Tissue Doppler Imaging: A New Prognosticator for Cardiovascular Diseases

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STATE-OF-THE-ART PAPER

Tissue Doppler Imaging

A New Prognosticator for Cardiovascular Diseases

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Tissue Doppler imaging (TDI) is evolving as a useful echocardiographic tool for quantitative assessment of left ventricular (LV) systolic and diastolic function. Recent studies have explored the prognostic role of TDI-derived parameters in major cardiac diseases, such as heart failure, acute myocardial infarction, and hypertension. In these conditions, myocardial mitral annular or basal segmental (Sm) systolic and early diastolic (Ea or Em) velocities have been shown to predict mortality or cardiovascular events. In particular, those with reduced Sm or Em values of <3 cm/s have a very poor prognosis. In heart failure and after myocardial infarction, noninvasive assessment of LV diastolic pressure by transmitral to mitral annular early diastolic velocity ratio (E/Ea or E/Em) is a strong prognosticator, especially when E/Ea is ≥15. In addition, systolic intraventricular dyssynchrony measured by segmental analysis of myocardial velocities is another independent predictor of adverse clinical outcome in heart failure subjects, even when the QRS duration is normal. In heart failure patients who received cardiac resynchronization therapy, the presence of systolic dyssynchrony at baseline is associated with favorable LV remodeling, which in turn predicts a favorable long-term clinical outcome. Finally, TDI and derived deformation parameters improve prognostic assessment during dobutamine stress echocardiography. A high mean Sm value in the basal segments of patients with suspected coronary artery disease is associated with lower mortality rate or myocardial infarction and is superior to the wall motion score. (J Am Coll Cardiol 2007;49:1903–14)

Echocardiography is now the most commonly used noninvasive tool for the assessment of cardiac anatomy and function. In addition to commonly established roles such as confirming diagnosis, etiologic work-up, complication screening, and disease monitoring, echocardiography plays an important clinical role in prognostic assessment. Conventional echocardiographic predictors of poor outcome, such as left ventricular (LV) ejection fraction (EF) and restrictive filling pattern have recently been supplemented by tissue Doppler imaging (TDI).

Tissue Doppler imaging is a robust and reproducible echocardiographic tool which has permitted a quantitative assessment of both global and regional function and timing of myocardial events (1,2). In clinical practice, the myocardial time-velocity curve can be reconstructed either on line as spectral pulsed TDI or off line from 2-dimensional (2D) color-coded TDI image loops. It is important to recognize that myocardial velocities obtained from the on-line spectral pulsed TDI curve are higher than those reconstructed off-line from 2D color-coded TDI images. Most published studies have examined the long-axis function of the heart by TDI from apical views. A number of parameters from TDI have been proposed to be useful in various cardiac diseases (Tables 1 and 2). In systole, potentially important prognosticators of TDI include peak systolic velocity in ejection period measured at mitral annulus (Sa) or at myocardial segments (Sm) (Fig. 1) as well as systolic dyssynchrony assessment. In diastole, potentially important prognosticators include peak myocardial early diastolic velocity measured at the mitral annulus (Ea) or myocardial segments (Em) (Fig. 1) as well as measurement of transmitral to TDI early diastolic velocity ratio (E/Ea). These myocardial velocity measurements with TDI have been shown to be useful in various diseases (3), including heart failure (HF), hypertension, and acute myocardial infarction (MI), and in patients undergoing stress echocardiography for suspected coronary heart disease.

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Peak Systolic Annular (Sa) or Basal Ventricular Velocity (Sm)

Mitral annular or basal LV velocities reflect the long-axis motion of the ventricle, which is an important component of LV systolic and diastolic function (4). Subendocardial

Abbreviations and Acronyms

CI = confidence interval
DT = deceleration time
Ea = early diastolic velocity at mitral annulus
EF = ejection fraction
Em = early diastolic velocity at myocardial segments
HF = heart failure
HR = hazard ratio
LV = left ventricle
LVEF = left ventricular ejection fraction
MI = myocardial infarction
Sa = peak systolic velocity at mitral annulus
Sm = peak systolic velocity at myocardial segments
TDI = tissue Doppler imaging

fibers make a substantial contribution to long-axis function, and these are particularly susceptible to disturbance by various diseases and pathologies. Because the LV apex is stationary, simple M-mode measurement of mitral annulus excursion provides a useful and sensitive measure of ventricular function which is rapidly affected by ischemia (4). The amplitude of long-axis motion during systole also correlates well with LVEF, which is also true for the right ventricle (5).

However, M-mode measurements of the mitral or tricuspid annulus amplitude are more laborious than measuring the peak systolic and diastolic velocities by TDI, and the time course of this movement is less readily obtained by M-mode. Peak myocardial systolic velocity averaged from 6 sites around the mitral annulus correlates well with LVEF, and a cut-off of >7.5 cm/s had a sensitivity of 79% and a specificity of 88% in predicting normal global LV function (6). The peak systolic velocity is also a sensitive marker of mildly impaired LV systolic function, even in those with a normal LVEF or apparently preserved LV systolic function, such as "diastolic heart failure" (7), or in diabetic subjects without overt heart disease (8). Reduced TDI velocities are present also in subjects with hypertrophic cardiomyopathy mutations at a time of subclinical disease when cardiac hypertrophy is not present (9). Therefore, TDI can be used for early identification of hypertrophic cardiomyopathy.

Given the above observations, it is not surprising that peak annular or basal systolic velocities are strong predictors of outcome in several conditions. Wang et al. (10) followed a cohort of 518 subjects (353 with cardiac disease and the rest normal) for 2 years after measuring the average mitral annular velocities from 4 sites (septal, lateral, anterior, and inferior) from color-coded TDI. They found that cardiac mortality was significantly higher when both Sm and Em were <3 cm/s (hazard ratios [HRs] 7.5 and 5.3, respectively), although in the multivariate analysis Em had a stronger impact on mortality than Sm. Survival curves (Fig. 2) for both Sm and Em clearly show the impact of Sm <3 cm/s on mortality. In a study of 185 patients with HF and LVEF <45% over a median follow-up of 32 months (11), only mean color Sm velocity (HR = 0.648 [95% confidence interval (CI) 0.460 to 0.912]; p = 0.013) and diastolic arterial pressure (HR = 0.966 [95% CI 0.938 to 0.994]; p = 0.016) were independent predictors of outcome. In a group of asymptomatic patients with severe mitral regurgitation but normal LVEF, Agricola et al. (12) showed that TDI of the lateral mitral annulus systolic velocity could predict those who would develop LVEF reduction after mitral valve surgery.

