JACC Vol. 28, No. 3
September 1996:658–64

Doppler Index Combining Systolic and Diastolic Myocardial Performance: Clinical Value in Cardiac Amyloidosis

CHUWA TEI, MD, FACC,* KARL S. DUJARDIN, MD, DAVID O. HODGE, MS,
ROBERT A. KYLE, MD, A. JAMIL TAJIK, MD, FACC, JAMES B. SEWARD, MD, FACC

Rochester, Minnesota

Objectives. This study was designed to determine the clinical value of a Doppler-derived index of combined systolic and diastolic myocardial performance in the assessment of cardiac amyloidosis.

Background. Cardiac amyloidosis is an infiltrative disease with diastolic and systolic dysfunction. Therefore, the index of myocardial performance combining systolic and diastolic time intervals could be a useful predictor of clinical outcome in cardiac amyloidosis.

Methods. The study included 45 patients with biopsy-proved amyloidosis and 45 age-matched normal subjects. All patients had typical echocardiographic features of amyloid cardiac involvement. A Doppler-derived index, defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time, was measured from left ventricular outflow and mitral inflow Doppler velocity profiles recorded during routine echocardiography. The index as well as conventional systolic or diastolic echocardiographic/Doppler variables were related to subsequent outcome.

Results. The isovolumetric contraction and relaxation times were prolonged and ejection time was shortened ($p < 0.001$) in patients with amyloidosis compared with that in normal subjects, resulting in a marked increase of the index from normal values ($p < 0.001$). In the amyloid group the index was highest in patients with a low stroke index or with both shortened mitral deceleration time and lower ejection fraction. By univariate analysis, New York Heart Association functional class, the index, ejection fraction and mitral deceleration time were significant predictors of outcome. However, by multivariate stepwise regression analysis, functional class and the index were the only independent predictors of survival.

Conclusions. The Doppler-derived index of combined systolic and diastolic myocardial performance correlates with global cardiac dysfunction and is a useful predictor of clinical outcome in patients with cardiac amyloidosis.

(J Am Coll Cardiol 1996;28:658–64)

In amyloidosis the cause of death is most commonly due to cardiac involvement (1–4). The hallmark of cardiac involvement in amyloidosis is the "stiff heart syndrome" (5,6), with relaxation abnormalities in the early stages and concurrent systolic dysfunction in advanced stages (7,8). Echocardiography is important in the diagnosis of cardiac involvement of amyloidosis (9–18). Severity and prognosis of cardiac amyloidosis are assessed using wall thickness and different variables of systolic and diastolic function as measured by M-mode, two-dimensional and Doppler echocardiography (1,7,17).

Cardiac dysfunction in cardiac amyloidosis has been described previously using systolic and diastolic time intervals of the left heart. Abnormalities of isovolumetric relaxation time or time constant (tau) have been demonstrated using M-mode (19) and Doppler echocardiography (20) or invasive manometric catheterization recordings (6,21). In addition, abnormalities of systolic time intervals in cardiac amyloidosis have been described using phonocardiographic and external carotid pulse tracing (22).

Intuitively, a measure of global cardiac performance combining systolic and diastolic time intervals could therefore be a useful predictor of outcome in cardiac amyloidosis. More recently, an easily measured index of myocardial performance, combining systolic and diastolic time intervals, was proposed (23). This index has been reported to be simple, reproducible and independent of heart rate and blood pressure and to correlate with severity of clinical congestive heart failure in patients with dilated cardiomyopathy (24). Conceptually, this index combines systolic and diastolic myocardial performance because it is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time. In the present study, we measured and compared this index in normal subjects and in patients with cardiac amyloidosis of variable severity. The purpose of this study was 1) to analyze how the Doppler index correlates with clinical and echocardiographic severity of cardiac dysfunction; and 2) to assess its incremental prognostic power in patients with cardiac amyloidosis.

From the Division of Cardiovascular Disease, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Dr. Dujardin was supported by a Fellowship of the Belgian-American Educational Foundation.

Manuscript received January 25, 1996; revised manuscript received April 12, 1996, accepted April 26, 1996.

*Present address and address for correspondence: Dr. Chuwa Tei, Department of Rehabilitation and Physical Medicine, Faculty of Medicine, Kagoshima University, Sakuragaoka 8-35-1, Kagoshima, 890, Japan.

Published by Elsevier Science Inc.

