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A Doppler echocardiography study.**

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Prognostic Significance of Doppler Measures of Diastolic Function in Cardiac Amyloidosis

A Doppler Echocardiography Study

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Background. We have previously characterized the left ventricular diastolic filling abnormalities in cardiac amyloidosis by Doppler methods. The various filling patterns were shown to be related to the degree of cardiac amyloid infiltration. The purpose of this study was to determine the value of Doppler diastolic filling variables for assessing prognosis in cardiac amyloidosis.

Methods and Results. We performed pulsed-wave Doppler studies of the left ventricular inflow and obtained clinical follow-up data in 63 consecutive patients with biopsy-proven systemic amyloidosis. All patients had typical echocardiographic features of cardiac involvement. The patients were subdivided into two groups according to deceleration time: Group 1 (33 patients) had a deceleration time of 150 msec or less, indicative of restrictive physiology, and group 2 (30 patients) had a deceleration time of more than 150 msec. Of the 63 patients, 32 (51%) died during a mean follow-up period of 18 ± 12 months. Of these deaths, 25 (78%) were cardiac deaths, and 19 of the 25 patients (76%) were from group 1. The 1-year probability of survival in group 1 was significantly less than that in group 2 (49% versus 92%, $p < 0.001$). Bivariate analysis revealed that the combination of the Doppler variables of shortened deceleration time and increased early diastolic filling velocity to atrial filling velocity ratio were stronger predictors of cardiac death than were the two-dimensional echocardiographic variables of mean left ventricular wall thickness and fractional shortening.

Conclusions. Doppler-derived left ventricular diastolic filling variables are important predictors of survival in cardiac amyloidosis. (*Circulation* 1991;83:808–816)

Cardiac amyloidosis is characterized as a “stiff heart” syndrome with impairment of diastolic function secondary to amyloid infiltration of the myocardium.¹ Recent Doppler echocardiography studies have revealed that this technique is useful in the assessment of left ventricular diastolic filling abnormalities in various disease states.^{2–9} We have recently characterized the left ventricular diastolic filling abnormalities in cardiac amyloidosis and have further demonstrated that Doppler filling patterns are closely related to the degree of amyloid infiltration, as measured by mean left ventricular wall

thickness.^{10–12} Early cardiac amyloidosis (with a mildly increased mean wall thickness of more than 12 but less than 15 mm) showed an abnormal relaxation pattern characterized by a decreased early filling velocity-to-atrial filling velocity ratio (E/A ratio), a normal-to-prolonged deceleration time, and a prolonged isovolumic relaxation time. In contrast, advanced cardiac amyloidosis (markedly increased mean wall thickness of 15 mm or more) showed a short deceleration time and an increasing E/A ratio, which are consistent with restrictive physiology.^{10–12}

A previous investigation using two-dimensional echocardiography has demonstrated that the combination of increased mean left ventricular wall thickness and decreased fractional shortening is the best predictor of poor outcome in cardiac amyloidosis.¹³ The value of Doppler filling patterns for determining prognosis in cardiac amyloidosis is unknown. Therefore, the purpose of the present study was to assess prospectively the value of left ventricular diastolic filling variables obtained by Doppler echocardiography for predicting outcome in cardiac amyloidosis.

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Methods

Study Population

All patients with biopsy-proven primary systemic amyloidosis and typical echocardiographic features of cardiac involvement¹³ seen between July 1986 and February 1988 were included in the study. All patients had a baseline pulsed-wave Doppler study of left ventricular inflow.

Patients were excluded if they had a documented history of prolonged hypertension (blood pressure of more than 140/90 mm Hg); senile, familial, or secondary amyloidosis;¹⁴ or regional wall motion abnormalities suggestive of coronary artery disease on two-dimensional echocardiography.

The resulting patient population comprised 63 consecutive patients (43 men and 20 women with a mean age of 59 ± 8 years). In all patients, at least one biopsy specimen from bone marrow, rectum, kidney, or subcutaneous fat was positive for amyloid. Seven patients had endomyocardial biopsy findings positive for amyloid. Fifty-three patients (84%) were part of an earlier study that related left ventricular inflow to characterization of disease states in cardiac amyloidosis.¹²

Doppler Echocardiography Examination

Comprehensive two-dimensional,¹⁵ spectral pulsed- and continuous-wave Doppler,¹⁶ and color flow Doppler studies in the standard views were obtained using a phased-array, commercially available Doppler echocardiography unit (Hewlett-Packard 77020A) with a 2.5-MHz duplex imaging transducer. A heat-sensitive nasal respirometer was used in most patients to record the phase of the respiratory cycle. Doppler hard-copy tracings were recorded at a speed of 50 or 100 mm/sec.

