

Noninvasive Doppler Echocardiographic Evaluation of Left Ventricular Filling Pressures in Patients With Cardiomyopathies: A Simultaneous Doppler Echocardiographic and Cardiac Catheterization Study

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Objectives. The purpose of this study was to examine the relation of the mitral flow velocity curves to left ventricular filling pressures in patients with two different types of myocardial problems: hypertrophic cardiomyopathy and severe left ventricular systolic dysfunction.

Background. Previous studies have suggested that assessment of Doppler-derived mitral flow velocity curves can be used to predict left ventricular filling pressures in specific disease entities. However, it is unclear whether information derived from specific mitral flow velocity curves obtained from one disease entity can be valid in other disease states.

Methods. The study group consisted of 42 patients with left ventricular systolic dysfunction (group A) and 55 patients with hypertrophic cardiomyopathy (group B); both groups underwent simultaneous cardiac catheterization and were studied by Doppler echocardiography. High fidelity measures of left atrial and left ventricular pressures were obtained simultaneously with mitral flow velocity curves.

Results. There was a significant relation between the Doppler

echocardiographic variables and mean left atrial pressure in group A patients. The left atrial pressure was directly related to the E/A ratio ($r = 0.49$, $p = 0.004$) and inversely related to the deceleration time ($r = 0.73$, $p < 0.001$). The sensitivity and specificity of the deceleration time, <180 m/s, which indicated a mean left atrial pressure ≥ 20 mm Hg, were both 100%. In group B patients, there was no significant relation between mean left atrial pressure and deceleration time.

Conclusions. Doppler echocardiographic mitral flow velocity curves are useful in predicting and estimating left ventricular filling pressures in patients with left ventricular dysfunction. However, because of the complexity of the multiple interrelated factors that determine diastolic filling of the left ventricle, these flow velocity curves cannot be used in patients with other disease entities, such as hypertrophic cardiomyopathy. Future studies of different disease states are necessary to fully understand the role of Doppler echocardiography in the assessment of diastolic filling.

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Diastolic dysfunction is thought to be responsible for signs and symptoms of heart failure in many disease entities (1,2). The final result of abnormalities of diastolic dysfunction is an elevation of left ventricular filling pressure, which is reflected back to the pulmonary circulation, causing pulmonary congestion. A noninvasive method to measure the filling pressures of the left ventricle would be ideal. Previous studies have suggested that certain Doppler-derived mitral flow velocity curve variables are related to filling pressures in specific diseases, such as dilated cardiomyopathy (3-6), ischemic heart disease

(7,8), restrictive cardiomyopathy (9) and aortic stenosis (10). However, the interpretation of these mitral flow velocity curves for assessment of filling pressures in other disease entities has not been fully evaluated.

There is a complex interplay between the multiple interrelated events that affect mitral flow velocity curves (11-13). The mitral flow velocity curves are determined not only by the left atrial pressure, but also by many other factors, such as the relative compliance of the left atrium and ventricle, rate of ventricular relaxation, diastolic suction, atrial systolic function and pericardial restraint. These other factors may differ markedly in different disease states. Thus, inferences regarding left ventricular diastolic pressures derived from specific mitral flow velocities that are accurate in one disease entity may not be valid in other disease states.

The purpose of this study was to examine the relation of the mitral flow velocity curves to left ventricular filling pressures in patients with two different types of myocardial problems:

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hypertrophic cardiomyopathy and left ventricular systolic dysfunction. For optimal assessment of this relation, variables from Doppler-derived mitral flow velocity curves were compared with left ventricular filling pressures assessed with *simultaneous* high fidelity left atrial and left ventricular pressure curves.

