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ORIGINAL RESEARCH

Prognostic Significance of Strain Doppler Imaging in Light-Chain Amyloidosis

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OBJECTIVES To clarify the prognostic value of strain and strain rate imaging in light-chain (AL) amyloidosis.

BACKGROUND Myocardial strain and strain rate Doppler imaging are objective measurements that may detect regional subtle myocardial functional abnormalities in patients with amyloidosis.

METHODS We prospectively examined 119 consecutive, untreated patients with biopsy-proven AL amyloidosis. The mean values of tissue velocity, strain, and strain rate were calculated from the basal, mid, and apical left ventricular (LV) multiple walls in apical 2- and 4-chamber views. The prognostic value of these parameters was compared with standard 2-dimensional echocardiographic and Doppler measurements of transmitral and pulmonary venous flow.

RESULTS Seventy patients had cardiac involvement defined as the mean value of LV wall thickness greater than 12 mm. Thirty-two patients (27%) (including 22 proven cardiac deaths) died during a mean follow-up period of 285 ± 136 days. No echocardiographic or Doppler features differentiated patients with cardiac involvement without congestive heart failure (CHF) from noncardiac amyloid group other than the pre-defined wall thickness and LV end-diastolic and end-systolic diameters. On the other hand, strain rate and strain imaging clearly detected differences of longitudinal LV myocardial deformation among 3 groups (noncardiac involvement group, cardiac amyloidosis without CHF group, and cardiac amyloidosis with CHF group). Univariate analysis showed that strain rate, strain, and tissue velocity values were statistically significant predictors of outcome at most of the sites. Multivariate analysis showed that the mean LV basal strain was the only independent predictor of both cardiac and overall deaths.

CONCLUSIONS Among patients with AL amyloidosis, the mean basal strain, a measure of longitudinal LV function, was a powerful predictor of clinical outcome and was superior to standard 2-dimensional echocardiographic, Doppler flow measurements, and simple tissue velocity indexes. (J Am Coll Cardiol Img 2010;3:333–42) © 2010 by the American College of Cardiology Foundation

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Primary light-chain (AL) amyloidosis is a plasma cell dyscrasia associated with the deposition of immunoglobulin-derived amyloid in multiple organs. In the heart, this results in an infiltrative cardiomyopathy, with increased left ventricular (LV) wall thickness, normal or decreased LV cavity size, and congestive heart failure (CHF) (1–5). Cardiac involvement is a major determinant of prognosis of AL amyloidosis, and previous studies have attempted to correlate echocardiographic abnormalities with survival (2,4).

LV wall thickness >15 mm, reduced LV systolic function (2), shortened deceleration time, and increased early-to-late diastolic filling ratio of transmitral flow have all been reported as predictors of death in cardiac amyloidosis (4).

Regional strain (change in length per unit length) and strain rate (SR), the temporal derivative of strain (6), have been validated in experimental models and are sensitive markers of systolic myocardial function (7). We have previously shown that, using these techniques, systolic dysfunction can be demonstrated in cardiac amyloidosis when it is not apparent by other echocardiographic techniques (8). We have further shown that the cyclic variation of integrated backscatter at the ventricular posterior wall, a parameter of intrinsic myocardial contraction (9), is a predictor of clinical outcome that is superior to standard echocardiographic/Doppler flow indexes in AL amyloidosis (10). We therefore hypothesized that strain and SR may be additional tools for defining prognosis in this disease, and we performed this study in order to clarify the prognostic value of strain/SR Doppler analysis in a consecutive series of patients with primary (AL) amyloidosis. We also sought to compare the prognostic value of strain/SR Doppler with that of the standard 2-dimensional echocardiography and Doppler (2,4).

ABBREVIATIONS AND ACRONYMS

CHF = congestive heart failure
LV = left ventricular
SR = strain rate
TV = tissue velocity

METHODS

Two hundred ten consecutive patients with biopsy-proven AL amyloidosis were examined at the Boston University Amyloidosis Treatment and Research Center between April 23, 2001, and March 12, 2002. The diagnosis of amyloidosis was made when a biopsy specimen of an involved organ demonstrated typical Congo Red birefringence under polarized light. AL amyloidosis was confirmed by the finding of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow when evaluated by immunohistochemistry (11). Patients with non-AL amyloidosis were not enrolled. Twenty-three patients with poor echocardiographic images (n = 10), atrial fibrillation (n = 5), history of hypertension (n = 7), or significant valvular disease (n = 1) were excluded. We also excluded 68 patients who had undergone intravenous melphalan therapy with stem cell transplantation before the initial echocardiographic examination as this therapy has been shown to prolong survival, but its effect on echocardiographic indexes is not known. Thus, the final population consisted of 119 patients, all of whom had evidence of a plasma cell dyscrasia.