In coronary heart disease, TDI-derived systolic velocities have been used as an adjunct to wall motion scores as a predictor of risk (13). In a study of 174 hypertensive patients with LV hypertrophy, TDI velocities were lower than in control subjects and univariate analysis showed that low Sm, Em, and late diastolic velocity (Am) were associated with cardiac mortality after 36 months of follow-up (14). However, in a multivariate analysis, Em emerged as the most powerful independent prognostic indicator.

Peak Early Diastolic Velocity (Em)

A number of diastolic parameters have been used for assessing prognosis, the commonest being a short deceleration time (DT) and a persistent restrictive filling pattern, which are well known to be associated with a poor prognosis in HF (15). Although Sm is a good predictor of outcome, in many studies Em appeared to be superior. In the study with

Table 1 Potentially Useful Parameters of Systolic and Diastolic Function by Tissue Doppler Imaging

Parameters	Period of Cardiac Cycle	Number of Segments Measured	Sampling Level
Systole			
Sa	Ejection period	Single or mean of 2 segments	Mitral septal or lateral annulus
Sm	Ejection period	Single or mean of 6 basal segments	Basal LV segments
Dyssynchrony	Time to peak or onset of Sm	Multiple, from 2 to 12 segments	Basal ± mid segments
Diastole			
Ea	Early diastole	Single or mean of 2 segments	Mitral septal or lateral annulus
Em	Early diastole	Single or mean of 6 basal segments	Basal LV segments
Aa or Am	Late diastole	1 or 2 for Aa, up to 6 basal segments for Am	Mitral annulus for Aa, basal segments for Am
Ea/Aa or Em/Am	Diastole	1 or 2 for Aa, up to 6 basal segments for Am	Mitral septal or lateral annulus for Ea/Aa, basal segment for Em/Am
E/Ea or E/Em (filling pressure)	Early diastole	Single or 2 locations	Mitral septal or lateral annulus for E/Ea, basal septal or lateral segment for E/Em

Aa = mitral annular velocity during late diastole; Am = myocardial segmental velocity during late diastole; E/Ea = transmitral to mitral annular early diastolic velocity ratio; E/Em = transmitral to basal septal myocardial early diastolic velocity ratio; Ea = mitral annular velocity during early diastole; Ea/Aa = mitral annular early to late diastolic velocity ratio; Em = myocardial segmental velocity during early diastole; Em/Am = myocardial early to late diastolic velocity ratio; LV = left ventricular; Sa = mitral annular systolic velocity; Sm = myocardial segmental systolic velocity.

Table 2 Summary of Studies Which Assessed the Prognostic Importance of Tissue Doppler Imaging (TDI) Parameters in Cardiac Diseases

Author	Parameters	Disease Group	Sample Size	Follow-Up Duration	End Point Measure	Predictors of Event	Other Findings
1. Resting echocardiography with TDI							
Wang et al. (10)	Mean Sm, Em, Am from 4 basal LV segments	Various heart diseases	353 patients 165 controls	23 months	Mortality	Sm ≤3 cm/s, Em <3 cm/s, Am ≤4 cm/s	Em adds independent prognostic value to clinical data and deceleration time
Richartz et al. (17)	Sa and Ea at septal and lateral mitral annulus	HF (idiopathic dilated cardiomyopathy)	40 patients 25 controls	Cross-sectional study	Acute pulmonary edema	Ea	Patients with recent onset acute pulmonary edema were associated with lower Ea than stable HF patients but had similar Sa
Wang et al. (16)	Mean Sm, Em, Am from 4 basal LV segments, E/Em	HF	182 patients	48 months	Cardiac mortality	Sm, Em, Am, E/Em	Em <3 cm/s and E/Em >15 had independent prognostic value to clinical data and deceleration time
Dokainish et al. (23)	E/Ea (Ea averaged from septal and lateral mitral annulus)	HF	116 patients	18 months	Cardiac mortality or HF hospitalization	E/Ea ≥15	E/Ea ≥15 adds independent prognostic value to BNP and ejection fraction
Yamamoto et al. (24)	E/Ea, Aa	HF	96 patients	29 months	Cardiac mortality or HF hospitalization	E/Ea ≥15, Aa ≥5 cm/s	Both E/Ea ≥15 and Aa ≤5 cm/s independently predicted a worse prognosis
Hillis et al. (27)	E/Ea	AMI	250 patients	13 months	Mortality	E/Ea ≥15	E/Ea ≥15 has independent predictive value
Wang et al. (14)	Sm, Em, Am	Hypertension	174 patients 78 controls	19 months	Cardiac mortality	Sm, Em, Am	Em <3.5 cm/s is an independent prognosticator, together with IVSd >1.4 cm
2. Stress echocardiography with TDI							
Marwick et al. (13)	Mean Sm from 6 basal LV segments	DSE for suspected CHD	576 patients	16 months	Mortality or AMI	Sm >6 cm/s	Sm >6 cm/s predicted a lower event rate, but not wall motion score
3. Dyssynchrony assessment with TDI							
Bader et al. (58)	Maximum difference of time to onset of Sm at 4 basal LV segments	HF	104 patients	12 months	HF hospitalization	Intraventricular dyssynchrony	Intraventricular but not interventricular dyssynchrony predicted HF events
Cho et al. (60)	Ts-SD or Ts-diff from 4 basal and 4 mid LV segments	HF and QRS ≤120 ms	106 patients	17 months	Mortality, cardiac transplantation, or HF events	Ts-SD >37 ms, Ts-diff >91 ms	Ts-SD >37 ms has sensitivity of 68% and specificity of 71%, and Ts-diff >91 ms has sensitivity of 70% and specificity of 68% to predict events
Bax et al. (65)	Septal-to-lateral wall delay in time to peak Sm	HF, received CRT	85 patients	12 months	Mortality or HF hospitalization	Septal-to-lateral wall delay	Septal-to-lateral wall delay ≥65 ms has a sensitivity and specificity of 80% to predict clinical improvement

AMI = acute myocardial infarction; CHD = coronary heart disease; CRT = cardiac resynchronization therapy; DSE = dobutamine stress echocardiography; HF = heart failure; IVSd = thickness of interventricular septum at end-diastole; LV = left ventricular; Ts-diff = maximum difference in time to peak systolic velocity; Ts-SD = standard deviation of time to peak systolic velocity; other abbreviations as in Table 1.