Methods

Patients. The patient cohort included 97 patients with either hypertrophic cardiomyopathy or left ventricular systolic dysfunction (ejection fractions <40%) referred to the Cardiac Catheterization Laboratory for hemodynamic assessment from November 1992 through February 1996. Group A included 42 patients with left ventricular systolic dysfunction documented by previous two-dimensional and Doppler echocardiography. The diagnosis was made on the basis of left ventricular dilation and an ejection fraction <40%. Of these patients, 20 were thought to have left ventricular systolic dysfunction on the basis of known ischemic heart disease, and the diagnosis in the remaining 22 patients was idiopathic dilated cardiomyopathy. Group B included 55 patients with the diagnosis of hypertrophic cardiomyopathy. All group B patients had comprehensive two-dimensional and Doppler echocardiographic evaluations before the procedure, and from these, the diagnosis of hypertrophic cardiomyopathy was made by previously described criteria (14). Of these group B patients, 45 had documented dynamic left ventricular outflow obstruction (peak velocity >3.0 m/s) and 10 had no rest outflow obstruction. The primary indication for the cardiac catheterization study was to assess the hemodynamic response by cardiac catheterization to dual-chamber pacing. The data on the response to dual-chamber pacing have, in part, been previously reported (15,16). The combined cardiac catheterization and Doppler echocardiographic procedure was approved by the Institutional Review Board, and informed consent was obtained from each patient.

Cardiac catheterization procedure. All patients were studied in the fasting state. To avoid left ventricular catheter entrapment in patients with hypertrophic cardiomyopathy, left ventricular inflow pressures were obtained (17). Transseptal catheterization was performed under combined fluoroscopic and echocardiographic guidance with an 8F Mullins sheath. After entering the left atrium, the sheath was advanced across the mitral valve into the left ventricular inflow tract. High fidelity pressure measurements of the left atrium and left ventricle were obtained by one of two methods. In the first method, two catheters, a 3F and a 2F high fidelity manometer-tipped catheter, were advanced through the sheath and out into the left ventricular inflow tract, and both pressures were zeroed and balanced to the fluid-filled left ventricular pressure. With the 3F high fidelity catheter positioned in the left ventricular inflow tract, the sheath and the 2F high fidelity catheter were withdrawn into the left atrium, approximately 1 cm proximal to the mitral valve. The left atrial high fidelity pressure was then balanced to the left ventricular high fidelity pressure during diastasis at long RR intervals induced by

premature ventricular contractions. In the second method, a specially designed 7F catheter with two high fidelity transducers placed 4 cm apart was used. This catheter was placed out the end of the Mullins sheath into the inflow tract of the left ventricle, and both high fidelity pressures were zeroed and balanced to the fluid-filled left ventricular pressure. With the distal transducer kept in stable position, the sheath and proximal end of the catheter were then withdrawn into the left atrium, approximately 1 cm proximal to the mitral valve. The left atrial high fidelity pressure was then balanced to the high fidelity pressure during diastasis at long RR intervals.

Both left atrial and left ventricular pressure curves were recorded at end-expiration directly onto a digital format at 5-ms intervals. Other femoral sites were used for a thermidilation catheter in the pulmonary artery, a multipurpose catheter in the ascending aorta and two temporary pacing catheters in the right ventricle and right atrial appendage as part of the previously reported pacing study (15,16).

Doppler echocardiographic procedure. A *simultaneous* Doppler mitral inflow velocity curve was obtained during measurement of the high fidelity pressure curves. A 2.5 MHz duplex imaging transducer was used to obtain a four-chamber apical view of the left ventricle. A pulsed wave sample volume was placed at the tip of the mitral valve leaflets as they opened into the left ventricle (18). The mitral flow velocity curves were then recorded at end-expiration onto a strip chart recorder at 100 mm/s for off-line analysis. The simultaneous high fidelity left atrial and left ventricular pressures were superimposed on the Doppler recordings.

Analysis. The high fidelity left atrial and left ventricular pressures were measured from the digitized recordings by a custom-designed computer program (19,20). An average of five beats was analyzed. Measurements included mean left atrial pressure, left ventricular end-diastolic pressure and the time constant of relaxation (τ). *Left ventricular end-diastolic pressure* was defined as the left ventricular pressure immediately preceding the onset of ventricular contraction. τ was calculated by the method of Weiss et al. (21), in which the left ventricular pressure from aortic valve closure to mitral valve opening is fit to a monoexponential equation assuming a zero asymptote. In eight patients with left ventricular systolic dysfunction, the mean left ventricular diastolic pressure was measured in place of direct left atrial pressure (22).