All patients underwent a physical examination by a cardiologist (R.H.F.) with particular emphasis on the presence or absence of signs and symptoms of CHF. CHF was defined as dyspnea on exertion, associated with orthopnea, paroxysmal nocturnal dyspnea, or a chest radiographic appearance of heart failure and/or the presence of elevated jugular venous pressure. Echocardiograms were reviewed by 2 readers to determine the presence or absence of cardiac involvement, defined as a mean value of LV thickness >12 mm in the absence of hypertension, valvular heart disease, or criteria for LV hypertrophy on the electrocardiogram (ECG) (3,12). Seventy patients met the echocardiographic criteria for cardiac involvement, and 49 patients had no features of cardiac amyloidosis. The latter group was defined as group 1 (noncardiac amyloid). Of the 70 patients with cardiac amyloidosis, 37 had prior or current evidence of CHF. These patients were defined as group 3 (CHF [+] group) and the remaining 33 were defined as group 2 (CHF [−] group). Follow-up data were obtained from correspondence with the patient, with his or her family, and/or from the referring physician. Death data and date of death were also ascertained through an on-line Social Security database. The protocol was approved by the institutional review board, and written informed consent was obtained from each patient.

Ultrasound examination and measurements. Ultrasound examinations were performed with a commercially available echocardiographic machine (Vivid Five System, Vingmed-General Electric, Milwaukee, Wisconsin). Standard M-mode measurements of the LV were made. Transmitral flow velocity pattern and pulmonary venous flow were recorded as described previously (8,10). Analysis of Doppler flow was performed using dedicated soft-

ware (Echopac 6.3.6, GE Vingmed Ultrasound). Three consecutive beats were measured and averaged for each measurement. Peak velocities of early- (E) and late-filling (A) waves, duration of A-wave, the E/A ratio, and deceleration time of the E-wave were measured from transmitral flow velocities, and the peak velocities of the systolic (S), diastolic (D), and A waves, duration of A-wave, and the D/S ratio were also measured from pulmonary venous flow.

Tissue Doppler data acquisition. Apical 2- and 4-chamber views were obtained (Fig. 1), and 2-dimensional color tissue Doppler recordings were recorded during brief apnea after expiration at a frame rate 97 to 132 frames per second (mean value 110 frames/s). Pulse repetition frequency was adjusted to avoid aliasing. The acquired raw data were transferred to a hard drive for offline analysis.

Tissue velocity, strain, and SR. Color 2-dimensional digital data from 3 consecutive cardiac cycles were analyzed offline using software incorporated in the Vivid Five System (Echopac 6.3.6, GE Vingmed Ultrasound). The investigator performing the tissue Doppler, strain/SRI analysis (J.K.) did not know which patients had CHF. Sample volumes were placed in the inner half of the myocardium to keep the angle between the Doppler beam and the longitudinal shortening direction of the wall (or the direction of endocardium) as small as possible (at least <30°). Measurements were made at the center of each basal, mid-, and apical LV segment at the septum, lateral, inferior, and anterior walls (Fig. 1). SR is equal to the spatial myocardial velocity gradient expressed by the equation: $SR = (v[r] - v[r+\Delta r])/\Delta r$ (where r = distance along ultrasound beam, v = tissue velocity). Strain is calculated by combining the SR values over a given time interval as described previously (6,7). An offset (r) of 10.8 or 11.1 mm was used in all studies. Tissue velocity (TV), strain, and SR curves were acquired from the same sample volume in the same image at each site and the mean values were calculated from 3 cardiac cycles (Fig. 1). Peak systolic strain was determined as the difference in strain measured from the onset of the QRS complex to the nadir of the strain tracing. For SR, peak systolic SR, peak early diastolic SR, and peak late diastolic SR were measured. TV waves were obtained from the same sample volumes, and peak systolic, early diastolic, and late diastolic TV were measured. Values at each wall are reported separately and were also averaged to give a mean basal, mid- and apical value.

Inter- and intraobserver variability were assessed by measuring 18 datasets of averaged mean basal, mid- and apical value derived from 6 patients

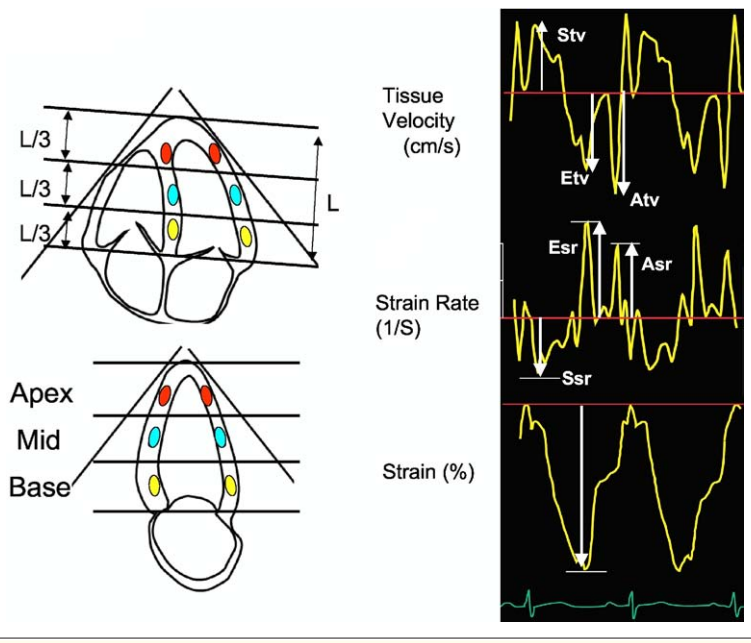

Figure 1. Sample Volume Positions and Analyzed Waveforms

(Left) Sample volume position in apical 2- and 4-chamber views. Sample volumes were placed in the septum and the lateral, inferior, and anterior walls at the base, mid-, and apical ventricular levels. **(Right)** Measurements of tissue velocity, strain rate, and strain. Asr = peak late diastolic strain rate; Atv = peak late diastolic tissue velocity; Esr = peak early diastolic strain rate; Etv = peak early diastolic tissue velocity; Ssr = peak systolic strain rate; Stv = peak systolic tissue velocity.