Left ventricular inflow velocities were obtained from the apical four-chamber view, using pulsed-wave Doppler echocardiography, by placing the sample volume at the leaflet tips of the mitral valve. Lowest filter settings were used.

Doppler Echocardiography Measurements

M-mode measurements, including left ventricular end-systolic and end-diastolic dimensions and ventricular septal and posterior wall thicknesses, were derived from visualization of the two-dimensional parasternal short-axis view at the papillary muscle level. Left ventricular fractional shortening was calculated as (end-diastolic dimension – end-systolic dimension)/end-diastolic dimension.¹⁷

The Doppler measurements included the left ventricular inflow early (E) and late (A) diastolic peak velocities as well as the E/A ratio for each cardiac cycle. The deceleration time was measured as the time required for the peak E velocity to decline to baseline (Figure 1). All measurements were made with a computer-interfaced digitizing tablet, except for the deceleration time, which was measured by hand. Mean values were obtained by averaging at least six beats (one beat for inspiration and expira-

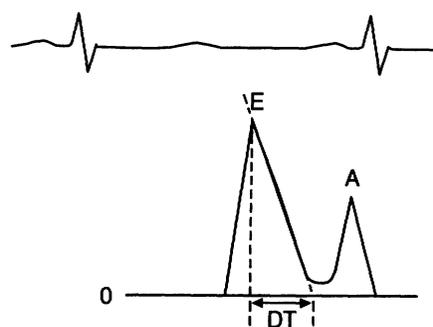


FIGURE 1. Left ventricular inflow velocity tracing using pulsed-wave Doppler echocardiography in a normal subject. Note that peak early diastolic filling wave (E) is greater than peak late diastolic filling wave (A). Deceleration time (DT) is time for peak E velocity to decline to baseline. A, atrial filling velocity; E, early diastolic filling velocity.

tion for three respiratory cycles). Mitral valve regurgitation was graded as mild, moderate, or severe by spatial mapping of the jet dimensions according to the method of Helmcke et al.¹⁸

Study Design

Baseline measurements included the clinical variables; the echocardiographic variables of left ventricular wall thickness, fractional shortening, and ejection fraction; and the Doppler variables of E/A ratio and deceleration time. The patients had clinical follow-up; if they died, their deaths were designated as either cardiac (i.e., the patient died of congestive heart failure or an arrhythmogenic death) or noncardiac (i.e., the patient died of an extracardiac cause such as renal failure). Clinical follow-up data were obtained by a review of the chart (hospital record and dismissal summary) and correspondence with the patient or referring physician.

Analysis of Patients

On the basis of our previous research demonstrating that a short deceleration time is indicative of restrictive physiology and is present in patients with advanced cardiac amyloidosis,¹¹ the study population was subdivided into two groups: Group 1 had a deceleration time of 150 msec or less (33 patients), and group 2 had a normal or prolonged deceleration time of more than 150 msec (30 patients).

Statistical Analysis

Cardiac mortality was compared between subgroups using log-rank tests. Relative risk (defined as the hazard ratio) was estimated for different patient subgroups based on the Cox proportional hazards model. Cardiac survival curves for the entire group and for various subgroups were computed with the Kaplan-Meier method.

The echocardiographic, Doppler, and clinical variables were compared regarding prognostic significance for predicting cardiac mortality by means of proportional hazards models. All univariate models

TABLE 1. Important Clinical and Echocardiographic Features of 63 Patients With Cardiac Amyloidosis

	Total (n=63)	Subgroup*	
		Group 1 (n=33)	Group 2 (n=30)
Age (yr)	59±11	61±13	57±10
Sex (M/F)	43/20	23/10	20/10
Heart rate (beats/min)	82±12	85±14	78±9
Systolic BP (mm Hg)	115±20	116±18	114±22
Diastolic BP (mm Hg)	70±14	70±89	71±17
CHF (n) (%)	41 (65)	26 (79)	15 (50)
NYHA class III or IV (n) (%)	25 (40)	16 (48)	9 (30)
MVWT (mm)	15.2±2.2	15.6±2.1	14.7±2.2
FS (%)	35±9	31±9	39±6
LA (mm)	42±8	45±8	41±6
MR grade of 2 or more (n)	6	6	0
Duration of follow-up (mo)	18±12	13±11	22±10

BP, blood pressure; CHF, congestive heart failure; NYHA, New York Heart Association; MVWT, mean left ventricular wall thickness; FS, fractional shortening; LA, left atrium; MR, mitral regurgitation.

