

Filling Patterns in Left Ventricular Hypertrophy: A Combined Acoustic Quantification and Doppler Study

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Objectives. The purpose of this study was to evaluate the potential of acoustic quantification compared with Doppler echocardiography for assessment of left ventricular diastolic dysfunction.

Background. Diastolic dysfunction usually accompanies left ventricular hypertrophy. Although Doppler echocardiography is widely used, it has known limitations in the diagnosis of diastolic abnormalities. The ventricular area-change waveform obtained with acoustic quantification technology may provide an alternative to assess diastolic dysfunction.

Methods. Potential acoustic quantification variables (peak rate of area change and mean slope of area change rate during rapid filling, amount of relative area change during rapid filling and atrial contraction) were obtained and compared with widely used Doppler indexes of ventricular filling (isovolumetric relaxation time, pressure half-time, peak early diastolic velocity/peak late diastolic velocity ratio, rapid filling, atrial contribution to filling)

in 16 healthy volunteers and 30 patients with left ventricular hypertrophy.

Results. Criteria for abnormal relaxation were present in 68% of patients by acoustic quantification and in 64% of patients by Doppler echocardiography. However, abnormal relaxation was identified in 80% of patients by one or both methods. Acoustic quantification indicated abnormal relaxation in the presence of completely normalized Doppler patterns and in patients with mitral regurgitation or abnormal rhythm with unreliable Doppler patterns.

Conclusions. Acoustic quantification potentially presents a new way to assess diastolic dysfunction. This technique may be regarded as complementary to Doppler echocardiography. The combined use of the methods may improve the diagnosis of left ventricular relaxation abnormalities.

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Assessment of left ventricular diastolic properties frequently requires the use of Doppler echocardiography (1,2). Patterns of velocity across the mitral valve characteristic for relaxation abnormalities and restrictive states have been described (3-5). However, the ventricular filling patterns provided by these Doppler recordings are strongly influenced by several factors, including volume status and left atrial pressure (6,7), and their use is limited in the presence of significant mitral regurgitation or nonsinus rhythm. The interrelation of several factors can result in an apparently normal Doppler pattern in the presence of diastolic dysfunction (8,9). Therefore, an alternative, noninvasive technique to assess diastolic function is desirable. Acoustic quantification is a recently developed technology, based on ultrasound backscatter, that has the ability to automatically track and

display the endocardial border and to measure the cross-sectional area of the ventricle in real time (10,11). The left ventricular area change waveform is displayed along with the two-dimensional image. Previous studies suggest that this waveform reflects cardiac cycle events (12,13), and variables based on its diastolic portion were shown to correlate with diastolic indexes obtained with other methods (12-15). The purpose of the present study was to compare acoustic quantification with Doppler echocardiography for assessment of the diastolic abnormalities expected in patients with left ventricular hypertrophy.

Methods

Study group. Thirty patients: (18 men, 12 women; mean [\pm SD] age 52 ± 22 years, range 20 to 89) with pathologic conditions known to cause left ventricular hypertrophy and concentric or asymmetric ventricular hypertrophy by two-dimensional or M-mode criteria, as well as high quality two-dimensional echocardiographic images, were included in the study. Thirteen patients had hypertrophic cardiomyopathy; 11 had systemic arterial hypertension, 4 had aortic stenosis; and 2 had previous aortic valve replacement. Mean left ventricular end-diastolic wall thickness was 18 ± 5 mm (range 13 to 28), and estimated left ventricular mass

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was in the hypertrophy range (>265 g) in 26 patients (16). No attempt was made to withhold or account for medications in this group. Sixteen healthy volunteers (11 men, 5 women; mean age 33 ± 3 years, range 29 to 42) with negative cardiovascular history, normal physical examination and normal two-dimensional and Doppler echocardiographic studies were used as a control group. Informed consent was obtained before the study in all subjects.

