

Electrophysiologic Abnormalities in AL (Primary) Amyloidosis With Cardiac Involvement

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Objectives. This study sought to determine the spectrum of electrophysiologic abnormalities found in patients with cardiac involvement due to AL (primary) amyloidosis and to evaluate the prognostic implications, particularly in relation to subsequent sudden death.

Background. Only case reports, but no series of invasive electrophysiologic studies, exist in patients with cardiac AL.

Methods. Twenty-five patients with biopsy-proven AL and cardiac involvement underwent standard invasive electrophysiologic studies.

Results. The function of the sinus and the atrioventricular node was preserved in most patients, but the infra-His (HV) conduction times were usually abnormal. The mean (\pm SD) HV interval for the 25 patients was 79 ± 18 ms (range 50 to 110), and 23 patients (92%) had an abnormally prolonged interval (>55 ms). Marked HV prolongation (≥ 80 ms) occurred in 12 patients, 6 of whom had an interval ≥ 100 ms. Among the 23 patients who died during

follow-up, HV prolongation was the sole independent predictor of sudden death by multivariate analysis ($p = 0.05$).

Conclusions. Patients with cardiac AL are prone to disease in the His-Purkinje system. Prolongation of the HV interval is common and may not be suspected from the surface electrocardiogram in the presence of a narrow QRS complex. These patients have a high prevalence of sudden death, of which the HV interval is an independent predictor. The association of HV prolongation and sudden death is probably multifactorial, representing either a marker of severe myocardial infiltration with an increased propensity to lethal ventricular arrhythmias or electromechanical dissociation, or indicating severe conduction system disease eventually leading to complete atrioventricular block and bradycardic death.

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AL amyloidosis (formerly known as primary amyloidosis) is a multisystem disease caused by plasma cell dyscrasia and characterized by the extracellular deposition of fibrils composed of immunoglobulin light chains within various organs. Clinical evidence of cardiac involvement, usually in the form of congestive heart failure, is present in ~30% to 50% of patients (1). The 12-lead electrocardiogram (ECG) reflects the generalized infiltrative nature of this disease with low voltage in the limb leads, pseudoinfarction patterns in the anterior precordial or inferior limb leads, or both, and abnormalities of conduction such as fascicular block or atrioventricular block of varying degree (2-4). When cardiac involvement is present, death is frequently sudden, accounting for 30% to 50% of all cardiac deaths (5). No adequate method for predicting sudden death exists in amyloid heart disease.

Histologic examination reveals that the amyloid fibrils may infiltrate the cardiac conduction system and may preferentially involve the His-Purkinje system (6,7). The widespread involvement of the myocardium and the conduction system implies that several different mechanisms may be responsible for sudden death in cardiac amyloidosis—namely, ventricular arrhythmias, atrioventricular (AV) block and acute electromechanical dissociation. Only two case reports have described electrophysiologic findings in AL and both showed prolonged infra-His (HV) conduction times (8,9).

The aims of the present study were therefore twofold: to determine the spectrum of electrophysiologic abnormalities found in cardiac AL and to evaluate the prognostic implications of any demonstrable abnormalities, particularly in relation to subsequent sudden death.

Methods

Study group. The study group consisted of 25 patients (18 men and 7 women, mean age 57.1 ± 9.0 years) with documented AL involving the heart; these patients were referred to Boston University Medical Center for evaluation of their disease. The diagnosis of systemic amyloidosis was confirmed by the occurrence of amyloid fibril deposits with the characteristic green birefringence after Congo red staining of biopsy

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Abbreviations and Acronyms

AH	= supra-His conduction time
AL	= amyloidosis, light chain (primary)
AV	= atrioventricular
cSNRT	= corrected sinus node recovery time
ECG	= electrocardiogram, electrocardiographic
H	= His bundle potential duration
HV	= infra-His conduction time
SNRT	= sinus node recovery time
VT	= ventricular tachycardia

tissue. Most patients had multiple biopsies taken, but the sites of biopsy from which the initial diagnosis was made were the heart in five patients, the rectum in five patients, the kidney in four patients, subcutaneous abdominal fat in three patients, the tongue in two patients, the submandibular lymph node in two patients and the stomach, bone marrow, lung and liver in one patient each. The diagnosis of AL was made in all 25 patients by evidence of plasma cell dyscrasia or by identification of an immunoglobulin light chain in their amyloid deposits, or both (10). All patients had a complete history and physical examination, a 12-lead ECG, serum electrolyte measurements, chest X-ray film and two-dimensional and Doppler echocardiograms. Twenty-four-hour Holter recordings were performed in 22 patients; signal-averaged ECGs were analyzed in 17 patients and not studied in 8 patients (due to a QRS complex duration ≥ 120 ms on the surface ECG in 5 patients).