Three consecutive beats of the mitral flow velocity curves obtained simultaneously with the high fidelity pressures were measured off-line by an observer who had no knowledge of the results of the catheterization. The peak initial velocity (E wave) and velocity at atrial contraction (A wave) were measured. The deceleration time was taken as the time from the peak E velocity to the point at which the deceleration of flow was extrapolated to the baseline. The *A wave duration* was defined as the time from the onset to the end of the A wave.

Statistics. All data are reported as the mean value \pm SD. The mitral flow velocity curve variables were compared with the catheter variables by simple linear regression analysis. Confidence bands for the regression line were calculated (23).

Table 1. Hemodynamic and Doppler Variables for the Study Patients

	Left Ventricular Systolic Dysfunction (group A, n = 35)		Hypertrophic Cardiomyopathy (group B, n = 54)	
	Mean \pm SD	Range	Mean \pm SD	Range
Age (yr)	67 \pm 8	42-88	58 \pm 14	25-81
Heart rate (beats/min)	79 \pm 14	49-99	66 \pm 9	46-91
Mean LAP (mm Hg)	21 \pm 10	3-42	18 \pm 8	3-36
LVEDP (mm Hg)	23 \pm 9	8-41	25 \pm 9	11-44
LVSP (mm Hg)	130 \pm 31	75-220	183 \pm 42	108-280
Tau (ms)	65 \pm 14	41-91	62 \pm 19	34-120
E velocity (m/s)	0.86 \pm 0.35	0.3-1.8	0.83 \pm 0.27	0.5-1.8
A velocity (m/s)	0.62 \pm 1.30	0.1-1.2	0.79 \pm 0.33	0.2-1.8
E/A ratio	2.12 \pm 1.6	0.4-7.0	1.22 \pm 0.66	0.4-4.0
DT (ms)	177 \pm 75	90-360	243 \pm 70	120-440

DT = deceleration time; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure.

Results

Left ventricular dysfunction in group A. Of the 42 patients in group A, 7 had to be excluded from analysis because the E and A velocities on the mitral flow velocity curves were fused by a long first-degree atrioventricular block. This left 35 patients (13 women, 22 men) for analysis. The mean age of these 35 patients was 67 ± 8 years (range 42 to 88).

The variables derived from Doppler echocardiography and cardiac catheterization for patients with left ventricular systolic dysfunction (group A) are reported in Table 1. The range of mean left atrial pressures was wide (3 to 42 mm Hg).

There was a significant relation between the Doppler echocardiographic variables and mean left atrial pressure in group A (Fig. 1). The left atrial pressure was directly related to the E/A ratio ($r = 0.49$, $p = 0.004$) and inversely related to the deceleration time ($r = 0.73$, $p < 0.001$) (Fig. 2, left). The sensitivity and specificity for an E/A ratio ≥ 2.0 , indicating a mean left atrial pressure ≥ 20 mm Hg, were 52% and 100%, respectively (Fig. 3, left). The sensitivity and specificity for a

deceleration time < 180 ms, indicating a mean left atrial pressure ≥ 20 mm Hg, were both 100%.

Hypertrophic cardiomyopathy in group B. Of the 55 patients in group B, one patient went into atrial fibrillation during the study and was excluded from the analysis. The remaining 54 patients had adequate Doppler flow velocity curves and cardiac catheterization pressure curves for analysis. The mean age of these patients (28 women, 26 men) was 58 ± 14 years (range 25 to 81).

The variables derived from Doppler echocardiography and cardiac catheterization for group B are reported in Table 1. The range of mean left atrial pressures was wide (3 to 36 mm Hg), as was the range of tau (34 to 120 ms). Comparisons of the various Doppler echocardiographic variables with mean left atrial pressure for the patients in group B are shown in Figures 2 (right), 3 (right), 4 and 5. There was no significant relation between the deceleration time and mean left atrial pressure (Fig. 2, right). There was a relation between the E/A ratio and mean left atrial pressure ($r = 0.42$, $p = 0.001$), but much scatter was present (Fig. 3, right).