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Table 1. Patients and Echocardiographic and Doppler Characteristics (n = 119)

	Group 1 (n = 49)	Group 2 (n = 33)	Group 3 (n = 37)
Age (yrs)	59.0 ± 9.8	56.5 ± 11	59.4 ± 10.4
Male/female	21/28	23/10	19/18
Heart rate (beats/min)	75 ± 13	78 ± 13	87 ± 16*
Systolic BP (mm Hg)	121 ± 21	115 ± 17	109 ± 15†
Diastolic BP (mm Hg)	72 ± 10	72 ± 10	69 ± 10
Mean LVThd (mm)	10.2 ± 1.2	14.5 ± 1.8‡	15.8 ± 2.7‡§
LVDd (mm)	49.3 ± 6.5	44.6 ± 6.3*	41.2 ± 5.0‡
LVDs (mm)	28.9 ± 6.3	25.8 ± 5.2†	29.8 ± 4.7§
LVFS (%)	42.7 ± 7.9	41.3 ± 8.6	28.2 ± 9.6‡‖
LAD (mm)	41.5 ± 7.5	45.0 ± 9.2	46.6 ± 6.9†
TMF-E (m/s)	0.66 ± 0.14	0.68 ± 0.21	0.86 ± 0.20‡¶
TMF-A (m/s)	0.67 ± 0.16	0.69 ± 0.22	0.38 ± 0.21‡‖
TMF-A duration (ms)	168 ± 32	159 ± 29	150 ± 27
TMF-E/A	1.08 ± 0.51	1.15 ± 0.72	2.71 ± 1.15‡‖
TMF E-DT (ms)	199 ± 50	205 ± 56	166 ± 82§
PVF-S (m/s)	0.52 ± 0.19	0.46 ± 0.18	0.25 ± 0.14‡‖
PVF-D (m/s)	0.45 ± 0.14	0.46 ± 0.18	0.58 ± 0.17*§
PVF-A (m/s)	0.23 ± 0.08	0.24 ± 0.07	0.20 ± 0.10
PVF-A duration (ms)	145 ± 26	132 ± 27	133 ± 39
PVF-D/S	1.03 ± 0.68	1.22 ± 0.97	2.95 ± 1.57‡‖

*$p < 0.01$ versus group 1; †$p < 0.05$ versus group 1; ‡$p < 0.0001$ versus group 1; §$p < 0.05$ versus group 2 (by Scheffé test); ‖$p < 0.0001$ versus group 2; ¶$p < 0.001$ versus group 2.
A = peak atrial filling wave velocity; BP = blood pressure; D = peak diastolic wave velocity; DT = deceleration time; E = peak early diastolic wave velocity; LAD = left atrial diameter; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVFS = left ventricular fractional shortening; LVThd = left ventricular thickness at end diastole; PVF = pulmonary venous flow; S = peak systolic wave velocity; TMF = transmitral flow.

randomly selected from each group, for a total of 18 patients. The second measurements were done several months after the first measurements for both inter- and intraobserver variability. Results are expressed as the linear regression between the 2 measurements and as the percent error.

Statistics. All data are expressed as mean ± SD. Statistical analyses were done with a commercially available software program (Stat View 5.0, SAS Institute Inc., Cary, North Carolina). Differences among 3 group characteristics were assessed with the chi-square test for categorical variables, and comparisons of continuous variables among 3 groups were made using the 1-way or factorial analysis of variance with repeated measures for segment and wall, followed by the Scheffé test. A difference was considered significant when the p value was <0.05.

The median value of variables was used to divide patients into 2 groups when survival free of cardiac death and overall survival were estimated using the Kaplan-Meier method (13). To determine a suitable cutoff value, we constructed the receiver-operator characteristic curve, and took values where sensitivity is as equal as possible to specificity. We also measured the area under the curve, which is a summary measure of performance determined by the receiver-operator characteristic curve (14). Univariate analyses were followed by a log-rank test. Multivariate analysis to determine the relative contribution of variables was examined by Cox's proportional hazards regression model (15). A stepwise regression analysis was performed to investigate the independence of mean LV basal strain from tissue E velocity and the deceleration time of the transmitral E-wave. A 0.05 level of significance was applied to determine whether variables were added or removed from the model (15).

RESULTS

Two-dimensional echocardiographic and Doppler measurements. Clinical characteristics are shown in Table 1. Systolic blood pressure was significantly lower and heart rate was significantly higher in group 3 than in the other 2 groups. No echocardiographic or Doppler features differentiated group 2 from group 1 other than the pre-defined wall thickness and LV end-diastolic and end-systolic diameters (Table 1), whereas patients in group 3 had more abnormalities than either of the other 2 groups. Left atrial diameter was significantly greater in group 3 than in group 1, and the LV fractional shortening was smaller in group 3 than in the other 2 groups. Patients in group 3 showed greater peak E velocity, peak E/A ratio, peak D-wave velocity, and the peak D/S ratio of pulmonary venous flow. Patients in group 3 also showed smaller values in the peak transmitral A-wave, peak S velocity of pulmonary venous flow, and deceleration time of transmitral E-wave than in the other 2 groups.