Cardiac amyloidosis was defined as otherwise unexplained low voltage on the ECG and/or an echocardiogram with wall thickening (mean left ventricular wall thickness >1.1 cm) in the absence of hypertension or significant valvular disease, with a tissue biopsy from any organ staining positive for the presence of amyloid deposits (11). We did not require an endomyocardial biopsy because, in such cases, cardiac biopsy almost invariably shows myocardial amyloid (12). Heart failure was considered present on physical examination in patients with jugular venous distention or with clinical or radiologic evidence of pulmonary venous congestion. Low voltage was defined as a mean QRS voltage amplitude of all ECG limb leads of <0.5 mV. A pseudoinfarction pattern was defined as pathologic Q waves (width ≥ 40 ms) or QS waves in the anteroseptal or inferior leads, or both, in the absence of a documented history of myocardial infarction. Intraventricular conduction disturbances were classified according to current guidelines (13). A late potential on the signal-averaged ECG was defined as present according to currently accepted standards (14).

Electrophysiologic studies. Nine patients were studied because of clinical indications (unexplained syncope in six, presyncope in two and sustained spontaneous ventricular tachycardia [VT] in one). The remaining 16 patients underwent electrophysiologic study as part of a prospective risk assessment. After written, informed consent was obtained, all patients underwent electrophysiologic study (approved by the

local Institutional Review Board) in a nonsedated, fasting state. All antiarrhythmic drugs were discontinued at least 48 h before the study. No patient had taken amiodarone during the past 6 months. Three electrode catheters were positioned one each in the right atrium, the His bundle and the right ventricle. Three surface ECG leads and the bipolar intracardiac electrograms (filtered at 40 to 500 Hz) were recorded simultaneously at a paper speed of 100 mm/s. His bundle electrograms were recorded with multipolar catheters with a 0.5-cm interelectrode distance. In an attempt to avoid recordings of right bundle branch potentials, the catheter was withdrawn proximally until both large atrial and ventricular electrograms were displayed, suggesting an AV location of recording electrodes. Validation of His potentials was attempted in most of the patients, using the responses to (single and coupled) atrial pacing. The supra-His (AH) conduction time was taken from the earliest reproducible rapid deflection of the atrial electrogram in the His bundle recording to the onset of the His deflection. His bundle potential duration (H) was taken from the earliest onset of the His deflection to its end, and the HV interval from the beginning of the His bundle deflection to the earliest onset of ventricular activation recorded from multiple surface ECG leads or the intracardiac electrograms. Normal conduction intervals were defined as follows (15): AH 60 to 125 ms, HV 35 to 55 ms and H 10 to 25 ms. Standard electrophysiologic methods (15) were used to determine the Wenckebach cycle length, the effective refractory period of the AV node, sinus node recovery time (SNRT) and maximal corrected sinus node recovery time (cSNRT). A programmable stimulator was used to deliver rectangular pulses 2 ms in duration at twice the diastolic threshold (threshold always ≤ 1.3 mA in the right atrium and ≤ 1 mA in the right ventricle). Programmed ventricular stimulation was performed using single and double extrastimuli introduced after an 8-beat drive train at cycle lengths of 600 and 400 ms, and diastole was scanned in 10-ms decrements. A third extrastimulus was delivered only at a basic drive cycle length of 400 ms. The end point of ventricular stimulation was the reproducible initiation of sustained monomorphic VT, defined as VT lasting >30 s or requiring termination because of hemodynamic collapse. Ventricular tachycardia was considered monomorphic if the QRS configuration was constant and the cycle length was >200 ms. The induction of polymorphic VT or ventricular fibrillation in these patients was not considered as a valid end point, but rather as a nonspecific response (16).

