Cardiac Arrhythmias in Systemic Amyloidosis: Correlation With Echocardiographic Abnormalities

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To determine the prevalence of cardiac arrhythmias in patients with systemic amyloidosis 24 hour electrocardiographic monitoring was performed in 27 patients with primary amyloidosis and in 6 patients with familial amyloid polyneuropathy. All patients underwent echocardiographic studies. Despite a high prevalence of conduction disturbances on standard electrocardiogram, clinically significant bradyarrhythmias were rare (one patient). Complex ventricular arrhythmias (multiform, paired or repetitive beats) occurred in 14 patients (47%) with primary amyloid and 3 patients (50%) with familial amyloid polyneuropathy. The presence of cardiac arrhythmia correlated with heart failure and, more strongly, with an abnormal echocardiogram. There were four sudden deaths, all in patients with abnormal echocardiograms and complex ventricular arrhythmias. These findings suggest that complex ventricular arrhythmia on Holter monitoring is common in cardiac amyloidosis and may be a harbinger of subsequent sudden cardiac death.

Systemic amyloidosis frequently involves the heart and results in death in approximately 50% of patients with AL (primary) amyloidosis (1) Several series have reported that sudden death is common, occurring in about 33% of patients (1–3) The standard electrocardiogram usually demonstrates abnormalities of conduction, such as atrioventricular block of varying degree or fascicular block, or both (4–7) In the hereditary form of amyloidosis, familial amyloid polyneuropathy, serial electrocardiograms have demonstrated the progression of conduction abnormalities, necessitating permanent pacemaker insertion for complete heart block in a few patients (8). There have been no corresponding studies on AL amyloidosis, although isolated case reports have documented sick sinus syndrome due to amyloid Pathologic studies (5,9) have shown marked abnormalities of the sinus and atrioventricular nodes due to either amyloid infiltration or fibrosis. These findings have led to the implication that sudden death in amyloidosis may be due to asystole or profound bradycardia, perhaps precipitated by the use of digoxin (3,9)

In both ischemic heart disease and hypertrophic cardiomyopathy, sudden death is common and usually due to ventricular fibrillation (10) even in patients with preexisting bifascicular block (11) In these patients, the presence of repetitive forms of ventricular arrhythmias during long-term electrocardiographic monitoring (Holter monitoring) correlates with subsequent sudden cardiac death (12,13) We postulated that sudden death in amyloid heart disease is due to ventricular arrhythmia rather than bradycardia and that Holter monitoring may reveal unsuspected complex ventricular arrhythmias This report documents our experience with Holter monitoring supplemented by exercise testing for the exposure of arrhythmias in patients with primary and heredofamilial amyloidosis

Methods

Study patients. The study population consisted of 33 consecutive patients with generalized amyloidosis admitted to this hospital between July 1980 and December 1982 Twenty-seven patients had primary amyloidosis and six had

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JACC Vol 3, No 1
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familial amyloid polyneuropathy The diagnosis was confirmed by the occurrence of the characteristic green birefringence after Congo red staining of biopsy tissue taken from liver, kidney, rectum, skin or abdominal fat pad All 33 patients had a complete history and physical examination, 12 lead electrocardiogram, serum electrolyte measurement, chest roentgenogram and M-mode echocardiogram, 24 patients also had a two-dimensional echocardiogram Heart failure was considered to be present in patients with jugular venous distension (with or without peripheral edema) or radiologic and clinical evidence of pulmonary venous congestion.

Echocardiography. M-mode echocardiography was performed with a commercially available instrument (Irex) and recorded with a multichannel strip chart recorder at a paper speed of 50 mm/s Echocardiographic measurements were made in accordance with the standards of the American Society of Echocardiography (14) Two-dimensional echocardiography was performed on a Diasonics instrument using standard echocardiographic views Recordings were made on a Sony videotape recorder All echocardiograms were reviewed by a cardiologist (R H F) Echocardiographic abnormalities considered compatible with the diagnosis of cardiac amyloidosis included increased left or right ventricular wall thickness, or both (in the absence of systemic hypertension, pulmonary or valvular disease), and thickened interatrial septum and increased echogenicity of valves and myocardium (''granular sparkling'') as seen on the two-dimensional study (Fig 1) (15–17)

