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Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis☆

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ABSTRACT

Background: Cardiac amyloidosis (CA) is associated with a poor prognosis with the proposed mechanism of sudden cardiac death in the majority of patients being pulseless electrical activity. However, the incidence of ventricular arrhythmias (VA) and implantable cardioverter-defibrillator (ICD) indications in CA patients are unclear. We performed a detailed evaluation of our CA population undergoing ICD implantation and assessed appropriate ICD therapy and survival predictors.

Methods: We included consecutive patients from June 2008 to November 2014 in five centers. ICDs were systematically interrogated and clinical data recorded during follow-up.

Results: Forty-five patients (35 males, mean age 66 ± 12 years) with CA who underwent ICD implantation (84.4% primary prevention) were included. CA types were hereditary transthyretin in 27 patients (60%), light chain (AL) in 12 (27%) and senile in 6 (13%). After a mean follow-up of 17 ± 14 months, 12 patients (27%) had at least 1 appropriate ICD therapy occurring after 4.7 ± 6.6 months. Patients with or without ICD therapy had no significant differences in baseline characteristics, amyloidosis type, LVEF, and type of prevention although there was a trend towards a better 2D global longitudinal strain in patients with ICD therapy ($P = 0.08$). Over the follow-up, 12 patients died (27%) and 6 underwent cardiac transplantation (13%). From multivariate analysis a worse prognosis was associated with higher NT-proBNP level (>6800 pg/mL, HR = 5.5[1.7–17.8]) and AL type (HR = 4.9[1.5–16.3]).

Conclusions: Appropriate ICD therapies are common (27%) in CA patients. No specific strong VA predictor could be identified. However, patients with advanced heart disease, especially with AL-CA, display a poorer outcome.
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1. Introduction

Amyloidosis is a severe systemic disease. Cardiac amyloidosis (CA) may occur in the three main types of amyloidosis and markedly impacts upon prognosis, with a median survival of <1 year after the onset of heart failure symptoms until quite recently. The mechanism of death has been traditionally attributed to pulseless electrical activity (PEA) and therefore implantable cardioverter-defibrillator (ICD) implantation has not been considered to be a beneficial therapeutic option.

Recent advances in amyloid specific therapy for light chain (AL) [1] or hereditary amyloidosis transthyretin related (ATTR) amyloidosis, as well as earlier diagnosis at the preclinical stage based on cardiac biomarkers [2] or more sensitive imaging technics [3–5], have contributed to a significant improvement in CA prognosis. Furthermore, many studies have shown that sustained ventricular arrhythmias (VA) on ECG-holter monitoring [6] or successful termination of VAs with appropriate ICD therapies [7,8] are not uncommon. However, no robust predictors

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for malignant VA have been identified. In addition, it has been recently suggested that non-sustained ventricular tachycardia (NSVT) can predict subsequent ICD therapy and should be a risk factor for prophylactic ICD implantation [8]. However, NSVT does not appear to correlate with sudden cardiac death (SCD) or survival in non-implanted CA patients [6].

Cardiac biomarkers seem to predict adverse outcome in AL patients [2,3,9], but there is no data to suggest that these biomarkers would predict further VA occurrence [10]. Finally, whether echocardiographic parameters (e.g. strain) associated with worse outcomes [3,11] would predict malignant VA in CA remain unclear. As a result, the consensus statement from the European Society of Cardiology is that there is insufficient data to provide recommendations on prophylactic ICD implantation in CA patients [12].

We aimed to assess the usefulness of ICD implantation in CA patients with analysis of: i) the occurrence of VA with appropriate ICD therapy and ii) predictors of a combined survival endpoint including death and cardiac transplant.

2. Methods

2.1. Patient characteristics

This study was approved by the local institutional review boards, and all patients provided informed consent to participate. All consecutive CA patients undergoing ICD implantation in our centers (5 centers in Paris) were included within this study.

Diagnosis of CA was determined by the presence of a positive endomyocardial biopsy or by a confirmed extra-cardiac histological diagnosis, in addition with thickened cardiac septum (≥12 mm by echocardiography with no other cardiac cause of hypertrophy) [13]. The definition of the CA type was based on genetic screening (ATTR) as well as the presence of a monoclonal gammapathy in serum electrophoresis, immunofixation on serum or urine and confirmed by positive immunohistochemical staining for kappa or lambda in the biopsy (AL).