TV, SR, and strain imaging. Peak values of tissue velocity, strain, and SR measured at each segment are shown in Figures 2A to 2C, and mean values for each wall are shown in Figure 2D (Table 2). Segmental values at the base, mid-ventricle, and apex trended in the same direction and were therefore pooled for statistical analysis of prognostic significance. As we have previously shown (8), peak systolic TV did not differ between group 1 and group 2 at any site, but was lower in group 3 at the base and mid-LV than in either of the other groups. In contrast to the indexes of systolic TV, peak early diastolic TV at the LV base was statistically different among all 3 groups. Whereas peak late diastolic

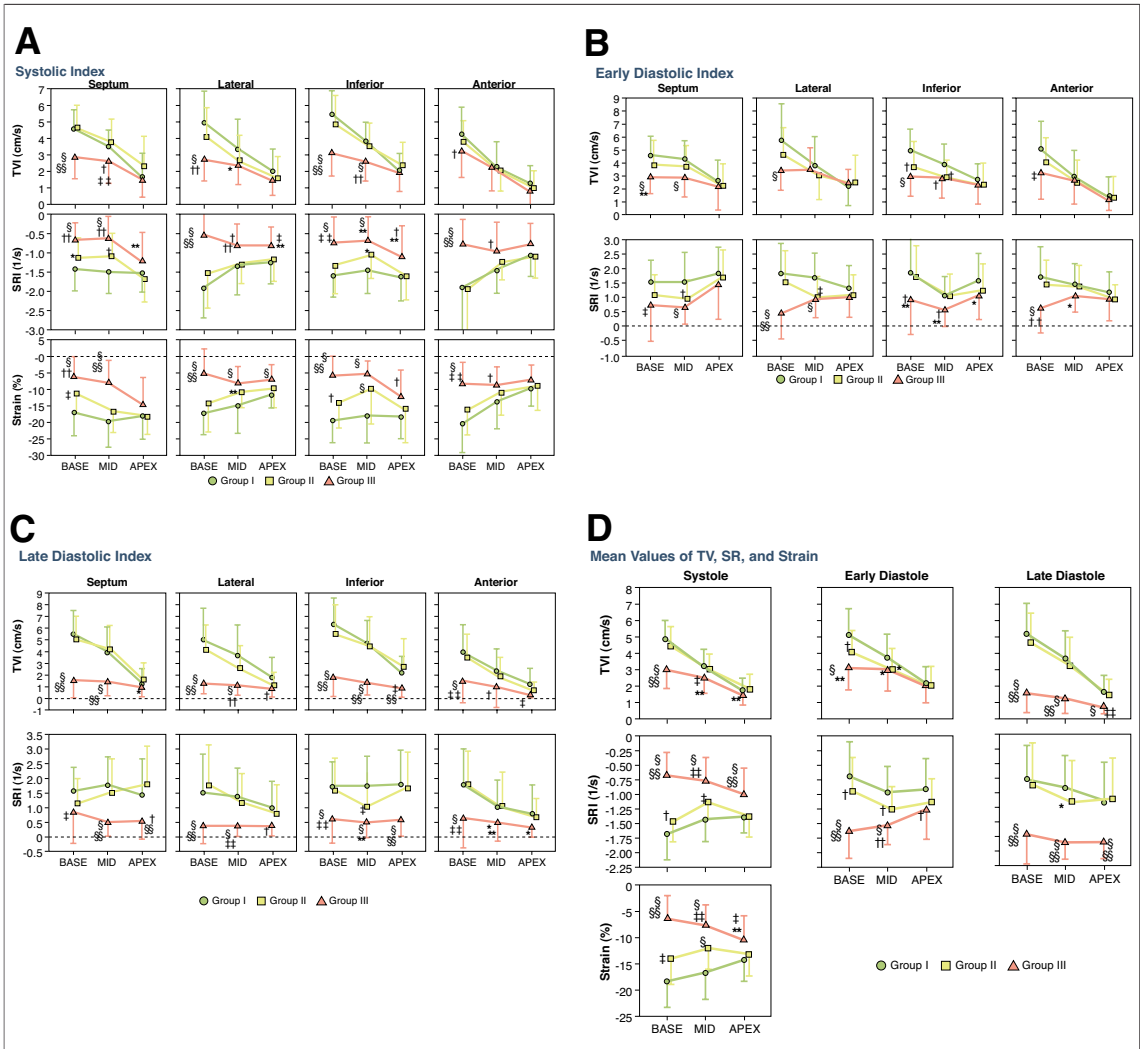

Figure 2. TV, SR, and Strain Measurements at Each Position

Peak systolic **(A)**, peak early diastolic **(B)**, and peak late diastolic values **(C)** of tissue velocity (TV), strain rate (SR), and strain at basal, mid-, and apical LV at the septum, lateral, inferior, and anterior walls. Mean values of TV, SR, and strain were calculated from 4 walls at the basal, mid, and apical LV **(D)**. Group 1, noncardiac amyloid; group 2, CHF (−); group 3, CHF (+). *$p < 0.05$ versus group 1, †$p < 0.01$ versus group 1, ‡$p < 0.001$ versus group 1, §$p < 0.0001$ versus group 1, **$p < 0.05$ versus group 2, ††$p < 0.01$ versus group 2, ‡‡$p < 0.001$ versus group 2, §§$p < 0.0001$ versus group 2.