Ambulatory electrocardiography. Twenty-four hour electrocardiographic monitoring was performed using a portable cassette recorder (Oxford) that recorded modified leads V_1 and V_5 Serum electrolytes were measured before monitoring and corrected if abnormal During recordings, patients were active and encouraged to perform as many daily activities as possible No patients were taking antiarrhythmic agents at the time of the recordings, and heart failure had been controlled with diuretic drugs when necessary Analysis of the 24 hour continuous electrocardiographic records was performed by trained technicians on an Oxford scanner, allowing visual display at 60 times real-time Hourly samples of cardiac rhythm and a printed record of any arrhythmia were obtained and interpreted by the cardiologist (R H F) Histograms of mean hourly atrial and ventricular premature beats were constructed, and ventricular rhythm disturbances were classified according to the grading system of Lown and Graboys (18) (Grade 1 = < 30 unifocal premature ventricular complexes/h, 2 = > 30 unifocal premature ventricular complexes/h, 3 = multiform beats, 4a = ventricular couplets, 4b = ventricular tachycardia)

Exercise testing. Nineteen of the 33 patients underwent exercise stress testing Fourteen patients were excluded because of severe congestive heart failure, severe postural hypotension or physical disability Stress testing was performed on a motorized treadmill according to the Bruce protocol Modified electrocardiographic leads V_2, V_5 and aVF were monitored simultaneously Electrocardiographic signals were displayed on a Marquette computerized system that automatically prints rhythm strips at 1 minute intervals and in the presence of ectopic beats, 12 lead electrocardiograms were recorded before exercise and every 3 minutes during exercise and recovery Blood pressure recordings were taken a minimum of every 3 minutes by a physician using a standard mercury sphygmomanometer Patients were encouraged to exercise to their maximal tolerance The physician terminated the test at the request of the patient or earlier if a decrease in systolic blood pressure or ventricular tachycardia (defined as three or more consecutive ventricular ectopic beats) occurred

Statistical analysis of data was performed using Fisher's exact probability test The study was approved by the Human Studies Committee of the Boston City Hospital.

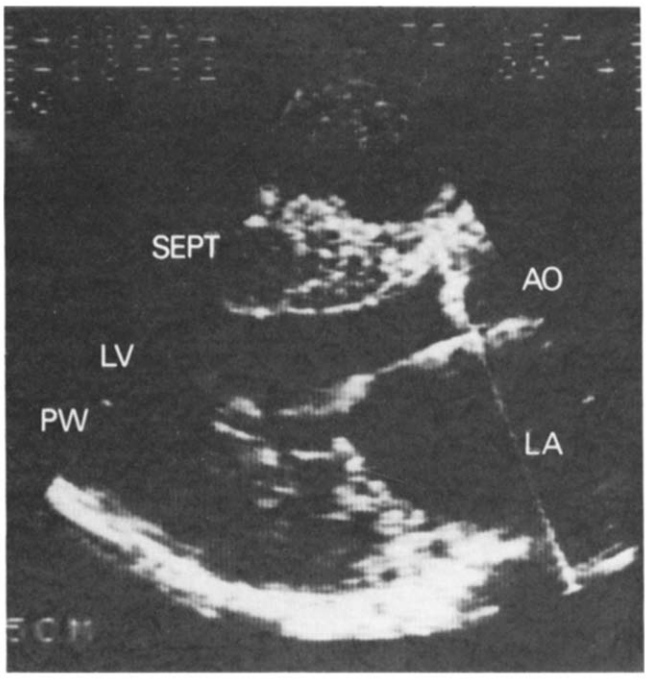


Figure 1. Parasternal long-axis view of two-dimensional echocardiogram in a typical case of cardiac amyloidosis (early diastole) The septum (SEPT) and posterior wall (PW) are thickened with the classic increased echogenicity seen with amyloid infiltration The cursor passes through a thickened aortic valve Left ventricular (LV) cavity size is normal AO = aorta, LA = left atrium