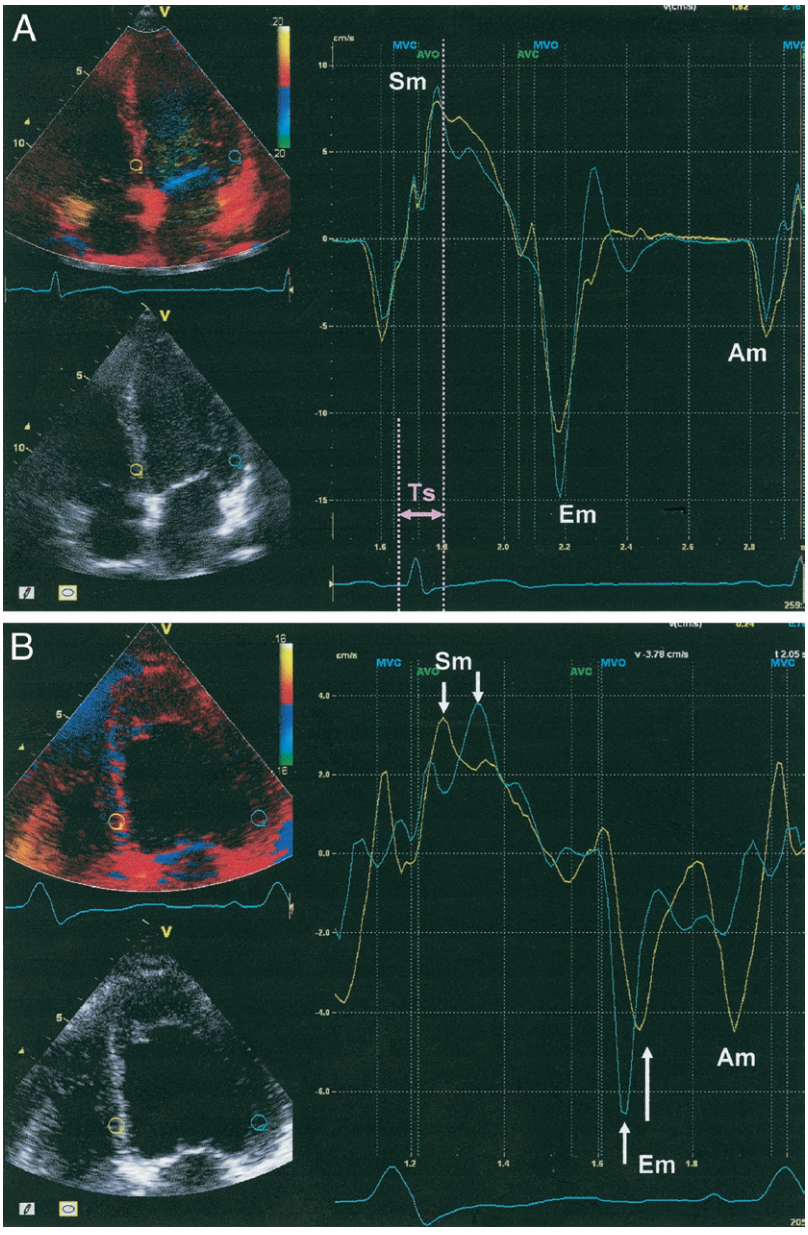

Figure 1 **Examples of Measures on Myocardial Velocity Curve**

Measurement of peak myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities, as well as the time to peak systolic velocity in ejection phase (Ts) at basal septal and basal lateral segments by 2-dimensional color-coded tissue Doppler imaging in a normal subject **(A)** and in a patient with systolic heart failure and wide QRS complex **(B)**. Myocardial velocity curves are reconstituted offline from the color tissue Doppler images. Note that in heart failure there is a reduction of Sm and Em. Systolic dyssynchrony is demonstrated by the delay of Ts in the basal lateral segment when compared with the basal septal segment. AVO and AVC = aortic valve opening and closure, respectively; MVO and MVC = mitral valve opening and closure, respectively.

a large population with various cardiac diseases, TDI measurements (Sm, Em, and Am) were significantly associated with outcome, independent of and incremental to clinical data and DT <160 ms, even after adjustment for age and LV/left atrium geometry (10). In the multivariate analysis, however, Em has the strongest impact on cardiac mortality among the TDI variables. Similarly, in patients with impaired LV systolic function, Wang et al. (16) found that an Em of <3 cm/s was the best prognostic index in long-term follow-up, and it added incremental value to indexes of systolic or diastolic function, including a DT of <140 ms and an E/Em of >15. Similar results were found by the same group in hypertensive subjects with LV hypertrophy, where again a low Em improved the outcome of a model that contained clinical risk factors, increased septal thickness, and either a pseudonormal or restrictive filling