*Group 1, patients with a deceleration time of 150 msec or less; group 2, patients with a deceleration time of more than 150 msec.

were considered, as were all bivariate models, and the likelihood ratio χ^2 statistics were computed and used to assess the relative predictive powers of various one- and two-variable combinations. The model χ^2 value was used to assess the multivariate predictive power of each set of combined variables. A probability of less than 0.05 was considered significant. Baseline descriptive data are given as mean±SD.

Results

Clinical and Echocardiographic Characteristics

The important clinical and echocardiographic features of the patient population are shown in Table 1. Group 1 patients showed a higher incidence of symptoms of congestive heart failure than group 2 patients, and group 1 patients had faster heart rates, lower mean fractional shortening, and more significant mitral regurgitation than group 2 patients. Mean durations of follow-up were 13.3±11.1 months in group 1 and 22.0±10.2 months in group 2. Three patients in group 1 had atrial fibrillation or high-grade atrioventricular block and were excluded from analysis.

Outcome

Of the 63 patients, 32 (51%) died during the mean follow-up period of 17.5±11.5 months: of the 32 patients, 21 (66%) were from group 1, and 11 (34%) were from group 2. Of the 32 deaths, 25 (78%) were cardiac deaths. Of the 25 patients with a cardiac death, 19 (76%) were from group 1, and six (24%) were from group 2 (Figures 2–5). The relative risk

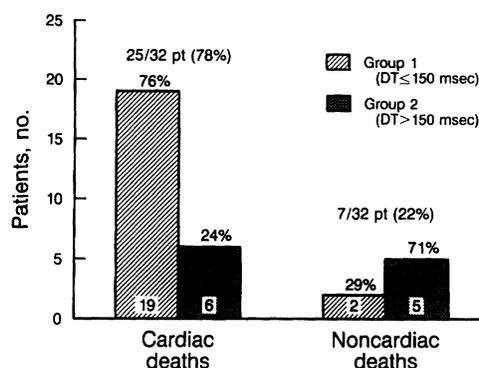


FIGURE 2. Bar graph of cardiac and noncardiac deaths in 63 patients with cardiac amyloidosis, according to deceleration time (DT). During the mean follow-up period of 17.5±11.5 months, 32 of the 63 patients (51%) died: 21 (66%) from group 1, and 11 (34%) from group 2. Of these 32 patients, 25 (78%) had a cardiac death, and seven (22%) had a noncardiac death. Of the 25 patients with a cardiac death, 19 (76%) were from group 1, and six (24%) were from group 2. Of the seven patients with a noncardiac death, two (29%) were from group 1, and five (71%) were from group 2. The relative risk for cardiac death was 4.87 times higher for group 1 than for group 2.

for cardiac death was 4.87 (95% confidence interval, 1.76–13.48) in group 1 compared with group 2.

Univariate Cox Model Analysis

Table 2 shows a ranking of the clinical, echocardiographic, and Doppler variables in decreasing order of strength for predicting cardiac deaths, as measured by the likelihood ratio χ^2 statistic from a proportional hazards model. All variables were significantly related to the risk of cardiac death. However, the single best predictor was the E/A ratio ($\chi^2=11.1$; $p<0.0009$).

Bivariate Cox Model Analysis

Table 3 ranks all two-variable combinations in decreasing order of strength for predicting risk of cardiac death, as measured by the model χ^2 . The partial χ^2 indicates the strength of the separate contributions of the individual variables to the combined model. The best combination was that of E/A ratio and New York Heart Association (NYHA) functional class (class III or IV versus I or II), with a model χ^2 of 16.2. In this model, the separate contributions of E/A and NYHA class are both strong and nearly additive. All of the two-variable combinations were associated with cardiac mortality. However, the combination of the Doppler filling variables (E/A ratio and deceleration time) was more predictive of cardiac death than was the combination of two-dimensional echocardiographic variables (mean left ventricular wall thickness and fractional shortening).