Results

Primary Amyloidosis

Clinical features (Table 1). The mean age of the group of 27 patients was 58 ± 11 years There were 18 men (mean age 58 ± 10 years) and 9 women (mean age 61 ±

Table 1. Clinical Features in 27 Patients With AL (Primary) Amyloidosis

Case	Age (yr) Sex	Clinical Features	ECG	Echocardiogram	Arrhythmia		Follow-Up
					Ventricular	Supraventricular	
1	52M	CHF, restrictive myopathy	1° AVB, LAH/RBBB	Thick walls and valves, ASH	1 3,4b	Occasional PAC	Alive
2	52M	CHF, restrictive myopathy	1° AVB, LAH, pseudo MI	Thick walls	2, 3, 4a, 4b	Frequent PAC	Sudden death
3	82F	CHF	AF	Thick walls and valves, normal cavity, GS	2, 3, 4a, 4b	Atrial fibrillation	Alive
4	62F	CHF, diabetes, macroglossia	Low voltage	Thick walls, normal cavity, GS	1, 4b	Occasional PAC	Alive
5	63F	Macroglossia, CHF	Low voltage, pseudo MI	Thick walls, GS	2, 3, 4a	SVT × 2	Sudden death
6	52F	CHF, restrictive myopathy	Low voltage	Abnormal diastolic motion	1, 4a	Frequent PAC	Sudden death
7	58F	CHF, angina	Low voltage, 1° AVB, LPH, pseudo MI	Thick walls, GS	2, 4a	Frequent PAC, frequent SVT	Died—CHF
8	60M	Nephrotic syndrome, CHF, neuropathy	Low voltage, LPH	Thick walls, GS	2, 3, 4a (4a on ETT)	Occasional PAC	Died—CHF
9	59M	CHF	AF, LPH, IVCD	Thick walls, GS	1	Atrial fibrillation, prolonged bout of SVT	Alive
10	43M	CHF, purpura	Low voltage, LPH	Thick walls, GS	1	0	Died—CHF
11	63M	CHF, gut involvement	Low voltage, 1° AVB, LAH, RBBB	Thick walls, GS	1	0	Alive
12	72M	CHF	Low voltage	Thick walls	0	0	Lost to follow-up
13	85M	CHF	Low voltage, 1° AVB, RBBB	Thick walls, GS	1	0, Sinus pauses (max 2 seconds)	Lost to follow-up
14	62M	Nephrotic syndrome	Low voltage	Thick walls	1, 4b	Frequent PAC and SVT, paroxysmal AF	Died—CVA
15	62M	Nephrotic syndrome, neuropathy	Low voltage, poor R wave progression	Thick walls, abnormal diastolic wall motion	2, 3, 4b	0	Alive
16	67M	Nephrotic syndrome	Low voltage	Thick walls	1, 4a	0	Sudden death
17	61F	Macroglossia, dysphagia, nephrotic syndrome	Low voltage, poor R wave progression	Normal	1, 4a	Frequent PAC, 1 SVT	Alive
18	72F	Salivary gland enlargement, macroglossia	Normal	Normal	1, 3	0	Alive
19	48M	Hepatomegaly proteinuria	LAH, RBBB	Thick walls, ASH	1, 3	Occasional	Alive
20	52F	Nephrotic syndrome	Low voltage, LAH	Normal	0	0	Alive
21	51M	Hepatomegaly, salivary gland enlargement	Low voltage, pseudo MI	Normal	1	Frequent PAC, SVT × 1	Died—hepatic failure
22	50M	Nephrotic syndrome	Normal	Normal	1	0	Died—renal failure
23	48M	Peripheral neuropathy	Normal	Normal	1	0	Alive
24	45F	Nephrotic syndrome	Normal	Normal	0	0	Alive
25	51M	Proteinuria	1° AVB, LPH	Normal	0	0	Alive
26	57M	Nephrotic syndrome	1° AVB, poor R wave progression	Normal	0	0	Died—renal failure
27	56M	Hepatomegaly	Normal	Normal	0	Occasional PAC	Died—hepatic failure