TV was significantly lower at all 3 segments in group 3 compared with either of the other groups, TV imaging could not distinguish between groups 1 and 2. In contrast to TV imaging, SR and strain imaging clearly detected differences of longitudinal LV myocardial deformation among all 3 groups both in systole and early diastole at the base and mid-LV. The SR at late diastole distinguished between groups 1 and 2 only at the mid-LV.

Prognostic value of echocardiogram/Doppler and tissue Doppler indexes. Of the 119 patients, 32 died during a mean follow-up period of 285 ± 136 days (censored periods range from 199 to 510 days), and 22 of the 32 deaths (68.8%) were either sudden or due to CHF. Patients with heart failure showed significantly poorer prognosis than the other 2 groups (Fig. 3, upper panels). Univariate analysis showed that strain, SR, and TV values were statistically significant predictors of outcome at most of the sites, although apical values tended not to differ among groups. The stepwise regression analysis showed that the mean LV basal strain, TVI-E-Apex, and the deceleration time of transmitral E-wave were independent predictors. Multivariate analysis of these 3 parameters showed that the only independent measurement predicting either death

Table 2. Strain, Strain Rate, and Tissue Doppler Score Characteristics

	Group 1 (CV%) (n = 49)	Group 2 (CV%) (n = 33)	Group 3 (CV%) (n = 37)
Tissue velocity imaging (TVI) (cm/s)			
TVI-S-Base	4.80 ± 1.13 (24)	4.36 ± 1.19 (27)	2.95 ± 1.12 (38)*†
TVI-S-Mid	3.23 ± 0.95 (29)	3.03 ± 0.90 (30)	2.44 ± 0.89 (36)‡#
TVI-S-Apex	1.74 ± 0.70 (40)	1.83 ± 0.85 (46)	1.40 ± 0.58 (41)#
TVI-E-Base	5.10 ± 1.60 (31)	4.07 ± 1.31 (32)‖	3.07 ± 1.32 (43)*#
TVI-E-Mid	3.75 ± 1.38 (37)	3.00 ± 1.27 (42)¶	2.71 ± 1.35 (50)¶
TVI-E-Apex	2.20 ± 0.96 (44)	2.05 ± 1.07 (52)	1.95 ± 0.97 (50)
TVI-A-Base	5.20 ± 1.84 (35)	4.60 ± 1.85 (40)	1.51 ± 1.18 (78)*†
TVI-A-Mid	3.67 ± 1.70 (46)	3.28 ± 1.65 (50)	1.21 ± 0.87 (72)*†
TVI-A-Apex	1.63 ± 0.99 (61)	1.50 ± 0.91 (61)	0.70 ± 0.40 (57)*§
Strain rate imaging (SRI) (1/s)			
SRI-S-Base	−1.72 ± 0.46 (27)	−1.48 ± 0.62 (42)‖	−0.70 ± 0.40 (57)*†
SRI-S-Mid	−1.44 ± 0.37 (26)	−1.13 ± 0.29 (26)‡	−0.78 ± 0.41 (53)*§
SRI-S-Apex	−1.38 ± 0.29 (21)	−1.39 ± 0.34 (24)	−0.99 ± 0.45 (45)*†
SRI-E-Base	1.72 ± 0.65 (38)	1.44 ± 0.63 (44)‖	0.67 ± 0.50 (75)†
SRI-E-Mid	1.41 ± 0.49 (35)	1.09 ± 0.42 (39)‖	0.77 ± 0.35 (45)*‖
SRI-E-Apex	1.47 ± 0.59 (40)	1.23 ± 0.44 (36)	1.09 ± 0.57 (52)‖
SRI-A-Base	1.64 ± 0.64 (39)	1.54 ± 0.79 (51)	0.59 ± 0.57 (97)*†
SRI-A-Mid	1.48 ± 0.60 (41)	1.23 ± 0.76 (62)#	0.44 ± 0.31 (70)*†
SRI-A-Apex	1.24 ± 0.71 (57)	1.26 ± 0.79 (63)	0.44 ± 0.31 (70)*†
Strain (%)			
Strain-Base	−18.3 ± 4.9 (27)	−13.9 ± 5.0 (36)‡	−6.5 ± 4.3 (66)*†
Strain-Mid	−16.6 ± 5.0 (30)	−12.2 ± 3.9 (32)*	−7.7 ± 3.9 (51)*§
Strain-Apex	−14.4 ± 3.9 (27)	−13.2 ± 4.1 (31)	−10.4 ± 4.4 (42)*#

*$p < 0.0001$ versus group 1, †$p < 0.0001$ versus group 2, ‡$p < 0.001$ versus group 1, §$p < 0.001$ versus group 2, ‖$p < 0.01$ versus group 1, ¶$p < 0.05$ versus group 1, #$p < 0.05$ versus group 2 (by Scheffé test).
CV = coefficient of variation (%); other abbreviations as in Table 1.

from any cause or cardiac death was basal systolic strain (Table 3).

