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Doppler Tissue Imaging: A Noninvasive Technique for Evaluation of Left Ventricular Relaxation and Estimation of Filling Pressures

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Objectives. **This investigation was designed 1) to assess whether the early diastolic velocity of the mitral annulus (E_a) obtained with Doppler tissue imaging (DTI) behaves as a preload-independent index of left ventricular (LV) relaxation; and 2) to evaluate the relation of the mitral E/E_a ratio to LV filling pressures.**

Background. **Recent observations suggest that E_a is an index of LV relaxation that is less influenced by LV filling pressures.**

Methods. **One hundred twenty-five study subjects were classified into three groups according to mitral E/A ratio, LV ejection fraction (LVEF) and clinical symptoms: 34 asymptomatic subjects with a normal LVEF and an E/A ratio ≥1; 40 with a normal LVEF, an E/A ratio <1 and no heart failure symptoms (impaired relaxation [IR]); and 51 with heart failure symptoms and an E/A ratio >1 (pseudonormal [PN]). E_a was derived from the lateral border of the annulus. A subset of 60 patients had invasive measurement of pulmonary capillary wedge pressure (PCWP) simultaneous with Doppler echocardiographic DTI.**

Results. **E_a was reduced in the IR and PN groups compared with the group of normal subjects: 5.8 ± 1.5 and 5.2 ± 1.4 vs. 12 ± 2.8 cm/s, respectively ($p < 0.001$). Mean PCWP (20 ± 8 mm Hg) related weakly to mitral E ($r = 0.68$) but not to E_a. The E/E_a ratio related well to PCWP ($r = 0.87$; PCWP = 1.24 [E/E_a] + 1.9), with a difference between Doppler and catheter measurements of 0.1 ± 3.8 mm Hg.**

Conclusions. **E_a behaves as a preload-independent index of LV relaxation. Mitral E velocity, corrected for the influence of relaxation (i.e., the E/E_a ratio), relates well to mean PCWP and may be used to estimate LV filling pressures.**

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Diastolic dysfunction is the primary mechanism responsible for dyspnea in patients with heart failure, irrespective of the presence or severity of systolic dysfunction (1–3). Doppler echocardiography has become the noninvasive technique of choice for the evaluation of diastolic function (4,5). However, current methods are limited by the dependence of the transmitral flow velocity and the isovolumic relaxation time (IVRT) on left ventricular (LV) relaxation and left atrial pressure (4–9). Increases in left atrial pressure override the effects of impaired relaxation (IR), resulting frequently in a "pseudonormalization" of the transmitral velocity.

Measurements of E wave velocity, IVRT and other variables from the transmitral velocity and pulmonary venous flow have been used in combination to estimate filling pressures noninvasively (10–19). The equations derived are based on the premise that the changes occurring in the transmitral velocity in response to increases in filling pressures (i.e., pseudonormalization) occur in the presence of IR. Consequently, the application of these equations requires differentiation of the pseudonormal (PN) pattern from the normal pattern. This differentiation is currently done by data derived from clinical and echocardiographic findings that suggest the presence of impaired LV relaxation or by inspection of the pulmonary vein velocity (13,14). A preload-independent noninvasive index of LV relaxation would facilitate this process and, more importantly, allow the evaluation of relaxation independent of loading conditions.

Doppler tissue imaging (DTI) is a new ultrasound modality that records systolic and diastolic velocities within the myocardium (20–24) and at the corners of the mitral annulus (25–27). The velocity of annular motion reflects shortening and lengthening of the myocardial fibers along a longitudinal plane. The early diastolic velocity recorded at the lateral corner of the annulus (E_a) has been recently demonstrated to decline progressively with age and to be reduced in pathologic LV hypertrophy (26), as well as in patients with restrictive cardiomyopathy (27). These findings suggest that E_a is an index of LV relaxation that may not be influenced by left atrial pressure.

The current investigation was therefore designed to assess first whether the E_a, as recorded with DTI, is a preload-independent index of LV relaxation that will distinguish a PN mitral inflow pattern from a normal one, and second to explore the hypothesis that correcting the transmitral E wave velocity

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Abbreviations and Acronyms

A_a = late diastolic velocity of mitral annulus
DTI = Doppler tissue imaging
E_a = early diastolic velocity of mitral annulus
IR = impaired relaxation
IVRT = isovolumetric relaxation time
LV = left ventricular
LVEF = left ventricular ejection fraction
PCWP = pulmonary capillary wedge pressure
PN = pseudonormal
S_a = systolic velocity of mitral annulus

for the influence of myocardial relaxation (i.e., the E/E_a ratio) improves its relation with filling pressures.