AF = atrial fibrillation, ASH = asymmetric septal hypertrophy, 1° AVB = first degree atrioventricular block, CHF = congestive heart failure, CVA = cerebrovascular accident, ETT = exercise treadmill test, GS = granular sparkling, IVCD = intraventricular conduction defect, LAH = left anterior hemiblock, LPH = left posterior hemiblock, MI = myocardial infarction, PAC = premature atrial complexes, pseudo MI = pseudomyocardial infarction pattern, RBBB = right bundle branch block, SVT = supraventricular tachycardia

JACC Vol 3, No 1
January 1984 107–13

11 years) Serum electrolytes at the time of Holter electrocardiographic monitoring were normal in all patients

Twenty-four patients (89%) had an abnormal electrocardiogram and 17 (63%) had an abnormal echocardiogram Electrocardiographic abnormalities included one or more of the following low voltage (15 patients), first degree atrioventricular block (7 patients), isolated left anterior hemiblock (2 patients), isolated left posterior hemiblock (3 patients), right bundle branch block (1 patient), bifascicular block (3 patients), pseudomyocardial infarction pattern (4 patients) and indeterminate intraventricular conduction defect (1 patient). The predominant echocardiographic abnormalities were thickened ventricular walls (15 patients), valve thickening (7 patients) and "granular sparkling" appearance on two-dimensional echocardiogram (11 patients) (16,17)

Holter electrocardiographic monitoring, performed in all patients, revealed complex ventricular arrhythmia (defined as multiform beats, paired beats or ventricular tachycardia) in 14 patients (47%). In the 15 patients who underwent exercise testing, only one (Case 8) had arrhythmia of a higher grade than that seen on Holter monitoring

Five patients (19%) had evidence of autonomic neuropathy judged by postural hypotension in the absence of hypovolemia There was no correlation between the presence of postural hypotension and high grade arrhythmia

Relations among heart failure, ventricular arrhythmias and echocardiographic abnormalities (Tables 2 and 3). Thirteen (48%) of the 27 patients with AL amyloidosis had heart failure Left ventricular cavity size was normal in all patients and ejection fraction was only reduced in three (Cases 1, 4 and 7). All patients with heart failure had an abnormal echocardiogram, as did four (29%) without heart failure (probability [p] < 0 05) Of the patients with heart failure, eight (62%) had complex arrhythmia (grades 3 to 4b) compared with six (43%) of those without heart failure.

Table 2. Relation of Heart Failure to Mortality, Arrhythmias and Echocardiographic and Electrocardiographic Findings in 27 Patients With Primary Amyloidosis

	Heart Failure* (n = 13) No (%)	No Heart Failure (n = 14) No (%)
Abnormal echocardiogram	13 (100)	4 (29)
Abnormal electrocardiogram	13 (100)	11 (79)
Arrhythmia		
Grade 3 to 4b	8 (62)	6 (43)
Grade 4a to 4b	8 (62)†	4 (29)
Died	6 (46)	6 (43)
Cardiac death	6 (46)†	1 (7)
Sudden death	3 (23)	1 (7)

*Two patients with heart failure were lost to follow-up †p < 0 05 (comparing patients with and without heart failure)

Table 3. Relation of Abnormalities on Echocardiogram to Mortality, Heart Failure, Arrhythmias and Electrocardiographic Findings in 27 Patients With Primary Amyloidosis

	Abnormal Echocardiogram* (n = 17) No (%)	Normal Echocardiogram (n = 10) No (%)
Heart failure	13 (76)*	0
Abnormal electrocardiogram	17 (100)	6 (60)
Arrhythmia		
Grade 3 to 4b	12 (71)†	2 (20)
Grade 4a to 4b	11 (65)†	1 (10)
Died	8 (47)	4 (40)
Cardiac death	7 (41)†	0
Sudden cardiac death	4 (24)	0