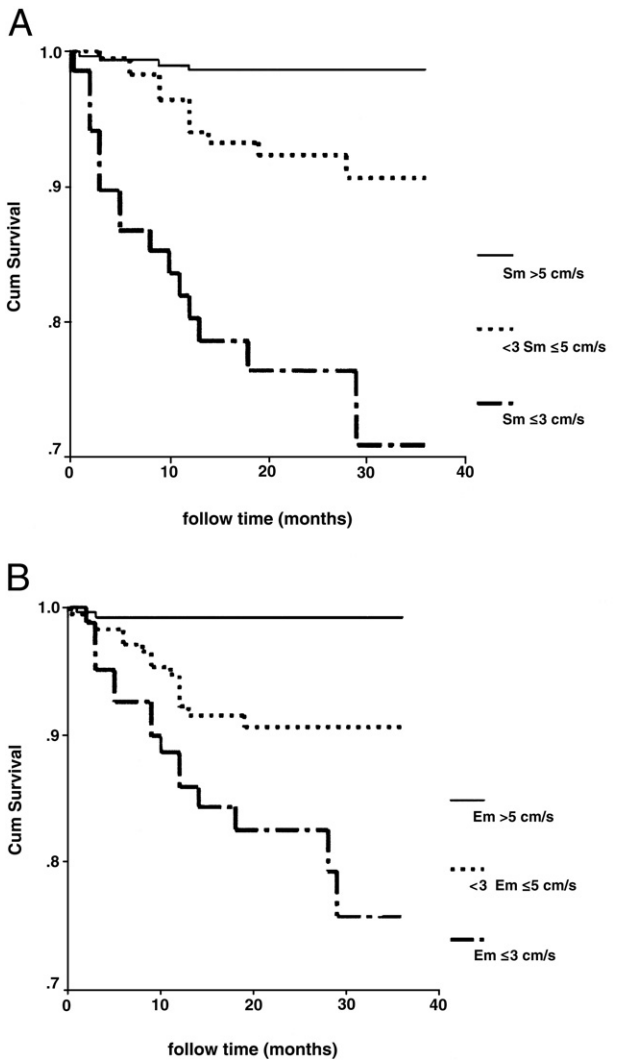

Figure 2 **Cumulative Cardiac Death in Patients Grouped by Tissue Doppler Imaging Parameters**

Tertiles of peak systolic velocity (Sm) and peak early diastolic velocity (Em) in a cohort of a variety of cardiac diseases. Reprinted with permission from Wang et al. (16).

pattern (14). In patients with idiopathic dilated cardiomyopathy, Em was significantly lower in those who recently had pulmonary edema than in those who were clinically stable (17). Clinical improvement also paralleled a rise in Em. Thus, it appears that Em alone may be a more sensitive marker and a more powerful predictor of outcome than Sm or possibly E/Em, although the latter is a useful index of LV filling pressure per se.

E/Ea (or E/E′) and E/Em

The early diastolic velocity of the longitudinal motion of the mitral annulus (Ea) reflects the rate of myocardial relaxation (18). The velocity of the mitral annulus can be recorded by TDI, and this has become an essential part of evaluating diastolic function by echocardiography (19–21). In normal subjects Ea increases as transmitral gradient increases with exertion or increased preload, whereas in patients with impaired myocardial relaxation Ea is reduced at baseline and does not increase as much as in normal subjects with increased preload (22). Lateral annulus early diastolic velocity is usually higher than septal annulus Ea. The Ea increases with increasing transmitral gradient in healthy individuals, so that E/Ea is similar at rest and with exercise (usually <8).

Decreased Ea is one of the earliest markers for diastolic dysfunction and is present in all stages of diastolic dysfunction (see the preceding text). Because Ea velocity remains reduced and mitral E velocity increases with higher filling pressure, the ratio between transmitral E and Ea (E/Ea, also written as E/E′), correlates well with LV filling pressure or pulmonary capillary wedge pressure (PCWP) (19–21). The PCWP is $\geq$20 mm Hg if E/Ea is $\geq$15 and normal if E/Ea is <8 (Fig. 3). Because PCWP has been shown to be a prognostic indicator in patients with HF, it is reasonable to expect E/Ea to be a similarly powerful prognosticator in various cardiac diseases. Indeed, both E/Ea $\geq$15 and B-type natriuretic peptide $\geq$250 pg/ml carried independent prognostic value in patients with HF (23). The independent predictive value of E/Ea $\geq$15 for cardiac mortality or HF hospitalization has been confirmed in 96 patients with LV dysfunction (24).

When the filling pressure index is calculated from the ratio between transmitral E and basal segmental Em, it is called E/Em. In a prospective study of 182 patients with impaired LV systolic dysfunction, Em (average from 4 annular sites) and E/Em were found to be good prognosticators after 48 months of follow-up (16). The E/Em was $\geq$15 in 97% of the deceased patients, among whom the average E/Em was 36 $\pm$ 18, compared with 25 $\pm$ 15 in the survivors.

In patients with acute MI, a restrictive filling pattern or a short DT are predictors of LV remodeling and mortality (25,26). The E/Ea ratio has also been found to be a strong predictor for survival after acute MI (27,28). In a study of 250 patients with acute MI, echocardiograms were performed 1 to 3 days after admission, and the patients were followed for a median of 13 months. A total of 73 patients (29%) had E/Ea $>$15, which was the most powerful independent predictor of survival (risk ratio 4.8) (Fig. 4). The addition of E/Ea $>$15 significantly improved the prognostic utility of a model containing clinical variables and conventional echocardiographic indices of LV systolic and diastolic function (Fig. 5) (27). Moreover, the Ea of the patients with E/Ea $>$15 was significantly lower than that of the patients with E/Ea $<$15 (4.67 vs. 7.27 cm/s; $p < 0.001$).

Because both LV remodeling with progressive LV dilatation and increased filling pressure expressed by E/Ea predict poor outcome after acute MI, they should be related. Therefore, 47 patients were examined 3 days and 8 weeks after their first MI. The E/Ea was much higher in patients who increased LV end-diastolic volume $>$15% (i.e., remod-

