Diastolic Heart Failure: Standard Doppler Approach and Beyond

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Evidence of normal systolic left ventricular function has been reported in up to 30–40% of patients with clinical signs of congestive heart failure, suggesting that diastolic dysfunction is an important predictor of prognosis and mortality. Doppler echocardiography as a noninvasive diagnostic procedure is able to provide immediate and relevant information on functional and structural changes underlying the clinical syndrome of heart failure. Four distinct early filling/late diastole (E/A) ratio patterns (normal, delayed relaxation, pseudonormal, restrictive) can be discerned if viewed within the context of other available clinical information. These patterns evolve from one to another in a single individual, with changes in disease evolution, treatment, and loading condition. They represent a continuum from normal to severe diastolic dysfunction, showing progressively increasing left ventricular (LV) chamber stiffness and subsequently decreasing deceleration time. The combination of Doppler restrictive filling pattern and decreased deceleration time provides important information that helps to differentiate gradations of diastolic dysfunction and has been found to be a potent predictor of prognosis and mortality in various cardiac conditions. When clinical and transthoracic data alone are not sufficient in guiding therapy of congestive heart failure, transesophageal echocardiography can be used to assess most Doppler flows, especially pulmonary venous and left atrial (LA) appendage flows. The use of the multiplane transducer in multiple intermediate scan planes further improves the possibility of optimizing the Doppler incident angle and obtaining the best Doppler recordings of the left upper or right upper pulmonary venous flow. Whereas LV diastolic dysfunction is common in patients with congestive heart failure and appears to be an important predictor of prognosis, little information is available about right ventricular (RV) diastolic dysfunction. The role of RV function in congestive heart failure has probably been underestimated and it is possible that RV diastolic dysfunction assessment is equally important in the follow-up of heart failure patients. Recently, 2 novel echocardiographic technologies for the assessment of ventricular wall dynamics have been developed—color kinesis and tissue Doppler imaging. Both techniques have recently been shown to provide global as well as regional information on LV contraction and filling. Complementary use of both techniques may allow a more complete noninvasive assessment of global and regional systo-diastolic LV function.

Am J Cardiol 1998;81(12A):115G–121G

The prevalence of left ventricular (LV) failure with a normal ejection fraction (diastolic heart failure) is as high as 30–40%,[1–3] with arterial hypertension being the most frequent etiologic cause. Less frequently, impaired diastolic filling may be related to abnormalities of the mitral valve, pericardial disease, or congenital heart disease.[4–6] Although measuring ventricular diastolic function has been a challenge to investigators, in the past few years Doppler echocardiography has emerged as a noninvasive and rapid bedside alternative to cardiac catheterization for the assessment of diastolic function. The objectives of this review are to (1) focus on the pathophysiologic entities that can benefit from Doppler evaluation; (2) point out established echocardiographic indexes of abnormal ventricular filling; and (3) to synthesize some recently described methods of quantifying diastolic function.

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PATHOPHYSIOLOGY OF DIASTOLIC HEART FAILURE

Impairment in diastolic filling is related to both abnormalities of the active relaxation of the myocardium and passive elastic properties as a result of hypertrophy, myocardial ischemia, decreased adrenergic tone, or increased myocardial connective tissue.[7–8] Impairment in relaxation increases myocardial wall tension in diastole, and loss of cardiac elastic properties causes a reduction in compliance, both of which lead to an increase in pulmonary venous pressures. Thus in diastolic heart failure, pulmonary venous congestion and/or decreased cardiac output occur as a result of impaired energy dependent filling or as a result of increased LV stiffness.

During the isovolumetric relaxation and the early stages of left ventricular filling, the continued fall of intraventricular pressure creates a suction pressure that is subject to the effects of sympathetic stimulation and augments diastolic ventricular filling. Impairment in ventricular relaxation produces an inability to increase end-diastolic volume during tachycardia, and this leads to a decreased stroke volume. Furthermore, the prolongation of diastolic myocardial tone causes an increase in LV diastolic pressure and an upward shift in the diastolic pressure–volume relation during exercise.

