Heart failure and cardiomyopathies

Original research

Predictors and outcomes of pacemaker implantation in patients with cardiac amyloidosis FREE

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Abstract

Objective We sought to investigate prevalence, incidence and prognostic implications of permanent pacemaker (PPM) implantation in patients with cardiac amyloidosis (CA), thereby identifying the predictors of time to PPM implantation.

Methods Seven hundred eighty-seven patients with CA (602 men, median age 74 years, 571 transthyretin amyloidosis (ATTR), 216 light-chain amyloidosis (AL)) evaluated at two European referral centres were retrospectively included. Clinical, laboratory and instrumental data were analysed. The associations between PPM implantation and mortality, heart failure (HF) or a composite endpoint of mortality, cardiac transplantation and HF were analysed.

Results 81 (10.3%) patients had a PPM before initial evaluation. Over a median follow-up time of 21.7 months (IQR 9.6–45.2), 81 (10.3%) additional patients (18 with AL (22.2%) and 63 with ATTR (77.8%)) underwent PPM implantation with a median time to implantation of 15.6 months (IQR 4.2–40), complete atrioventricular block was the most common indication (49.4%). Independent predictors of PPM implantation were QRS duration (HR 1.03, 95% CI 1.02 to 1.03, p<0.001) and interventricular septum (IVS) thickness (HR 1.1, 95% CI 1.03 to 1.17, p=0.003). The model to estimate the probability of PPM at 12 months and containing both factors showed a C-statistic of 0.71 and a calibration of slope of 0.98.

Conclusions Conduction system disease requiring PPM is a common complication in CA that affects up to 20.6% of patients. QRS duration and IVS thickness are independently associated with PPM implantation. A PPM implantation at 12 months model was devised and validated to identify patients with CA at higher risk of requiring a PPM and who require closer follow-up.

Data availability statement

Data are available upon reasonable request.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Conduction system disorders are a known complication in cardiac amyloidosis (CA), but data about their incidence, prevalence, risk factors and prognostic implications are scarce.

WHAT THIS STUDY ADDS

In this multicentre, retrospective cohort study, 787 patients affected by CA demonstrated a permanent pacemaker (PPM) prevalence of 10.3% at baseline and an estimated incidence rate of 4.45% person/year over a median follow-up time of 21.7 months. Independent predictors of PPM implantation identified were QRS duration and interventricular septum thickness and, when combined, they constitute a model assessing the probability of PPM at 12 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Conduction system disease requiring PPM is confirmed to be a common complication in CA, and the use of simple predictors could help clinicians in identifying patients at higher risk and who require closer follow-up.

Introduction

Cardiac amyloidosis (CA) is an infiltrative disorder caused by extracellular fibril protein deposition in the myocardium leading to the development of irreversible restrictive cardiomyopathy.1 There are two major types of CA, immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), characterised by specific monomers combining to form fibrils. In ATTR, monomers tend to dissociate and misfold to form fibrils due to either destabilising mutations (hereditary transthyretin amyloidosis (ATTRv)) or homeostatic imbalance (wild-type transthyretin amyloidosis (ATTRwt)). The latter occurs typically with ageing, though, to date, its precise mechanism remains elusive.2 AL, in turn, is associated with plasma cell dyscrasias,3 and its precursor protein is a clonal immunoglobulin light chain or light-chain fragment.

Conduction system impairment caused by extracellular fibril deposition is common in CA.4 Indeed, atrioventricular (AV) conduction abnormalities have been described in 43% of AL-CA and in 58% of patients with ATTR-CA5–7 with prevalence of PPM ranging from 3.0% to 4.7% in AL-CA8 and 9.5% in patients with ATTR-CA.9

With the very effective new pharmacological treatments for CA already available in the clinic and others in development, improvement of how to predict and prevent conduction problems in patients with CA constitutes an unmet medical need.