Methods

The investigational protocol was approved by the Institutional Review Boards of The Methodist Hospital and Baylor College of Medicine, and all patients gave written informed consent before participation. The study group consisted of 125 patients; 65 underwent echocardiographic evaluation in our laboratory for assessment of cardiac structure and function and 60 were studied simultaneously during right heart catheterization in the intensive care unit (n = 45) or in the catheterization laboratory (n = 15). Criteria for inclusion included the presence of sinus rhythm, absence of mitral stenosis or prosthetic mitral valve and adequate echocardiographic two-dimensional imaging.

The 125 patients were divided into three groups: the normal group, the IR group and the PN group. The normal group included 34 patients with no symptoms or previous history of heart failure, hypertension or coronary artery disease. They all had a normal echocardiographic examination, including LV size and function, left atrial volumes and pulmonary artery systolic pressures by Doppler echocardiography. The IR group consisted of 40 patients with hypertension, coronary artery disease and/or LV hypertrophy, normal ejection fraction and a mitral inflow pattern with an early to late transmitral flow velocity (E/A) ratio <1.0. None of these patients had symptoms of heart failure. Twenty patients with hypertension were receiving beta-blockers or calcium channel blockers, or both; subjects with coronary artery disease were also receiving nitrates. A subgroup of 26 patients with invasive hemodynamic data had a mean pulmonary capillary wedge pressure (PCWP) ≤12 mm Hg (10 ± 1.5). The PN group consisted of 51 patients with symptoms of pulmonary congestion and elevated (>40 mm Hg) pulmonary artery systolic pressure by Doppler echocardiography, accompanied by an E/A ratio ≥1.0 and an IVRT ≤70 ms. Seventeen patients had idiopathic dilated cardiomyopathy; 20 were status post myocardial infarction (12 anterior, 8 inferoposterior); and 14 had normal systolic function with symptoms of heart failure. A subgroup of 34 patients with invasive hemodynamic data had a mean PCWP >12 mm Hg (23 ± 6). Five patients in the IR group and five in the PN group had bundle branch block (three with left bundle branch block).

Echocardiographic studies. The patients studied in the echocardiography laboratory were imaged in the left lateral decubitus position with an Acuson XP-128 instrument equipped with a multifrequency transducer as well as the DTI program. A complete echocardiographic study was performed using standard views and techniques. All Doppler echocardiographic and DTI recordings were obtained during normal respiration. From the apical window, the pulsed Doppler sample volume was placed at the mitral valve tips and 5 to 10 cardiac cycles were recorded. Using continuous wave Doppler echocardiography, the cursor was positioned midway between LV outflow and mitral inflow to record the IVRT. Pulmonary venous flow velocity was recorded from the right pulmonary vein guided by color Doppler echocardiography. The DTI program was set to the pulsed wave Doppler mode. Filters were set to exclude high frequency signals, and the Nyquist limit was adjusted to a velocity range of −15 to 20 cm/s. Gains were minimized to allow for a clear tissue signal with minimal background noise. From the apical four-chamber view, a 5-mm sample volume was placed at the lateral corner of the mitral annulus and subsequently at the medial (or septal) corner. The resulting velocities were recorded for 5 to 10 cardiac cycles at a sweep speed of 100 mm/s and stored on a ½-in. VHS videotape for later playback and analysis. The same set of echocardiographic data was obtained in the supine position in the subgroup of patients studied during right heart catheterization.

Echocardiographic measurements were performed by an observer who had no knowledge of the clinical and hemodynamic data on a computerized off-line analysis station (Digisonics EC500) equipped with two-dimensional and Doppler software. The LV ejection fraction was calculated using the multiple diameter method (28). Left atrial volumes were derived with the method of discs (29) and, when possible, estimation of pulmonary artery systolic pressure was obtained with the tricuspid regurgitant jet (30,31). The mitral inflow velocity was traced and the following variables derived: peak velocity of early (E) and late (A) filling, deceleration time of the E wave velocity and atrial filling fraction (10). The IVRT was measured as previously described (10,14,17). The pulmonary venous flow was analyzed for the peak velocity and the velocity–time integral of each of the systolic, diastolic and atrial reversal signals (12–14).