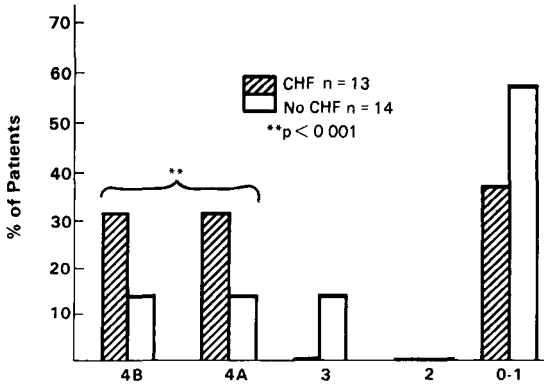
*Two patients, both with cardiac involvement, were lost to follow-up †p < 0 05 (comparing patients with a normal and an abnormal echocardiogram)

This difference was not significant If consideration was limited to grades 4a and 4b arrhythmias, there was a difference in patients with and without failure: eight (62%) versus four (29%), respectively (p = 0.001) (Fig 2).

An analysis of the relation between the presence of echocardiographic abnormality compatible with amyloidosis and ventricular arrhythmia on 24 hour monitoring (Table 3) demonstrated a highly significant relation. Of the 17 patients with an abnormal echocardiogram, 12 (71%) had complex ventricular arrhythmia compared with 2 patients (20%) with a normal echocardiogram (Fig 3) Only one patient with a normal echocardiogram had ventricular couplets and none had ventricular tachycardia.

Thus, patients with a history of heart failure had echocardiographic evidence of myocardial amyloidosis and a high incidence of complex ventricular arrhythmia on 24 hour monitoring In those patients with complex ventricular ar-

Figure 2. Comparison of highest grade of ventricular arrhythmia seen on 24 hour monitoring in 27 patients with AL (primary) amyloidosis in relation to congestive heart failure (CHF) (for grading system see Methods)



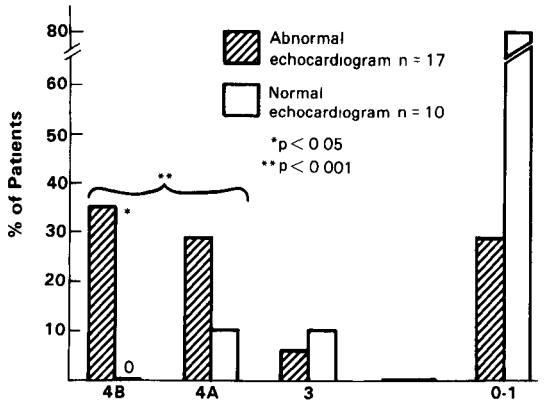


Figure 3. Comparison of highest grade of ventricular arrhythmia seen on 24 hour monitoring in 27 patients with primary amyloidosis in relation to abnormal echocardiograms

rhythmia without heart failure, an abnormal echocardiogram was frequently found This suggests a relation between an abnormal echocardiogram in systemic AL amyloidosis and the presence of complex ventricular arrhythmia, even in the absence of a history of heart failure

Atrial arrhythmias. Frequent premature atrial complexes and supraventricular tachycardia or atrial fibrillation, or both, were seen on Holter monitoring in 10 subjects (37%) Sustained atrial fibrillation occurred in two patients, one of whom (Case 9) also had a prolonged episode of junctional tachycardia lasting 3 days Paroxysmal atrial fibrillation occurred in one patient (Case 14), supraventricular tachycardia in seven and atrial premature beats greater than 20/h in six patients Of the 13 patients with heart failure, 6 (46%) had supraventricular arrhythmia compared with 4 (28%) of 14 without heart failure This difference was not statistically significant When echocardiographic evidence of cardiac involvement was considered, 8 (47%) of 17 patients with an abnormal echocardiogram had atrial arrhythmias compared with 2 (20%) of 10 with normal echocardiograms