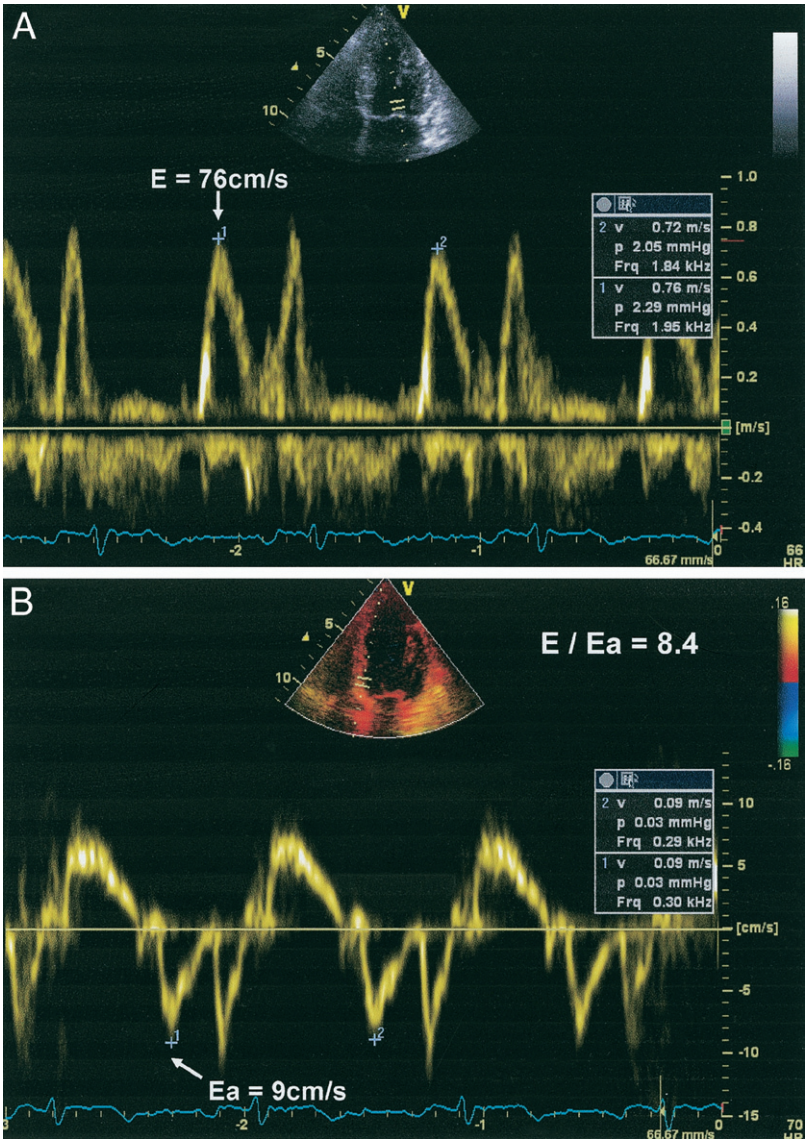

Figure 3 **Estimation of Left Ventricular Diastolic Pressure by Tissue Doppler Imaging**

Estimation of left ventricular diastolic pressure by the ratio of transmitral E **(A)** and mitral septal annular velocity **(B)**, E/Ea. The E/Ea ratio in this patient is 8, which is within normal limits. His Ea is also within normal limits. *Continued on next page.*

eled) compared with the value in patients without remodeling (19 vs. 10) (28). Patients with E/Ea >15 had a greater increase in indexed LV end-diastolic volume (9.3 vs. 1.7 ml/m^2).

Although patients with dilated cardiomyopathy have similar global systolic dysfunction, their clinical symptoms and hemodynamic status (diastolic filling pattern, pulmonary arterial systolic pressure, severity of mitral regurgitation) can differ markedly. One group of these patients may be minimally symptomatic, whereas another group may have chronic HF symptoms. Doppler and color-flow imaging provide important hemodynamic information that is helpful in assessing LV filling pressures, management strategy, and prognosis. The evolution of diastolic dysfunction from an impaired relaxation pattern to a restrictive filling pattern was demonstrated elegantly in an animal model with tachycardia-induced cardiomyopathy (29,30). The Ea was reduced from an early stage of reduced LV systolic function and remained reduced even with increased filling pressure. The diastolic filling variables (E, DT, and E/Ea), which have a good correlation with PCWP, have an incremental prognostic power over what LVEF can provide. The shorter the DT and the higher the E/Ea, the worse the prognosis (31,32). As a patient's HF is treated, diastolic filling becomes less restrictive and DT increases. The persistence of the restrictive filling after therapy is associated with a