0735-1097/96/$15.00
PII S0735-1097(96)00202-1

Methods

Study patients. This was a retrospective study of 45 patients (29 men, 16 women; mean [±SD] age 60 ± 10 years, range 42 to 76) with biopsy-proved amyloidosis and typical echocardiographic features of cardiac involvement, including refractoriness and thickening of myocardium, pericardial effusion, thickening of interatrial septum and valvular tissue, as defined in previous studies (7–9,14,15). Patients coded as having excellent echocardiographic images typical of cardiac amyloidosis recorded between December 1989 and April 1995 were selected from the Mayo Clinic echocardiography data base. The diagnosis was further established by the presence of amyloid at biopsy (bone marrow, abdominal fat aspirate, rectal, liver or renal biopsy) in all patients. Fourteen patients also underwent cardiac biopsy to confirm cardiac involvement. Patients with atrial fibrillation and atrioventricular (AV) block were excluded. Of 45 patients, primary amyloidosis was diagnosed in 39 (33 lambda/6 kappa), familial amyloidosis in 3 and senile amyloidosis in 3. At the time of the echocardiographic study, there was evidence of previous or concurrent congestive heart failure in 23 patients (51%). Twenty five patients (56%) were in New York Heart Association functional class I or II, and 20 (44%) in class III or IV. Eight patients were taking digoxin (18%); 12 angiotensin-converting enzyme inhibitors (27%); 37 diuretic agents (82%); 6 calcium blocking agents (13%); 1 beta-adrenergic blocking agent (2%); and 29 intermittent melphalan-prednisolone (64%). Follow-up data were obtained for each patient from the history charts, written correspondence or by phone. The mean duration of follow-up was 16.2 months. The cause of death was determined on the basis of hospital admission charts, death certificates or information from attending physicians. Forty-five age- and gender-matched normal subjects were selected from a previous study of Doppler echocardiography in healthy volunteers (25). All normal subjects had no symptoms suggestive of cardiovascular disease and physical examination, chest roentgenographic, electrocardiographic and two-dimensional/Doppler echocardiographic results were normal.

Echocardiographic examination. Complete two-dimensional and Doppler echocardiograms were recorded as previously described using commercially available ultrasound instrumentation (26,27). A parasternal short-axis view at the mid-left ventricular level was used for the following measurements: left ventricular end-systolic and end-diastolic dimensions, ventricular septal and left ventricular posterior wall thickness. Mean left ventricular wall thickness was measured as half of the sum of the septal and free wall thickness. Left ventricular ejection fraction was measured by the method of Quinones et al. (28). The mitral inflow velocity pattern was recorded from the apical four-chamber view with the pulsed wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole. The left ventricular outflow velocity pattern was recorded from the apical long-axis view with the pulsed wave Doppler sample volume positioned just below the aortic valve.

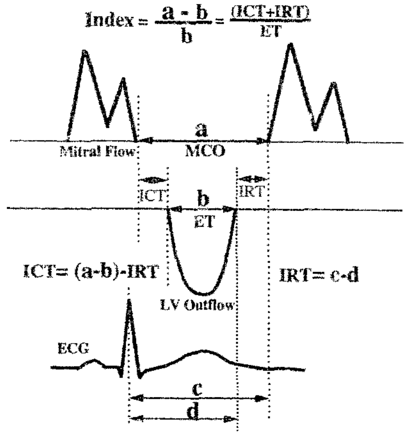


Figure 1. Schema for measurements of Doppler time intervals. The index is defined as $(a - b)/b$, where a is the interval between cessation and onset of the mitral inflow, and b is the ejection time (ET) of left ventricular (LV) outflow. Isovolumetric relaxation time (IRT) is measured by subtracting the interval c between the R wave and the cessation of left ventricular outflow from the interval d between the R wave and the onset of mitral flow. Isovolumetric contraction time (ICT) is obtained by subtracting isovolumetric relaxation time from $a - b$. ECG = echocardiogram; MCO = interval from cessation to onset of mitral flow.

Two-dimensional and Doppler tracings were recorded at a paper speed of 50 or 100 mm/s on 0.75-in. videotape.

