Prophylactic pacemaker implantation in familial amyloid polyneuropathy

Vincent Algalarrondo, MD,*† Sylvie Dinanian, MD,*† Christophe Juin, MD,*† Denis Chemla, MD, PhD,*‡
Soumiya L. Bennani, MD,*† Claude Sebag, MD,*† Violaine Planté, MD,§
Dominique Le Guludec, MD, PhD,‖ Didier Samuel, MD, PhD,*¶ David Adams, MD, PhD,*#
Michel S. Slama, MD*†

*From the *French Referral Center for FAP and Other Rare Peripheral Neuropathies (NNERF), Kremlin Bicêtre, France
Univ Paris-Sud, France, †Cardiology Department, CHU Antoine Béclère, Univ Paris-Sud, AP-HP, Clamart, France,
‡EA4533 - Réanimation Médicale - CHU de Bicêtre, Univ Paris Sud, AP-HP, Kremlin Bicêtre, France, §Neurology
Department, CHU Henri Mondor, Université Paris XII, APHP, Créteil, France, ‖Nuclear Medicine Department, CHU
Xavier Bichat, Université Paris Diderot-Paris VII, AP-HP, Paris, France,¶Centre Hépato-Biliaire, CHU Paul Brousse,
Univ Paris-Sud, AP-HP, Villejuif, France, and #Neurology Department, CHU Kremlin Bicêtre, Univ Paris-Sud, AP-HP,
Bicêtre, France.*

BACKGROUND Familial amyloid polyneuropathy (FAP) is an autosomic dominant disease with a high rate of conduction disorders and increased risk of sudden death. Prophylactic cardiac pacing may be considered in asymptomatic patients with FAP. However, the potential benefits are unknown.

OBJECTIVE To document conduction disorders in a large series of FAP and the incidence of high-degree atrioventricular (AV) block in patients with prophylactic pacemaker (PM).

METHODS From January 1999 to January 2010, 262 patients with FAP were retrospectively evaluated. Prophylactic PM was implanted in patients with His-ventricular interval ≥70 ms, His-ventricular interval >55 ms associated with a fascicular block, a first-degree AV block, or a Wenckebach anterograde point ≤100 beats/min. The spontaneous AV conduction was then analyzed by temporarily inhibiting the PM.

RESULTS As compared with patients with prophylactic PM (n = 100) and patients implanted given a class I/IIa indication (n = 18), the patients who did not require PM (n = 144) were younger and displayed less severe cardiac involvement. Follow-up after prophylactic PM implantation was analyzed in 95 of the 100 patients over 45 ± 35 months, and a high-degree AV block was

documented in 24 of the 95 patients (25%). The risk of high-degree AV block was higher in patients with first-degree AV block or Wenckebach anterograde point ≤100 beats/min (hazard ratio 3.5; 95% confidence interval 1.2–10) while microvoltage on surface electrocardiogram reduced the risk (hazard ratio 0.2; 95% confidence interval 0.1–0.7).

CONCLUSION In FAP with conduction disorders, prophylactic PM implantation prevented major cardiac events in 25% of the patients over a 45-month mean follow-up. It is suggested that prophylactic PM implantation prevented symptomatic bradycardia in these patients.

KEYWORDS Familial amyloid polyneuropathy; Sudden death; Pacing; Electrocardiography

ABBREVIATIONS **AV** = atrioventricular; **ECG** = electrocardiogram; **EPS** = electrophysiological study; **FAP** = familial amyloid polyneuropathy; **HR** = hazard ratio; **HV** = His-ventricular; **ICD** = implantable cardioverter-defibrillator; **PCWP** = pulmonary capillary wedge pressure; **PM** = pacemaker; **WA** = Wenckebach anterograde

Introduction

Familial amyloid polyneuropathy (FAP) is an autosomic dominant disease caused by mutated transthyretin. Cardiac deposition of amyloid fibrils is a common feature of amyloidosis.[1] Cardiomyopathy due to FAP is characterized by cardiac infiltration leading to rhythmic disorders, such as sinus node dysfunction, conduction disorders, atrioventric-

ular (AV) blocks, and intraventricular blocks.[2] This may lead to syncope or sudden death.[3] Yet, the evaluation of dizziness in symptomatic patients with FAP is difficult because of the high incidence of orthostatic hypotension.[4] Autonomic nervous dysfunction and cardiac denervation have been reported in FAP, and it is likely that the combination of conduction disturbances and autonomic denervation makes the patients especially prone to develop serious symptoms due to bradycardia.[5,6] Conduction disorders are unpredictable, and the optimal management of asymptomatic patients with evidence of conduction disorders is still challenging. The follow-up must include serial ECG and

Address for reprint requests and correspondence: Dr Vincent Algalarrondo, MD, Cardiology Department, A. Béclère Hospital, 157 Av de la porte de Trivaux, 92140 Clamart, France. E-mail address: vincent.algalarrondo@abc.aphp.fr.