Echocardiographic studies. A complete study, including M-mode and two-dimensional echocardiography, Doppler pulsed wave interrogation of the mitral valve and the left ventricular outflow tract and Doppler color flow imaging, was performed according to standard techniques using a Sonos 1500 ultrasonograph (Hewlett-Packard Co. Medical Products Group) with 2.5- or 3.5-MHz transducers.

Wall thickness measurements. Interventricular septum and posterior wall thickness were measured at end-diastole by M-mode technique using the standards recommended by the American Society of Echocardiography (17). In one patient with apical hypertrophic cardiomyopathy and in five patients after septal myectomy for hypertrophic cardiomyopathy, single end-diastolic two-dimensional frames were used for thickness measurements in the area of interest. Left ventricular hypertrophy was defined as the presence of ≥ 13 -mm wall thickness in any wall segment. This value was selected because it excludes 95% of normal subjects in an adult group with an average body surface area (18). Left ventricular mass was estimated by plotting the left ventricular internal chamber diameter and the mean of the interventricular septal and left ventricular posterior wall on a nomogram (16).

Acoustic quantification imaging. The methods used in our laboratory have been described elsewhere (19). After an optimal parasternal short-axis view of the left ventricle at papillary muscle level is obtained, the acoustic quantification system is activated, and the lateral gain control circuit is used for enhancing endocardial echoes. The automated border detection capability is then activated, and the system displays a border following the detected cavity-wall interface. A study is considered satisfactory if at least two thirds of the endocardial contour are correctly tracked by visual assessment. A region of interest is traced manually so that the right ventricular cavity is excluded and only the left ventricular cross-sectional area is included throughout the cardiac cycle. The left ventricular area and the rate of area change (dA/dt) waveforms versus time are then displayed along with the electrocardiogram (ECG) and the real-time two-dimensional image (Fig. 1). Acoustic quantification was satisfactory in all 30 patients who were originally selected for high quality two-dimensional echocardiographic images.

Doppler recordings. After two-dimensional imaging is completed, a spectral Doppler recording of the mitral inflow is made at 50- and 100-mm/s paper speed from the apical four-chamber view with the pulsed wave sample volume positioned at the tips of the mitral valve leaflets, as previously described (5). The sample volume is then placed in the

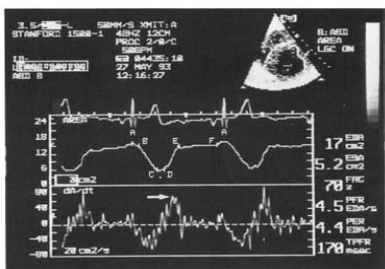


Figure 1. Acoustic quantification waveforms. Miniaturized two-dimensional image in upper right section with waveforms in panels below. Electrocardiogram (ECG) shown along upper edge of the waveform panels. Upper panel, Area versus time waveform (cm^2). Lower panel, Rate of area change versus time (dA/dt) waveform (cm^2/s). A = end-diastole (Q wave of the ECG); B = beginning of ejection; C = end of ejection; D = mitral valve opening; E = end of rapid filling; F = beginning of atrial contraction. Arrow = peak rate of area change during the rapid filling phase.

left ventricular outflow tract near the aortic valve, so that a recording of both the left ventricular outflow and the mitral inflow are obtained for isovolumetric relaxation time measurements (20). All studies are recorded on a standard S-VHS videotape.