The following measurements were made from the DTI recordings (Fig. 1): peak systolic velocity (S_a), early (E_a) and late (A_a) diastolic velocities, acceleration time of E_a (measured from onset to peak E_a) and deceleration time derived by linear extrapolation of E_a to baseline. Mean acceleration and deceleration rates were calculated as E_a divided by their respective time intervals. Measurements were made in three to five cardiac cycles and averaged.

Pressure measurements. A pulmonary artery balloon-occlusion catheter was used to acquire the PCWP. The wedge

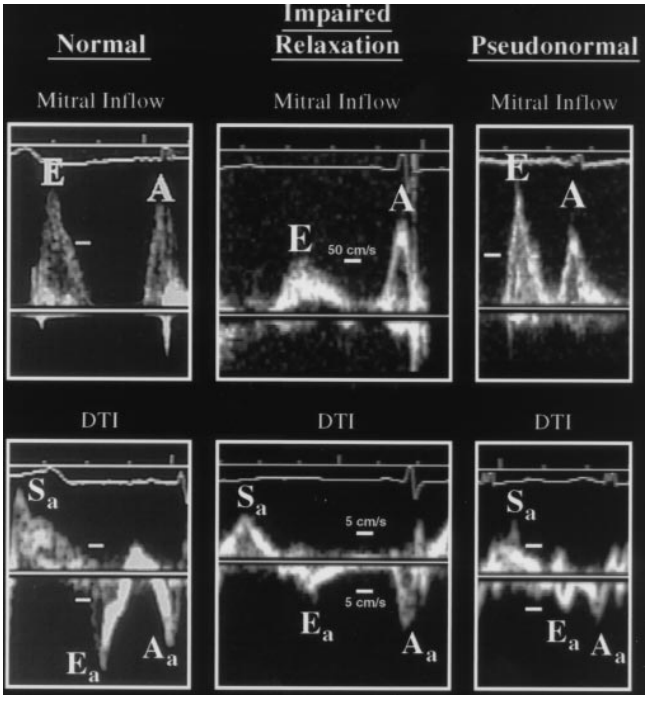

Figure 1. Representative examples of DTI annular velocities and transmitral velocity from the three study groups.

position was verified by observing the typical changes in pressure waveforms and documenting an increase in oxygen saturation >95%. The patients studied in the cardiac catheterization laboratory also had the benefit of fluroscopic guidance. Medex transducers were balanced before acquisition of hemodynamic data with the zero level at the midaxillary line. Measurements were made at end-expiration, and the average of three to five cardiac cycles was used.

Assessment of reproducibility. Intraobserver and interobserver reproducibilities were assessed in five randomly selected patients. The latter involved the second observer acquiring as well as measuring the data. Variability was expressed as the mean percent error, derived as the absolute difference between the two sets of observations, divided by the mean of the observations.

Statistics. Data are presented as mean value ± SD. Analysis of variance and the Bonferroni *t* test were used to compare differences between groups (see Results). Least-squares linear regression analysis was chosen to correlate continuous variables with each other. Significance was set at $p < 0.05$.

Results

Clinical characteristics and Doppler echocardiographic variables for the three groups are listed in Table 1. No significant differences were observed between the three groups in terms of age, heart rate or blood pressure. Both the normal and PN group displayed a higher E wave and E/A ratio, a lower atrial filling fraction and a shorter IVRT compared with the IR group. These variables were not different between the normal and PN groups. Ejection fraction was significantly reduced in the PN group compared with the other two groups.

Table 1. Clinical Characteristics and Doppler Variables in the Three Study Groups

	Normal (n = 34)	Impaired Relaxation (n = 40)	Pseudonormal (n = 51)
Age (yr)	59 ± 10	63 ± 11	61 ± 10
Male/female	17/17	19/21	30/21
Heart rate (beats/min)	79 ± 10.5	80 ± 15	83 ± 11
SBP (mm Hg)	129 ± 18	134 ± 22	122 ± 21
LVEF (%)	67 ± 5	65 ± 4	34 ± 12*
Mitral E (cm/s)	80 ± 16	53 ± 17*	82 ± 20
Mitral E/A ratio	1.4 ± 0.3	0.66 ± 0.14*	1.7 ± 0.5
IVRT (ms)	67 ± 9	99 ± 17*	60 ± 12
AFF	0.29 ± 0.06	0.39 ± 0.07*	0.28 ± 0.08