Holter ECG recordings as pacemaker (PM) implantation may be required.[7,8]

The ESC 2007 guidelines for cardiac pacing have recommended permanent pacing in amyloidosis with AV block as well as in other progressively deteriorating conditions such as sarcoidosis or neuromuscular diseases.[9] However, to the best of our knowledge, the benefits of prophylactic pacing in amyloidosis with conduction disorders have not yet been documented.

The aim of the present retrospective study was to document conduction disorders in a large series of FAP and to assess the incidence of AV block episodes in FAP patients with prophylactic PM implantation. The FAP patients with second- or third-degree AV blocks were analyzed separately. Prophylactic PM was implanted as it was hypothesized that the surface ECG in the setting of FAP may not accurately reflect the severity of conduction disease and that a significant proportion of patients will likely progress to high-degree AV block. The PM was used to accurately track the occurrence of arrhythmias that may remain undetected during conventional follow-up.

Methods
Patients
In the present single-center, retrospective study, all patients hospitalized in our French reference center for FAP (CRMR-NNERF) between January 1999 and January 2010 were identified from the administrative database by using the diagnosis code "amyloidosis" (n = 312). Fifty patients were excluded because amyloidosis was due to an etiology other than FAP. All genetically proven patients with FAP (n = 262) underwent a systematic cardiac evaluation according to our routine protocol.[5,6,10] Arrhythmias and conduction evaluation included standard 12-lead ECG, 24-hour Holter ECG recording, and electrophysiological study (EPS). During the EPS, atrial-His and His-ventricular (HV) conduction intervals were measured under spontaneous sinusal rhythm. Microvoltage was defined as maximum QRS amplitude <0.5 mV (5 mm) in limb leads. Normal HV interval was defined as HV <55 ms, and prolonged HV interval was defined as HV ≥70 ms. The development of intra- or infra-His block was searched by incremental atrial pacing. Wenckebach anterograde (WA) point was determined by progressive rapid atrial pacing. Programmed ventricular stimulation was performed from the right ventricular apex. Cardiac thickening was evaluated by echocardiography. Relative wall thickness was calculated by using the following formula: (2 × PWTd)/LVIDd, where PWTd is the posterior wall thickness and LVIDd is the left ventricle internal diameter at end-diastole. An interventricular septum thicker than 12 mm or a relative wall thickness >0.42 was considered abnormal. Right heart catheterization was performed in all patients. A right ventricular dip-plateau, pulmonary capillary wedge pressure (PCWP) >15 mm Hg or right atrial pressure >10 mm Hg attested to restrictive pattern. The study complied with the Declaration of Helsinki. The locally appointed ethics committee (CPP -

Hôpital de Bicêtre) approved the research protocol. An informed consent was obtained for all patients.

PM implantation and AV conduction follow-up
In patients with FAP, the PM was implanted either given a class I/IIa indication or for prophylactic pacing indications, namely, (1) prolonged HV interval (≥70 ms) or (2) an abnormal HV interval (>55 ms) associated with a fascicular block on ECG (right bundle branch block, left bundle branch block, left anterior hemiblock, left posterior hemiblock), or a first-degree AV block (PR interval ≥200 ms), or a WA point ≤100 beats/min. Our retrospective study focused on the evolution of spontaneous AV conduction after prophylactic PM implantation. Dual-chamber PM insertion was performed under local anesthesia. The type of PM was decided by the cardiologist in charge of the patient. In the subgroup of patients, PM was programmed in the AAI Safe R mode (Sorin Group, Clamart, France) and AV conduction disorders were monitored through the memory of the PM.[11] Episodes were counted by the device, and the mean incidence was calculated for each patient and the values were averaged out.

During follow-up, AV conduction status was assessed as follows:

- For each patient, the Holter memory of the device was scanned in order to identify episodes of atrial or ventricular tachyarrhythmias.
- Spontaneous heart rhythm was assessed by using the temporary pacing inhibition test. In cases where high-degree AV block was noted, the test result was considered abnormal.
- The incidence of conduction disorders and the mean percentage of pacing in each chamber (atrial and ventricular) were checked.

The patient's dependency on PM was confirmed in cases of permanent high-degree AV block diagnosed during the outpatient visit (second-degree AV block type II or third-degree AV block) or of complete absence of spontaneous ventricular activity. First-degree and second-degree AV block Mobitz I were not considered high-degree AV block. Causes of death were collected during the follow-up period and were adjudicated by 2 physicians from the French reference center for FAP (CRMR-NNERF).

Statistical analysis
Continuous variables were presented as mean ± SD, or as median and range. Categorical variables were presented as percentages. Comparisons between normal continuous variables were performed by using the Mann-Whitney test. Categorical unpaired variables were compared by using Fisher's exact test. The correlation between continuous variables was tested by using the Spearman test. Univariate Cox regression models were used to detect whether preoperative parameters were associated with the end point. Results are expressed as hazard ratio (HR) and 95% confidence interval. Based on significant predictors from the univariate