Waveform analysis. Off-line analysis was performed using the calibration and measurement systems built into the ultrasonograph. Values for three cardiac cycles were averaged for each measurement. The following points were defined on the area waveforms (Fig. 1): point A, at the peak of the R wave on the ECG (end-diastole); points B and C, at the beginning and end of the abrupt downslope of the curve (beginning and end of left ventricular ejection period); point D, at the beginning of the abrupt upslope of the curve (opening of the mitral valve and beginning of the rapid filling period); point E, at the end of this segment (completion of the rapid filling period); point F, at the beginning of the upslope segment near end-diastole after the P wave on the ECG (beginning of area change due to atrial contraction). End-diastolic and end-systolic areas were taken at points A and C, respectively, and the area at the end of the rapid filling period and at the beginning of atrial contraction were taken at points E and F, respectively (Fig. 1). The amount of total area change that occurred by the end of the rapid filling period was defined as rapid filling fractional area change and was calculated as follows: Rapid filling fractional area change = $(E \text{ area} - C \text{ area}) / (A \text{ area} - C \text{ area})$. The amount of total area change that occurred during atrial contraction was defined as atrial filling fractional area change and calculated as follows: Atrial filling fractional area change =

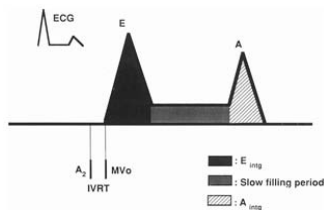


Figure 2. Schematic showing the method of Doppler tracing analysis. A = peak velocity during atrial contraction; A₂ = aortic valve closure click; A_{integ} = time-velocity integral during atrial contraction; E = peak velocity during early filling; E_{integ} = time-velocity integral during rapid filling; ECG = electrocardiogram; IVRT = isovolumetric relaxation time; MVo = mitral valve opening click.

(A area - F area)/(A area - C area). The mean rate of rapid filling was measured as the mean slope of the D-E segment. The greatest upward peak in early diastole on the dA/dt waveform was considered to represent the peak rate of area change during rapid ventricular filling.

Doppler analysis. The following measurements were made off-line from the mitral inflow velocity tracings using the Doppler analysis package of the echocardiographic system (Fig 2): peak early (E) and, peak late (A) diastolic velocities, E/A ratio, pressure half-time of early mitral flow (5), time-velocity integral during rapid filling (E_{integ}) and during atrial contraction (A_{integ}) and total time-velocity integral of ventricular filling (TF_{integ}). The rapid filling and atrial filling contributions to total filling were calculated as E_{integ}/TF_{integ} and A_{integ}/TF_{integ}, respectively. Isovolumetric relaxation time was measured as the time interval from the closure click of the aortic valve to the opening click of the mitral valve. The Doppler pattern would not be considered reliable for analysis of filling patterns in two patients with more than mild mitral regurgitation by qualitative color-flow criteria (21) and in three patients without sinus rhythm, and these five patients were analyzed separately.

Data analysis. The following groups were studied: group A = 16 normal subjects; group B = 25 patients with left ventricular hypertrophy and reliable Doppler studies; group C = 5 patients with unreliable Doppler studies. Data were expressed as maximal, minimal and median values and the Mann-Whitney test was used to assess group differences. Statistical significance was considered to be $p < 0.05$. The values found in the normal group defined the normal range for diastolic Doppler and acoustic quantification indexes (Table 1). A method was considered to indicate abnormal relaxation in an individual patient if at least two of its indexes were abnormal. The available Doppler and acoustic quantification data of the patients in group C were measured and are reported separately.

Table 1. Acoustic Quantification and Doppler Variables Used to Identify Study Patients With Abnormal Filling Dynamics

AQ Indexes	Doppler Indexes
RFS <20 cm/s	IVRT >133 ms
PRAC <28 cm ² /s	PHT >73 ms
RFFAC <0.16	RFC <0.51
AFFAC >0.32	AFC >0.3
RFFAC/AFFAC <2.2	RFC/AFC <1.72
	E/A <1

Abnormal relaxation was considered to be present if two or more indexes by one method were abnormal. AFC = atrial filling contribution; AFFAC = atrial filling fractional area change; AQ = acoustic quantification, E/A = ratio of peak early diastolic and late velocity; IVRT = isovolumetric relaxation time; PHT = pressure half-time; PRAC = peak rate of area change during rapid filling; RFC = rapid filling contribution; RFFAC = rapid filling fractional area change; RFS = slope of rapid filling segment.