*$p < 0.001$ compared with each of the other two groups. Data presented are mean value ± SD or number of patients. AFF = atrial filling fraction; E/A = early to late transmitral flow velocity; IVRT = isovolumetric relaxation time; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

Doppler tissue imaging annular velocities (Table 2). The systolic velocity (S_a) measured at the lateral border of the mitral annulus was significantly reduced ($p < 0.05$) in the PN group (6 ± 1.5 cm/s) compared with the normal (10 ± 1.5 cm/s) and IR groups (8.4 ± 1.7 cm/s). In addition, S_a correlated significantly ($r = 0.6$, $p < 0.001$) with ejection fraction. A significant relation was observed between the early diastolic velocity (E_a) measured at the lateral border of the mitral annulus and the same velocity derived from the septal corner of the annulus ($r = 0.88$, $p < 0.0001$; lateral E_a = [1.05 × septal E_a] + 1.3). The lateral velocities were slightly higher than the septal velocities, as shown by the regression equation, and were often easier to quantify. For this reason, they were chosen for the rest of the statistical analysis. No relations were observed between any of the DTI variables and

Table 2. Doppler Tissue Imaging Annular Velocities in the Three Study Groups

	Normal (n = 34)	Impaired Relaxation (n = 40)	Pseudonormal (n = 51)
E_a (cm/s)	12 ± 2.8*	5.8 ± 1.5	5.2 ± 1.4
AT_a (ms)	68 ± 12	76 ± 21	74 ± 19
DT_a (ms)	84 ± 22*	168 ± 50	156 ± 42
AR_a (cm/s^2)	166 ± 24*	78 ± 21	72 ± 24
DR_a (cm/s^2)	132 ± 41*	40 ± 20.5	43 ± 18
A_a (cm/s)	8.4 ± 2.4	9.5 ± 2.1	7.9 ± 2.3†
E_a/A_a ratio	1.4 ± 0.4*	0.62 ± 0.2	0.66 ± 0.2
S_a (cm/s)	10 ± 1.5	8.4 ± 1.7	6 ± 1.5‡
E/E_a ratio	7.7 ± 3	7.8 ± 3.5	18 ± 4*

*$p < 0.001$ compared with the other two groups. †$p < 0.01$ compared with the impaired relaxation group. ‡$p < 0.05$ compared with the other two groups. Data presented are mean value ± SD. A_a = late diastolic velocity; AR_a = acceleration rate of E_a; AT_a = acceleration time of E_a; DR_a = deceleration rate of E_a; DT_a = deceleration time of E_a; E_a = early diastolic velocity; S_a = systolic velocity.

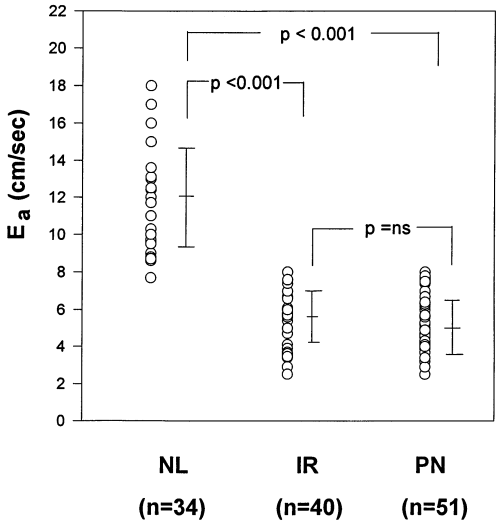

Figure 2. Comparison of E_a among the three study groups. NL = normal.

