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Prognostic value of fragmented QRS in cardiac AL amyloidosis

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ABSTRACT

Background: In light-chain (AL) cardiac amyloidosis, the 12-lead electrocardiogram (ECG) reflects myocardial amyloid infiltration with low limb voltages, pseudoinfarction patterns, and conduction abnormalities. Moreover, it is not unusual to see "aspecific" QRS complex abnormalities, such as notches and RsR′ pattern in the absence of QRS prolongation, i.e. a fragmentation of QRS complexes (fQRS), that has been associated with myocardial scars and prognosis. Since cardiomyocyte damage and interstitial fibrosis are associated with cardiac amyloid deposition, aim of the present study was to analyze the prevalence and the potential prognostic value of fQRS in patients with cardiac amyloidosis.
Methods: We enrolled 375 consecutive untreated patients in whom a first AL amyloidosis diagnosis was concluded between 2008 and 2010, 264 with and 111 without heart involvement. Patients with a positive history of coronary disease were excluded from the analysis.
Results: The prevalence of fQRS was significantly higher in patients with cardiac AL amyloidosis (28.5% vs. 11.7%; $p = 0.0008$). After a median follow-up of 561 days, Kaplan–Meier survival analysis revealed a significantly higher mortality in the fQRS group when compared with the "normal" QRS group ($p = 0.0008$). No association was found between the presence of fQRS and the duration of PQ, QRS, and QTc intervals, the presence of peripheral low voltages or pseudonecrosis, NT-proBNP serum levels or cardiac wall thickness.
Conclusions: In patients with cardiac AL amyloidosis, the presence of fQRS at diagnosis has an independent prognostic value. Such a simple and cheap analysis in patients' diagnostic work-up may improve diagnosis and prognostic stratification.

1. Introduction

Amyloidoses constitute a large group of diseases in which aggregates of insoluble toxic protein are deposited in forms of fibrils in several tissues [1,2]. The most common form of systemic amyloidosis is AL amyloidosis, in which fibrils are composed mainly by the N-terminus of a monoclonal immunoglobulin light-chain; the incidence is approximately 1 case per 100,000 person-years in Western countries and in such patients cardiac involvement is not only frequent but also the most common cause of death [3,4]. In primary (AL) amyloidosis, not only is survival dependent on the presence of cardiac involvement, but heart dysfunction also limits the feasibility of intensive and effective therapy [5–7].

The 12-lead electrocardiogram (ECG) reflects the generalized infiltrative nature of this disease with low voltages in the limb leads, pseudoinfarction patterns in the anterior precordial and/or the inferior limb leads, and conduction abnormalities such as fascicular block or atrioventricular block of varying degrees [4,8–10]. Moreover, it is not unusual to see "aspecific" abnormalities of the QRS complexes, such as notches and RsR′ pattern in the absence of QRS prolongation, that have been never described in detail. It has been suggested that alterations in QRS morphology, leading to a terminal conduction delay or a fragmentation of QRS complexes (fQRS) on the 12-lead ECG are associated with regional myocardial scars, in the setting of ischemic heart disease, dilated cardiomyopathy, and repaired tetralogy of Fallot [11–13]. In detail, the definition of fQRS includes various RSR′ patterns with different morphologies of the QRS complexes with or without the Q wave on a resting 12-lead ECG. Various patterns include an additional R wave (R′) or notching in the nadir of the S wave, or the presence of >1 R′ fragmentation in 2 contiguous leads, corresponding to a major coronary artery territory [14]. These different fQRS morphologies probably represent intramyocardial conduction abnormalities and peri-infarction conduction block due to myocardial necrosis or scar [15]. It is important to note that myocardial scar and/or fibrosis may alter QRS morphology