The receiver-operator characteristic analysis for the total patient group indicated that a basal strain value of −13.0% was the most suitable cutoff value to predict all death, and a strain value of −12.0% best predicted cardiac death (Fig. 3, middle panels). Because CHF is a strong predictor of adverse outcome (Fig. 3, upper panels), we also analyzed the groups without CHF (groups 1 and 2) separately from group 3 (Fig. 4). In the groups without CHF, a receiver-operator characteristic curve–derived cutoff value of strain at the basal LV of −13.0% predicted cardiac death ($p = 0.047$). This value is similar to that of the total group, but the value was statistically less robust. In group 3, all of whom had heart failure by definition, strain was still capable of adding prognostic value; a cutoff basal strain of <−4.6% best predicted death from any cause, similar to the value for cardiac death (−4.4%).

Reproducibility. The inter- and intraobserver variabilities of are shown in Table 4. The reproducibility of strain was better than that of the other parameters, and the measurements of TV and SR at the apex were less reproducible than at the basal and mid-LV.

Effect of treatment on prognosis. Thirty-four patients received high-dose intravenous melphalan therapy with stem cell transplantation, and the remaining 85 had oral regimens. These treatments were based on the best judgment of evaluating physicians after echocardiographic assessment. As shown in Figure 5, there was no statistical difference between intravenous and oral regimens in both all-cause and cardiac death.

DISCUSSION

Cardiac involvement in AL amyloidosis is the commonest cause of death, and therefore, an objective method to assess the cardiac prognosis in untreated patients is desirable (2,4,5,10,16,17). We previously showed that, despite echocardiographic evidence of amyloid infiltration, longitudinal systolic function in AL amyloidosis appeared normal when evaluated by TV imaging until the onset of

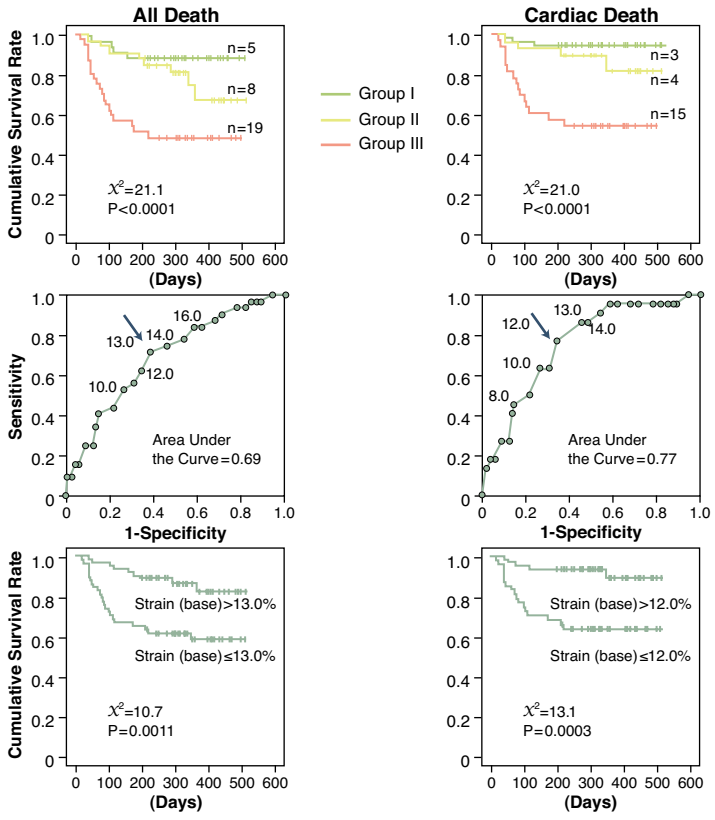

Figure 3. Overall Survival and Survival Free of Cardiac Death in Patients With AL Amyloidosis

(Upper), overall survival and survival free of cardiac death in each group. Group 3 showed poorer outcome than in the other 2 groups. Small **vertical lines** in graphs represent censor time. Group 1, noncardiac amyloid; group 2, cardiac involvement without CHF; and group 3, cardiac involvement with CHF. **(Middle)**, receiver-operator characteristic curve–derived cutoff values (13.0% for all death, and 12.0% for cardiac death). **(Lower)**, overall survival and survival free of cardiac death in patients with light-chain (AL) amyloidosis in all groups (n = 119).

CHF (18). We subsequently evaluated myocardial strain/SR imaging in these patients, and demonstrated that this technique can detect longitudinal systolic dysfunction even before the onset of heart failure (8). In the present study, we have shown that SR imaging is not only useful for demonstrating systolic dysfunction, but is also a powerful prognostic indicator of survival.

Several non-Doppler–derived echocardiographic parameters such as increased mean LV wall thickness, decreased fractional shortening, and LV inflow filling variables have been reported to be important independent predictors of cardiac mortality in small series of patients with cardiac amyloidosis (2,4,10,16), although there is some inconsistency of these findings between studies (10,17). Cyclic-dependent variation of myocardial integrated backscatter, a parameter considered to correlate with changes in intrinsic myocardial contractility (9), was found to be the most sensitive marker predicting poor outcome among multiple ultrasonic variables in amyloidosis, including LV inflow filling indexes (10). Although this finding supported the concept that sensitive markers of intrinsic myocardial contraction may be predictors of clinical outcome in patients with AL amyloidosis, that study did not include tissue Doppler, strain, or SR.