We hereby present a multicentre retrospective study investigating the prevalence and incidence of PPM in patients with CA, with the aim of identifying predictors of PPM

implantation, evaluating their potential prognostic implications and developing a model to predict the risk of PPM implantation in the following 12 months.

Methods

Study population and design

This is a multicentre, retrospective cohort study comprising consecutive patients with a definite diagnosis of CA evaluated at two European amyloidosis centres (IRCCS S. Orsola Hospital, University of Bologna, Italy, and Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain) between 1986 and 2020 in Bologna and between 2008 and 2020 in Madrid. Inclusion criteria were patients ≥18 years old diagnosed with ATTRv-CA, ATTRwt-CA or AL-CA with amyloidotic cardiomyopathy defined as left ventricle (LV) end-diastolic interventricular septum (IVS) thickness of ≥12 mm on echocardiography, in the absence of any other cause of hypertrophy.

ATTR-CA was diagnosed by one of the following criteria: (1) demonstration of transthyretin amyloid deposits on endomyocardial biopsy; (2) typical echocardiographic/cardiac magnetic resonance findings associated with demonstration of transthyretin amyloid deposits on extracardiac biopsy; and (3) typical echocardiographic/cardiac magnetic resonance findings associated with (1) cardiac uptake grade 2 or 3 on 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid, 99mTc-pyrophosphate or 99mTc-hydroxymethylene diphosphonate and (2) clonal plasma cells dyscrasia excluded by serum free light-chain assay and serum and urine protein electrophoresis with immunofixation. In all cases, genetic testing confirmed the absence or presence of mutations in the transthyretin gene. AL-CA was diagnosed by one of the following: (1) demonstration of light-chain amyloid deposits on endomyocardial biopsy; (2) light-chain amyloid deposits on extracardiac biopsy associated with echocardiographic or cardiac magnetic resonance features suggestive of CA, in the absence of an alternative diagnosis.10

Data collection and outcomes

Demographics, clinical data, ECGs, transthoracic echocardiograms at baseline evaluation were extracted from available hospital records. Valve disease was defined as at least moderate left-side valve disease or previous valve replacement or repair, and advanced renal failure was defined as need for chronic dialysis, renal transplant or estimated glomerular filtration rate of <30 mL/min/1.73 mq. Troponin levels were not considered in the final analysis because of the variability of assays between the two centres and over the study period.

Time to follow-up started at the time of first evaluation at each centre. Cardiovascular parameters noted during follow-up included New York Heart Association functional class at last evaluation, PPM implantation, implantable cardioverter defibrillator implantation,

atrial fibrillation onset, stroke or transient ischaemic attack, hospitalisation for heart failure (HF) and heart transplantation.

The PPM implantation endpoint was defined as time to implantation from date of first evaluation.

PPM type and indication were derived from operative reports and clinical notes. Indications were classified succeeding the latest 2021 European Society of Cardiology guidelines on cardiac pacing and cardiac resynchronisation therapy11 into the following categories: advanced AV block (permanent or paroxysmal third-degree or second-degree type 2, infranodal 2:1 or high-degree AV block), second-degree type 1 AV block, bifascicular block (with or without electrophysiological study high-risk features), sinus node dysfunction and other indications (ablate and pace or indications for cardiac resynchronisation therapy).

Worsening HF during follow-up was defined by at least one hospitalisation for HF or urgent evaluation for HF.

Overall and cardiovascular mortality were defined as mortality due to any cause or due to cardiac complications.

Statistical analysis

Continuous variables were reported as median and IQR and were compared by means of Mann-Whitney U test. Categorical variables were reported as frequencies and percentages and were compared with the $\chi 2$ or Fisher exact test.

Univariate Cox proportional hazard models were estimated to identify factors associated with PPM implantation during follow-up. Multivariable Cox proportional hazards modelling was subsequently performed to identify independent factors associated with PPM implantation during follow-up. Nine variables selected at the univariable analysis ($p<0.05$) and clinically relevant between baseline clinical, ECG and echocardiographic data were entered in the multivariable model with a backward stepwise selection procedure. Survival was evaluated from diagnosis or from PPM implantation with Kaplan-Meier curves; the equality of the survival distributions by PPM was tested using the log-rank test. For all tests, a two-sided p value of <0.05 was required for statistical significance.