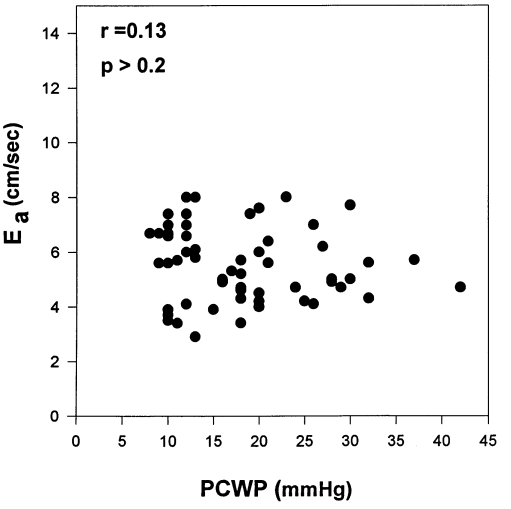

Figure 3. Plot of E_a versus mean PCWP. Note the lack of relation between the two variables.

heart rate or systolic blood pressure. In addition, there was no relation between any of the diastolic velocity measurements and ejection fraction.

Figure 1 illustrates examples of DTI velocities in representative cases from the three groups. In the normal group, E_a ranged from 7.5 to 18 cm/s, averaging 12 ± 2.8 cm/s. A significant inverse relation was observed between E_a and age ($r = -0.60$, $p < 0.001$) in the normal group. The E_a was significantly reduced in the PN (5.2 ± 1.4) and IR groups (5.8 ± 1.5) compared with the normal group ($p < 0.001$) (Fig. 2). The E_a was also reduced in the 14 PN patients with preserved systolic function (5.6 ± 2 cm/s). The E_a/A_a, acceleration rate and deceleration rate was similar to that of E_a. Deceleration time was longer in the two patient groups when compared with the normal group ($p < 0.001$). The ratio of the transmitral E wave velocity to E_a was elevated in the PN group compared with the other two groups ($p < 0.001$). Significant correlations were observed between E_a and the transmitral E wave velocity and E/A ratio using data from the normal and IR groups combined ($n = 74$; $r = 0.55$ and 0.5, respectively; $p < 0.01$). In contrast, no relation was found between these variables in the PN group.

Relation of filling pressures to Doppler echocardiographic and DTI variables. Sixty patients had measurements of mean PCWP; 26 belonged to the IR group and 34 to the PN group. Mean PCWP (20 ± 8 mm Hg [range 7 to 42]) correlated with the individual variables derived from the transmitral velocity, with a wide distribution of r values ranging from −0.32 for the mitral A wave to 0.72 for the E/A ratio. Of the pulmonary vein measurements, the systolic filling fraction had the best relation with PCWP ($r = -0.7$). No relation was observed between mean PCWP and E_a (Fig. 3). In contrast, the ratio of the transmitral E wave velocity to E_a related significantly with mean PCWP, with an r value of 0.87 ($R^2 = 0.76$, SEE = 3.87, $p < 0.001$) (Fig. 4A). Bland-Altman analysis (Fig. 4B) demonstrated a mean difference of 0.1 ± 3.8 mm Hg between catheter measurements and Doppler estimates of mean PCWP using the following regression equation; Mean PCWP = 1.91 + (1.24 E/E_a). The ratio of E wave velocity to the other variables derived from the diastolic annular velocity did not provide better results than E/E_a. An E/E_a ratio >10 was associated with the most optimal sensitivity (91%) and specificity (81%) for PCWP >12 mm Hg. Using a ratio of 8 resulted in a higher sensitivity (97%) but a lower specificity (62%), whereas a ratio of 12 resulted in a higher specificity (88%) but a lower sensitivity (68%). An E/E_a ratio >10 detected a mean PCWP >15 mm Hg, with a sensitivity of 97% and a specificity of 78%.

Reproducibility. The interobserver and intraobserver reproducibilities are shown in Table 3. Small differences were noted in all DTI variables. In addition, small differences were present in E/E_a and the Doppler estimate of mean PCWP. In absolute values, the interobserver and intraobserver differences for the Doppler estimate of mean PCWP ranged from 2 to 5 and 1 to 4 mm Hg, respectively.

Discussion

Doppler tissue imaging is a new development in ultrasonography that applies the Doppler principle (both in the pulsed wave and color modes) to record tissue velocities. Therefore, DTI can be used to quantitate the velocity of mitral annulus displacement during systole and diastole. These velocities reflect the longitudinal vector of myofiber shortening and lengthening, with each corner of the annulus being influenced more by the adjacent LV wall. Earlier studies using M-mode and two-dimensional echocardiography have demonstrated the importance of the longitudinal vector of contraction to global LV function (25,32). It is therefore not surprising that in the current investigation, a significant relation was observed between the systolic annular velocity (S_a) at the lateral border and ejection fraction. The primary aim of the study, however,