In the present investigation, regional variations in strain and SR were noted both in patients with normal echocardiograms and those with evidence of cardiac amyloidosis. The values in our group 1 patients demonstrate a slightly lesser degree of apical than basal strain and SR, and are very similar to the slight regional variation found by Andersen and Poulsen (19) in normal subjects. Basal strain was superior to traditional diastolic Doppler flow parameters and was also a stronger predictor of outcome than early diastolic measurements of TV or SR. It is of interest that, although the presence of

Table 3. Univariate Mantel-Cox and Multivariate Cox Proportional Hazards Analysis (Log-Rank Test, n = 119)

	All-Cause Death (n = 32)		Cardiac Death (n = 22)	
	Chi-Square	p Value	Chi-Square	p Value
Univariate*				
%FS (39)	5.00	0.0254	8.38	0.0038
LVThdm (12.6)	9.34	0.0022	10.00	0.0015
TMF-E/A (1.12)	6.33	0.0118	9.12	0.0025
TMF-DT (186)	6.31	0.0120	5.74	0.0166
PVF-D/S (1.13)	11.40	0.0007	10.60	0.0011
Strain-Base (−13.28)	9.31	0.0023	13.60	0.0002
Strain-Mid (−11.69)	5.08	0.0241	10.30	0.0013
SRI-S-Mid (−1.11)	9.99	0.0016	9.16	0.0025
SRI-A-Mid (0.97)	6.81	0.0091	8.44	0.0037
SRI-A-Apex (0.85)	7.57	0.0059	8.70	0.0032
TVI-S-Base (4.14)	5.75	0.0165	4.95	0.0260
TVI-S-Apex (1.56)	8.90	0.0029	6.66	0.0099
TVI-E-Base (4.26)	5.16	0.0232	7.87	0.0050
TVI-E-Mid (3.20)	7.34	0.0067	6.64	0.0100
TVI-E-Apex (2.1)	10.40	0.0013	9.62	0.0019
TVI-A-Base (4.02)	5.11	0.0237	7.83	0.0051
Multivariate*				
Strain-Base (−13.28)	5.210	0.0225	7.022	0.0081
TMF-DT (186)	3.95	0.0468	3.088	0.0789
TVI-E-Apex (2.1)	1.39	0.2385	2.210	0.1371

*Median value.
%FS = percent fractional shortening; other abbreviations as Tables 1 and 2.

heart failure was associated with a very poor prognosis, an analysis of basal strain limited to this group demonstrated its independent prognostic value.

A cardiovascular magnetic resonance study demonstrated a characteristic pattern of global late gadolinium enhancement with a dominant subendocardial distribution that matches the transmural distribution of amyloid protein (20). It can be speculated that subendocardial dominant deposition of amyloid protein reduces subendocardial contraction, which contributes to longitudinal LV shortening and could lead to longitudinal LV dysfunction and poor cardiac prognosis (21).

The patients were treated by various therapies after the echocardiography study, based on clinical assessment of their disease, including high-dose chemotherapy. Although high-dose chemotherapy with autologous stem cell transplant has been shown to be beneficial in some patients with AL amyloidosis (22), there are data to suggest that less aggressive therapies (as received by some patients) are equally effective in high-risk cardiac patients (23). From our results, we are not convinced that stem cell therapy would necessarily have had an additional impact on outcome in cardiac amyloidosis—a group of patients known for a very upfront mortality with stem cell therapy.

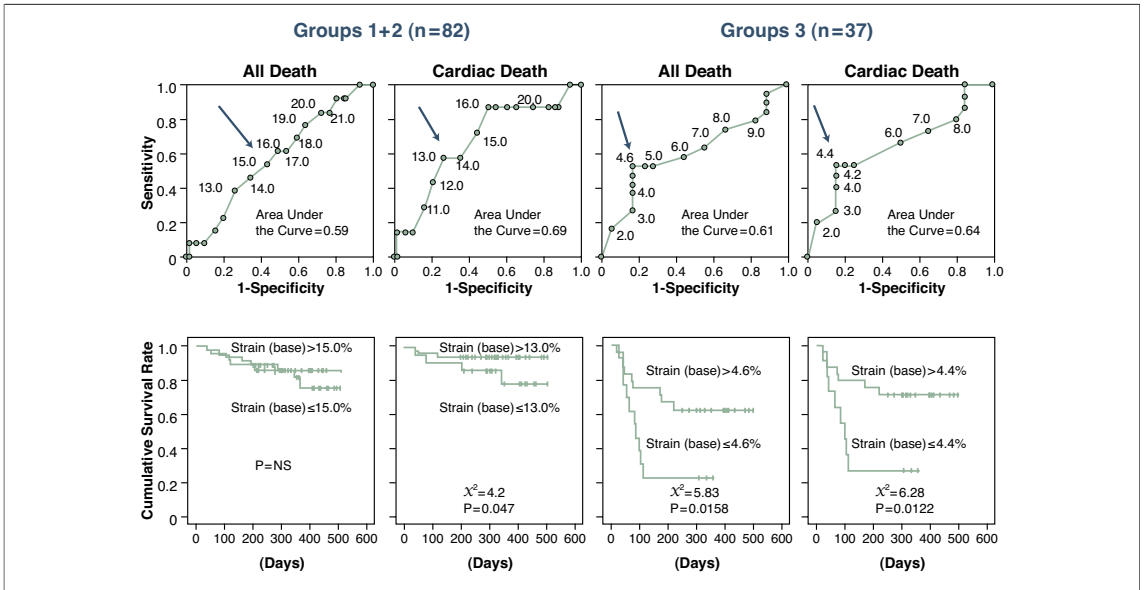

Figure 4. Analysis in Groups Without CHF (1 + 2) and Group With CHF

Receiver-operator characteristic curve–derived cutoff value of 13.0% predicted cardiac death in the subgroup 1+2. In group 3, receiver-operator characteristic cutoff value of 4.6% best predicted all death and 4.4% best predicted cardiac death.