Doppler measurements. Measurement of Doppler recordings was carried out on an off-line commercial digitizing system (Freeland Systems analyzer). Five consecutive beats were measured and averaged for each measurement. Doppler time intervals were measured from mitral inflow and left ventricular outflow velocity time intervals (Fig. 1). The interval a from the cessation to the onset of mitral inflow is equal to the sum of isovolumetric contraction time, ejection time and isovolumetric relaxation time. Left ventricular ejection time b is the duration of left ventricular outflow velocity profile. Thus, the sum of isovolumetric contraction time and isovolumetric relaxation time was obtained by subtracting b from a. The index of combined left ventricular systolic and diastolic function (the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time) was calculated as $(a - b)/b$ (23). In addition, isovolumetric relaxation time was measured by subtracting the interval d between the R wave and cessation of left ventricular outflow from the interval c between the R wave and the onset of mitral inflow (25). Isovolumetric contraction time was calculated by subtracting the isovolumetric relaxation time from $a - b$ (Fig 1). Doppler measurements were made by independent observer (C.T.) with no knowledge of patient outcome.

Statistical analysis. Continuous data are expressed as mean value ± SD and categoric data as percentages. Comparisons of all measurements between normal subjects and patients with cardiac amyloidosis, or comparison between two subgroups of cardiac amyloidosis defined by different grades of

JACC Vol. 28, No. 3
September 1996:658–64

Table 1. Clinical Profile and General Echocardiographic/Doppler Findings

	Normal Subjects (n = 45)	Patients With Cardiac Amyloidosis (n = 45)	p Value
Age (yr)	55 ± 15	60 ± 10	NS
Male/female	29/16	29/16	NS
NYHA functional class			
I/II		25 (56%)	
III/IV		20 (44%)	
History of CHF		24 (53%)	
Heart rate (beats/min)	63 ± 8	81 ± 12	< 0.0001
Systolic BP (mm Hg)	128 ± 13	114 ± 21	< 0.01
Diastolic BP (mm Hg)	76 ± 8	72 ± 12	NS
Ejection fraction (%)	62 ± 4	50 ± 15	< 0.0001
LV wall thickness (mm)	10 ± 1	16 ± 3	< 0.0001
LVDd (mm)	49 ± 4	44 ± 5	< 0.0001
LAD (mm)	36 ± 5	44 ± 6	< 0.0001
Mild MR		22 (49%)	
Moderate or severe MR		6 (13%)	
Mild		15 (33%)	
Moderate or severe TR		5 (11%)	

Data presented are mean value ± SD or number (%) of patients. BP = blood pressure; CHF = congestive heart failure; LAD = left atrial dimension; LV = left ventricular; LVDd = left ventricular end-diastolic dimension; MR = mitral regurgitation; NYHA = New York Heart Association; TR = tricuspid regurgitation.

New York Heart Association functional class (I/II vs. III/IV), ejection fraction (<50% vs. ≥50%), wall thickness (≤15 vs. >15 mm), mitral deceleration time (≤150 vs. >150 ms) and stroke index (<25 vs. ≥25 ml/min per m^2) were made using the unpaired *t* test. Values were considered significantly different at $p < 0.05$. Survival free of cardiac death and overall survival were estimated in patients with cardiac amyloidosis using the Kaplan-Meier method (29). The relation of specific factors to end points of interest were investigated both univariately and multivariately using the Cox proportional hazards model (30). The stepwise selection technique was used to construct the multivariate model. A 0.05 level of significance was applied to determine whether variables were added or removed from the model (30).