Results

Patients versus normal subjects. A significant difference was found between groups A and B for all acoustic quantification and Doppler indexes except for the rapid filling contribution (Table 2). Analysis of Doppler data showed that left ventricular hypertrophy was associated with a longer isovolumetric relaxation time and pressure half-time, increased contribution to filling during atrial contraction, decreased ratio of early versus late contribution to filling and decreased E/A ratio. Acoustic quantification indexes in patients with left ventricular hypertrophy showed reduced slope of the rapid filling area change, less area change during rapid filling phase, increased area change during atrial contraction and decreased ratio of area change during rapid filling phase to that during atrial contraction.

Doppler and acoustic quantification results in patients with left ventricular hypertrophy and reliable Doppler studies. Although as a group the 25 patients with left ventricular hypertrophy were significantly different from the normal subjects, considerable overlap was found for most Doppler indexes between patients and control subjects, with group B patients (28%) having all Doppler indexes within normal limits. Widely used indexes, such as isovolumetric relaxation time, E/A ratio and pressure half-time, were within normal limits in >50% of group B patients (Table 3). The atrial contribution to filling was least likely to be normal in this group (8 [32%] of 25 patients with normal values).

Although mean group values were significantly different between normal subjects and patients, acoustic quantification indexes also showed considerable individual overlap (Table 3), with five patients (20%) having all acoustic quantification indexes within normal limits. The rapid filling fractional area change was least likely to be normal in this group (7 [28%] of 25 patients with normal values).

Comparative results of the methods. Acoustic quantification classified 17 (68%) of the 25 patients as having abnormal filling dynamics compared with 16 (64%) of 25 patients so classified by Doppler studies ($p = NS$) (Fig. 3). However, 20 of the 25 patients were classified as abnormal by either

Table 2. Doppler and Acoustic Quantification Values in Normal Subjects and Patients With Left Ventricular Hypertrophy

	Normal Subjects (n = 16)	Pts With LVH (n = 25)	p Value
Doppler Echocardiography			
IVRT (ms)			
Max	123	190	
Min	69	65	
Median	84.0	109	0.003
PHT (ms)			
Max	72.9	112	
Min	32.5	40	
Median	55.6	68.5	0.03
E/A			
Max	4	3.5	
Min	1	0.57	
Median	1.9	1	0.0001
RFC			
Max	0.75	0.84	
Min	0.51	0.25	
Median	0.62	0.58	NS
AFC			
Max	0.3	0.75	
Min	0.09	0.11	
Median	0.21	0.38	0.0001
RFC/AFC			
Max	8.4	6.2	
Min	1.72	0.33	
Median	2.72	1.54	0.0003
Acoustic Quantification			
RFFAC			
Max	0.92	1	
Min	0.66	0.2	
Median	0.74	0.56	0.0001
AFFAC			
Max	0.32	0.8	
Min	0.08	0	
Median	0.18	0.4	0.0001
RFFAC/AFFAC			
Max	11.2	9	
Min	2.17	0.25	
Median	4.28	1.5	0.0001
RFS (cm²/s)			
Max	55.3	48	
Min	20.3	2.2	
Median	37.1	21	0.0003
PRAC (cm²/s²)			
Max	79.9	57.3	
Min	28.5	10.8	
Median	50	37.3	0.006

LVH = left ventricular hypertrophy; Max = maximum; Min = minimum; Pts = patients; other abbreviations as in Table 1.

Doppler or acoustic quantification; thus, the combined yield of the two methods was 80%. Thirteen of the 25 patients were identified by both methods as having abnormal ventricular filling, and 5 patients were classified as normal by both methods (Table 4); thus, the two methods agreed in 72% (18 of 25) of the patients and disagreed in 28%.