There was no significant relation between the deceleration time and mean left atrial pressure in a subgroup of group B patients aged 50 to 75 years.

Discussion

Doppler echocardiography provides a noninvasive means of assessing hemodynamic variables (24). Volumetric flow rates, intracardiac pressures, valve gradients and valve areas can be accurately and reliably measured by Doppler echocardiography. In the early 1980s, there was interest in the use of Doppler echocardiography to assess diastolic filling of the left ventricle by a pulsed wave tracing of the inflow across the mitral valve during diastole (25-27). These mitral velocity curves were initially thought to represent volumetric filling rates (28-30). The abnormally low peak filling rates found in various disease states were thought to represent abnormal diastolic relaxation. Subsequent studies, however, showed that mitral velocity curves depend on many other factors, such as atrial pressure,

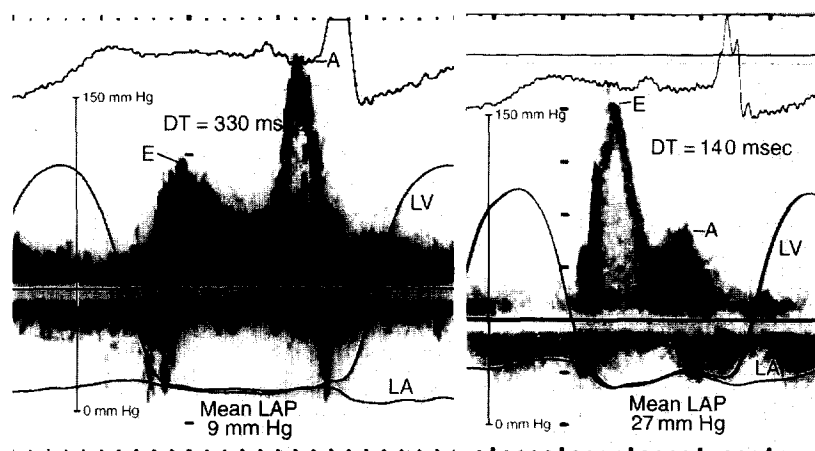
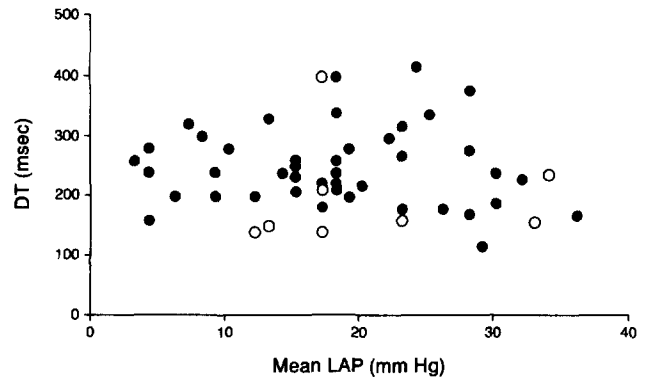
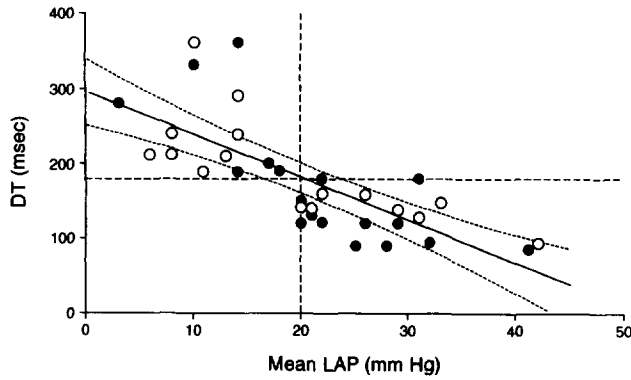


Figure 1. High fidelity left ventricular (LV) and left atrial (LA) pressure curves with simultaneous mitral flow velocity curves in patients with left ventricular dysfunction. The E velocity, A velocity and measured deceleration time (DT) are shown. **Left,** The mean left atrial pressure (LAP) is 9 mm Hg, with a low E velocity, a high A velocity and prolongation of deceleration time. **Right,** The mean left atrial pressure is 27 mm Hg, with a high E velocity, a low A velocity and a short deceleration time.



atrial compliance, atrial systolic function, ventricular compliance, diastolic suction and the viscoelastic forces of the myocardium (11,12,31). It is because of these complexities that the mitral flow velocity curves cannot be looked on as representing either normal or abnormally low filling rates.