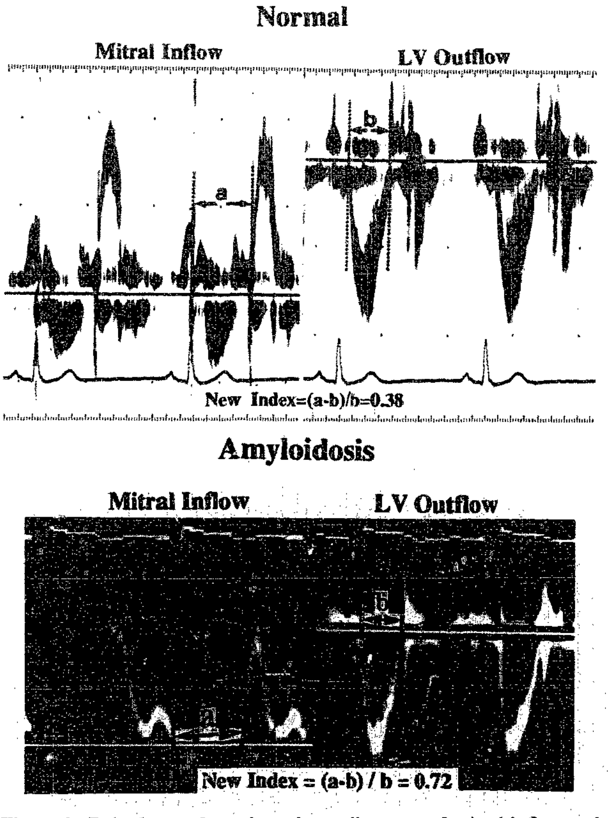


Figure 2. Pulsed wave Doppler echocardiograms of mitral inflow and left ventricular (LV) outflow in a normal 38-year old male subject (ejection fraction 63%) and a 49-year old male patient with cardiac amyloidosis (ejection fraction 51%). The value of the index $(a - b)/b$ is 0.38 in the normal subject and 0.72 in the patient with cardiac amyloidosis.

Results

Patient characteristics. Clinical characteristics and general echocardiographic/Doppler findings are shown in Table 1. Mean left ventricular wall thickness, heart rate and left atrial dimension were significantly increased in patients with cardiac amyloidosis compared with those in normal subjects, whereas blood pressure and left ventricular dimension were significantly decreased. Mean ejection fraction was also lower in patients with cardiac amyloidosis, but ejection fraction was preserved (≥50%) in 24 (53%) of 45 patients.

Doppler measurements. Figure 2 shows an example of a measurement of the index in a normal subject and in a patient with cardiac amyloidosis. Both the isovolumetric contraction time and isovolumetric relaxation time were significantly prolonged, whereas ejection time was significantly shortened in patients with cardiac amyloidosis compared with that in normal subjects (Fig. 3). Thus, the index combining these variables was even more significantly different between cardiac amyloidosis and normal subjects (Fig. 4). Table 2 summarizes the measurements of Doppler time intervals. Doppler-derived time intervals were significantly different between patients with cardiac amyloidosis and a mean ejection fraction <50% versus ≥50%. However, these Doppler time intervals were not significantly different among patients with cardiac amyloidosis and a mean wall thickness ≤15 versus >15 mm (Table 2).

Comparison of Doppler index. The mean value of the index tended to be higher in patients in functional class III/IV than class I/II, with an ejection fraction <50% versus ≥50% or mitral flow deceleration time ≤150 versus >150 ms, but this finding did not reach statistical significance. However, there was a significant difference between patients (0.90 ± 0.11, n = 15) with both ejection fraction <50% and decleration time ≤150 ms and patients (0.73 ± 0.15, n = 19) with both ejection fraction ≥50% and deceleration time >150 ms ($p < 0.01$). In addition, the mean value of the index was significantly higher in patients (0.88 ± 0.16, n = 21) with less than the median

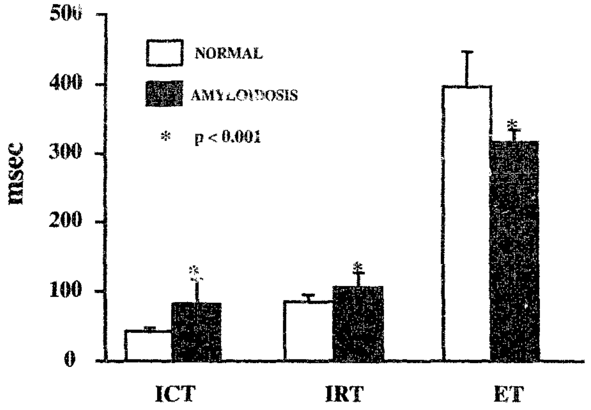


Figure 3. Comparison of Doppler time intervals between normal subjects and patients with cardiac amyloidosis. Left ventricular isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) were significantly prolonged, whereas left ventricular ejection time (ET) was significantly shortened in patients with cardiac amyloidosis compared with that in normal subjects.

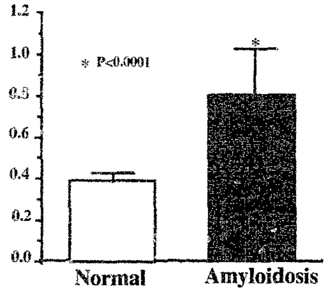


Figure 4. Comparison of the index of combining systolic and diastolic myocardial performance between normal subjects and patients with cardiac amyloidosis. The index is significantly prolonged in patients with cardiac amyloidosis compared with that in normal subjects.

value of the stroke index (<25 ml/min per m^2) than in patients (0.72 ± 0.13, n = 20) with a stroke index ≥25 ml/min per m^2 ($p < 0.01$).