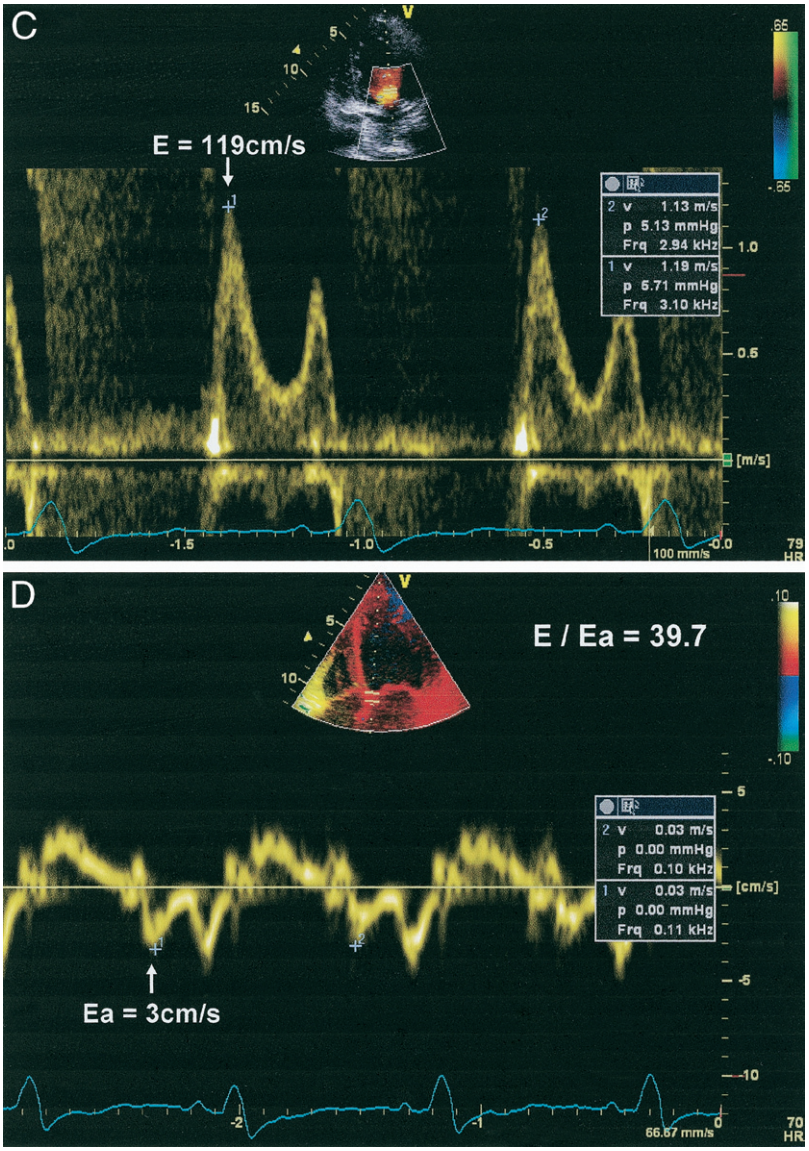

Figure 3 Continued

(C and D) A patient with elevated left ventricular diastolic pressure and E/Ea ratio of 40, which is significantly elevated. Note also that the Ea is severely reduced to only 3 cm/s. Both of these parameters were associated with poor prognosis.

high mortality and transplantation rate. Patients with reversible restrictive filling have a high probability of improvement and excellent survival (33).

Prognostic Significance of the Stress Response by TDI

Stress echocardiography is a valuable tool for predicting outcome in patients with known or suspected coronary heart disease: The risk of a major event in a patient with a negative test is ≤1% per year. However, the prognostic significance of ischemia is more ambiguous, with an event rate of approximately 20% over 2 to 3 years, implying a spectrum of risk among patients with positive test results. Although wall motion scoring is a means of discriminating a mildly from a markedly positive test, this technique has some variability between sites and observers (34).

The stress response of TDI has been studied as an adjunct to wall motion scoring for the prediction of outcome in patients undergoing dobutamine stress echo (13). In that study, color tissue velocity imaging and tissue tracking were performed in the basal and middle segments of the heart, the apex being ignored because tissue velocity in that area is close to 0. Peak velocities derived from post-processing of color images were averaged, to account for the contractile response not only in the area with abnormal wall motion but also the ability of remote segments to compensate. Average

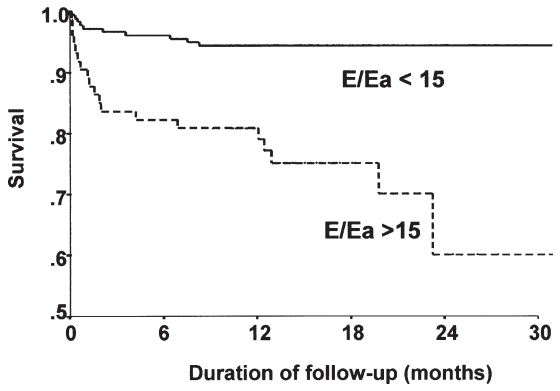

Figure 4 **Survival Curve Stratified by E/Ea in Patients With Acute Myocardial Infarction**

Patients with E/Ea >15 were associated with a significantly higher mortality. Reprinted with permission from Hillis et al. (27). E/Ea = transmitral to mitral annular early diastolic velocity ratio.

peak myocardial velocity or displacement was then correlated with outcome over a follow-up of 16 months. In 251 patients with an abnormal test, 22 died and 7 had nonfatal MIs. The average wall motion score was not significantly different in patients with and without events (1.8 ± 0.5 vs. 1.7 ± 0.5; p = NS), but the average peak systolic velocity in patients with events was significantly lower than in those without events (4.9 ± 1.7 cm/s vs. 6.4 ± 6.5 cm/s; $p < 0.001$). Similarly, the average tissue displacement in patients with events was significantly lower than in those without events (4.5 ± 1.5 cm vs. 5.7 ± 3.1 cm; $p < 0.001$). Development of receiver operating characteristic curves demonstrated an area under the curve of 0.74 for a prediction of adverse outcome in patients with a positive test, and the optimal cut-off was identified as a mean basal velocity of 6 cm/s (Fig. 6).

These data suggest that quantification of function using TDI is able to supplement visual wall motion analysis. The findings are consistent with angiographic comparisons that identify patients with coronary heart disease based upon failure to augment tissue velocity with stress (35) as well as with studies of valvular disease demonstrating that tissue velocity responses correspond to the presence of myocardial contractile reserve (36). Nonetheless, tissue velocity has a fundamental limitation of examining tissue movement in relation to the transducer rather than relative to adjacent segments. Therefore, measurements within a segment may be colored by the behavior of adjacent segments. This may pose a particular limitation to the prognostic assessment of patients with positive scans, because problems with wall motion assessment particularly relate to segments with hypokinesia at rest, where difficult judgments are required as to whether the tissue has improved or deteriorated function in response to stress. A more site-specific approach such as strain rate or strain imaging could overcome this limitation. Moreover, these alternative measurement approaches would permit assessment of apical function, which is difficult with tissue Doppler measurements alone.

Prognostic Significance of Resting Strain

Over the last 5 years, myocardial deformation imaging has become possible initially with tissue Doppler (37), and more recently with myocardial speckle-tracking using 2D echocardiography (38). Unlike simple tissue velocity measurements, deformation measurements are specific for the region of interest and therefore not subject to cardiac tethering. Measurements of myocardial deformation with these techniques have been validated using microcrystals and magnetic resonance (39,40). Signal noise and angle dependency are particularly problematic with the tissue Doppler approach, and although the speckle-tracking approaches may be less sensitive to these problems issues related to image quality are likely to be even more important (41). These techniques are less robust and more technically challenging than TDI velocity measurement and probably not ready for routine clinical use.