Survival was measured from the time of the electrophysiologic study until death or to heart transplantation in the two patients who underwent this procedure. Our analyses are based on the assumption that heart transplantation is an equivalent of dying of congestive heart failure, because both patients were hospitalized and terminally ill due to refractory heart failure at the time of their heart transplantation. Sudden death was defined as natural unexpected death that occurred either instantaneously (including during sleep) or within 1 h after the onset of symptoms.

Table 1. Clinical and Electrophysiologic Characteristics of 25 Study Patients

Male/female	18/7 (72%/28%)
History of syncope or presyncope	9 (36%)
PR interval >200 ms	13 (52%)
Pathologic Q waves	16 (64%)
LAFB	6 (24%)
LPFB	2 (8%)
QRS duration \geq 120 ms	5 (20%)
RBBB	2 (8%)
LBBB	2 (8%)
IVCD	1 (4%)
Mean maximal cSNRT (ms)	401 \pm 237
Mean AH interval (ms)	121 \pm 33
Mean HV interval (ms)	79 \pm 18

Data presented are number (%) of patients or mean value \pm SD. cSNRT = corrected sinus node recovery time; IVCD = nonspecific intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; RBBB = right bundle branch block.

Statistical analysis. Continuous data are presented as mean value \pm SD. Overall survival data are presented as median values. Univariate statistical analyses were done by the chi-square test for proportions or *t* tests for intergroup differences of continuous variables; median survival times were analyzed by the Mann-Whitney *U* test. A *p* value \leq 0.05 was considered significant; 95% confidence intervals are given if appropriate. Multivariate analysis (logistic regression with stepwise selection of predictor variables) was performed using the Statistical Analysis System Software (version 6.11, SAS Institute Inc.), including all variables presenting *p* values \leq 0.15 by univariate analysis.

Results

Surface ECG. The 12-lead ECG was abnormal in all 25 patients (Table 1).

Electrophysiologic findings (Table 1). Electrophysiologic testing revealed normal maximal cSNRT in all but three patients. The effective refractory period of the AV node determined by atrial extrastimuli delivered during a drive cycle length of 600 ms was not abnormally prolonged in any patient. For the 25 patients, the mean AH interval was 121 \pm 33 ms (range 70 to 210). Nine patients had an AH interval greater than the upper limit of 125 ms. Measurements of the HV intervals contrasted markedly with the findings in the proximal conduction system. The mean HV interval for the 25 patients was 79 \pm 18 ms (range 50 to 110), and 23 patients had an abnormally prolonged interval ($>$ 55 ms). Marked HV prolongation (\geq 80 ms) occurred in 12 patients, six of whom had an interval \geq 100 ms. Rapid incremental atrial pacing resulted in block below the His bundle in only one patient. Ventricular stimulation induced monomorphic VT in four patients. In three patients this was induced by double extrastimuli and required overdrive pacing or cardioversion for termination. All three of these patients had a positive late potential. The fourth

patient had a self-terminating 40-beat run of monomorphic VT induced by triple extrastimuli. His signal-averaged ECG was normal.

Relation between surface ECG and electrophysiologic findings. First-degree AV block on the ECG occurred in 13 patients, 8 of whom had a prolonged AH interval, but all 13 had HV prolongation. The mean HV interval in the 20 patients with a QRS duration $<$ 120 ms was 77 \pm 18 ms, whereas it was 88 \pm 17 ms in the five patients with a QRS duration \geq 120 ms (*p* = 0.28). Nine of our 20 patients with a QRS complex $<$ 120 ms in duration showed first-degree AV block on the surface ECG. Fourteen of these 20 patients showed abnormal HV conduction, with an HV interval $>$ 55 ms and $<$ 80 ms in five patients and a markedly (\geq 80 ms) prolonged HV interval in nine patients (Fig. 1). In five patients, prolonged HV conduction (first-degree block in the His bundle with a total duration of the His bundle deflection of \geq 30 ms, often with a notched or fragmented deflection) was present. There was no significant relation between the HV interval and either a history of syncope or presyncope, septal thickness or left ventricular ejection fraction.