Correlation of heart rate and echocardiographic/Doppler variables. Table 3 shows the correlation between heart rate and echocardiographic/Doppler variables in normal subjects and patients with cardiac amyloidosis. The interval *a* between cessation and onset of mitral inflow and the ejection time *b* were significantly related to heart rate in normal subjects as well as in patients with cardiac amyloidosis; however, the index $(a - b)/b$ was independent of heart rate.

Correlation of blood pressure and echocardiographic/Doppler variables. All Doppler variables were unrelated to blood pressure in normal subjects, but there was a significant relation between systolic or diastolic blood pressure and intervals *a* and *b* and the isovolumetric relaxation time in patients with cardiac amyloidosis (Table 4), whereas the index was independent of systolic and diastolic blood pressures.

Prognostic value of Doppler index. During a follow-up period of up to 3 years, 29 of 45 patients died (cardiac related in 23, noncardiac related in 4, unknown in 2). Of all the echocardiographic/Doppler variables, the index was the best predictor of cardiac death by univariate analysis (Table 5). Multivariate stepwise regression analysis showed that functional class and index were the only independent predictors of cardiac death (Table 6). Figure 5 shows the survival curves based on the two subgroups with an index value either less than or greater than the median value of the index, indicating that the group with the higher value (>0.77) had a worse outcome than the group with the lower value (≤0.77). Figure 6 shows that the index also predicted overall mortality.

Discussion

Cardiac amyloidosis is characterized by varying degrees of systolic and diastolic dysfunction, which appear to have independent prognostic value (7,17). Thus, a measure of combined systolic and diastolic myocardial performance could be a useful predictor of outcome in these patients. Abnormalities of systolic and diastolic time intervals of the left heart cycle have been described in cardiac amyloidosis (6,20–22). However, there have been no previous studies in cardiac amyloidosis that have attempted to relate these intervals to other measurements of systolic and diastolic performance and clinical prognosis in cardiac amyloidosis. In the present study, the index of myocardial performance combining systolic and diastolic time intervals was compared with conventional Doppler echocardio-

Table 2. Summary of Doppler Measurements (mean ± SD)

	E/A	DT (ms)	ICT (ms)	ET (ms)	IRT (ms)	Index [(ICT + IRT)/ET]
Normal subjects (n = 45)	1.3 ± 0.4	195 ± 35	41 ± 11	317 ± 19	84 ± 13	0.39 ± 0.04
Pts with amyloidosis (n = 45)	2.2 ± 1.4*	176 ± 60	82 ± 31*	236 ± 36*	106 ± 22*	0.81 ± 0.21*
Wall thickness						
≤15 mm (n = 21)	2.0 ± 1.3	188 ± 68	73 ± 25	246 ± 33	110 ± 25	0.75 ± 0.13
>15 mm (n = 24)	2.4 ± 1.4	168 ± 50	88 ± 34	230 ± 33	103 ± 19	0.86 ± 0.25
Ejection fraction						
<50% (n = 21)	2.6 ± 1.2	144 ± 33	98 ± 29	219 ± 33	98 ± 20	0.91 ± 0.22
≥50% (n = 24)	1.9 ± 1.4	205 ± 63†	68 ± 27†	251 ± 32†	112 ± 23‡	0.73 ± 0.17†

*$p < 0.001$. †$p < 0.01$. ‡$p < 0.05$. DT = mitral deceleration time; E/A = early/late diastolic peak velocity; ET = ejection time; ICT = isovolumetric contraction time; IRT = isovolumetric relaxation time; Pts = patients.

