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Are classic predictors of voltage valid in cardiac amyloidosis? A contemporary analysis of electrocardiographic findings

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ABSTRACT

Background: Low voltage electrocardiography (ECG) coupled with increased ventricular wall thickness is the hallmark of cardiac amyloidosis. However, patient characteristics influencing voltage in the general population, including bundle branch block, have not been evaluated in amyloid heart disease.
Methods: A retrospective analysis was performed of patients with newly diagnosed cardiac amyloidosis from 2002 to 2014. ECG voltage was calculated using limb (sum of QRS complex in leads I, II and III) and precordial (Sokolow: S in V1 plus R in V5–V6) criteria. The associations between voltage and clinical variables were tested using multivariable linear regression. A Cox model assessed the association of voltage with mortality.
Results: In 389 subjects (transthyretin ATTR 186, light chain AL 203), 30% had conduction delay (QRS > 120 ms). In those with narrow QRS, 68% met low limb, 72% low Sokolow and 57% both criteria, with lower voltages found in AL vs ATTR. LV mass index as well as other typical factors that impact voltage (age, sex, race, hypertension, BSA, and smoking) in the general population were not associated with voltage in this cardiac amyloidosis cohort. Patients with LBBB and IVCD had similar voltages when compared to those with narrow QRS. Voltage was significantly associated with mortality ($p < 0.001$ for both criteria) after multivariable adjustment.
Conclusion: Classic predictors of ECG voltage in the general population are not valid in cardiac amyloidosis. In this cohort, the prevalence estimates of ventricular conduction delay and low voltage are higher than previously reported. Voltage predicts mortality after multivariable adjustment.

1. Introduction

Amyloidosis is a protein misfolding disorder characterized by fibrillary protein deposition into tissue. Cardiac amyloidosis (CA) almost exclusively results from pathologic deposition of immunoglobulin light chains (AL) or the transthyretin protein (ATTR). This leads to fibrosis, myocardial dysfunction and conduction disease.

Low voltage electrocardiography (ECG) coupled with increased ventricular wall thickness on echocardiography is the classic hallmark of amyloid cardiomyopathy. This phenomenon was first described by Carroll utilizing limb and precordial (Sokolow) voltage indices [1]. Nevertheless, low voltage is not ubiquitous in amyloid heart disease. Previous reports suggest that only about 60% of patients with AL and 25–40% with ATTR meet low voltage criteria [2]. In another analysis, low limb voltage was found in approximately 35% of patients, while 60% had low Sokolow voltage ≤15 mm [3].

There are many factors impacting ECG voltage in the general population; body mass index [4–7] and smoking [7] have been associated with a lower ECG voltage while blood pressure [4,5], African American race [5,8] and male gender [5,7] yield higher voltage measurements. Similarly, bundle branch block and pacing have been shown to alter measured ECG voltage compared to normal conduction [9–11]. Studies of amyloidosis have commonly excluded patients with bundle branch block and paced rhythms as a result. Anecdotally, conduction delay is quite common in cardiac amyloidosis, yet the precise frequency of these ventricular conduction abnormalities is unknown.

We sought to assess whether the classic factors that impact voltage in the general population are valid in amyloid heart disease. Similarly, because voltage predicts cardiovascular outcomes in the general population [12], we set to investigate whether this held true in cardiac amyloidosis.

2. Methods

2.1. Patient population

A retrospective cohort study was performed in patients with cardiac amyloidosis at our institution diagnosed between 2002 and 2014. Patients were considered to have cardiac amyloidosis and included in

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the study if they met diagnostic criteria as defined below. Clinical, electrocardiographic and echocardiographic data were collected for all patients within 3 months of a diagnosis of cardiac amyloidosis. Patients were excluded from the analysis in cases of incomplete clinical data and unavailable electrocardiography or echocardiography.

The diagnosis of cardiac amyloidosis was made based upon a clinical concern along with endomyocardial biopsy or advanced imaging confirmation. In patients included based upon an endomyocardial biopsy, tissue typing was used to differentiate AL from ATTR. In patients included based upon confirmatory non-invasive imaging, modalities included at least one of the following: cardiac magnetic resonance imaging (CMR), echocardiography with strain, or (99m) technetium pyrophosphate (TcPYP) scintigraphy. Morphologic criteria consistent with cardiac amyloidosis on CMR and echocardiography included left ventricular (LV) wall thickening ≥ 12 mm in the absence of another cause of LV hypertrophy, right ventricular or intra-atrial septal thickening, biatrial enlargement, low tissue Doppler velocities and short deceleration time. CMR was consistent with the disease if there was significant diffuse subendocardial or transmural delayed gadolinium enhancement of the left ventricular myocardium. Strain echocardiography was consistent with the disease if there was apical sparing of peak systolic longitudinal strain [13]. TcPYP scans were considered positive or negative based upon expert clinician interpretation and utilization of region of interest count statistics of the LV as compared to the contralateral lung field [14]. In patients without an endomyocardial biopsy, AL was differentiated from ATTR based upon the analysis of serum free light chains, extracardiac biopsy including bone marrow, TCPYP scintigraphy and TTR genetic testing.