Strain rate or strain measurements have been used as sensitive indicators for subclinical diseases including hypertension, diabetes, Fabry's disease, and infiltrative disorders (42). Indeed, reduction of strain and strain rate has been correlated with myocardial fibrosis, which itself is a marker of risk in patients with cardiac disease (43). In addition to their role as sensitive diagnostic techniques, they have also been used in following the response of the myocardium to therapy (44). Although the prognostic implications of strain responses with therapy are undefined, it seems likely that increases in deformation would be associated with improved

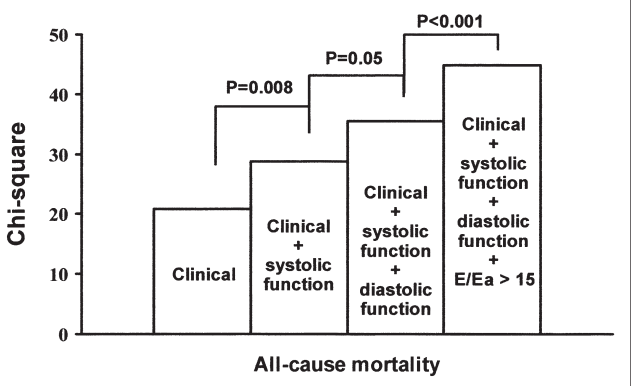

Figure 5 **Incremental Value of E/Ea >15 in Predicting All-Cause Mortality**

The addition of left ventricular ejection fraction (LVEF), deceleration time (DT), and the ratio of transmitral E and mitral annular velocity (E/Ea) resulted in significant incremental improvements in the predictive value of a model including clinical variables (age, Killip class ≥2 on admission, anterior myocardial infarction, and myocardial revascularization during the index admission): chi-square = 20.8 for clinical factors; chi-square = 28.8 for clinical factors plus LVEF; chi-square = 33.2 for clinical factors plus LVEF plus DT ≤140 ms; and chi-square = 43.0 for clinical factors plus LVEF plus DT ≤140 ms plus E/Ea >15. Reprinted with permission from Hillis et al. (27).

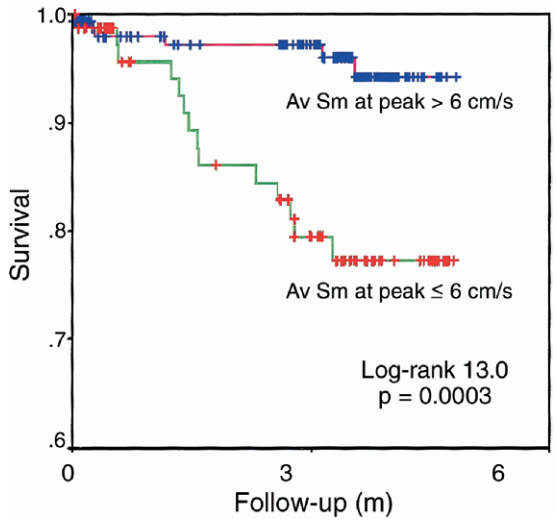

Figure 6 **Survival Curves of Patients With Suspected CHD Undergoing DSE and TDI**

Patients with an average peak basal systolic velocity (Av Sm) of >6 cm/s were associated with a higher mortality than those Av Sm ≤6 cm/s. Reprinted with permission from Marwick et al. (13). CHD = coronary heart disease; DSE = dobutamine stress echocardiography; TDI = tissue Doppler imaging.

outcome, and improvements in the techniques may give this modality a valuable role in following up the LV response to therapy.

Prognostic Significance of Strain Responses to Stress

Augmentation of strain rate and strain with dobutamine is a marker of myocardial viability, evidenced either by the identification of viable tissue using other techniques such as positron emission tomography (45) or by detection of recovery after revascularization (46). The likelihood of prognostic benefit after revascularization of viable tissue increases in proportion to the number of viable segments (47). Whether the presence and extent of deformation with low-dose dobutamine can be anticipated to predict outcome (rather than functional recovery) remains unproven.

The transmural extent of infarction (TME) may be identified from late enhancement of magnetic resonance images after gadolinium injection (48). The TME is another determinant of the functional recovery of myocardium that may be prognostically important. Although subendocardial infarction has been identified with tissue Doppler-based strain in experimental models (49), the distinction between subendocardium and subepicardium is challenging at greater imaging depths in humans, because of the low lateral resolution of the technique. However, the degree of impairment of longitudinal strain rate has been reported to correlate with TME (50). Radial and circumferential 2D strain may be potential markers of TME (51).

Deformation parameters change with myocardial ischemia, but the use of these data as a diagnostic tool presents some significant challenges related to signal noise at peak stress. Nonetheless, one study has shown the technique to have incremental benefit to wall motion analysis in the identification of myocardial ischemia (52). Moreover, myocardial deformation at peak stress is related to the likelihood of cardiac events, incremental to regional wall motion assessment (53).

Rationale for the Assessment of Systolic Dyssynchrony by TDI

Electromechanical delay is caused by delay of electrical propagation within the LV resulting in mechanical dyssynchrony. During propagation of the electrical impulse in the LV, an area of functional electrical conduction delay usually occurs in the anterior wall. This results in a "U-shaped" endocardial activation pattern that starts from the septum, curves around the apex, and causes delayed activation of the LV free wall (54,55). These patients will have prolonged QRS duration, although this is not an exclusive phenomenon. In HF subjects, systolic dyssynchrony is potentially a marker for disease severity and may act as a prognosticator. Therefore, systolic dyssynchrony is now included as part of the HF assessment by echocardiography.

Echocardiography is the most widely used tool to assess mechanical dyssynchrony, and TDI has been found to be the most useful among different echocardiographic modalities. Although myocardial velocity curves can be constructed either on line from spectral pulse TDI or off line from 2D color TDI, the latter approach is preferable, because multiple segments can be compared within the same heart beat (Fig. 1). To assess systolic dyssynchrony, the time to peak or onset of systolic velocity is measured from individual segments (56,57). In addition, other parameters of systolic dyssynchrony, such as strain dyssynchrony, can be derived from these raw data.

Prognostic Importance of Systolic Dyssynchrony

The prognostic importance of systolic dyssynchrony was initially reported by Bader et al. (58), who examined 104 HF patients with an EF of ≤45% (mean 31%) who were followed for 1 year. Intraventricular delay was examined by spectral pulsed TDI in the apical 4- and 2-chamber views to delineate the LV long-axis motion. The time to the onset of ejection phase contraction in the systolic wave was measured from the basal segments of septal, lateral, anterior, and inferior walls, and the maximal time difference among the 4 segments was calculated as an index of intraventricular dyssynchrony. Interventricular dyssynchrony was calculated as the difference between aortic and pulmonary pre-ejection period. At 1-year follow-up, although there was no mortality, 86 patients (83%) were admitted for worsening HF. Intraventricular dyssynchrony, but not interventricular dyssynchrony, was found to be the most important independent

predictor of HF event (β = 1.47; p < 0.001) by the Cox multivariate analysis model. The other 2 independent predictors included LVEF <25% (β = 1.34; p < 0.001) and QRS >140 ms (β = 0.82; p = 0.04) (58).