Table 3. Frequency of Findings Classified as Abnormal by Acoustic Quantification and Doppler Indices in 25 Study Patients

Index	Acoustic Quantification		Doppler Echocardiography	
	Abnormal Finding (%)		Index	Abnormal Finding (%)
RFS	44		IVRT	32
PFR	38		PHT	45
RFFAC	72		RFC	32
AFFAC	56		AFC	68
RFFAC/AFFAC	64		RFC/AFC	60
			E/A	48

Abbreviations as in Table 1.

Thirteen of the 25 patients had an E/A ratio >1. The atrial contribution to filling was the only Doppler index that was statistically different between these 13 patients and normal subjects. However, all of the mean acoustic quantification indexes remained significantly different between the two groups. Moreover, the configuration of the acoustic quantification waveform and the calculated acoustic quantification indexes suggested abnormal filling in two of the seven patients with completely normal Doppler filling patterns (Fig. 4). One of the five patients with completely normal acoustic quantification patterns was identified as abnormal by Doppler criteria.

Two patients with significant mitral regurgitation, two others with atrial fibrillation and one with ventricular paced rhythm and mitral regurgitation were analyzed separately. At least one Doppler index (either pressure half-time or isovolumetric relaxation time) was abnormal in four of these five patients. At least one acoustic quantification index was abnormal in three of them.

Discussion

Automatic real-time detection of the left ventricular endocardial-blood interface by the ultrasound backscatter signal processing system has previously been reported as accurate (10,11). Few data are available on the value of the acoustic quantification technology for diastolic function assessment in patients with known or expected left ventricular dysfunction. The studies available to date have focused mainly on demonstrating good correlation between ventricular filling indexes derived from the acoustic quantification waveform and similar indexes provided by other techniques. We (12) and others (14) have shown that the amount of left ventricular cross-sectional area change during the rapid filling and atrial filling phases as measured by acoustic quantification correlates with the relative contribution to filling of these two phases as measured by Doppler echocardiography. The rate of area increase during early rapid ventricular filling as measured by acoustic quantification was shown to correlate with the rate of ventricular expansion assessed by cineventriculography (22). Preliminary data from our group (12) and others (15) suggest that acoustic

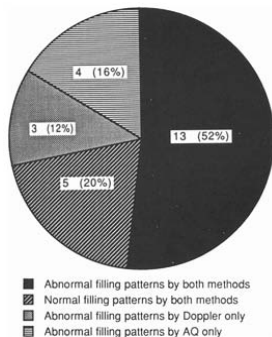


Figure 3. Relative distribution of findings by acoustic quantification (AQ) and Doppler echocardiography in 25 patients with left ventricular hypertrophy and reliable Doppler studies.

quantification indexes can differentiate between normal and abnormal diastolic function, but little is known about the comparative value of acoustic quantification and Doppler echocardiography for identifying diastolic abnormalities (23). To address this issue, acoustic quantification and Doppler studies were prospectively performed in patients with a high prevalence of diastolic abnormalities and in a group of normal subjects.

Doppler studies. As expected, mean group values were significantly different between normal subjects and patients with ventricular hypertrophy and were consistent with a relaxation abnormality in the latter group. However, overlap of values was noted between individual patients in each group. The readily available E/A ratio is commonly used as an index of abnormal relaxation, but it would have misidentified 13 of 25 patients as having normal relaxation. The finding of a normal E/A ratio in patients with organic heart disease has been extensively reported and is often associated with increased filling pressures (24-26). Although the isovolumetric relaxation time and pressure half-time were shorter in those with a normal E/A ratio (>1), they were still in the pathologic range in some of them. These findings indicate pseudonormalization of the mitral inflow pattern due to increased filling pressures (8,9). The Doppler index appar-