Model development

The risk model was obtained by fitting clinical and instrumental variables into a multivariable Cox regression model. The proportional hazards assumption was tested with the Schoenfeld residuals.

The discrimination was assessed using Harrell's C-statistic. A value of 0.5 for C-index indicates no discrimination, and a value equal to 1 indicates perfect discrimination. Calibration was evaluated by the D'Agostino and Nam modification of the Hosmer-Lemeshow $\chi 2$ approach for survival data, with a p value of <0.05 indicating poor calibration. Kaplan-Meier estimates and survival curves were generated for descriptive purpose.

Model validation

The model was internally validated using the bootstrap method. According to Steyerberg et al,12 we applied the regular bootstrap procedure (1000 iterations) and estimated the optimism of each bootstrap sample.

Statistical analyses were performed using STATA/IC V.16.1 (StataCorp LP, College Station, Texas, USA) and SPSS Statistics V.27. Data extraction was performed on 21 March 2021.

Results

Baseline characteristics

A total of 787 patients with CA were included in the study. Six hundred two patients were male (76.5%); the median age was 74.2 years (IQR 63.7–80.5); 155 (19.7%) had ATTRv; 416 (52.9%) had ATTRwt; and 216 (27.4%) had AL. A total of 81 patients (10.3%) had prior PPM implantation. Baseline characteristics of the entire cohort and of patients with and without PPM at baseline are shown in the table 1. Patients with previous PPM were older and presented more frequently with ATTRwt and a longer disease duration compared with patients without PPM at first evaluation.

Table 1

Baseline characteristic of the whole cohort and in the groups with or without PPM before the first evaluation

Follow-up

Follow-up data were available in all patients without PPM implantation before first evaluation except four (0.6%), resulting in a final study population of 702 patients. After a median follow-up of 21.7 months (IQR 9.6–45.2), of 663 patients, 267 (40.1%) had

worsening HF; 20 (2.9%) had undergone cardiac transplantation; and 311 (44.3%) had died. For 65 patients, the cause of death was unknown; 151 patients (48.5%) died for worsening HF; 21 (6.7%) died suddenly; 8 (2.6%) died for other cardiovascular reasons and 66 (21.2%) for non-cardiovascular reasons. A new PPM was required in 81 patients (11.5% of final study population) with a median time to implantation of 15.6 months (IQR 4.2–40). In 68 patients, the indication for PPM implantation had a class of recommendation I, following the latest ESC guidelines,11 in particular 40 patients had a third-degree AV block (49,4%); 9 patients had a second-degree type 2 AV block or infrandoal 2:1 AV block (11.1%); 10 patients had a symptomatic sinus node dysfunction (12.3%); 2 patients had an unexplained syncope with bifascicular block and high-degree features at the electrophysiological study (2.5%); and 7 patients had an indication for cardiac resynchronisation therapy (8,6%). Furthermore, two patients (2.5%) experienced syncope with bifascicular block, but they did not undergo electrophysiological study due to their advanced age and frailty (class of recommendation IIb for PPM implantation), and one patient (1.2%) with atrial fibrillation, who was intolerant to rate and rhythm control therapy, underwent AV node ablation and subsequently received a PPM implantation (class of recommendation IIa). In 10 patients, the indications for PPM implantation were not clearly defined (12.3%).

After PPM implantation, only five patients (6.2%) had a device-related complication.

Baseline characteristics according to PPM implantation during follow-up are shown in table 2. Notably, distribution of type of CA did not differ between patients requiring PPM implantation and patients not requiring PPM implantation during follow-up (p=0.347). Both groups had also similar median age, disease duration, medical history and comorbidities.