The important prognostic value of systolic dyssynchrony not only applies to patients with HF and prolonged QRS duration but is also confirmed in patients with narrow QRS complexes. In fact, systolic dyssynchrony is a common condition in HF, with a prevalence range from 27% to 43% depending on methodologies (56,57,59). In a study of 106 HF patients with EF <35% (mean 28%) and QRS duration ≤120 ms, intraventricular dyssynchrony was measured from both basal and middle LV segments on apical 4- and 2-chamber views, and the standard deviation of the time to peak systolic velocity (Ts-SD) was derived from the 8 LV segments through off-line analysis (60). During the follow-up period of 17 ± 11 months, HF decompensation or cardiac transplantation occurred in 35 patients (33%) and mortality in 18 (17%). From the receiver-operating characteristic curves, a Ts-SD value of >37 ms has a sensitivity of 68% and specificity of 71% to predict event-free survival, and these figures were 70% and 68% respectively for a maximum difference in time to peak systolic velocity (Ts-diff) value of >91 ms (60). The hazard ratio for the cut-off values for Ts-SD and Ts-diff were 3.89 and 4.26, respectively. Importantly, QRS duration was not an independent prognosticator. Therefore, all of these studies suggested that assessment of systolic dyssynchrony in HF patients provides prognostic information independent of QRS duration.

Prognostic Implications of Systolic Dyssynchrony in the Cardiac Resynchronization Therapy (CRT) Era

The assessment of systolic dyssynchrony is particularly valuable in the cardiac resynchronization therapy (CRT) era. Currently, patients with New York Heart Association functional class III or IV HF despite optimal medical treatment, an EF of <35%, and dilated left ventricle who had prolonged QRS duration >120 to 130 ms are eligible for CRT with biventricular pacemaker or biventricular defibrillator therapy. From these criteria, QRS duration is the only parameter to suggest the presence of electromechanical delay. Because this parameter only has modest sensitivity and specificity to predict the presence of electromechanical delay, some patients may not show a favorable response if there is no evidence of baseline mechanical dyssynchrony despite wide QRS complexes (56). Previous studies had reported that the prevalence of nonresponders was about 30% by clinical definition; or about 40% when echocardiographic definitions of improvement in systolic function or LV reverse remodeling were used (61).

The application of TDI and post-processing imaging to assess systolic dyssynchrony has been shown to be helpful in predicting a favorable clinical response. From a recent review, it appears that most of the indices of dyssynchrony with defined cut-off values were derived from TDI or related technologies (62). In essence, these indices mostly examined the time to peak myocardial contraction from 2 (e.g., septal-to-lateral wall delay) to 12 (Ts-SD or Ts-diff) LV segments. These studies suggested that the assessment of systolic dyssynchrony by TDI before pacemaker implantation may help to predict short- to medium-term echocardiographic responders with a reasonably high sensitivity (87% to 97%) but variable specificity (55% to 100%). Currently the role of dyssynchrony assessment by applying tissue Doppler strain to predict CRT response is a topic of further investigation (63,64), although strain rate did not appear to be useful (59).

Apart from predicting responders after CRT, TDI also has a role in predicting the long-term clinical outcome. In a study of septal-to-lateral wall delay by off-line 2D color TDI analysis (65), a delay of 65 ms not only predicted a favorable clinical response (sensitivity and specificity of 80%) and LV reverse remodeling (sensitivity and specificity of 92%) after treatment for 6 months but also predicted a lower event rate in 85 patients who received CRT. At 1-year follow-up, a total of 16 events (7 deaths and 9 HF hospitalizations) occurred in 80 patients, and those with septal-to-lateral wall delay of >65 ms were associated with a much lower cardiovascular event rate (6% vs. 50%) (65). The link between baseline systolic dyssynchrony and long-term prognosis in HF patients could be explained by the fact that those patients with severe systolic dyssynchrony had early LV reverse remodeling (66). In another study, 141 patients who received CRT were followed for a mean period of 23 months. Either the presence of significant pre-pacing septal-to-lateral wall delay (6.6% vs. 21.8%; log-rank chi-square = 4.46; p = 0.03) or early LV reverse remodeling within 3 months to 6 months of CRT (6.9% vs. 30.6%; log-rank chi-square = 13.26; p = 0.0003) was a significant predictor of all-cause mortality in a univariate model. However, by Cox multivariable regression analysis, LV reverse remodeling was the only independent predictor of all-cause or cardiovascular mortality (66). Therefore, significant baseline systolic dyssynchrony is a marker of severe disease in HF patients that will be promptly improved by CRT (67). The CRT will alter the clinical course of the disease and improve HF outcome.

Conclusions

Tissue Doppler imaging has evolved as a new quantitative tool for the assessment of cardiac systolic function, diastolic function, and the hemodynamics of LV filling. From tissue Doppler velocity analysis, a number of parameters have been shown to be useful to predict long-term prognosis, in particular, Sm, Em, and E/Ea. The use of threshold values of Em (<3 cm/s) and E/Ea (≥15) has provided independent and incremental prognostic information in a number of major cardiac diseases, such as HF, acute MI, and hypertension. Systolic dyssynchrony assessment not only predicts

HF events and mortality, but may also predict favorable LV reverse remodeling and long-term clinical outcome after CRT. In patients with suspected coronary heart disease, a high basal segmental Sm value (>6 cm/s) after dobutamine stress echocardiography is associated with lower mortality and MI and is superior to wall motion score. Although a number of post-processing techniques can be derived from TDI, such as strain and strain rate, the clinical utility of these modalities as prognosticators has not been established. Because tissue Doppler velocity imaging is readily available in most of the current echocardiographic systems, this information is now ready to apply toward optimal clinical management for patients who are vulnerable to the development of cardiovascular events.

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