Survival

The 1-year probability of avoiding cardiac death for group 1 patients was significantly less than that

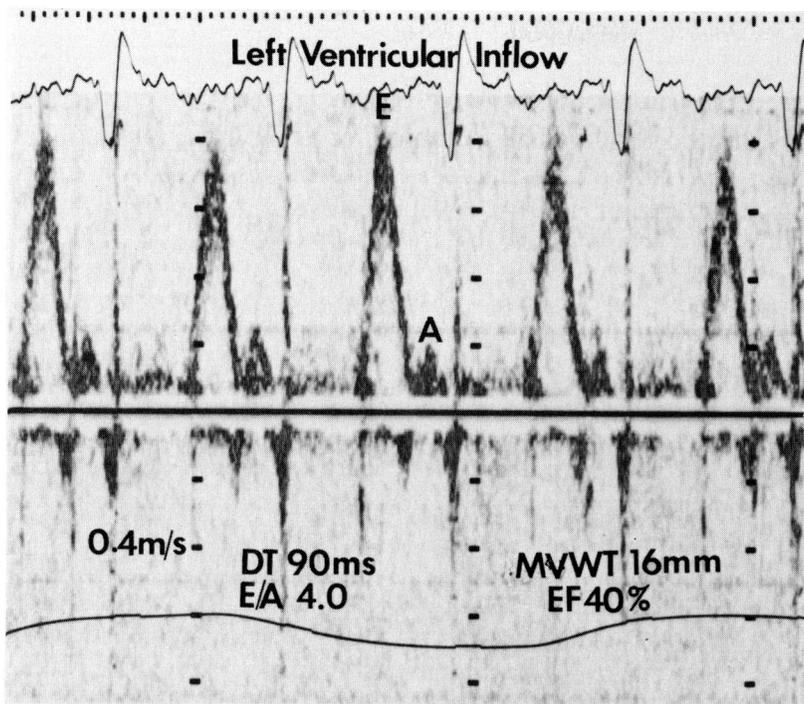


FIGURE 3. Shown is restrictive flow pattern of left ventricular inflow in a group 1 patient who died of congestive heart failure. Pulsed-wave Doppler recording is of a left ventricular inflow profile in a very symptomatic (New York Heart Association functional class IV) 70-year-old man who showed an increased mean left ventricular wall thickness (MVWT) of 16 mm and a decreased ejection fraction (EF) of 40% on two-dimensional echocardiography. Note markedly shortened deceleration time (DT) of 90 msec and increased early diastolic filling velocity-to-atrial filling velocity (E/A) ratio of 4.0, which are findings characteristic of restriction.

for group 2 patients (49% versus 92%, $p < 0.001$) on the basis of a log-rank test (Figure 6). Similarly, the 1-year cardiac survival of patients with an increased E/A ratio (2.1 or more, and more than 1 SD above normal) was less than that of patients with a normal or decreased E/A ratio (less than 2.1) (53% versus 81%, $p = 0.11$ by log-rank test). The combination of a short deceleration time (150 msec or less) and an increased E/A ratio (2.1 or more) yielded the lowest

1-year survival compared with the other combinations (Figure 7).

Discussion

Systemic amyloidosis is a multisystem disorder in which amyloid fibrils are deposited in several organs, including the heart, kidney, and nervous system. Cardiac complications with congestive heart failure or arrhythmias constitute the most common cause of

