfaces and with the helical angle changing continuously between the endocardium and epicardium, such that the midwall fibers have a circumferential orientation forming a sort of equator of the heart (76–78). As with contraction, the endocardial and epicardial onset of relaxation is temporally discrete beginning in the apical subendocardium just before closure of the aortic valve with subepicardial relaxation beginning at the base after aortic valve closure (79). Different from contraction, however, relaxation of the helixes is in the opposite direction, apex to base for subendocardium and base to apex for subepicardium. The temporal and spatial differences in LV relaxation are critical for the creation of forces required for diastolic suction (79). Because of the intrinsic spiral geometry of the LV myofibers, shortening and lengthening of the myocardial wall results in rotary movements. The counter-directional rotation of the LV apex with respect to the base is referred to as LV twist or torsion. By convention, rotation is described from the apical end of the LV, with clockwise and counterclockwise rotations shown in negative and positive degrees, respectively (Fig. 8). Our now better understanding of myocardial form and myofiber architecture paralleled with advances in ultrasound signal processing have allowed the subtleties of myocardial motion to be characterized and quantified (80).

In the end, the heart is simply a pump, albeit a complex and sophisticated one that serves to deliver blood to the body. Although we can now begin to decipher the complex motion needed to complete this task, intriguing are techniques that can also decipher the complexities of the final common purpose of cardiac pump function, blood flow (81). Perhaps systolic and diastolic dysfunction will no longer be viewed clinically as dichotomous terms but rather voiced as just "cardiac dysfunction." The echocardiography laboratory will evolve into a cardiovascular physiology and pathophysiology laboratory able to decipher the subtle morphologic and physiological characteristics of a heterogeneous group of cardiovascular diseases (82). We will then be able to evolve a new paradigm of what we define as "disease" with "echophysiology" providing insights allowing for more active intervention for prevention strategies. Perhaps in another decade all inscriptions on the Rosetta Stone will be deciphered and we will realize that the translation was not just that of diastology but rather cardiovascular physiology and pathophysiology. Until then. . .

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Figure 8   **VVI Illustrating the Rotation Motion of the LV Apex**

(Left) Systole where the apical rotation is predominantly anticlockwise; **(right)** systole where the apical rotation (now untwisting) is predominantly in the clockwise direction. LV = left ventricular; VVI = Velocity Vector Image.

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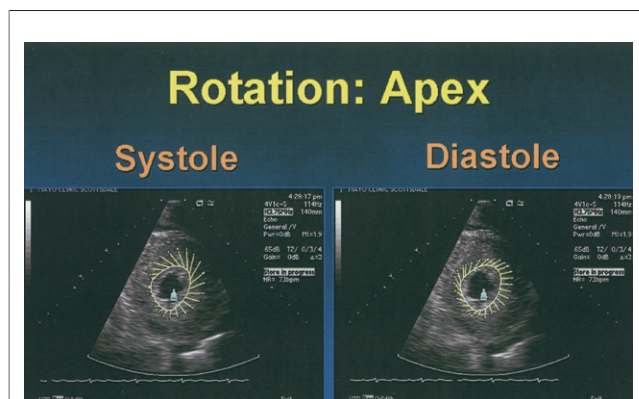
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