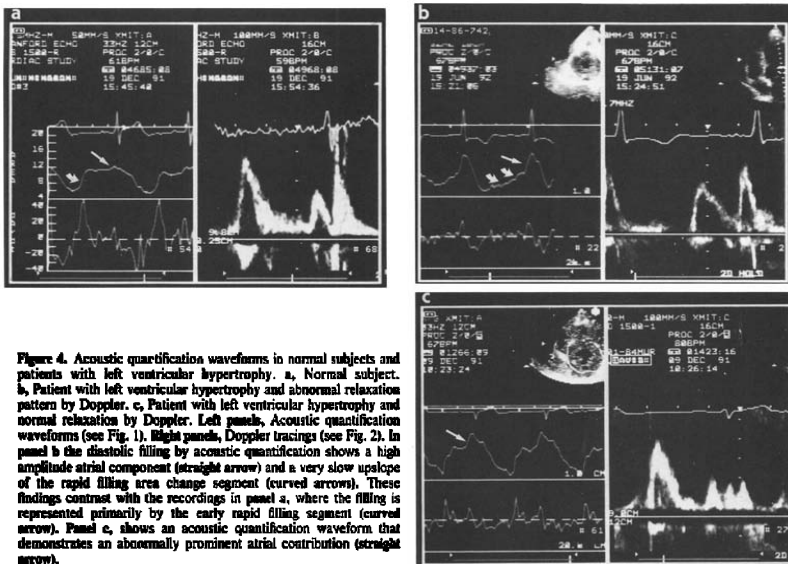


Figure 4. Acoustic quantification waveforms in normal subjects and patients with left ventricular hypertrophy. **a**, Normal subject. **b**, Patient with left ventricular hypertrophy and abnormal relaxation pattern by Doppler. **c**, Patient with left ventricular hypertrophy and normal relaxation by Doppler. **Left panels**, Acoustic quantification waveforms (see Fig. 1). **Right panels**, Doppler tracings (see Fig. 2). In panel **b** the diastolic filling by acoustic quantification shows a high amplitude arial component (straight arrow) and a very slow upslope of the rapid filling area change segment (curved arrows). These findings contrast with the recordings in panel **a**, where the filling is represented primarily by the early rapid filling segment (curved arrow). Panel **c**, shows an acoustic quantification waveform that demonstrates an abnormally prominent arial contribution (straight arrow).

ently most sensitive to this form of diastolic dysfunction was the atrial contribution to filling, which was within normal limits in only 8 of the 25 patients. All of the other Doppler indexes were negative as well in seven of these patients. Few data are available on the sensitivity and specificity of various Doppler indexes for detection of a ventricular relaxation abnormality. Shapiro and Gibson (27) studied 50 patients with left ventricular hypertrophy of various etiologies using digitized M-mode, Doppler echocardiography and apexcardiography. They found abnormal values for the E/A ratio, velocity half-time and isovolumetric relaxation time, with prevalences of 30%, 66% and 42%, respectively. The atrial contribution to total filling, by time-velocity integrals, was not measured in their study, but the relative height of the A wave by apexcardiogram was normal in only 5 of the 50 patients. If one accepts the assumption that the Doppler time-velocity integral during atrial contraction reflects the volumetric atrial contribution to filling (2), the volume of blood entering the hypertrophied left ventricle with atrial contraction may still be increased compared with the normal left ventricle despite a normalized E/A ratio.

Acoustic quantification studies. Acoustic quantification indexes behaved similarly to the Doppler indexes, showing a significant difference from normal subjects, but with considerable overlap of individual values, when group mean values were compared. The index least likely to be within normal limits in this group with hypertrophy was the amount of area change during rapid filling. This contrasts with the Doppler method by which the contribution of the rapid filling phase to total filling was a poor discriminator between patients and normal subjects. The duration of the rapid filling phase, as identified by acoustic quantification, was consistently shorter than that measured by the Doppler method in a previous study (19) from this laboratory. We postulated that a significant decrease in the filling rate may occur before the mitral flow velocity signal decreases to the low values of the slow filling period. This finding highlights the different phenomena assessed by the two methods: atrioventricular pressure-gradient by Doppler and cavity expansion by acoustic quantification.