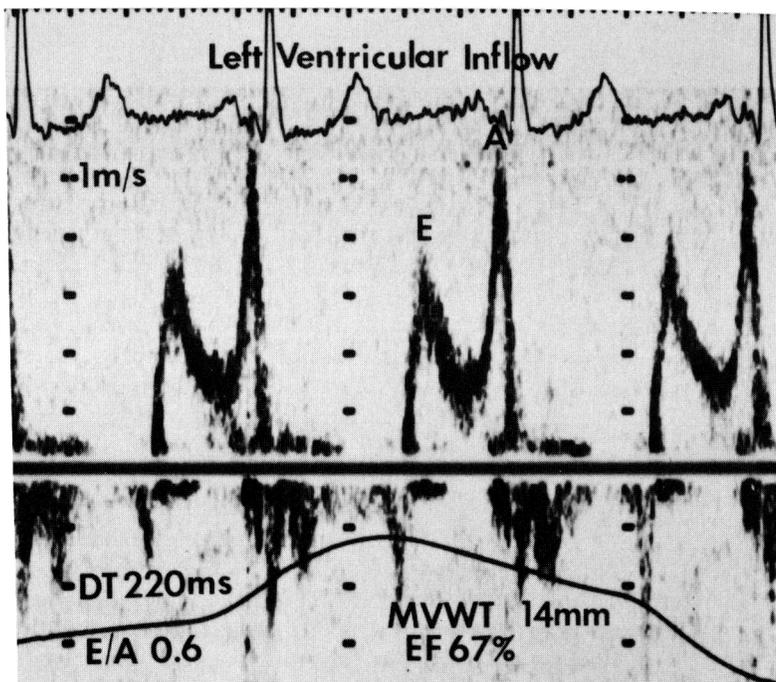


FIGURE 4. Shown is abnormal relaxation flow pattern of left ventricular inflow in a group 2 patient who was alive at the time of this report. Pulsed wave Doppler recording is of a left ventricular inflow profile in an asymptomatic 60-year-old woman who showed a mildly increased mean left ventricular wall thickness (MVWT) of 14 mm and a normal ejection fraction (EF) of 67% on two-dimensional echocardiography. Note the upper normal deceleration time (DT) of 220 msec and decreased early diastolic filling velocity-to-atrial filling velocity (E/A) ratio of 0.6. Duration of follow-up in this patient was 2 years.

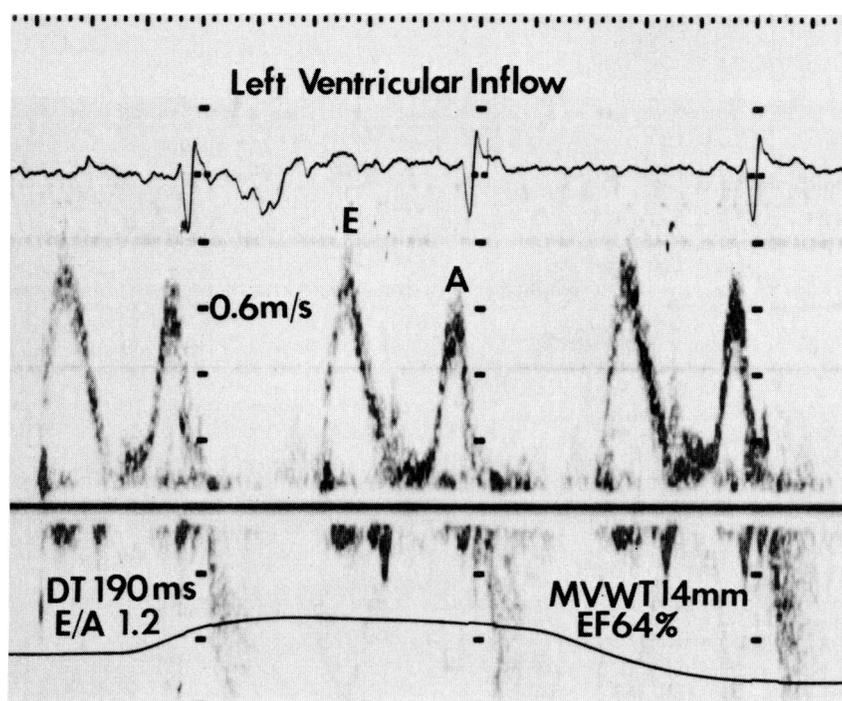


FIGURE 5. Shown is normal flow pattern of left ventricular inflow in a group 2 patient who had a noncardiac death. Pulsed-wave Doppler recording is of a left ventricular inflow profile in an asymptomatic 50-year-old man who showed a mildly increased mean left ventricular wall thickness (MVWT) measuring 14 mm and a normal ejection fraction (EF) of 64%. Note the normal deceleration time (DT) of 190 msec and a normal early diastolic filling velocity-to-atrial filling velocity (E/A) ratio of 1.2. This patient died of renal failure; duration of follow-up was 3 months.

death in this systemic disease, accounting for at least 40% of the deaths.^{14,19}

Previous studies from our institution have shown that echocardiography is useful for assessing prognosis in patients with cardiac amyloidosis.¹³ Cueto-Garcia et al^{13,20} demonstrated that an increased mean left ventricular wall thickness (an indirect measure of diastolic function) and decreased fractional shortening (a measure of systolic function) are the most important echocardiographic predictors of poor outcome in cardiac amyloidosis. The combination of a decreased fractional shortening of less than 20% and a mean left ventricular wall thickness of 15 mm or more was associated with an actuarial median survival of only 4 months.