Table 3. Correlation of Echocardiographic/Doppler Variables With Heart Rate in Normal Subjects and Patients With Cardiac Amyloidosis

	Normal Subjects		Patients With Cardiac Amyloidosis	
	r	p Value	r	p Value
DT	0.25	NS	0.16	NS
E/A	0.30	< 0.05	0.14	NS
EF	0.10	NS	0.26	< 0.05
Dd	0.42	< 0.01	0.19	NS
Ds	0.34	< 0.05	0.10	NS
SI	0.30	< 0.05	0.18	NS
CI	0.32	< 0.05	0.30	< 0.05
MCO (*a*)	0.42	< 0.01	0.42	< 0.01
ET (*b*)	0.31	< 0.05	0.48	< 0.0001
IRT	0.17	NS	0.22	NS
ICT	0.32	< 0.05	0.01	NS
ICT+IRT	0.41	< 0.01	0.13	NS
Index	0.23	NS	0.17	NS

CI = cardiac index; Ds = end-systolic dimension; SI = stroke index; MCO = interval from cessation to onset of mitral flow; other abbreviations as in Tables 1 and 2.

Table 4. Correlation of Echocardiographic/Doppler Variables With Blood Pressure in Patients With Cardiac Amyloidosis

	Systolic		Diastolic	
	r	p Value	r	p Value
DT	0.26	< 0.05	0.26	< 0.05
E/A	0.38	< 0.01	0.33	< 0.05
EF	0.24	NS	0.13	NS
SI	0.39	< 0.01	0.28	NS
CI	0.23	NS	0.26	NS
MCO (*a*)	0.47	< 0.0001	0.41	< 0.001
ET (*b*)	0.47	< 0.0001	0.31	< 0.05
IRT	0.25	< 0.05	0.35	< 0.01
ICT	0.09	NS	0.09	NS
ICT+IRT	0.23	NS	0.29	< 0.05
Index	0.13	NS	0.03	NS

Abbreviations as in Tables 1 to 3.

graphic variables of left ventricular function and was related to clinical status and outcome of patients with cardiac amyloidosis.

Isovolumetric contraction and relaxation times were prolonged and ejection time was shortened significantly in patients with amyloidosis compared with that in normal age-matched subjects. This caused a marked increase in the value of the index. All these intervals, except the index, demonstrated significant blood pressure or heart rate dependence. Thus, there was no need for normalization of the index. The index correlated with global dysfunction and was significantly higher in the subgroup of patients with a lower stroke index, shortened mitral deceleration time and lower ejection fraction. In the multivariate model, only functional class and index were independent predictors of clinical outcome. The index therefore had significant prognostic power in addition to functional class. Univariately, both ejection fraction and deceleration time were predictors of outcome in this patient cohort. However, in the multivariate analysis they had no independent prognostic power. They did not add any prognostic information to that already conferred by functional class and the index. Use of the index may thus enhance the ability to plan management, especially if orthotopic cardiac transplantation is to be considered.

Comparison with previous work. The results of Doppler measurements of the individual time intervals are consistent with previous work in amyloid cardiomyopathy (6,20,22,31). A previous study demonstrated prolongation of isovolumetric relaxation time in early amyloidosis only, but the interval tended to be shortened in advanced stage with restrictive filling (20,31). In the present study, isovolumetric relaxation time was significantly prolonged, even in patients with advanced amyloidosis characterized by a mean left ventricular wall thickness >15 mm. This may be explained by the shortened ejection time, with earlier closure of the aortic valve. In addition, it has been shown by invasive manometry that the negative peak rate of left ventricular pressure increase (−dP/dt) is significantly abnormal in more advanced stages of cardiac amyloidosis (6). Left atrial pressure increase causes earlier mitral valve opening, which tends to shorten isovolumetric time. Our results demonstrate that the net result is prolongation of isovolumetric relaxation time, even in advanced cardiac amyloidosis.

Prolongation of the preejection period previously observed in amyloid heart disease (22) is consistent with the prolongation of isovolumetric contraction time observed in the present study. Even when ejection fraction is normal in early amyloid heart disease, isovolumetric contraction time is prolonged. This suggests that some degree of systolic dysfunction may be present in early cardiac amyloidosis. The isovolumetric contraction time may be a more sensitive measure of systolic dysfunction than ejection fraction.

Shortening of the ejection time has also been previously demonstrated (22). Because left ventricular end-diastolic volumes cannot increase in cardiac amyloidosis, shortening of the ejection time is associated with a decreased left ventricular stroke volume. This explains the higher value of the index in advanced amyloidosis, when the stroke volume starts to decrease.