Results of signal-averaged ECG. The signal-averaged ECGs were recorded in 22 patients and analyzed in the 17 patients with a surface ECG QRS duration $<$ 120 ms. Ventricular late potentials were present in seven and absent in 10 patients. The mean HV interval duration in patients with late potentials was 84 \pm 19 ms, and in those without late potentials, 72 \pm 19 ms (*p* = 0.24).

Therapeutic management. Two patients underwent pacemaker insertion and one patient prophylactic implantation of a cardioverter-defibrillator. These procedures were performed at the discretion of the referring physician on the basis of neurologic symptoms (syncope in all three patients) and electrophysiologic abnormalities (significant infranodal disease in one patient, combination of sinus node dysfunction and infranodal disease in one patient and induction of ventricular fibrillation in one patient).

Follow-up. Twenty-three of the original 25 patients died or underwent heart transplantation during follow-up, with a median duration of survival of 3 months (range 0.5 to 50). The most common cause of death was sudden death, which occurred in 10 patients, including all three patients with permanent pacemakers or implantable cardioverter-defibrillators. Seven patients died from congestive heart failure and two patients underwent heart transplantation due to refractory heart failure. Four patients died from noncardiac causes (hepatic failure in two and renal insufficiency in two). The median time to death or heart transplantation was 2 months in patients with sudden death, compared with 5 months in those with a nonsudden death or those undergoing heart transplantation (Mann-Whitney *U* test, *p* = 0.08).

Predictors of death. Univariate and multivariate analyses were performed in the 23 patients who died or underwent heart transplantation to evaluate any predictive factors. Univariate analysis revealed a significant association between a markedly prolonged HV interval (\geq 80 ms) and the occurrence

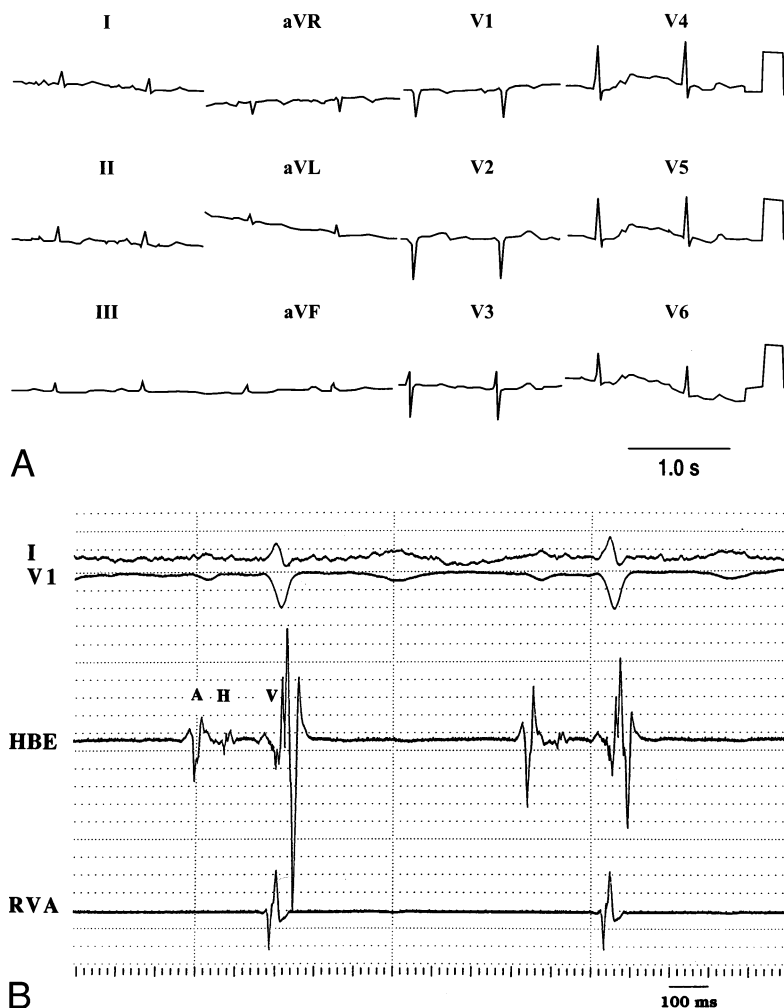


Figure 1. **A**, Twelve-lead ECG showing low voltage in the limb leads, a pseudoinfarction pattern in lead V_2 , a borderline PR interval of 200 ms and a narrow QRS complex (QRS duration 100 ms). **B**, His-bundle electrocardiogram (HBE) of the same patient showing a normal AH interval of 100 ms, but a prolonged H duration of 30 ms and a markedly prolonged HV interval of 90 ms. A = atrial electrogram; H = His potential; RVA = right ventricular apex; V = ventricular electrogram.