LV hypertrophy in response to increased afterload

is initially an adaptive mechanism in hypertensive heart disease, serving to restore the increased wall stress toward normal. With chronic pressure overload, the increasing cardiac mass leads to a progressive impairment in diastolic filling. The noncompliant left ventricle has a more pronounced pressure–volume relation than the normal ventricle, and this results in large changes in the diastolic pressure for relatively small changes in volume. The exaggerated response to a relatively small degree of volume loading causes high pulmonary venous pressures that may be clinically manifest as pulmonary edema. The increased wall tension, combined with increased myocardial collagen content and elevated myocardial angiotensin-converting enzyme levels, leads to the development of diastolic dysfunction in hypertensive heart disease.[9,10]

Myocardial ischemia causes diastolic impairment at the cellular level through abnormalities in the sequestration of the calcium ion into the sarcoplasmic reticulum, a process requiring energy and thus impaired by myocardial hypoxia and hypoxemia.[11,12] Patients with coronary artery disease exhibit abnormalities of diastolic relaxation and filling that have been shown to improve after angioplasty and coronary artery bypass surgery.[13,14]

Aging provides a decline in LV diastolic function secondary to alteration in passive elasticity from age-related changes that result in a decrease in LV cavity size and decreased rates of ventricular filling.[15–17]

TRANSTHORACIC ECHOCARDIOGRAPHY

In the early 1980s, there was considerable enthusiasm for the new technique of pulsed Doppler echocardiography that made it possible to measure LV diastolic filling in humans. By placing a gated Doppler sample volume near the tips of the mitral valve, it was possible to generate a tracing of the velocity profile of the blood flowing from the left atrium to the left ventricle during diastole and to quantify and analyze every aspect of the Doppler ventricular filling profile. Animal and human studies continued characterizing the complex and dynamic processes that result in normal and abnormal diastolic filling patterns.[18–24] The major determinant of LV filling is the pressure gradient between the left atrium and the left ventricle. The gradient responsible for early filling is dependent primarily on the negative pressure (suction) created by active ventricular relaxation and on the left atrial (LA) pressure. The gradient during late diastole is dependent primarily on the pressure increase generated by LA contraction and on passive ventricular pressure. An alteration of these factors will alter the Doppler LV filling pattern.

Further studies led to the recognition that 4 distinct early filling/late diastole (E/A) ratio patterns[20,25–27] can be distintiguished if viewed within the context of other available clinical information (Figure 1). In the first pattern, which is seen in healthy young subjects, early filling is dominant such that the E/A ratio is >1. In the second pattern (delayed relaxation), there is decreased peak early LV filling, which results in a reversed E/A ratio of <1, increased deceleration time, and increased isovolumetric relaxation time. This is attributable to a decreased early diastolic gradient between the left atrium and the left ventricle, resulting from a slowed relaxation and vigorous compensatory atrial contraction. Ventricular ischemia, hypertrophy, and aging are associated with impaired relaxation. The third pattern of LV abnormal filling, which has been termed "pseudonormalization," shows an E/A ratio >1, as in young normals, and results from an increase in LA pressure that compensates for the slowed rate of LV relaxation. This pattern is distinguished from normal filling by a shortened early deceleration time. This represents an intermediate stage between impaired relaxation and restrictive filling as a result of disease progression, ischemia, or increased loading conditions.[25,28]

In the fourth pattern of ventricular filling, which has been termed "restrictive," the early filling is increased abnormally due to a rapid increase in ventricular pressure during early diastolic filling and little subsequent filling because of chamber stiffness. This results in an increased E/A ratio often >2 and a short deceleration time and isovolumetric relaxation time.[29] The momentum of rapid blood flow into the stiff ventricle may cause ventricular pressure to increase quickly and exceed atrial pressure during diastole, reversing the direction of flow and leading to diastolic mitral and tricuspid regurgitation.[18,28,30] The restrictive pattern is seen in patients with severe diastolic dysfunction, pulmonary congestion, and end-stage dilated cardiomyopathy.