Clinical interpretation of mitral flow velocity curves. It has been proposed that these mitral flow velocity curves be looked on not in terms of peak filling rates, but rather as representing the relative pressure gradients between the left ventricle and the left atrium during diastole (18,24,32). Multiple studies have demonstrated the consistent changes that are evident in the mitral flow velocity curves when there are isolated alterations in preload, afterload and contractility in the same patient (33,34). An increase in afterload, which prolongs the rate of ventricular relaxation, results in a lower initial E velocity, a prolongation of the time of deceleration of flow and a higher velocity at atrial contraction. This result is due to the slower rate of decrease in left ventricular pressure, which continues into mid and even late diastole and supports the previous clinical notion that a lower early filling rate indicates an abnormal prolongation of relaxation. However, an increase in left atrial filling pressure results in a higher initial E velocity and a shorter deceleration time, because there is a higher driving pressure across the mitral valve at the onset of mitral valve opening. A lower left atrial filling pressure causes an opposite effect in the mitral flow velocity curve, with a lower E velocity, a lower A velocity and a longer deceleration time.

On the basis of this conceptual framework, distinct patterns

Figure 2. Relation of deceleration time (DT), assessed by Doppler echocardiography, to left atrial pressure (LAP), assessed by cardiac catheterization. **Left,** In patients with left ventricular dysfunction, a significant inverse correlation exists between the deceleration time and mean left atrial pressure. **Solid circles** = idiopathic dilated cardiomyopathy; **open circles** = ischemic cardiomyopathy. **Right,** In patients with hypertrophic cardiomyopathy, there is no significant relation between the deceleration time and mean left atrial pressure. **Solid circles** = patients with outflow obstruction; **open circles** = patients without outflow obstruction.

of the mitral flow velocity curves have been identified and applied to clinical practice. Normal values based on age, gender and heart rate for the variables measured from the mitral flow velocity curves have been established. Abnormal relaxation is said to be present when the E/A ratio is low, the deceleration time is prolonged and there are normal filling pressures. A "pseudonormalization" pattern occurs when there is an elevated left atrial pressure together with a baseline

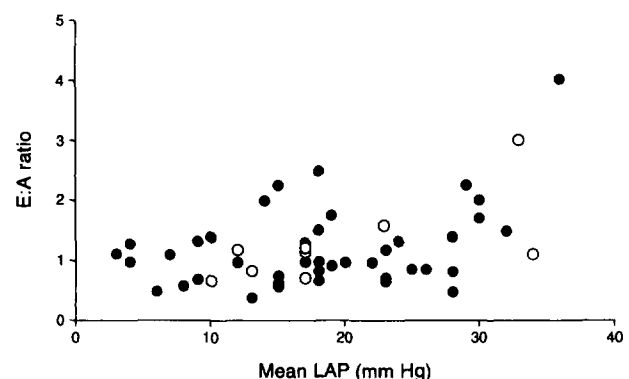
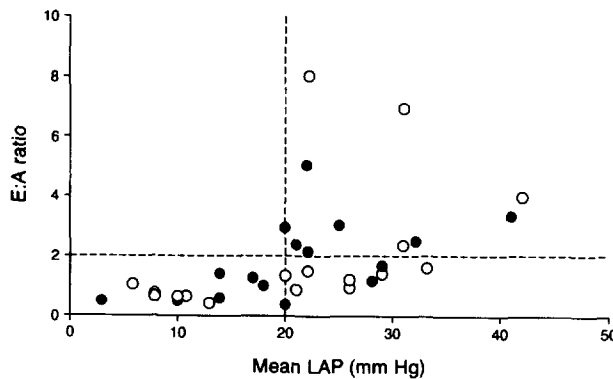