Table 5. Univariate Cox Model Analysis

Variable	Chi-Square	p Value
NYHA functional class	12.4	< 0.001
Index	11.2	< 0.001
Ejection fraction	6.9	0.009
DT	4.4	0.04
ICT	3.9	0.05
Heart rate	3.7	0.05
Wall thickness	0.6	0.46
E/A	0.4	0.51
IRT	0.2	0.63

Abbreviations as in Tables 1 to 3.

Table 6. Multivariate Cox Regression Analysis Using Clinical and Echocardiographic Variables

Variable	Chi-Square	p Value
NYHA functional class	7.4	0.007
Index	4.6	0.032

Abbreviations as in Tables 1 and 2.

Several studies (7,17) have related two-dimensional and Doppler echocardiographic variables to outcome in cardiac amyloidosis. In the present study, the univariate analysis confirms the predictive value of functional class, ejection fraction and mitral deceleration time. However, wall thickness and mitral early/late diastolic peak velocity ratio did not have a significant predictive value in a univariate analysis. This may be due to selection bias, because the study included only a few patients with early cardiac involvement.

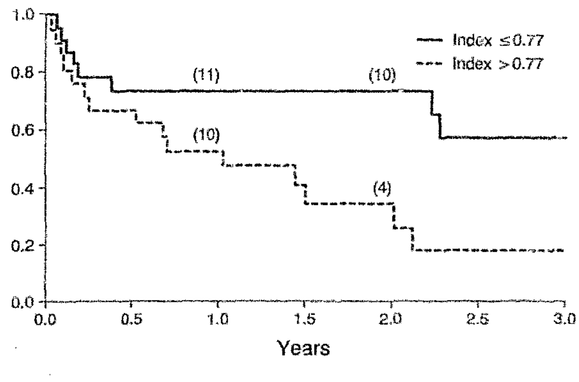
Study limitations. Interpretation of the individual time intervals is limited because of their dependency on loading conditions and heart rate. This problem was partially addressed by demonstrating lack of correlation of the index with either heart rate or blood pressure (24). The influence of load dependency must ultimately be addressed in an experimental model. However, despite this possible limitation, the index provided relevant clinical information in patients with advanced cardiac amyloidosis and appeared to be unaffected by heart rate or blood pressure. Moreover, other conventional echocardiographic variables, such as ejection fraction or deceleration time, display significant load dependency, but this has not limited their clinical applicability.

By design and selection, the majority of patients had advanced cardiac involvement. This may imply that the diagnosis of cardiac involvement was convincing and obviated the need for further scrutiny. However, the present study was primarily designed to show the value of the index in predicting outcome in this patient population.

Patients with atrial fibrillation and AV block were excluded from the study. This exclusion may limit extrapolation of this survival analysis to all patients with cardiac amyloidosis. Finally, the cause of death was based on clinical judgment. However, the index was related to overall survival, regardless of cause of death.

Conclusions. A simple measure of Doppler index, combining systolic and diastolic time intervals as an expression of global myocardial performance, correlates with overall cardiac function and seems to be a useful predictor of clinical outcome in patients with cardiac amyloidosis.

Figure 5. Survival free of cardiac death in patients with cardiac amyloidosis. The group with an index greater than the median value (>0.77) has a higher mortality risk than that with an index lower than the median value (≤0.77). **Numbers in parentheses** are number of patients.



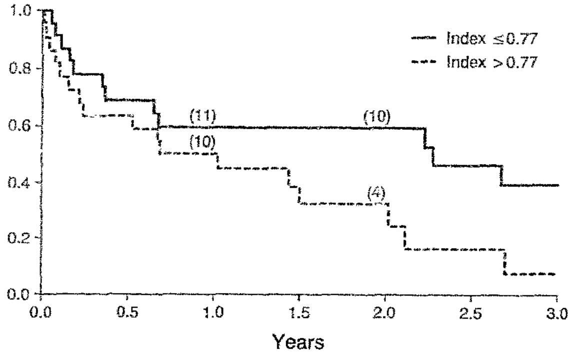


Figure 6. Overall survival in patients with cardiac amyloidosis. The group with an index greater than the median value (>0.77) has a higher mortality risk than that with an index lower than the median value (≤0.77). The index predicts overall mortality, regardless of cause of death. **Numbers in parentheses** are number of patients.