Left Ventricular Inflow Filling Variables and Outcome

We previously documented a spectrum of right and left ventricular diastolic filling abnormalities related

TABLE 2. Univariate Cox Model Rankings of Doppler Echocardiography Variables in Predicting Cardiac Deaths in 60 Patients* With Cardiac Amyloidosis

Variable	χ^2	<i>p</i>
E/A	11.08	0.0009
NYHA class	9.22	0.0024
DT	6.69	0.0097
LVMWT	6.56	0.0104
FS	6.24	0.0123

E/A, ratio of early diastolic filling velocity to atrial filling velocity; NYHA, New York Heart Association; DT, deceleration time; LVMWT, left ventricular mean wall thickness; FS, fractional shortening.

*Number of patients is 60 because of three patients with atrial fibrillation or high-grade atrioventricular block.

to the degree of amyloid infiltration in cardiac amyloidosis. The restrictive filling pattern was seen only in the advanced stages of disease.^{10-12,21}

The present study clearly demonstrates that left ventricular diastolic filling variables are also important independent predictors of cardiac mortality in cardiac amyloidosis.

Group 1 patients (deceleration time of 150 msec or less) showed a markedly increased frequency of cardiac deaths compared with group 2 patients (normal or prolonged deceleration time). A short deceleration time by Doppler echocardiography has been shown to correspond to the "dip-and-plateau" pattern of cardiac catheterization, which is indicative of restrictive physiology.²² This restrictive pattern is usually seen in patients with an advanced form of cardiac disease.²³ Recently, Appleton et al²³ correlated the restrictive left ventricular inflow pattern with an increased rapid filling wave and pulmonary capillary wedge pressure during cardiac catheterization in patients with various diseases, including dilated cardiomyopathy, coronary artery disease, and restrictive myocardial disease.

In contrast, group 2 patients (deceleration time of more than 150 msec) had a more favorable prognosis because such patients usually have mild-to-moderate disease with less amyloid infiltration as measured by mean left ventricular wall thickness.^{11,12,24} Only six of the 25 patients (24%) who had a cardiac death did not show a restrictive physiology. The likely explanation is that these patients could have evolved from an abnormal relaxation pattern through a "normal" or pseudonormal pattern toward restriction during the follow-up period.²³

TABLE 3. Bivariate Cox Model Ranking of Combinations of Two-dimensional and Doppler Echocardiographic Variables in Predicting Cardiac Deaths in 60 Patients* With Cardiac Amyloidosis

Variable	Partial χ^2	<i>p</i>	Model χ^2
E/A	7.7	0.02	16.2
NYHA	5.7	0.01	
E/A	8.7	0.003	13.7
LVMWT	4.2	0.04	
DT	4.0	0.05	13.6
NYHA	5.4	0.02	
FS	3.5	0.05	12.6
NYHA	6.3	0.01	
LVMWT	3.4	0.07	12.3
NYHA	6.0	0.01	
E/A	3.7	0.06	11.1
DT	1.1	NS	
E/A	5.6	0.02	10.9
FS	0.8	NS	
DT	3.9	0.05	10.2
LVMWT	2.6	0.10	
DT	2.8	0.09	9.1
FS	1.5	NS	
LVMWT	2.5	0.12	8.1
FS	2.4	0.12	

E/A, ratio of early diastolic filling velocity to atrial filling velocity; NYHA, New York Heart Association class; LVMWT, left ventricular mean wall thickness; DT, deceleration time; FS, fractional shortening.

*Number of patients is 60 because of three patients with atrial fibrillation or high-grade atrioventricular block.

Univariate and Bivariate Analyses

Univariate analysis of the Doppler echocardiography variables showed that all the clinical, echocardiographic,

and Doppler variables were individually significantly important for predicting cardiac deaths, with a high E/A ratio being the best predictor.