of sudden death (chi-square, $p = 0.024$). The mean HV interval in patients with sudden death was 86 ± 14 ms, compared with a mean HV interval of 71 ± 18 ms in those who died nonsuddenly or underwent heart transplantation (two-tailed t test, $p = 0.038$). Figure 2 shows the number of patients who had sudden death, nonsudden death or heart transplantation within each category of HV interval duration. There was also a significant association between a history of syncope or presyncope and the occurrence of sudden death by univariate analysis (chi-square, $p = 0.026$) (Table 2). Only four patients had inducible monomorphic VT, two of whom died suddenly and two from noncardiac complications of AL. In a multivariate model that examined the HV interval, history of syncope or presyncope, presence of a late potential and age, only a prolongation of the HV interval was an independent predictor of sudden death ($p = 0.05$), with an odds ratio of 2.26 for a 10-ms increase in the HV interval.

Discussion

In this series of patients with cardiac AL, AV node conduction was borderline or within normal limits, whereas distur-

bances in the His-Purkinje system were common and marked prolongation of the HV interval was often seen, even in the presence of a narrow QRS complex. Moreover, we found a significant association between HV interval prolongation and the occurrence of sudden death among those patients who died during follow-up.

Pathophysiology of HV prolongation. The finding of HV prolongation in the majority of these patients, even when the QRS complex was relatively narrow, implies that the distal conduction system is extensively infiltrated. The rarity of bundle branch block on the surface ECG is in contrast to electrophysiologic studies in other forms of heart disease, in which a prolonged HV interval of this degree is almost always associated with an abnormally wide QRS complex (17,18). In nonamyloid heart disease, it is postulated that the coexistence of HV prolongation and bundle branch block reflects a non-homogeneous involvement of the bundle branches by the underlying pathologic process (18,19). Our finding may reflect the widespread, generalized infiltration seen in amyloid heart disease and described in pathologic studies (2,8). This typically homogeneous involvement of both bundle branches may explain the rare occurrence of a complete unilateral bundle

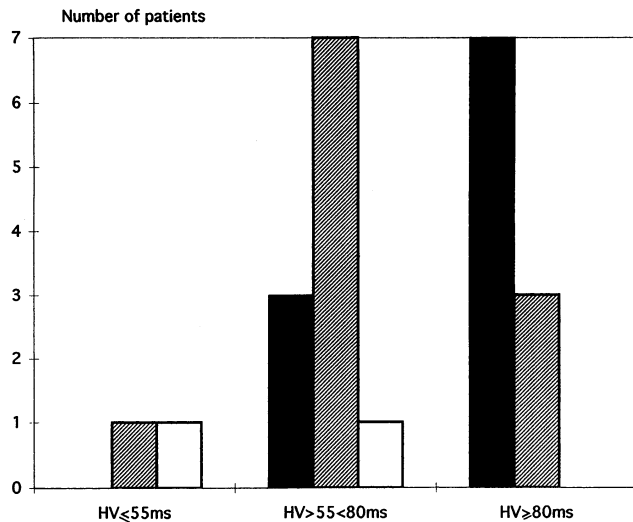


Figure 2. Bar graph showing number of patients who had sudden death (solid bars) or nonsudden death (hatched bars) or those undergoing heart transplantation (open bars) within each category of HV interval duration.

branch block in these patients. An equivalent conduction delay in both bundle branches would result in a narrow QRS complex but a prolonged HV interval.