References

1. Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necropsy patients. Am J Cardiol 1983;52:137–46.
2. Kyle RA, Greipp PR. Amyloidosis: clinical and laboratory features in 229 cases. Mayo Clin Proc 1983;58:665–83.
3. Falk RH, Rubinow A, Cohen AS. Cardiac arrhythmias in systemic amyloidosis: correlation with echocardiographic abnormalities. J Am Coll Cardiol 1984;3:107–13.
4. Gertz MA, Kyle RA. Amyloidosis: prognosis and treatment. Semin Arthritis Rheum 1994;24:124–38.
5. Chew C, Wiady GM, Raphael MJ, Oakley CM. The functional defect in amyloid heart disease. The "stiff heart" syndrome. Am J Cardiol 1975;36:438–44.
6. Swanton RH, Brooksbey IAB, Davies MJ, Coltart DJ, Jenkins BS, Webb-Peploe MM. Systolic and diastolic ventricular function in cardiac amyloidosis. Am J Cardiol 1977;39:658–64.
7. Cueto-Garcia L, Reeder GS, Kyle RA, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. J Am Coll Cardiol 1985;6:737–43.
8. Hongo M, Ikeda S. Echocardiographic assessment of the evolution of amyloid heart disease: a study with familial amyloid polyneuropathy. Circulation 1983;73:249–56.
9. Child JS, Krivokapich J, Abbasi AS. Increased right ventricular wall thickness on echocardiography in amyloid infiltrative cardiomyopathy. Am J Cardiol 1979;44:1391–5.
10. Tyberg TI, Goodyer AVN, Hurst VWM, Alexander J, Langou RA. Left ventricular filling in differentiating restrictive amyloid cardiomyopathy and constrictive pericarditis. Am J Cardiol 1981;47:791–6.
11. Siquero-Filho AG, Cunha CLP, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation 1981;63:188–96.
12. Nicolosi GL, Pavan D, Lestuzzi C, Burelli C, Zardo F, Zanuttini D.

Prospective identification of patient with amyloid heart disease by two-dimensional echocardiography. Circulation 1984;70:432–7.

13. Cueto-Garcia L, Tajik AJ, Kyle RA, et al. Serial echocardiographic observations in patients with primary systemic amyloidosis: an introduction to the concept of early (asymptomatic) amyloid infiltration of the heart. Mayo Clin Proc 1984;59:589–97.
14. Falk RH, Plehn J, Deering T, et al. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. Am J Cardiol 1987;59:418–22.
15. Klein AL, Oh JK, Miller FA, Seward JB, Tajik AJ. Two-dimensional and Doppler echocardiographic assessment of infiltrative cardiomyopathy. J Am Soc Echocardiogr 1988;1:48–59.
16. Kinoshita O, Hongo M, Yamada H, et al. Impaired left ventricular diastolic filling in patients with familial amyloid polyneuropathy: a pulsed Doppler echocardiographic study. Br Heart J 1989:61·198–203.
17. Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. Circulation 1991;83:808–16.
18. Hamer JPM, Janssen S, Van Rijswijk MH, Lie KI. Amyloid cardiomyopathy in systemic non-hereditary amyloidosis. Eur Heart J 1992;13:623–7.
19. Hongo M, Misava T, Kinoshita O, et al. Computerized M-mode echocardiographic assessment of left ventricular diastolic function in patients with familial amyloid polyneuropathy. Jpn Circ J 1990;54:32–42.
20. Klein AL, Hatle LK, Burstow DJ, et al. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 1989;13:1017–26.
21. Hirota Y. A clinical study of left ventricular relaxation. Circulation 1980;62:756–63.
22. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the non-invasive diagnosis of cardiac amyloidosis. Am Heart J 1982;103:468–73.
23. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995;26:135–6.
24. Tei C, Lieng HL, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357–66.
25. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KL, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. Mayo Clin Proc 1994;69:212–24.
26. Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification, and validation. Mayo Clin Proc 1978;53:271–303.
27. Nishimura RA, Miller FA Jr, Callahan MJ, Benassi RC, Seward JB, Tajik AJ. Doppler echocardiography: theory, instrumentation, technique, and application. Mayo Clin Proc 1985;60:321–34.
28. Quinones MA, Waggoner AD, Reduto LA, et al. A new simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744–53.
29. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
30. Cox DR. Regression models and life-tables (with discussion). J R Statist Soc B 1972;34:187–220.
31. Klein AL, Hatle LK, Taliercio CP, et al. Serial Doppler echocardiographic follow-up of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 1990;16:1135–41.