Figure 3. Relation between the E/A ratio from the Doppler mitral flow velocity curves and mean left atrial pressure (LAP) assessed by cardiac catheterization. **Left,** Among patients with severe left ventricular dysfunction, all those with a mean left atrial pressure <20 mm Hg had an E/A ratio <2.0. **Solid circles** = idiopathic dilated cardiomyopathy; **open circles** = ischemic cardiomyopathy. **Right,** Of those patients with hypertrophic cardiomyopathy, two with a very high E/A ratio (≥ 3.0) had a high left atrial pressure. However, there is a wide scatter in the remaining patients. **Solid circles** = patients with outflow obstruction; **open circles** = patients without outflow obstruction.

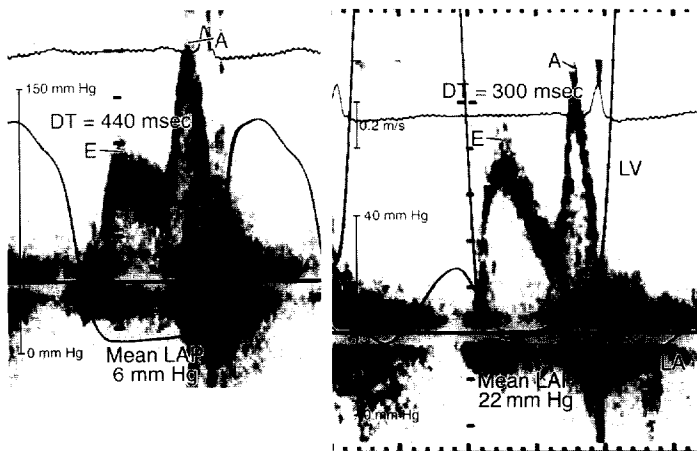
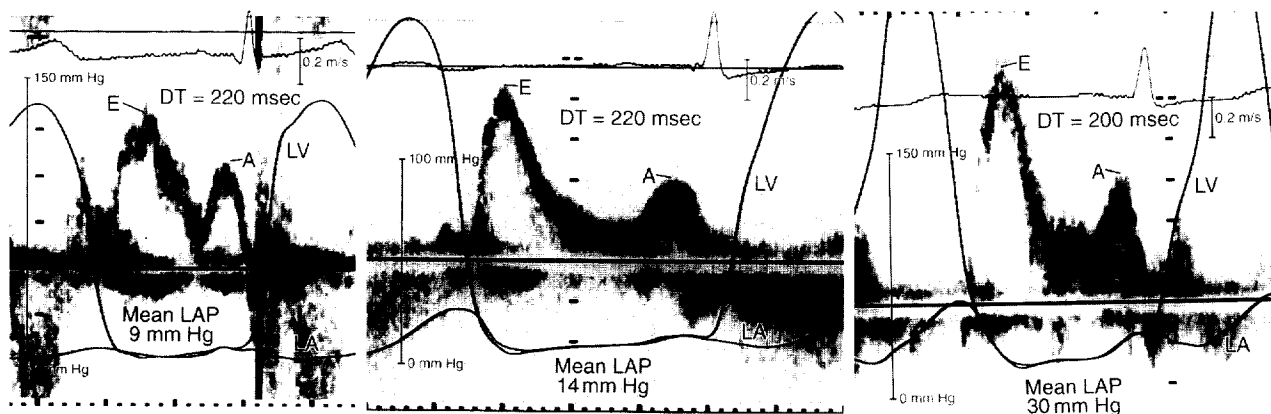


Figure 4. Simultaneous left ventricular (LV) and mean left atrial pressure (LAP) and the simultaneous mitral flow velocity curves in two patients with hypertrophic cardiomyopathy. The mitral flow velocity curves are labeled for the E velocity, A velocity and deceleration time (DT). Both patients have an E/A ratio <1.0 and prolongation of deceleration time. However, the patient on the left had a normal mean left atrial pressure and the patient on the right had a high mean left atrial pressure.

abnormal relaxation pattern. The increased driving pressure across the mitral valve will raise the initial E velocity and shorten the deceleration time back to "normal" values. Restriction to filling is identified by an abnormally high E/A ratio and a shortened deceleration time.