Interaction of HV prolongation and sudden death. Cardiac AL is a rapidly fatal disease. Although we found a significant association between HV prolongation and subsequent sudden death, this finding does not necessarily imply that death is due to asystole resulting from complete heart block. We have previously shown (20) that an abnormal signal-averaged ECG is a predictor of sudden death in a larger series of patients with AL—a finding interpreted as indicating a role for tachyarrhythmias in sudden death. We do not believe these two findings are contradictory but would suggest that the association between HV prolongation and sudden death is multifactorial. In some patients, HV prolongation may represent a marker of more severe myocardial infiltration, possibly increasing the propensity to sudden death due to lethal ventricular arrhythmias or to acute electromechanical dissociation. In other patients, it may be a marker of severe conduction system disease indicative of a propensity to complete heart block and bradycardic death. At present, we have no way to differentiate the significance of a markedly prolonged HV interval in an individual patient with AL.

Prolongation of the HV interval was common even in patients with AL without a history of syncope or presyncope. Thus, caution should be applied in interpreting this finding in a patient with AL who presents with syncope. This is anecdotally demonstrated in the two patients who died suddenly despite appropriately functioning permanent pacemakers inserted because of syncope and HV prolongation. Earlier studies of patients with prolonged HV intervals and bifascicular block (21,22) found a markedly prolonged HV interval to be predictive of sudden death. However, the cause of sudden

death, when documented, was more often due to ventricular tachyarrhythmias than to complete AV block (23,24). Consequently, we would urge caution in using the HV interval as a guide to pacemaker implantation in amyloid heart disease.

Inducibility of ventricular arrhythmias and sudden death.

In patients with coronary artery disease and a previous myocardial infarction, the lack of inducibility of VT has been proposed as a beneficial prognostic marker in relation to subsequent sudden death (25). In contrast, failure to induce VT does not imply a benign outcome in patients with nonischemic cardiomyopathies (26). Similarly, the lack of inducibility of sustained monomorphic VT in the majority of our patients did not portend a favorable prognosis in terms of sudden death. Thus, in cardiac AL, as in other forms of nonischemic cardiomyopathies, noninducibility has little prognostic value.

Study limitations. Amyloidosis is a rare disease, thereby limiting the size of our study group. Nevertheless, despite our cohort size, we were able to show consistent abnormalities and significant associations.

Our patients had light-chain associated amyloidosis and these data should not be extrapolated to patients with familial amyloidosis, in whom a high prevalence of conduction disturbances has been shown and a requirement for permanent pacing due to high degree AV block is relatively frequent (27-29).

Conclusions. This study demonstrates that patients with cardiac AL are prone to disease in the His-Purkinje system. Prolongation of the HV interval is common and may not be suspected from the surface ECG in the presence of a narrow QRS complex. Patients with cardiac AL have a high prevalence

Table 2. Univariate Analysis of Characteristics of All 23 Patients Who Died During Follow-Up

	Sudden Death Group (n = 10)	Nonsudden Death Group* (n = 13)	p Value
Age at time of EP study (yr)	52.6 ± 10.1	60.1 ± 7.3	0.066
Male	6 (60%)	10 (77%)	0.38
HV interval (ms)	86 ± 14	71 ± 18	0.038
HV interval ≥80 ms	7 (70%)	3 (23%)	0.024
LAFB or LPFB	3 (30%)	4 (31%)	0.97
QRS duration ≥120 ms	2 (20%)	3 (23%)	0.86
Positive SAECG†	4/6 (67%)	3/10 (30%)	0.15
Inducibility of monomorphic VT	2 (20%)	2 (15%)	0.77
History of syncope or presyncope	6 (60%)	2 (15%)	0.026
Septal thickness (cm)	1.6 ± 0.3	1.6 ± 0.3	0.94
LVEF (%)	49 ± 13	48 ± 12	0.82
Heart failure	9 (90%)	12 (92%)	0.85

*The nonsudden death group includes both patients who underwent heart transplantation. †Signal-averaged electrocardiographic records were analyzed in only 16 patients who died subsequently. Data are presented as mean value ± SD or number (%) of patients. EP = electrophysiologic; LVEF = left ventricular ejection fraction; SAECG = signal-averaged electrocardiogram; VT = ventricular tachycardia; other abbreviations as in Table 1.

of sudden death, of which the HV interval is an independent predictor. Prolongation of the HV interval may serve as a marker for the propensity to lethal tachyarrhythmias, bradyarrhythmias or acute electromechanical dissociation.

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