2.2. Measurement techniques

A 12-lead electrocardiogram was performed with standard equipment at the time of the diagnosis of amyloid heart disease and reviewed in a blinded fashion to identify characteristics suggestive of CA. Limb lead voltage was calculated by the sum of the entire QRS complex voltage of leads I, II and III with low voltage being defined as each lead ≤5 mm. Low voltage in the precordial leads was defined by the Sokolow criteria (S wave in V1 plus R wave in V5 or V6 ≤ 15 mm). Voltage-to-mass ratio was calculated as the limb or Sokolow voltage divided by the LV wall cross sectional area indexed to body surface area as defined by Carroll [1]. Left bundle branch block, right bundle branch block and nonspecific intraventricular conduction delay were defined in standard fashion [15].

Transthoracic echocardiography was performed using commercially available Vivid 7 or Vivid 9 (GE Medical, Milwaukee) or EPIQ (Philips Medical Systems, Bothell, WA) ultrasound systems. Longitudinal strain measurements in patients who underwent echocardiography on GE machines were performed offline using automated software (EchoPAC Version 113, Advanced Analysis Technologies; GE Medical Systems) as previously described [13]. Echocardiographic parameters including measurements of LV mass were retrospectively measured in a blinded fashion in a manner consistent with the American Society of Echocardiography guidelines [16]. CMR was performed using 1.5 T or 3 T MR scanners (Philips Achieva, Best, Netherlands). TCPYP scintigraphy were performed using SPECT-CT with Siemens Symbia T6 cameras after patients received 20 mCi of TCPYP intravenously. Endomyocardial biopsy was obtained after informed consent by experienced physicians and read in blinded fashion by two cardiac pathologists experienced in cardiac amyloidosis.

2.3. Statistical analysis

Continuous variables are expressed as either mean ± standard deviation or median [interquartile range] and analyzed by the student's t-test or Wilcoxon rank test for parametric and non-parametric variables, respectively. Categorical variables are expressed as n (%) and were compared by the Fisher's Exact test. Box and scatter plots were used to graphically represent data. Multivariable linear regression models were created to assess the association between clinical, echocardiographic and ECG variables and voltage measurements as a continuous variable.

Survival analysis was performed using an endpoint of time to all-cause mortality. Patients were censored at the time of last follow up or at the time of heart transplantation or left ventricular assist device. A Cox proportional hazards model was generated for each voltage index after adjusting for age, sex, race, body surface area (BSA), hypertension, smoking, LV mass index and type of bundle branch block.

Mortality was assessed by electronic medical records, and patients who had no follow-up within the past 6 months were contacted by telephone to assess vital status and interim heart transplantation or LVAD. All statistical tests were 2-sided and p values <0.05 were considered significant. All model assumptions were examined including linearity, collinearity, additivity, and proportional hazards. Statistical analysis was performed using Stata (version 13, StataCorp LP, College Station, Texas). The study was approved by the Cleveland Clinic Institutional Review Board.

3. Results

3.1. Patient characteristics

There were 389 consecutive patients (ATTR 186 and AL 203) who met inclusion criteria, with 69% diagnosed based upon endomyocardial biopsy. In those without endomyocardial biopsy, 49% had positive bone marrow or extracardiac biopsy and 16% had a TTR genetic mutation. Cardiac involvement was confirmed based upon CMR in 29%, TcPYP scintigraphy in 24%, and echocardiography with strain in 47%. Table 1 depicts the baseline demographics of the cohort. Patients with ATTR were older and more likely to be white, male, obese, hypertensive and have a history of smoking, atrial fibrillation, coronary artery and renal disease. Anteroseptal thickness and LV mass index and were larger and QRS duration longer in the ATTR subtype as compared to AL. Patients with AL showed significantly lower limb voltages and a trend toward lower Sokolow voltage as compared to ATTR. There was no difference in voltage-to-mass ratio between subtypes. The supplemental table shows the baseline characteristics in ATTR subdivided into wild type, hereditary and untyped.

3.2. Voltage assessment

Of the 389 patients, 118 had a prolonged QRS > 120 ms (30.3%). Table 2 shows the unadjusted comparison of voltage parameters stratified by each category of conduction abnormality. In patients with a narrow QRS, 68% met low limb (76% in AL and 56% in ATTR, $p = 0.001$), 72% met low Sokolow (77% in AL and 65% in ATTR, $p = 0.052$), and 57% met low voltage by both criteria (64% in AL and 45% in ATTR, $p = 0.004$). Patients with right bundle branch block and paced rhythms had significantly higher limb voltages and lower precordial voltages as compared to those with a narrow QRS (example in Fig. 1).

Fig. 2 shows scatter plots of LV mass index as compared to ECG voltage in patients without conduction disease. There was no association between either index of ECG voltage and LV mass index. This lack of association remained when groups were divided by amyloid subtype (AL vs ATTR).

Results of multivariable linear regression analysis are seen in Table 3. Patients with AL type were found to have a lower Sokolow voltage than those with ATTR. LBBB and IVCD patterns were not significantly associated with either voltage measurement. RBBB and paced rhythms predicted significantly higher limb and lower Sokolow voltages. Age, sex, race, history of hypertension, smoking, BSA and LV mass index were