These patterns evolve from one to another in a single individual, with changes in disease evolution, treatment, and loading condition. They result from a variable combination of delayed early relaxation, increased LA pressure, and increased LV chamber stiffness. They represent a continuum from normal to severe diastolic dysfunction, showing progressively increasing LV chamber stiffness and subsequently decreasing deceleration time. The combination of Doppler restrictive filling pattern and decreased deceleration time provides important information that helps to differentiate gradations of diastolic dysfunction and has been found to be a potent predictor of prognosis and mortality in various cardiac conditions.[31–40]

Since the qualitative staging of diastolic dysfunction in "delayed relaxation," "pseudonormal," and "restrictive" patterns may be confounded by the degree of preload compensation, attempts have been made to derive or infer the time constant of LV relaxation (τ) from isovolumic relaxation time duration and other noninvasive parameters, such as the downslope of the mitral regurgitation Doppler profile.[41,42] These techniques should be tested in future prospectively acquired data sets to assess the degree of accuracy in most clinical situations.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

When clinical and transthoracic data alone are not sufficient in guiding therapy of congestive heart fail-

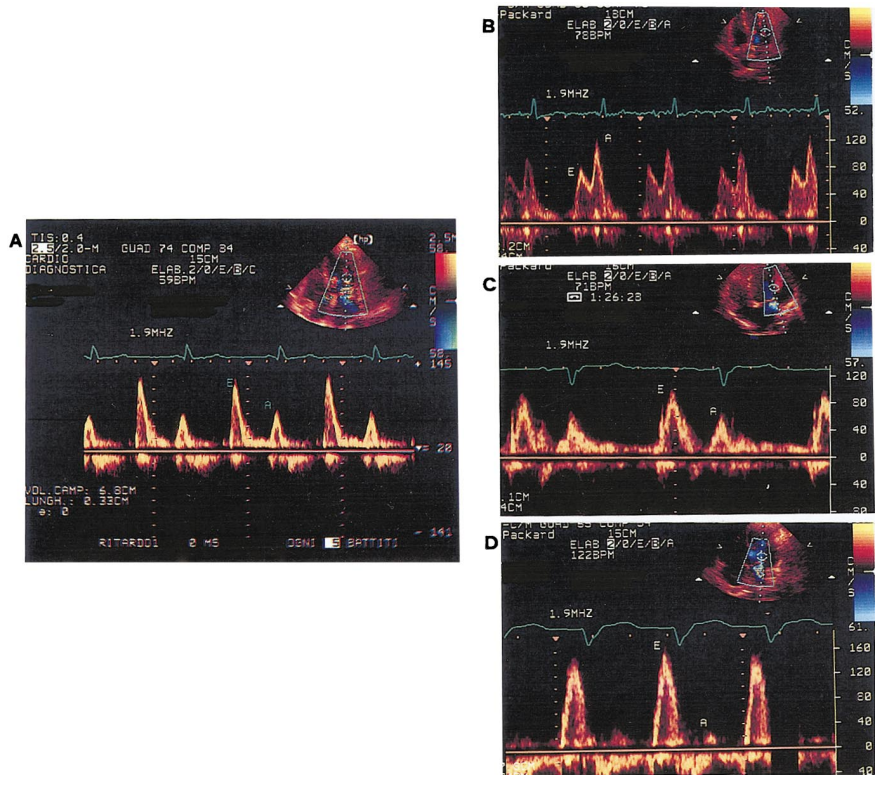

FIGURE 1. Mitral Doppler flow profiles and E/A ratios of the normal young subject (*A*), delayed relaxation (*B*), pseudonormal filling (*C*), and restriction (*D*).

ure, transesophageal echocardiography can be used to assess most Doppler flows, especially pulmonary venous and LA appendage flows.[43,44] It has been shown that the pulmonary venous flow velocity pattern obtained by transesophageal echocardiography (Figure 2) provides valuable information in distinguishing systo-diastolic from diastolic ventricular dysfunction in patients with congestive heart failure.[45] Pulmonary venous flow patterns may serve as an "eyeball index" of mean LA pressure, since the level of mean LA pressure or pulmonary capillary wedge pressure is related to the systolic fraction of pulmonary venous flow.[46] The respective influence on this relation of factors such as LA expansion, descent of the mitral anulus, and LV contractile function, as well as the relation of pulmonary venous flow to mitral inflow,[47] have been tested.