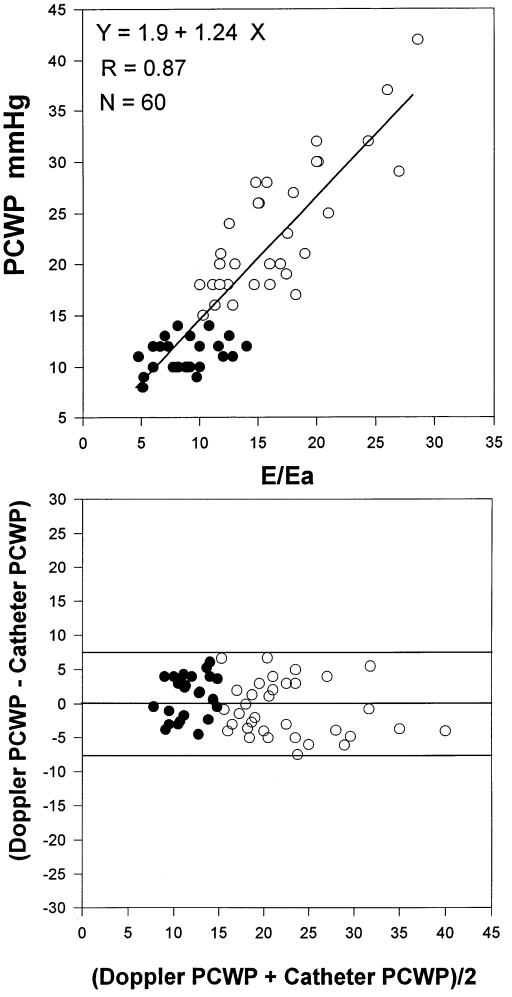

Figure 4. **Top,** Relation of E/E_a to PCWP. **Bottom,** Plot of the difference between Doppler-estimated and catheter-measured PCWP versus the average of both observations. **Solid circles** = patients with impaired relaxation; **open circles** = patients with a PN mitral inflow pattern.

was to assess the early diastolic velocity as an index of ventricular relaxation.

Diastolic annular velocity as a marker of myocardial relaxation. There is a growing body of evidence demonstrating that the early diastolic velocity recorded at the lateral border of the mitral annulus is a marker of myocardial relaxation. Left ventricular relaxation is known to decline with increasing age (33). Older individuals frequently display a transmitral velocity with a low E/A ratio and a prolonged deceleration time and IVRT (34,35). Rodriguez et al. (26) have recently shown a progressive decline in E_a with advancing age. We observed a similar trend in our normal group. When data from the normal group and the IR group were combined, E_a related significantly with the E wave velocity and the E/A ratio, again supporting the concept that this variable reflects myocardial relaxation. Furthermore, the early diastolic velocity of the posterior wall, recorded with DTI, has been recently

Table 3. Reproducibility of Doppler Tissue Imaging Measurements

	Interobserver Error (%)	Intraobserver Error (%)
E	4 ± 3	3 ± 2
E_a	5 ± 2	3 ± 2
A_a	5.5 ± 3	4.6 ± 2
E_a/A_a ratio	7 ± 4	5 ± 4
S_a	4 ± 2	4 ± 4
DT_a	11 ± 4	10 ± 6
DR_a	7 ± 6	10 ± 4
E/E_a ratio	6 ± 5	5 ± 4
PCWP	9 ± 4	7 ± 6

Data presented are mean value ± SD. PCWP = pulmonary capillary wedge pressure; other abbreviations as in Table 2.

demonstrated by Oki et al. (36) to relate inversely with the time constant of LV relaxation.

Impaired relaxation is a common denominator in patients with heart failure with or without systolic dysfunction (1–3). When these patients are in heart failure, the left atrial pressure increases in response to a reduction in LV compliance. This increase masks the influence of IR on the transmitral velocity and produces a PN pattern with an E/A ratio >1.0 and shortening of the IVRT and deceleration time (5,37,38). These patients, however, continue to have abnormal myocardial relaxation, which can be demonstrated with invasive measurements of the time constant of relaxation (38) and more recently with the flow propagation velocity of LV inflow assessed by color M-mode echocardiography (39–41). The present investigation demonstrates that E_a can also detect IR in patients with elevated LV filling pressures. The values for E_a observed in these patients were in the same range as those in the patients with IR and normal filling pressures. Furthermore, this variable showed no relation with mean PCWP.