VIEW INLINE VIEW POPUP

Table 2

Baseline characteristics of the population without PPM at first evaluation and in the groups with or without PPM implantation during the follow-up

ECG at first evaluation demonstrated a more prolonged PR interval (218 (189–257) vs 184 (161–212), p<0.001) and increased QRS duration (118 (98–152) vs 102 (120–190) ms, p<0.001) with higher rate of intraventricular blocks (p<0.001), both left and right bundle branch block (16% vs 6% (p=0.005) and 21% vs 11% (p=0.016), respectively), in patients requiring PPM implantation during follow-up.

The echocardiogram showed a more dilated left atrium, larger LV mass index (174 (143–223) vs 163 (137–199) g/m2, p=0.016) and wall thickness (IVS thickness: 18 (16–21) vs 17 (15–19) mm, p=0.003, and posterior wall thickness: 16 (14–19) vs 15 (13–18) mm, p=0.031) with similar systolic and diastolic functions (no differences in LV ejection fraction, global

longitudinal strain and transmitral flow pattern). No differences were found regarding medications that could affect cardiac conduction such as beta blockers, calcium channel blockers and antiarrhythmic drugs.

These results remained similar when the three different types of CA (ATTRv, ATTRwt and AL) were analysed separately as shown in online supplemental table 1.

Supplemental material

[heartjnl-2022-322315supp001.pdf]

Univariable and multivariable Cox regression analysis

Univariable and multivariable analyses of factors associated with PPM implantation during follow-up are shown in table 3. For the entire population of patients without PPM at baseline evaluation, independent predictors of time to PPM implantation included QRS duration (HR 1.03, 95% CI 1.02 to 1.03, p<0.0001) and IVS thickness (HR 1.1, 95% CI 1.03 to 1.17, p=0.003). In the subgroup of patients with sinus rhythm at first ECG collected (513, 73.2%) independent predictors of time to PPM implantation included also PR interval of ≥200 ms, as shown in online supplemental table 2.

Supplemental material

[heartjnl-2022-322315supp002.pdf]

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Table 3

Univariate and multivariate Cox regression analyses for predictors of time to PPM implantation in the overall population

Once QRS duration and LV wall thickness had been identified as the independent predictors of PPM implantation during follow-up, we fitted a Cox proportional hazard model by adjusting also for age. Furthermore, we verified that the proportional hazard assumption holds. The estimates of the HRs and the corresponding CIs are shown in table 4. There is an 2.6% increase in the expected hazard relative to a 1 ms increase of QRS duration holding IVS thickness and age constant while the expected HR increases by 10.6% for each millimetre of IVS thickness holding QRS duration and age constant. The probability of PPM at 12 months for a single patient is given by:

Embedded Image

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Table 4

Time to permanent pacemaker implantation risk prediction model at 12 months

where Embedded Image is the estimated survival function at time t=12 months, and Embedded Image 1, Embedded Image 2 and Embedded Image 3 are the estimated coefficients of QRS, IVS thickness and age, respectively.

The predicted risks of PPM implantation at 12 months, combining IVS thickness and QRS duration, are presented in figure 1.

Figure 1

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Figure 1

Predicted risk of PPM implantation at 12 months combining IVS thickness and QRS duration and adjusted for the age of 74 years (median age of the study population). Each box indicates the minimum and maximum predicted risk for PPM implantation at 12 months. Green boxes identify a maximum risk less than 2% at 12 months; yellow boxes identify a maximum risk between 2.1% and 5% at 12 months; salmon boxes identify a maximum risk between 5.1% and 10.0% at 12 months; and red boxes identify a maximum risk greater than 10% at 12 months. IVS, interventricular septum; PPM, permanent pacemaker.

The discrimination accuracy measured by the C-statistic was. 0.71 (95% CI 0.634 to 0.785). The result of modified Hosmer-Lemeshow test p value was 0.44.

The model was internally validated by bootstrap method. The mean optimism (0.027) was then subtracted from the apparent performance measure (C-statistic=0.71) to estimate the internally validated performance that resulted in a C-statistic of 0.68 with a calibration slope of 0.98.