Table 4. Intraobserver and Interobserver Variability of TV, SR, and Strain Measurements

	Systole		Early Diastole		Atrial Filling	
	Intraobserver	Interobserver	Intraobserver	Interobserver	Intraobserver	Interobserver
Tissue velocity						
Base R^2	0.970	0.988	0.987	0.987	0.989	0.996
SE (cm/s)	0.045	0.026	0.028	0.028	0.028	0.017
Mid R^2	0.968	0.966	0.970	0.991	0.971	0.979
SEE (cm/s)	0.044	0.045	0.041	0.023	0.043	0.038
Apex R^2	0.895	0.966	0.936	0.963	0.855	0.935
SEE (cm/s)	0.073	0.046	0.056	0.044	0.094	0.061
Strain rate						
Base R^2	0.983	0.995	0.937	0.964	0.972	0.970
SEE (1/s)	0.032	0.017	0.065	0.049	0.043	0.045
Mid R^2	0.962	0.976	0.934	0.966	0.974	0.993
SEE (1/s)	0.051	0.039	0.068	0.042	0.041	0.022
Apex R^2	0.902	0.930	0.974	0.965	0.877	0.982
SEE (1/s)	0.090	0.076	0.040	0.047	0.095	0.042
Strain						
Base R^2	0.996	0.998	—	—	—	—
SEE (%)	0.015	0.012	—	—	—	—
Mid R^2	0.996	0.998	—	—	—	—
SEE (%)	0.015	0.009	—	—	—	—
Apex R^2	0.996	0.992	—	—	—	—
SEE (%)	0.017	0.023	—	—	—	—

SEE = standard error of the estimate; SR = strain rate; TV = tissue velocity.

Study limitations. Strain Doppler measurements are angle dependent (6,7), and the angle between the ultrasound beam and LV wall must be small. Because of curvature of the apex, the measurement of apical LV strain may be artifactually related to Doppler alignment, and this may be the reason why the basal, not apical parts of the LV seem to indicate prognostic relevance. However, this should not have affected the results of the study. With the method used, a limitation of SR

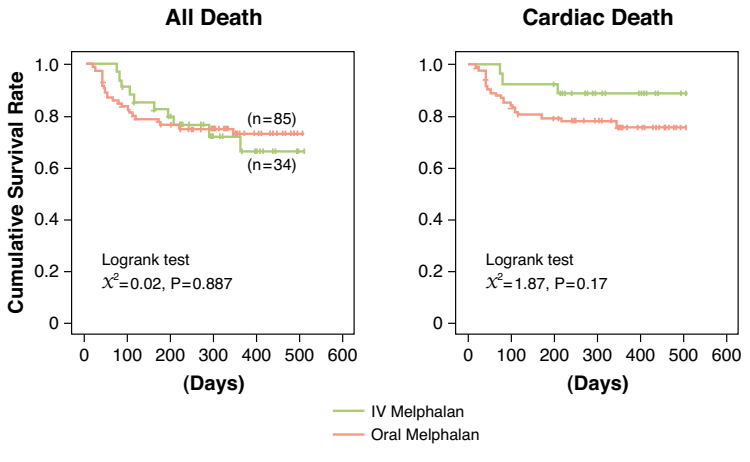

Figure 5. Overall Survival and Survival Free of Cardiac Death in High-Dose Intravenous and Oral Melphalan Therapy Groups

Overall survival and survival free of cardiac death in high-dose intravenous melphalan with autologous stem cell transplantation group (n = 34) and oral melphalan therapy group (n = 85). The treatments were selected based on the best judgment of evaluating physicians after echocardiographic evaluation. There was no statistical difference between 2 regimens in both all-cause and cardiac death.

is a relatively poor signal-to-noise ratio. To minimize this effect we measured and averaged 3 cardiac cycles.

We did not randomize patients into high-dose intravenous or oral regimens group after echocardiographic assessment; there is insufficient evidence to suggest that therapy choice would have modified patients' prognosis.

CONCLUSIONS

This study demonstrates that systolic basal strain is a predictor of clinical outcome in patients with AL amyloidosis, and is superior to Doppler flow measurements and to diastolic TV or SR indexes. It has an additive prognostic value even when heart failure is present. This finding may help to select patients with AL amyloidosis for treatment, particularly when high-dose intravenous melphalan with autologous stem cell transplantation is considered, as this therapy, although successful in producing a hematologic remission in a significant proportion of patients, is associated with a high prevalence of cardiac complications that limit its utility in potentially high-risk patients with cardiac involvement from their disease (22,23).

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