Complementary value of the methods. Doppler echocardiography measures atrioventricular diastolic flow velocity (6); digitized M-mode echocardiography measures the rate and timing of changes in ventricular dimensions (27); and radionuclide ventriculography measures the rate and timing of radioisotope flow through the heart (28). The variables derived from the new acoustic quantification method are based on changes of the ventricular cross-sectional area during diastole. The left ventricular cross-sectional area at the papillary muscle level has been used for ventricular volume calculation without measurements of the long-axis length (29). It may be assumed, in the absence of gross distortions of the ventricular shape or severe regional wall motion abnormalities, that the pattern of area change reflects the pattern of volume change (13,22). Combining the flow velocity pattern provided by Doppler with a reflection of

volume change provided by acoustic quantification approaches the ideal noninvasive assessment of diastolic function using pressure-volume relations. Gorcsan et al. (30) have combined acoustic quantification with invasive pressure measurement to assess ventricular systolic function. Because the methods presently tested observe different aspects of diastolic behavior, they may be complementary, and their combined use should improve the noninvasive identification of diastolic dysfunction. Indeed, in the present study Doppler echocardiography identified abnormalities in 16 (64%) of 25 patients compared with 17 (68%) of 25 patients identified by acoustic quantification. When used together, the two methods identified 20 (80%) of 25 patients as having abnormal relaxation.

Study limitations. The main limitation of the present study is the assumption that diastolic dysfunction was present in all 30 patients with left ventricular hypertrophy. This was not tested further with another method, such as radionuclide ventriculography or catheterization and ventriculography. In the absence of this validation, defining diagnostic yields for Doppler echocardiography and acoustic quantification may be imperfect. However, previous studies consistently have demonstrated the presence of filling abnormalities in patients with left ventricular hypertrophy associated with arterial hypertension (31,32), aortic stenosis (33) and hypertrophic cardiomyopathy (34). In view of the selection criteria for our patients, it seems reasonable to assume that they had ventricular filling and myocardial relaxation abnormalities. Using two or more abnormal indexes per method as diagnostic criterion, we found the prevalence of relaxation abnormalities in our patients to be 80% by either acoustic quantification or Doppler echocardiography, which is similar to the prevalence of 87% reported by Spirito et al. (34), using digitized M-mode echocardiography in patients with hypertrophic cardiomyopathy. Conversely, there was no reason to expect diastolic abnormalities in the normal group.

A further limitation deals with understanding the apparently normal studies in some of the patients with left ventricular hypertrophy. This occurred in nine patients by Doppler echocardiography, eight patients by acoustic quantification and five patients by both acoustic quantification and Doppler studies. Development of Doppler patterns in very abnormal ventricles that are similar to those seen in normal subjects is well documented and partially understood (3,8,9). The Doppler variables seem to be preload and afterload dependent. It may be assumed that the acoustic quantification variables also are dependent on these factors but perhaps in different ways. The clinical characteristics of these patients with hypertrophy support a low probability for truly normal diastolic function and are more consistent with pseudonormalization. Another problem is the technical difficulty of obtaining studies with acoustic quantification. A prolonged learning period is required to perform acoustic quantification with acceptable reproducibility, but we had extensive experience with it before this study (19). We

selected patients for excellent two-dimensional images, so diagnostic yield cannot be addressed here. Nevertheless, the still undefined relation of acoustic quantification-measured area and change in area to volume and change in volume is a further limitation of the study.

Conclusions. Neither Doppler echocardiography nor acoustic quantification diastolic indexes were superior to the other because each had similar rates of positive and negative findings in this study group with left ventricular hypertrophy. However, their combined use enhanced identification of the expected abnormal relaxation. The ability of acoustic quantification to help identify abnormal relaxation in the presence of a pseudonormalized Doppler pattern is of special interest. From a practical standpoint, the combined use of the two methods may help to identify patients with suspected diastolic dysfunction not recognizable by either method alone.

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