Delayed LV relaxation, altered LV passive elastic properties, decreased LV suction or elastic recoil, increased extracardiac constraints, and a stiffened left atrium are frequently observed in the presence of heart failure. The abnormal mitral flow velocity pattern that is seen in patients with LV diastolic dysfunction can be normalized in association with elevated LA filling pressures.[48–50] In patients with impaired ventricular relaxation but with relatively normal chamber stiff-

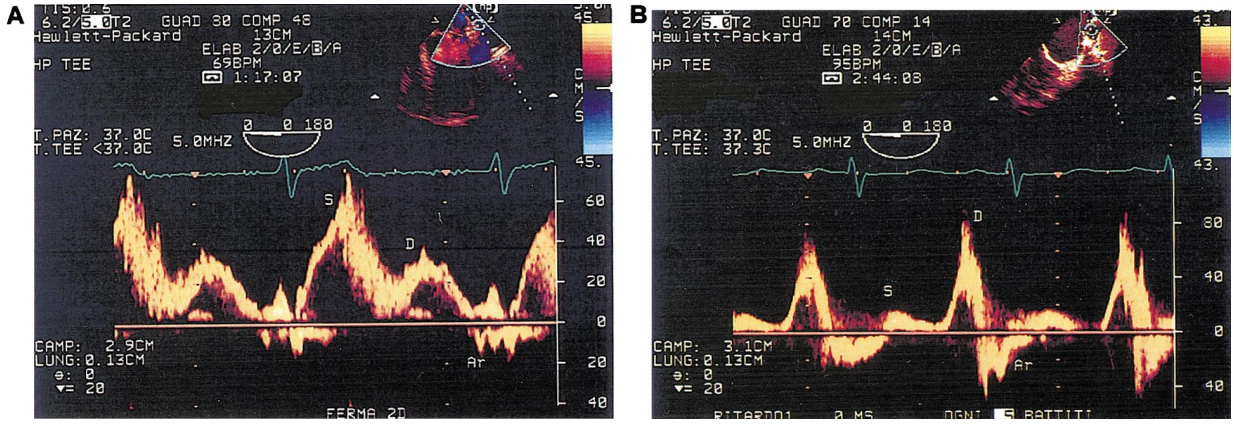

FIGURE 2. Transesophageal pulmonary venous Doppler flow profiles in a normal subject (*A*) and a patient with altered diastolic function (*B*) showing increased diastolic flow "D" velocity.