Clinical outcomes

Clinical outcomes in patients without PPM at baseline revealed that PPM implantation was associated with a significantly higher all-cause mortality (43/81: 53.1% vs 268/621: 43.2% with an HR of 1.58, 95% CI 1.14 to 2.18 and p=0.005), HF (31/80 38.75% vs 222/583 38.08%, respectively, with 4 and 17 patients for whom time to event was unknown and excluded from the analysis, with an HR of 1.71, 95% CI 1.14 to 2.56 and p=0.009), and a composite of all-cause mortality, heart transplantation and worsening HF (50/81: 61.73%

vs 327/621: 52.66% and one patient for each group without the time to the event excluded from the analysis, with an HR of 1.65, 95% CI 1.22 to 2.23 and p=0.001) as shown in figures 2 and 3.

Figure 2

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Figure 2

Kaplan-Meier curves showing survival probabilities in patients with cardiac amyloidosis stratified by PPM implantation during follow-up (log-rank test, p=0.005). PPM, permanent pacemaker.

Figure 3

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Figure 3

Kaplan-Meier curves showing probabilities of worsening heart failure, cardiac transplantation or death in patients with cardiac amyloidosis stratified by PPM implantation during follow-up (log-rank test, p=0.001). PPM, permanent pacemaker.

Discussion

This report of 787 patients constitutes, to the best of our knowledge, the largest study investigating the prevalence, incidence, predictors and clinical implications of PPM implantation in patients with CA (both ATTR and AL), allowing the development of a model for PPM implantation risk at 12 months. The main findings of this study can be summarised as:

A total of 81 patients (10.3%) were already implanted with PPM at baseline. Of the remaining, 81 patients (11.5%) underwent PPM implantation due mainly to either high degree or complete AV block with an estimated incidence rate of 4.45% person/year. These findings confirm the central role that cardiac conduction impairment plays in the natural history of CA. This applies not only to ATTR (particularly wild type) but also to AL form (8.8% of patients with AL required PPM in our study).

QRS duration and IVS thickness were the only factors independently associated with PPM implantation.

A model estimating the risk of PPM implantation at 12 months was developed, and its discriminatory capacity was internally validated by bootstrapping. The analysis demonstrated a 2.6% increase in PPM implantation risk for each millisecond increase in QRS duration and 10.6% for each millimetre increase in IVS thickness. This allowed accurate risk stratification, thereby identifying patients requiring closer follow-up.

PPM implantation was associated with an increased risk of death from any cause, worsening HF and a composite endpoint that included death, HF hospitalisation and cardiac transplantation.

The pathophysiology of conduction disease in CA remains elusive, being most likely the result of the interplay between a variety of mechanisms: autonomic dysfunction, especially in patients with AL or ATTRv and polyneuropathy13 14; direct amyloid infiltration of the conduction system impairing action potential propagation that may involve the sinoatrial node and His-Purkinje system; cytotoxicity induced by amyloid precursors that are known to cause apoptosis and replacement fibrosis.15 16

In keeping with the aforementioned hypotheses, a recent histopathological study on 23 CA autopsies described diverse pathological mechanisms affecting the conduction system, namely, sinoatrial node fibrosis (30% of cases), as well as atrophy (30%) and bundle branch fibrosis (23%), with 3 cases demonstrating histological evidence of amyloid infiltration.17

The present study documented a high prevalence and incidence of PPM implantation in patients with CA. In line with previous studies,5–9 advanced AV block was the main indication for PPM implantation (48 patients, 59.2%) with only 10 patients (12.3%) requiring a PPM due to sinus node dysfunction. Despite a slightly larger frequency of PPM implantation in patients with ATTR-CA, no statistically significant differences in rates of PPM implantation were found between different CA types.

In keeping with the notion that conduction system impairment is part of CA natural history,18 PPM implantation incidence increased with disease progression as evidenced by increased PPM implantation rates with increased wall thickness and QRS duration likely indicating a higher degree of amyloid infiltration and fibrosis.