The increased E/A ratio may reflect increased rapid filling of the ventricle, decreased atrial contribution to diastolic filling of the stiff ventricles, or both.⁷ Plehn et al²⁵ postulated that the increased E/A ratio in cardiac amyloidosis was the result of atrial systolic failure secondary to amyloid infiltration of the atria. Recently, we showed that prominent atrial reversal flow velocities in the pulmonary vein occur with cardiac amyloidosis, which suggests that atrial failure is less likely to be the cause of the increased E/A ratio but emphasizes the decreased compliance of the left ventricle at the time of atrial contraction (increased atrial afterload).¹²

Bivariate analysis of combinations of the variables showed that E/A ratio and NYHA functional class were the best predictors of poor outcome. It is important to note that the combination of the Doppler variables of an increased E/A ratio and a short deceleration time was a better overall predictor of cardiac mortality than the traditional measures of mean left ventricular wall thickness and fractional shortening. This finding emphasizes that an increased E/A ratio and a short deceleration time, which are markers of restrictive physiology,^{7,22} are associated with poor outcome in patients with cardiac amyloidosis. These findings are not surprising because the Doppler factors are more direct measures of hemodynamic function than mean left ventricular wall thickness, which is an indirect measure of impaired diastolic function. The use of Doppler variables adds independent value to the estimation of prognosis in patients with cardiac amyloidosis. Patients with mildly increased wall thickness may still have restrictive physiology, which suggests a poorer outcome than that predicted by the measurement of the wall thickness alone.

Mechanisms

Recently, we postulated that there is a continuum of impaired right and left ventricular diastolic filling abnormalities by Doppler echocardiography in car-

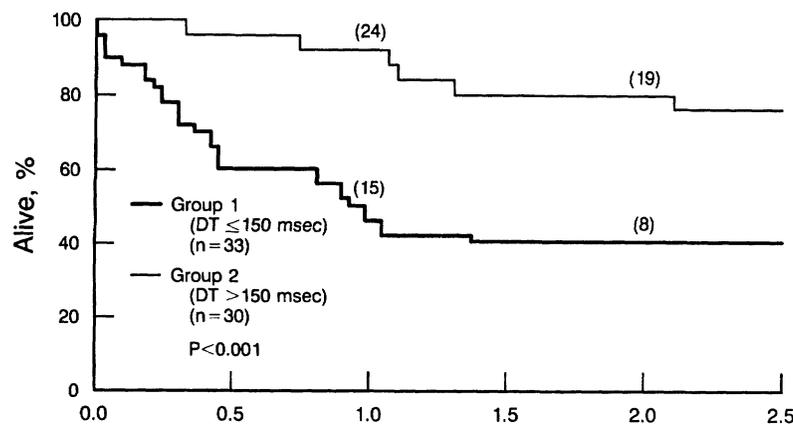


FIGURE 6. Survival in 63 patients with cardiac amyloidosis, as assessed by the effect of deceleration time (DT) on cardiac death. The 1-year probability of avoiding cardiac death for group 1 patients was significantly less than that for group 2 patients (49% versus 92%, $p < 0.001$).

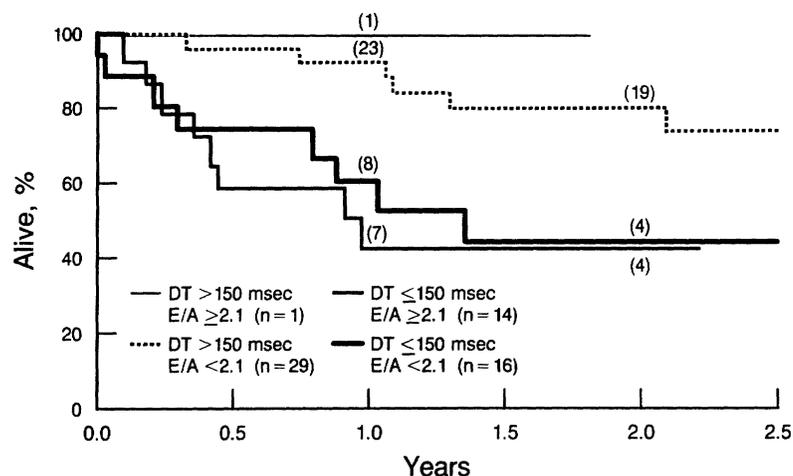


FIGURE 7. Survival in 60 patients with cardiac amyloidosis, as assessed by the effect of the combination of the Doppler variables of early diastolic filling velocity-to-atrial filling velocity (E/A) ratio and deceleration time (DT) on cardiac death. Patients with an increased E/A ratio and a shortened deceleration time characteristic of restriction showed the lowest 1-year survival (50%).