Progression of these mitral flow patterns during the course of disease has been identified (32). In patients with amyloid heart disease, an infiltrative cardiomyopathy that produces rapidly progressive diastolic dysfunction, the mitral flow velocity curves progress from an abnormal relaxation pattern to pseudonormalization and then finally to a restrictive pattern at the end stage of the disease (35). Prognosis can be determined by the initial appearance of the mitral flow velocity curves in patients with amyloid heart disease, with a restrictive pattern identifying those with the poorest prognosis. A similar prognostic value of the mitral flow velocity curves has been found in patients with dilated cardiomyopathy (36-39).

Figure 5. Simultaneous left ventricular (LV) and mean left atrial pressure (LAP) are shown with the simultaneous mitral flow velocity curves in three patients with hypertrophic cardiomyopathy. All three patients have an E velocity greater than the A velocity and a deceleration time (DT) between 200 and 220 ms. However, mean left atrial pressure varies widely, ranging from 9 (left) to 14 mm Hg (middle) to 30 mm Hg (right).



Estimation of left ventricular filling pressures. *Previous studies.* The mitral flow velocity curves have been used to estimate left ventricular filling pressures, which are the end result of both diastolic and systolic dysfunction produced by myocardial disease. These studies have been based on the alteration in mitral flow velocity curves produced by changes in preload in individual patients, i.e., that a higher preload causes a higher early E velocity and a shorter deceleration time (33,34). In several comparison studies, variables derived from the mitral flow velocity curves were related to filling pressures of the left ventricle (3-5,7,8,13). Higher filling pressures correlated with higher E velocities, higher E/A ratios and shorter deceleration times. Regression analyses based on these studies have been done for noninvasive calculation of filling pressures (8).

These studies demonstrated a good correlation between variables from the mitral flow velocity curves and left ventricular filling pressures in certain subgroups of patients. The most common disease entity studied has been coronary artery disease, usually in patients aged 50 to 75 years (7,8). Other studies, as well as the current one, have shown a relation between variables from mitral flow velocity curves and left ventricular filling pressures in patients with left ventricular systolic dysfunction (3-6). A deceleration time <180 ms was highly sensitive and specific for a high mean left atrial pressure. An E/A ratio >2.0 was specific but not sensitive for a high

mean left atrial pressure. This relation is supported by clinical reports in which mitral flow velocity curve patterns are related to symptoms and exercise tolerance in patients with severe left ventricular systolic dysfunction (40,41), because exercise tolerance depends, in part, on the filling pressure of the left ventricle. It should be emphasized that because of the large confidence intervals, an absolute left atrial pressure cannot be calculated from the mitral flow velocity curves in an individual patient. However, in this subset of patients with left ventricular systolic dysfunction, determination of the presence or absence of a high left atrial pressure is possible.

Previous studies that demonstrated an excellent relation between the mitral flow velocity curves and left ventricular filling pressures did not include patients with normal hearts or more unusual types of cardiac diseases. Use of mitral flow velocity curves in predicting left ventricular filling pressures is based on 1) the assumption that there is a gradual increase in E/A velocity ratio from abnormal relaxation to pseudonormalization to restriction as the filling pressure increases, and 2) the fact that most patients are in the age range in which E/A ratios >1.5 in normal subjects are distinctly unusual. Some patients with normal left ventricular diastolic function have mitral velocity curves similar to those with the pseudonormalization pattern. Unless these types of patients with normal diastolic function can be identified and excluded, correlation between the mitral velocity curves and left ventricular filling pressures would not be good. In addition, younger patients (age <40 years) were not included in these previous studies. An age-related change in the mitral flow velocity curves is due to the "suction" effect in the younger age group and slower relaxation in the older age group (42). Thus, a poorer relation between the mitral flow velocity curve variables and left ventricular filling pressures would be suspected if younger patients or those with normal ventricles had been included in previous studies.