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without lengthening its duration, thereby resulting in an additional R′ or notch in either the R or S wave within a narrow QRS complex. The presence of fQRS has been correlated with prognosis in the setting of ischemic heart disease [16–19], dilated cardiomyopathy [19,20], and acquired long QT syndrome [21], although this is not predictive of successful response to cardiac resynchronization therapy [22], or prophylactic ICD implantation [23]. Since in the setting of cardiac amyloidosis cardiomyocyte damage and amyloid deposition may contribute to similar alteration in QRS morphology, aim of the present study was on the one hand to analyze the prevalence of fQRS in patients with cardiac amyloidosis, and on the other hand to assess whether this finding has a prognostic value in predicting advanced heart failure and sudden cardiac death. Indeed the majority of patients with cardiac amyloidosis die for major cardiac events, which are often sudden cardiac death due to either tachy- or bradyarrythmias leading to electromechanic dissociation [7].

To this aim, consecutive patients with AL amyloidosis were recruited in the years 2008, 2009, and 2010, with a median follow-up of 18.7 months in order to assess the prevalence of fQRS, the relationship with clinical, structural, functional and biochemical data, and their possible prognostic significance.

2. Methods

We enrolled all consecutive untreated subjects undergoing extensive multiteam evaluation c/o the Amyloidosis Research and Treatment Center of Pavia and the Regional Amyloid Center of the Careggi Hospital of Florence, Italy in whom first diagnosis of primary AL amyloidosis was concluded between 2008 and 2010. Diagnosis was made according to the International Society of Amyloidosis criteria, as well as assessment of organ involvement at baseline [24]. The presence of heart involvement was defined according to either the demonstration of amyloid deposits on the endomyocardial biopsy or by echocardiographic evidence of cardiac amyloidosis in the setting of a defined systemic disease. Echocardiographic features of amyloidosis included diastolic dysfunction, and a mean left ventricular wall thickness (septum and posterior wall) greater than 12 mm in the absence of hypertension or other potential causes of left ventricular hypertrophy. The presence of low voltages on 12-lead electrocardiography (all limb leads less than 5 mm in height) was a clue to cardiac involvement by amyloid. Elevation of the N-terminal pro-brain natriuretic peptide (NT-proBNP), and elevation of cardiac troponins were compared with echocardiography [25–29]. No patient with cardiac AL was found to have NT-proBNP in the normal range. Patients were also divided according to the Mayo staging system as proposed by Dispenzieri and coworkers [30]. At presentation, all patients provided informed consent for anonymous publication of scientific data. The authors of this manuscript have certified that they comply with the "Principles of Ethical Publishing in the International Journal of Cardiology".

2.1. 12-lead ECG

Analysis of the standard 12-lead electrocardiogram (Esaote P8000 Power 1e30, filter range 0.05 to 50 Hz, 25 mm/s, 10 mm/mV) was performed by 2 independent readers (F.S. and F.C.) blinded to the organ involvement, echocardiographic data and levels of cardiac biomarkers as well as clinical data. There was 97% concordance in defining fQRS between the 2 readers. Beyond the usual electrocardiographic parameters (PQ, QRS, QT intervals), peripheral and total QRS scores were also calculated as the sum of QRS voltages in all the 6 peripheral leads and in all the 12 peripheral and precordial leads, respectively.

2.2. fQRS definition criteria

Fragmented QRS was defined by the presence of various RSR' patterns with or without a Q wave and included an additional R wave (R), notching of the R wave, notching of the downstroke or upstroke of the S wave, or the presence of >1 R′ in 2 contiguous leads corresponding to a major coronary artery territory (Fig. 1) [14]. Electrocardiograms were compared with previous electrocardiograms (if available) to confirm that fQRS or pathologic Q waves were of recent onset.