diac amyloidosis.^{10-12,21} In early cardiac amyloidosis, we speculate that there is an alteration of the relaxation process of diastole, which accounts for prolonged or impaired relaxation and a shift of diastolic filling to late diastole with enhanced atrial contribution as a form of compensatory response.^{26,27} This stage is similar to the Doppler flow patterns described in hypertension,⁴ coronary artery disease,³ hypertrophic cardiomyopathy,⁵ and the aging process.^{28,29} In contrast, in advanced disease, there is a greater infiltration of the amyloid fibrils of the myocardial cells, which may cause a very stiff ventricle and restriction to filling with a greater rise of ventricular pressure for a small change in volume (dip-and-plateau pattern).¹⁰⁻¹² In some patients, the Doppler tracing may be normal, which could represent a pseudonormal phase, that is, a transition phase from abnormal relaxation toward restriction as left atrial pressure increases.^{10-12,23}

Limitations

A limitation of the present study is that multiple factors can influence left ventricular diastolic filling variables,³⁰ including the aging process,^{28,29} loading conditions,^{30,31} heart rate,³² and valvular regurgitation.⁵ The effect of age probably played a minor role in our results because the predominant pattern in the group 1 patients was restrictive, which is opposite to that seen with the aging process, which more closely resembles a pattern of abnormal relaxation.³³ Similarly, the heart rate was increased in group 1 compared with group 2 patients; however, this increase would be unlikely to affect the results because tachycardia would cause a pattern of abnormal relaxation and not a restrictive pattern, which was seen in the group 1 patients.³² Also, mitral regurgitation was predominantly mild in 56 of the 63 patients (89%) and therefore unlikely to affect the restrictive filling pattern.¹²

Another limitation is the lack of endomyocardial biopsies in our study group; however, previous research from our institution has demonstrated that

patients with biopsy-proven systemic amyloidosis and the typical echocardiographic features of cardiac involvement have confirmation by endomyocardial biopsy or autopsy.²⁰

The determination of the cause of death as either cardiac or noncardiac has its shortcomings because patients with systemic amyloidosis often have simultaneous multiorgan involvement, and it could be difficult to determine the exact cause of death. However, all seven patients in the present study who had a noncardiac death were asymptomatic for cardiac symptoms and had progressive renal disease.

It should also be noted that the use of a single Doppler echocardiography study to assess prognosis has limitations because left ventricular inflow patterns may change during short-term follow-up. Serial studies of left ventricular inflow patterns have suggested that patients with cardiac amyloidosis evolve from an abnormal relaxation pattern to restriction, through a pseudonormal phase.³¹ We recently demonstrated that in short-term follow-up (13.6 months), left ventricular inflow patterns show significant change in patients with early cardiac amyloidosis (mean ventricular wall thickness of less than 15 mm). This finding corroborates the hypothesis that in cardiac amyloidosis, diastolic filling deteriorates as the disease advances.^{34,35}

Cardiac Transplantation

The present study assumes special importance because of renewed interest in cardiac transplantation for cardiac amyloidosis.^{36,37} Inclusion criteria for heart transplantation in this group at the Mayo Clinic include 1) patients being less than 60 years old, 2) no evidence of multiple myeloma, 3) a 24-hour protein urine collection with less than 1 g protein, 4) an alkaline phosphatase value of less than twice that of normal, and 5) no evidence of hepatomegaly unless it results from passive congestion. In the assessment of patients for cardiac transplantation, the left ventricular inflow velocity variables may be used as one of the important criteria for transplantation. Because

patients with restrictive physiology have worse cardiac prognosis, they may be earlier candidates for transplantation. In the group 1 patients in the present study, only six (18%) would have been definite candidates for cardiac transplantation on the basis of current criteria.

Clinical Importance

The present study is the first to document that Doppler-derived left ventricular diastolic filling variables can be important independent prognostic indicators of poor outcome in cardiac amyloidosis. We believe that these findings will be useful to the clinician, who could potentially modify treatment (such as the use of calcium channel blockers³⁸) to improve left ventricular diastolic function and accurately predict the outcome of patients with cardiac amyloidosis. Furthermore, these Doppler observations will be especially important in the selection of candidates for cardiac transplantation.^{36,37}

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