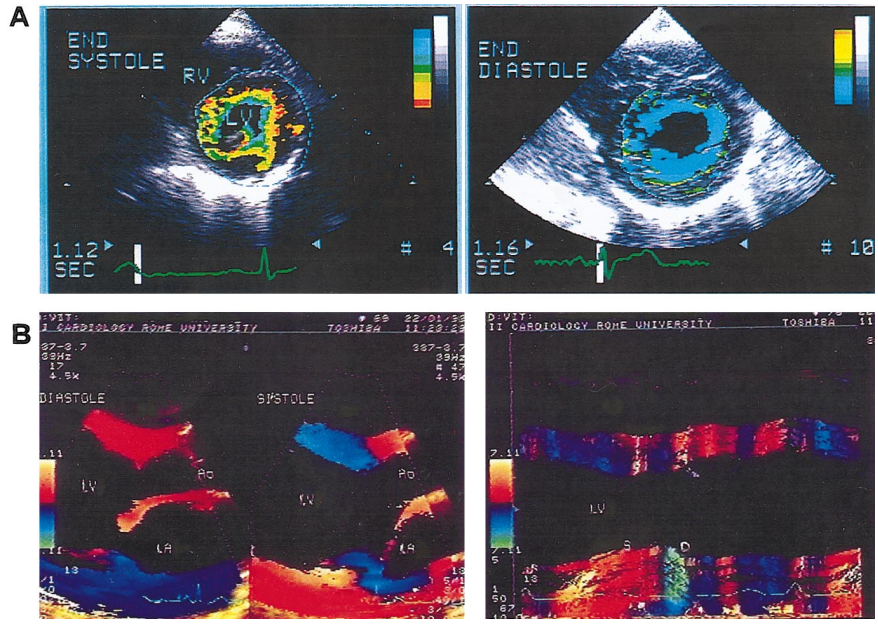

FIGURE 3. (*A*) Color kinesis images obtained in the parasternal short-axis view at end-systole and end-diastole. From early systole to end-systole (*left*) and from early diastole to end-diastole (*right*), an increasing number of colors is added with progressive inward and outward endocardial excursion. (*B*) Tissue Doppler image, M-mode (*right*), and parasternal long-axis view (*left*) of the left ventricle (LV), showing the distribution of color-coded myocardial velocities and the normal contraction and relaxation pattern of septal and posterior wall in systole "S" and diastole "D." Motion toward the transducer is color-coded red and motion away from the transducer is color coded blue.

ness, the reduction in early ventricular filling produces a higher atrial preload and forceful atrial contraction (low E/A ratio, increased deceleration time and isovolumic relaxation time). The opposite may occur when ventricular filling pressures are elevated, imposing a higher afterload on the left atrium and a shift in ventricular filling toward early diastole (high E/A ratio, decreased deceleration time and isovolumic relaxation time). In the spectrum of LV dysfunction, a combined assessment of pulmonary venous peak diastolic velocity, mitral E velocity, and isovolumetric relaxation time is useful in distinguishing those patients with predominant diastolic impairment (normal or nearly normal LV ejection fraction, high E and diastolic velocities) from patients with systolic impairment (low LV ejection fraction, low systolic venous fraction).

Pulmonary venous flow patterns can also be obtained with transthoracic echocardiography, but the quality of the tracings is considerably poorer and qualitative and quantitative analysis of the different waves is more difficult. Operator-related, patient-related, and equipment-related limitations of the transthoracic approach can make the examination difficult and, in some cases, the results of questionable reliability. Transesophageal Doppler examination is more accurate than transthoracic examination in evaluating pulmonary venous flow because the transducer can be located nearer to the pulmonary vein; there are few obstacles between the transducer and pulmonary vein by transesophageal approach. The difficulty of obtaining good narrow-band Doppler signals of pulmonary venous flow by the transthoracic approach may be a possible explanation for the discrepancy in the findings between transthoracic and transesophageal studies. Even if it has been shown recently[51] that transthoracic tracings provide reliable quantitation of the pulmonary venous flow pattern in patients with cardiac disorders, the transesophageal approach was considered to be better than the transthoracic in terms of the detection rate. Moreover, the use of the multiplane transducer in multiple intermediate scan planes further improves the possibility of optimizing the Doppler incident angle and obtaining the best Doppler recordings of the left upper or right upper pulmonary venous flow.

DOPPLER ASSESSMENT OF RV DIASTOLIC DYSFUNCTION

Whereas LV diastolic dysfunction is common in patients with congestive heart failure and appears to be an important predictor of prognosis, little information is available about RV diastolic dysfunction. Difficulty assessing RV diastolic performance by means of transtricuspid flow velocities is partially due to the fact that tricuspid flow depends significantly on respiration.[52–54] It has been shown that respiration affected only the maximum velocity of the E wave when the flow was measured on the ventricular side of the tricuspid valve.[52] In a recent study of RV diastolic function after repair of tetralogy of Fallot,[55] the effect of restrictive physiology was apparent in measure-

ments recorded at both end inspiration and end expiration. By averaging values measured at end expiration and end inspiration, clinically relevant information can be derived to separate patients with abnormal RV diastolic function from normal individuals.[56]