Current study. In the current study, the mitral flow velocity curve variables and the mean left atrial pressure were not related in the patients with hypertrophic cardiomyopathy. This lack of correlation existed even when very young and very old patients were excluded. In a disease such as hypertrophic cardiomyopathy, a wide spectrum of abnormalities in diastolic function is related to abnormalities in both relaxation and compliance (17,43,44). Because mitral flow velocity curves depend on multiple, interrelated events that contribute to diastolic filling of the left ventricle, these curves might be thought not to be closely associated with left ventricular filling pressures (17). Several patients in the hypertrophic cardiomyopathy group had normal left ventricular filling pressures and a normal tau, indicating that diastolic filling was not severely impaired in the rest state. Alternatively, tau values in some patients with hypertrophic cardiomyopathy were over 2½ times the normal value, an indication of severe impairment of relaxation. This lack of relation has been suggested indirectly by previous studies in which mitral flow velocity curves were not correlated with the degree of hypertrophy, symptoms or

exercise capacity in patients with hypertrophic cardiomyopathy (45,46).

Comparison with other studies. There were other differences between this study and previous studies examining the relation of the mitral flow velocity curves to left ventricular filling pressures. In most of the previous studies, Doppler echocardiography was performed at a time different from that of cardiac catheterization, so that the loading condition on the left ventricle may have been altered between the two studies. For proper examination of this relation, Doppler echocardiographic and cardiac catheterization studies should be simultaneous. Fluid-filled catheters, with the potential for artifacts of overdampening and underdampening of the pressure curves, were used in the previous studies, whereas high fidelity, manometer-tipped catheters were used in this study. Different catheter measurements of left ventricular filling pressures were used in previous studies, including left ventricular end-diastolic pressure, pulmonary capillary wedge pressure and a "pre-A wave" pressure. These other measurements may differ from the direct measurement of mean left atrial pressure used herein, especially in the diseased heart (22,47-49).

Study limitations. One major limitation of this study is that all possible information obtainable from Doppler echocardiography was not incorporated in assessing diastolic filling of the left ventricle. Interrogation of pulmonary venous flow velocities may add information to the mitral flow velocities in this assessment, as the velocities at atrial contraction have been shown to be predictive of left ventricular end-diastolic pressure (50-52). However, the purpose of this study was to look specifically at the diagnostic accuracy of the mitral flow velocity curves routinely obtained in all echocardiographic laboratories.

The calculation of tau was done by the method of Weiss et al. (21). In some patients with cardiomyopathies, there may be marked asynchrony of relaxation and the decrease in left ventricular pressure may not be exponential. Although this limitation does not affect the results of the study directly, it does influence our understanding of the mechanism by which relaxation interacts with the mitral flow velocity curves.

We did not investigate measurement variability between two diseases. Small differences in the location of the Doppler sample volume have been shown to change the contour of the mitral flow velocity curves because of the nonlaminar velocity profile through the mitral valve (53). The velocity profile may differ in various diseases because it is related to left atrial driving pressure as well as to the rate of ventricular relaxation (54). The sample volume was placed at the tip of the mitral valve leaflets as they opened into the left ventricle, the location at which the velocity profile changes least throughout diastole (18). Intraventricular pressure gradients occur and may affect measurement of the left ventricular diastolic pressures by high fidelity manometer-tipped catheters (11). These intraventricular pressure gradients may be different in the different disease states (54). However, these differences should not occur with measurement of mean left atrial pressure (55).

Another major limitation of the study is that it examined

only two specific groups of patients. It will be necessary to extend this type of analysis to other disease processes with a greater number of patients. In addition, the sensitivity and specificity of the thresholds in patients with left ventricular dysfunction need to be prospectively studied in a future set of patients.

Conclusions. Doppler echocardiographic mitral flow velocity curves cannot be used in all types of patients for estimation of left ventricular filling pressures. Because of the complexity of the multiple, interrelated factors that determine diastolic filling of the left ventricle, the final mitral flow velocity curve depends on many factors other than the filling pressure. When mitral flow velocities are used for noninvasive assessment of diastolic filling of the left ventricle, the individual disease process must be taken into consideration. Future studies of the different disease states are necessary to fully understand the role of Doppler echocardiography in the assessment of diastolic filling.

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