2.2. ICD indication and programming

For our CA cohort, ICD exclusion criteria were: patient age > 80 years or expected survival <1 year when not qualifying for a cardiac transplant. ICD was implanted for secondary prevention for patients who experienced sustained VT or sudden cardiac arrest. Patients were implanted for primary prevention if they were listed for a cardiac transplant, if they had non-postural syncope of suspected arrhythmic origin; when LVEF was ≤35% or after a multidisciplinary team assessment of VA risk, when patients had an altered LV two-dimensional global longitudinal strain (2D-GLS ≥ −15%) [11] associated with a pacing indication and/or ventricular hyper-excitability on ECG-Holter monitoring (NSVT, frequent premature ventricular complexes). Indeed, in CA patients LVEF impairment is a late marker of cardiac dysfunction whereas abnormal strain indices seem to be a better and earlier criterion to assess LV systolic dysfunction [11,14,15]. In symptomatic patients with LVEF <50%, bi-ventricular ICD was implanted if one of the additional following characteristics were documented: prolonged QRS duration (>130 ms), second or third degree atrioventricular block or prolonged PR interval > 350 ms [16,17].

All patients had a standard ICD programming with a VT zone starting at 170 bpm. usually with a long detection time (e.g. number of intervals to detect = 30/40) and a ventricular fibrillation (VF) zone starting at 220 bpm. Anti-tachycardia pacing including three bursts and three ramps followed by shocks was set for the VT zone (i.e. 170–220 bpm.), while high energy shocks only (with 1 anti-tachycardia pacing attempt during charge) were programmed for the VF zone (i.e. VF or VT > 220 bpm).

2.3. Baseline evaluation

All baseline clinical, echocardiographic, ECG-Holter data and laboratory test results were collected in heart failure units, before ICD implantation. We performed a standard echocardiographic assessment followed by two-dimensional color tissue Doppler recordings with second harmonic imaging collected during a brief breath hold, for the offline assessment of longitudinal strain. The 2D-GLS was calculated as the average of the longitudinal systolic peak negative values obtained from the 16 LV segments in the apical 4-, 2-, and 3-chamber views.

2.4. Data collection and follow-up

Following ICD implantation, patients were followed at 1 month, 3 months and then every 6 months or sooner if clinically indicated. The primary end-point was the occurrence of appropriate ICD therapies determined by ICD interrogation. Only reviewed episodes with detailed electrograms were counted. For patients who died during the follow-up, post-mortem ICD interrogation was performed when possible. To assess our secondary endpoint, all-cause mortality or heart transplant, we performed a telephone interview with all patients or relatives at the closure of follow-up.

2.5. Statistical analysis

Statistical analyses were performed using SPSS for Windows release 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distributions were expressed as mean ± standard deviation. Categorical variables were expressed as counts and percentages. To compare patients with or without ICD therapy, univariate survival Cox proportional hazards regression model was used. Time 0 was the implant date and event time was the first diagnosed VA with subsequent appropriate ICD therapy. Patients without VA since implant were censored at death or last study visit or last tele-transmission. To assess the risk of major event (mortality or heart transplantation), univariate Cox proportional hazard regression model was also used and all variables that were significant at the 0.1 level were further analyzed using the multivariate Cox proportional hazards regression model. Before multivariate analysis, significant quantitative variables were dichotomized based on ROC curve providing the best cutoff in our cohort. Adjusted hazard ratio (HR) and 95% confidence interval (CI) were derived from this model. Survival data were illustrated using Kaplan-Meier curves. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

From June 2008 to November 2014, 45 consecutive CA patients (12 AL, 27 ATTR and 6 SSA) met the inclusion criteria and were enrolled in our study. Clinical characteristics are summarized in Table 1. The main indication for ICD placement was primary prevention (84.4%) and 12 patients (26.7%) received a bi-ventricular ICD. LVEF was decreased (<50%) in 68.9% of cases and ≤35% in one third of our population. All but 2 patients had a NT-proBNP >332 ng/L and interventricular septal wall thickness > 15 mm was present in 75% of cases. Interestingly, because of the extra-cardiac severity of the amyloidosis and particularly the neuropathy associated with severe hypotension only 35.6% patients were treated with beta-blockers. Patients concomitantly received specific anti-amyloid therapies: all AL patients underwent chemotherapy, ATTR patients received either tafamidis, or liver transplantation (n = 7 patients, 26%) whereas no specific treatment was available for patients with senile amyloidosis [18].

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