Follow-up. Follow-up was available in 25 patients (95%) Twelve patients (Cases 2, 5 to 8, 10, 14, 16, 21, 22, 26 and 27) died a mean of 8 2 months after the initial visit (range 1 to 22) There were seven cardiac deaths, four of which were sudden (Cases 2, 5, 6 and 16) and the remainder due to congestive heart failure All patients dying of cardiac causes had evidence of cardiac amyloidosis when seen initially, one of these (Case 16) was symptom-free All patients who died suddenly and two who died of congestive heart failure had grade 4a or 4b arrhythmia Five noncardiac deaths occurred, all in patients without evidence of congestive heart failure Causes of death were hepatic failure (Cases 21 and 27), renal failure (Cases 22 and 26) and stroke (Case 14) The latter patient had paroxysmal atrial fibrillation on Holter monitoring and an embolic cause of his stroke cannot be excluded because no autopsy was performed Four patients, all with heart failure, underwent autopsy Extensive cardiac amyloidosis was present in each patient, and was considered to be the cause of death Thirteen patients were known to be alive a mean of 17 months after the initial visit (range 11 to 33)

Familial Amyloid Polyneuropathy

Clinical features (Table 4). The mean age of the six patients was 54 years Patients 1 to 3 had symptomatic amyloidosis while the others were asymptomatic and had first degree relatives with a diagnosis of familial amyloidosis Examination of these latter three patients revealed abnormalities compatible with amyloidosis and tissue biopsy confirmed the diagnosis The electrocardiogram was abnormal in five of the six patients Two had left anterior hemiblock, one had left posterior hemiblock with first degree atrioventricular block and a pseudomyocardial infarction pattern, one left bundle branch block and one nonspecific T wave changes All patients had normal voltage in the electrocardiogram

Ventricular arrhythmia and echocardiographic findings. Echocardiograms were abnormal in four patients, with findings compatible with cardiac amyloidosis (Table 4) No patient had symptoms suggestive of heart failure Holter monitoring revealed ventricular tachycardia in three patients (50%), frequent premature ventricular complexes and episodes of sinus arrest in one and normal rhythm in two patients Exercise testing was feasible in four patients but failed to provoke any repetitive forms of arrhythmia Two brothers who underwent exercise testing (Patients 31 and 32) had a blunted heart rate and blood pressure response compatible with autonomic nervous system dysfunction All four patients with abnormalities on 24 hour electrocardiographic monitoring had an abnormal echocardiogram, the two patients with normal findings had a normal echocardiogram No patient with familial amyloid polyneuropathy had died at a mean follow-up time of 23 months (range 18 to 30)

Discussion

Electrocardiographic conduction defects and cardiac arrhythmias. The standard electrocardiographic changes associated with cardiac amyloidosis have been well described (4–8), although emphasis has been placed on conduction defects rather than the presence of ventricular arrhythmia In 23 patients who died of amyloidosis, Ridolfi et al (5) noted premature ventricular complexes on prior electrocardiograms in 7 (30%) and atrioventricular conduction disturbances in 16 (70%) We confirmed the high incidence of atrioventricular or intraventricular conduction disturbances on the standard electrocardiogram, and demonstrated a high prevalence of complex ventricular arrhyth-

JACC Vol 3, No 1
January 1984 107–13

Table 4. Clinical Features in Six Patients With Familial Amyloid Polyneuropathy (FAP)

Case	Age (yr) & Sex	Clinical Features	Electrocardiogram	Echocardiogram	Arrhythmias		Follow-Up
					Ventricular	Supraventricular	
28	61M	Peripheral neuropathy, dysphagia	1° AVB, LPH, pseudo MI	Thick walls, GS	1, 4a, 4b	Occasional PAC	Alive
29	39F	Postural hypotension, syncope, peripheral neuropathy	LBBB	Thick walls, GS	2	Frequent PAC, sinus arrest	Alive with pacemaker
30	64M	Family history of FAP, mild peripheral neuropathy	LAH	Thick walls	1, 3, 4b	2 to 15 PAC/h	Alive
31	62M	Family history of FAP, (brother of Case 30), peripheral neuropathy	LAH	Thick walls	2, 4a, 4b	Frequent PAC, frequent SVT	Alive
32	65M	Peripheral neuropathy	Normal	Normal	0	0	Alive
33	32M	Family history of FAP	T wave changes	Normal	0	0	Alive