The QRS median duration was 104 ms in the overall population and 118 ms in patients with PPM implanted. These ECG data are consistent with a previous study by Donnellan

and coworkers in 369 patients where the only ECG feature predicting PPM implantation was QRS duration, with durations greater than 120 ms being associated with development of high-grade AV block and a QRS duration of <100 ms associated with a reduced risk of high-grade AV block.9

Despite being a feature of advanced disease, conduction system impairment is not limited to these patients. Indeed, patients with or without PPM implantation during follow-up, in addition to having similar median age, medical history, comorbidities including renal function and medications (hence reducing the likelihood of any confounding factor), did not differ in terms of New York Heart Association class, NTpro-BNP levels, as well as systolic and diastolic echocardiographic parameters at baseline. Regardless of these similarities between groups, our study showed that PPM implantation is associated with worse outcomes both in terms of mortality and HF. This may be explained by the fact that conduction system disease may represent a more advanced disease stage as well as the impact of systolic desynchrony caused by the high rate of RV pacing as previously described.19

Clinical implications

The latest 2021 ESC guidelines on cardiac pacing and cardiac resynchronisation therapy describe CA as one of the intrinsic causes of bradycardia with several studies demonstrating increased pacing needs in patients with CA with cardiac implantable electronic devices.20 Nonetheless, current evidence is insufficient to justify pacing indications different from the general population in these patients with CA.11 Identifying possible red flags associated with increased need of PPM implantation may allow delineation of a specific group of patients to whom close clinical and electrocardiographic surveillance should be applied.

From the univariate and multivariate analyses conducted in this study, easily attainable variables such as QRS duration and IVS thickness were shown to predict PPM implantation in patients with CA. Moreover, a model containing the aforementioned factors was developed to predict the individual risk of PPM implantation at 12 months. This model was internally validated by bootstrapping showing excellent reproducibility and good performance. Therefore, our model could be used to identify patients with CA who should be followed up closely and in whom additional monitoring strategies could be considered. In this sense, tests that may prove crucial in the follow-up of these high-risk patients include 24-hour-ECG Holter and implantable loop recorder, which may in some instances anticipate the diagnosis of advanced blocks leading to prompt PPM implantation.

Study limitations

The principal limitations of this study are represented by its retrospective design and relatively short follow-up, which did not allow for complete data collection. Another

limitation of this study is the absence of an additional cohort for external validation. Moreover, the recent availability of specific therapies for patients with ATTR and the small number of subjects undergoing treatment in our population precluded us from making any definitive conclusions regarding the implications of these therapies for conduction system diseases. Lastly, no information on the timing of PPM implantation was available in patients who had it already at baseline evaluation.

Conclusions

Among patients with CA, PPM was required in 11.5% of patients without prior PPM. Independent predictors of new PPM implantation included QRS duration and IVS thickness. A model was created and internally validated to identify patients at higher risk of PPM implantation who would require closer follow-up. PPM implantation adversely affects mortality, HF hospitalisation and a composite of overall mortality, HF and cardiac transplantation.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by the ethics committee of IRCCS S. Orsola Hospital, University of Bologna A.O.U. Bologna, U.O. Cardiologia Galiè (number ID: 789/2020/Oss/AOUBo (PM-AMI)). The participants gave informed consent to participate in the study before taking part.

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Footnotes

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PG-P and SLon contributed equally.

Contributors GS, FDF, MS, PG-P and SLon contributed to the design of the study. GS, FDF, MS, EG-L, FD, AP, EC, AGC, SLoz, PM, MC-M, AA, VC-U, AG, JT-R, CG, MG-B, RR-T, EB, JS, NG, PG-P and SLon collected the data and contributed to the analysis of the results and to the writing of the manuscript. EN conducted the statistical analysis. SLon is the guarantor and is responsible for the overall content of the study. All the authors reviewed and approved the final version of the manuscript.

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