2.3. Echocardiography

Echocardiographic data were collected with the patient in a supine left lateral decubitus position. Two-dimensionally targeted M-mode echocardiography was performed after the longitudinal parasternal view had been checked to avoid angulation of the ultrasonic beam and consequent changes in the LV shape. LV internal dimensions, posterior wall thickness, and interventricular septum thickness were analyzed by a single reader according to the standards of the American Society of Echocardiography [31]. LV mass was indexed to body surface area (g/m^2). Endocardial shortening fraction (SFendo) was calculated as the difference between the end-diastolic and the end-systolic diameters divided by the end-diastolic diameter and then multiplied by 100. Transmitral flow velocity in early (E) and late (A) diastole was measured by conventional pulsed Doppler in the apical 4-chamber view. Moreover, pulsed TDI-derived early diastolic peak velocity at lateral (E' lateral) mitral annulus was evaluated as an index of LV relaxation [32]. The E to E′ ratio was also assessed.

2.4. Statistics

Continuous variables are expressed as median values and interquartile ranges, and categorical variables as frequencies and percentages. Comparisons of continuous variables were based on ANOVA followed by 2-tail Mann–Whitney's *U* test, and comparisons of proportions were based on chi-square tests. Prevalence of fQRS was assessed as the number of patients showing this electrocardiographic abnormality divided by the total study population. Survival curves were plotted according to Kaplan–Meier and differences in survival were tested for significance by the log-rank test. Receiver Operator Characteristic (ROC) analysis was performed to assess the ability (by calculating the area under the curve) of the biochemical, echo- and electrocardiographic parameters to identify patients who died within 12 months from diagnosis. Cox proportional regression models were fitted to compute hazard ratios (HR) and 95% confidence interval for death for a series of potential predictors, namely the presence of fQRS, NT-proBNP and Troponin I serum levels (as prognostically validated biochemical markers of cardiac dysfunction), LVMI (as an index of the extent of cardiac involvement), E/E′ ratio, and Endocardial Shortening Fraction (as indices of diastolic and systolic dysfunctions, respectively). Moreover, Cox proportional regression models were fitted to compute hazard ratios (HR) for death for the presence of fQRS, and for the Mayo staging system, that has been prognostically validated [30]. All analyses were performed using MedCalc® version 11.6.1.0.

3. Results

3.1. Study population

The study population included 418 consecutive patients, diagnosed between 2008 and 2010. To avoid any possible interference of ischemic heart disease on the presence of fQRS, patients with a positive history of coronary disease were excluded from the analysis. 43 patients without all echocardiographic, electrocardiographic and biochemical data were excluded. A cohort of 375 patients (age 65 ± 17 years; 202 males) was included in the final analysis. The cohort was divided into two groups depending on the presence (n = 264) or absence (n = 111) of heart involvement by amyloidosis. Patients with bundle branch blocks (n = 14) and with ICD or PM (n = 3) were included, following the criteria for definition of fQRS in this case as suggested by Das et al. [18].

3.2. ECG presentation

As expected, the presence of cardiac involvement was associated with a peculiar electrocardiographic pattern, with a 63.9% proportion of low voltages and a 52.2% proportion of pseudonecrosis, as defined by the presence of a pathological Q wave in two or more contiguous leads in the absence of history of ischemic heart disease and/or evidence of akinetic/dyskinetic wall segments [4]. Moreover, when compared with patients without cardiac amyloidosis, the presence of myocardial involvement was associated with prolonged PQ, QRS and QT intervals. Overt atrio-ventricular block was present in 24.8% of patients with cardiac AL, and complete bundle branch block was evident in 28% of patients with cardiac involvement. In both cases the prevalence of atrio-ventricular and intra-ventricular conduction delays was significantly higher than in patients without cardiac involvement ($p = 0.0295$ and $p = 0.0306$, respectively).

3.3. Echocardiographic presentation

Table 1 reports the values of septal and posterior wall end-diastolic thicknesses, left ventricular mass index, end-diastolic and end-systolic chamber volumes, ejection fraction, early-to-atrial transmitral flow velocity ratio (E/A ratio), and tissue Doppler E/E′. As expected, cardiac amyloidosis was associated with left ventricular concentric hypertrophy with preserved ejection fraction and evident diastolic dysfunction (all $p < 0.01$ vs. patients without cardiac involvement). This was associated with a marked increase in NT-proBNP and