Abbreviations as before

mia revealed by 24 hour electrocardiographic recording Only one patient with familial amyloidosis (Case 29) had symptoms suggestive of cardiac-related syncope, she also had episodes of sinus arrest on Holter monitoring In one other patient (Case 13), clinically insignificant bradycardia was noted In contrast, complex ventricular arrhythmias were common and correlated highly with the presence of an abnormal echocardiogram Although we did not have myocardial biopsy tissue to unequivocally confirm that abnormal echocardiographic findings were caused by amyloid infiltration, our patients with an abnormal echocardiogram manifested findings highly suggestive of amyloidosis (15–17), which in the clinical setting, and in the presence of biopsy-documented amyloid in other tissues, was taken as confirmatory evidence of myocardial involvement Because complex ventricular arrhythmias correlated with echocardiographic abnormalities, it is likely that myocardial amyloidosis was the responsible factor We postulate that the infiltration of the myocardium by amyloid fibrils produces these arrhythmias by disruption and replacement of the normal cellular architecture

Prognosis of ventricular arrhythmias. It is not surprising that amyloidosis is associated with ventricular arrhythmias, as these are seen in a wide variety of heart disease Less clear is the prognostic implication of these arrhythmias In coronary artery disease and hypertrophic cardiomyopathy, complex ventricular arrhythmia is associated with subsequent sudden death (12,13) whereas there is conflicting evidence in congestive cardiomyopathy (19,20) In view of the relatively few patients who died in our series, it is not possible to make a definitive statement concerning the relation between sudden death and ventricular arrhythmias in amyloidosis. However, that 4 of 12 patients with grade 4a or 4b ventricular arrhythmia died suddenly suggests that, as in other forms of heart disease, these arrhythmias are a harbinger of sudden cardiac death In the rare patient with amyloidosis dying suddenly in whom a terminal rhythm was documented, ventricular tachycardia or fibrillation was seen (21)

Atrial arrhythmias. The 37% incidence rate of atrial arrhythmias in this series may be, in part, attributed to amyloid involvement of the atrium, a frequent pathologic finding Of note is the fact that in the cases with atrial fibrillation there was a slow ventricular response, possibly due to amyloid involvement of the atrioventricular node (5,9)

Clinical course. The clinical course of AL (primary) amyloid and familial amyloid polyneuropathy differs In the latter, congestive heart failure is uncommon and peripheral or autonomic neuropathy, or both, is a prominent feature (7,22) Nevertheless, cardiac involvement is common, manifesting as conduction disturbances or myocardial infiltration (7,8) Symptomatic sick sinus syndrome and high degree atrioventricular block necessitating permanent pacemaker implantation have been described in both AL and familial amyloidosis although they are more common in the latter (8,23) Despite the lack of symptoms of heart failure, echocardiographic abnormalities such as thickened interventricular septum and hyperrefractile appearance on two-dimensional imaging have been described in about 70% of patients with familial amyloidosis (24)

None of the six patients with familial amyloid polyneuropathy in our series had congestive heart failure yet four had an abnormal echocardiogram, associated with ventricular tachycardia on Holter monitoring in three patients and frequent premature ventricular complexes and sinus node arrest in the fourth Thus, as in AL amyloidosis the presence of an abnormal echocardiogram was a predictor of potentially serious rhythm disturbances However, apart from the patient with sinus node dysfunction who had several syn-

copal episodes and required a permanent pacemaker, none of the patients were symptomatic from their arrhythmia and none have died

Conclusions. Complex forms of ventricular arrhythmias and frequent supraventricular arrhythmias are common in patients with both amyloidosis and familial amyloid polyneuropathy, even in the absence of congestive heart failure The strong association between these arrhythmias and echocardiographic abnormalities suggests a causal relation between myocardial amyloidosis and arrhythmia Given the rarity of bradyarrhythmia noted in this series, it is likely that, as in other forms of heart disease, sustained ventricular arrhythmias are the cause of sudden death previously noted in patients with amyloidosis Although there was a tendency for patients with high grade ventricular arrhythmias in our series to die suddenly, a longer follow-up is required to establish the exact prognostic significance of these arrhythmias in amyloidosis

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