The importance of E_a as a preload-independent index of LV relaxation goes beyond a simple distinction of the PN mitral inflow pattern from normal, because in most patients this distinction can often be deduced from clinical and echocardiographic variables that suggest the presence of impaired relaxation and by inspection of the pulmonary vein velocity. Of greater importance is the possibility that E_a could be used as a variable to follow noninvasively the effect of interventions on LV relaxation independent of the influence of these interventions on left atrial pressure. Future studies will be needed to demonstrate the sensitivity of E_a to changes in myocardial relaxation in the presence of different loading conditions.

Application of DTI annular velocities in the estimation of LV filling pressures. The mitral E wave velocity is directly influenced by left atrial pressure and inversely altered by changes in the time constant of relaxation (7,8). It is therefore not surprising that by itself, the E wave velocity relates poorly with left atrial pressure (10,12,14,17,18), given that abnormal relaxation and high filling pressures commonly coexist in the cardiac patient. However, it is conceivable that correcting E wave velocity for the influence of relaxation will improve its

relation with left atrial pressure. Studies using the early propagation velocity of LV inflow by color M-mode echocardiography support this hypothesis. The propagation velocity behaves as an index of LV relaxation (39–41), and the ratio of E wave velocity to propagation velocity (or its inverse) relates well with mean PCWP (42–44). This investigation demonstrates that dividing the E wave velocity by E_a provides an alternative method to correct the transmitral velocity for the influence of relaxation. We have observed an excellent correlation between E/E_a and mean PCWP in patients with a wide range of clinical conditions and rest ejection fractions. In comparison to propagation velocity, E_a is easily recorded and measured with DTI and is independent of systolic LV function, whereas propagation velocity is currently measured with different methods (39–41) and appears to have some relation to systolic performance (44).

Several regression equations have been proposed by previous investigators, including us, to estimate left-sided filling pressures using one or more variables derived from the transmitral or pulmonary vein velocity, or both (10–19). Some are simpler than others and all have been properly validated. To date, there are no studies comparing the accuracy of one method with another. The 95% confidence limit (2 SD) of E/E_a was 7.6 mm Hg, and thus, this method provides only an estimate of filling pressures close to that provided by several of the published equations. However, the E/E_a is relatively simple to obtain and conceptually has the potential for providing a reasonable estimate of filling pressures throughout a wide range of relaxation abnormalities. Furthermore, an E/E_a ratio >10 may be used to detect patients with high filling pressures.

Study limitations. Annular velocities may vary with the site of sampling, and thus, the utility of this method is dependent on the location of the sample volume. We chose the lateral aspect of the mitral annulus, because this site is easy to obtain from the apical window and, in contrast to the parasternal window, the velocities should not be influenced by anteroposterior translation. Analysis of the lateral annular motion is in part affected by the underlying regional function; thus, ischemia or infarction of the basal lateral wall can significantly lower E_a. Fortunately, the base of the lateral wall is seldom involved in ischemic heart disease.

Mean PCWP was obtained with fluid-filled catheters and was used as a measure of left atrial pressure. Although micromanometer-tipped catheters would have been ideal, this would have limited our sample size. Furthermore, the method used is the standard used in the clinical setting and has been well validated (45,46).

Our study group included only patients in sinus rhythm. The performance of this method in the presence of nonsinus rhythms is currently unknown. However, we have recently observed that the ratio of E wave velocity to propagation velocity by color M-mode echocardiography relates directly with LV filling pressures in patients with atrial fibrillation (43). Consequently, it is likely that the E/E_a ratio will allow estimation of filling pressures in the absence of atrial contraction. This concept, however, requires further evaluation. None of the patients in this investigation had more than mild mitral regurgitation, and thus, the utility of this method in patients with severe mitral insufficiency is unknown.

Conclusions. The current investigation demonstrated that E_a may be used as an index of LV relaxation. Using E_a we identified patients with relaxation abnormalities independent of the filling pressures and, consequently, differentiated the PN group from the normal group. Furthermore, the ratio of the transmitral E velocity to E_a related significantly with mean PCWP, suggesting that this simple measurement can be used as an index of filling pressures. In addition, E_a has the potential to be used for detecting serial changes in LV relaxation during interventions that may alter filling pressures.

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