Several cardiac conditions affect both the left and right ventricle, and LV failure may secondarily impair right ventricular diastolic performance through elevation of the pulmonary artery pressure or ventricular interdependence.[57–59] The role of RV function in congestive heart failure has probably been underestimated. An abnormal RV filling has been reported in children with dilated cardiomyopathy.[60] A prolonged RV isovolumic relaxation time and reversed tricuspid E/A ratio occurs in >50% of patients with congestive heart failure.[56] Impaired RV diastolic function in heart failure patients can be related to pulmonary artery hypertension secondary to increased LA pressure. However, abnormalities of RV diastolic function are still common in patients with heart failure and normal pulmonary artery pressure, partially due to the disease process (ischemic or dilated cardiomyopathy), but also caused indirectly by coexistent LV diastolic dysfunction resulting from ventricular interaction. Because LV diastolic function, particularly the restrictive filling pattern, has been shown to provide important prognostic information, it is possible that RV diastolic dysfunction assessment is equally important in the follow-up of these patients to increase the accuracy of predictions of outcome and prognosis.

FUTURE APPROACHES

Recently two novel echocardiographic technologies for the assessment of ventricular wall dynamics have been developed. Color kinesis is a new echocardiographic algorithm for evaluation of LV wall motion based on the acoustic quantification. Tissue Doppler imaging is a modification of conventional color Doppler technology from which quantitative data regarding myocardial velocity can be extracted. Both techniques (Figure 3) have been recently shown to provide global as well as regional information on LV contraction and filling.

Acoustic quantification has been previously described[61,62] and validated against a variety of techniques.[63–66] Analysis of the tissue backscatter data identifies the border between blood and tissue and automatically tracks endocardial motion throughout the cardiac cycle. Color kinesis is a further extension of automatic border detection, which defines endocardial motion by color encoding for inward and outward motion and facilitates the on-line assessment of systolic and diastolic ventricular function by creating a color map of regional wall motion.[67–71] Similar to acoustic quantification and other ultrasound-based techniques, the ability of color kinesis to adequately track endocardial border is dependent on the quality of the two-dimensional images. However, with repeated data acquisitions and analyses, color kinesis reproducibility proved to be similar to other methodologies based on manual tracing of endocardial border. Endocardial tracking is achieved in all LV segments, except for a decreased ability to track boundaries in the apical lateral wall, because of anisotropy of myocardium in those zones. Color kinesis can also be activated during diastole to identify whether endocardial expansion has occurred in a given pixel area. This feature is of particular clinical value because coronary artery disease first manifests itself as a segmental diastolic dysfunction, and abnormalities in regional LV filling and relaxation represent early signs of myocardial ischemia. Even if color kinesis appeared sensitive and specific for the detection of coronary artery disease, further improvements are needed in imaging software and quantitative analysis.

Transmural velocity gradients can be measured by tissue Doppler imaging, and the normal transmural gradient of velocities between subendocardium and subepicardium has been shown to be decreased in patients with ischemic heart disease and dilated cardiomyopathy.[71–75] In this respect, tissue Doppler imaging has recently allowed a quantitative evaluation of dobutamine stress echocardiography. By quantifying changes in myocardial velocity throughout the cardiac cycle, tissue Doppler imaging may also be beneficial in the assessment of diastolic dysfunction. Compared with normal controls, hypertensive patients have been shown to exhibit decreased peak early diastolic velocity in both the ventricular septum and posterior wall subendocardium and prolonged LV isovolumic relaxation time. A satisfactory pulsed wave tissue Doppler can be obtained independent of quality of LV wall motion, but the velocities recorded are influenced by the incident angle of Doppler ultrasound and by the whole heart motion, some issues for tissue Doppler imaging which remain to be resolved. Moreover, early diastolic parameters calculated from tissue Doppler imaging may not be reliable in patients with elevated LV end-diastolic pressure. Complementary use of both techniques (color kinesis and tissue Doppler imaging) may enhance the possibilities for noninvasively assessing global and regional systo-diastolic LV function.

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