Cardiovascular Topics

Assessment of Tp–Te interval in patients with cardiac AL amyloidosis

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Abstract

Background: Prolonged Tp–Te interval is strongly associated with fatal ventricular arrhythmias and mortality. This association has been demonstrated in various diseases. However, the current literature does not give any information on Tp–Te interval in cardiac amyloid light-chain (AL) amyloidosis.

Methods: We retrospectively screened 116 cardiac AL amyloidosis patients and 35 patients were included in the study. Demographic, laboratory, 12-lead electrocardiographic (QTc, Tp–Te V1–V6) and transthoracic echocardiographic data of the patients were analysed and compared with 35 healthy controls.

Results: QTc and Tp–Te V2–V5 were significantly prolonged in the cardiac AL amyloidosis group ($p < 0.05$). Also, there was a positive and statistically significant correlation between the parameters of QTc and Tp–Te V3–V6, and also between the parameters of interventricular septum thickness at end-diastole and Tp–Te V2–V5.

Conclusion: We present the first strong evidence of prolonged Tp–Te intervals in patients with cardiac AL amyloidosis. There may also be a relationship between prolonged Tp–Te interval and the development of arrhythmia in this patient group, as in some other groups. There is a need for prospective studies examining the relationship of prolonged Tp–Te interval with arrhythmias and its prognostic significance in cardiac AL amyloidosis.

Keywords: Tp–Te interval, immunoglobulin light-chain amyloidosis, cardiac amyloidosis, arrhythmia

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Thirty-six human amyloid proteins have been described in the literature, which may cause limited or systemic amyloidosis or both.[1] Localised or systemic deposition of insoluble amyloid precursor proteins in various tissues causes the different clinical faces of amyloidosis.[2,3] The mechanism of amyloid light-chain (AL) amyloidosis is the deposition of immunoglobulin light chains or fragments of a particular light chain in the tissues, and it can affect every organ and system other than the central nervous system.[4] Regardless of the type of amyloidosis, accumulation of these misfolded proteins in the tissues causes organ dysfunction by disrupting the tissue architecture.[5,6] Although it is a rare disease, amyloidosis is one of the frequent causes of infiltrative restrictive cardiomyopathies, and cardiac involvement is the main determinant of survival.[7,8]

As is well known, atrial and ventricular arrhythmias, conduction disease, prolonged QT and sudden death are common in cardiac amyloidosis.[9-11] Management of cardiac involvement has great importance as it is the primary determinant of survival in this patient group. The pathogenesis of arrhythmias in cardiac amyloidosis is highly complex and poorly understood due to limited data. Current data indicate that remodelling and fibrosis of the left ventricle, amyloid deposition in the conduction system, and micro-/macrovascular myocardial ischaemia caused by amyloid deposition play a role in ventricular arrhythmias that occur in cardiac amyloidosis.[12]

It has been demonstrated that prolonged transmural dispersion of repolarisation is associated with ventricular tachyarrhythmias

in higher-risk populations.[13] Electrophysiological studies have demonstrated that even if the QT interval also reflects ventricular repolarisation, the total T-wave area, late T-wave area and T peak to T end (Tp–Te) interval are better indicators of action potential duration at 90% repolarisation.[14] Various studies have revealed that Tp–Te, which corresponds to transwedge dispersion of the action potential duration, predicts malignant arrhythmias. It might be the best predictor in certain populations, and even prolonged Tp–Te is related to a higher risk of death from any cause in every population.[15-19]

However, the current literature does not yield any information on Tp–Te interval in cardiac AL amyloidosis. Our study aimed to investigate Tp–Te interval in cardiac AL amyloidosis patients.

Methods

All patients with a cardiac AL amyloidosis diagnosis, followed up in our haematology division between 2010 and 2022, were retrospectively screened. Systemic AL amyloidosis had been demonstrated by tissue biopsies in all patients. Cardiac involvement had been revealed by typical clinical, laboratory and echocardiographic findings in all patients, and cardiac magnetic resonance imaging in most patients.

The main exclusion criteria of the study were history of previous arrhythmia, ischaemic heart disease and chronic use of drugs that could affect the cardiac conduction system or cause QT prolongation.

Demographic data and 12-lead electrocardiographies (ECGs) were obtained from the patients' files and laboratory results, and the transthoracic echocardiography reports were from the hospital's electronic database. The data of QTc and Tp–Te V1–V6 from the electrocardiogram and left ventricular ejection fraction (LVEF), interventricular septum thickness at end-diastole (IVSd), left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter in transthoracic echocardiography were included in the analysis. For better standardisation, all the laboratory and electro-/echocardiographic data were obtained from the time of diagnosis of cardiac amyloidosis.

The control group consisted of healthy individuals with no chronic history of disease. To avoid incidental cardiac disorders, the control group underwent a physical examination, laboratory tests (complete blood count, glomerular filtration rate, electrolyte levels, high-sensitivity troponin T, and NT-proBNP) and transthoracic echocardiography.

All electrocardiograms were performed in the supine position with a 12-lead ECG, Cardioline Ar2100adv at 25 mm/s and 10 mm/mV. QTc and Tp–Te intervals were evaluated by two experienced doctors, and the CardioCalipers v3.3 application was used for measurements. QRS intervals were measured from the beginning of the Q wave or, in the absence of the Q wave, from the beginning of the R wave to the junction of the end of the S wave and the isoelectric line. Tp–Te intervals were measured from the peak of the T wave to the end of the T wave. The end of the T wave was defined as the intersection of the downslope of the T wave and the isoelectric line. If the T wave could not be clearly identified, the leads were excluded. The average of three readings for each lead was included in the analysis.

This study was approved by the Istanbul Faculty of Medicine clinical research ethics committee (number: E-29624016-050.99-1005733). All procedures performed complied with the ethical standards of the 1964 Helsinki Declaration.

Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation or median (minimum–maximum) for discrete and continuous numerical variables, and categorical variables as number of cases and percentage (%). Cross-table statistics were used to compare categorical variables (chi-squared and Fisher). Normally distributed parametric data were compared with the Student's *t*-test and ANOVA, and non-parametric data that were not normally distributed were compared with the Mann–Whitney *U*- and Kruskal–Wallis tests. Comparisons between multiple groups were achieved by *post hoc* Tukey analysis. The inter-scale correlation was evaluated with Spearman's rho and Pearson tests, taking into account the distribution of variables. Results with a p-value of < 0.05 were defined as statistically significant.

Results

A total of 116 cardiac AL amyloidosis patients were retrospectively screened. Thirty patients were excluded due to non-available electrocardiograms, nine due to non-available echocardiography, six due to low-quality electrocardiogram records, 18 due to co-morbidities, 12 due to drug use that might have affected repolarisation time, and six due to electrolyte imbalance (Fig. 1). After the exclusion, a total of 70 cases, including 35 cardiac AL amyloidosis and 35 healthy controls, were included in the study.

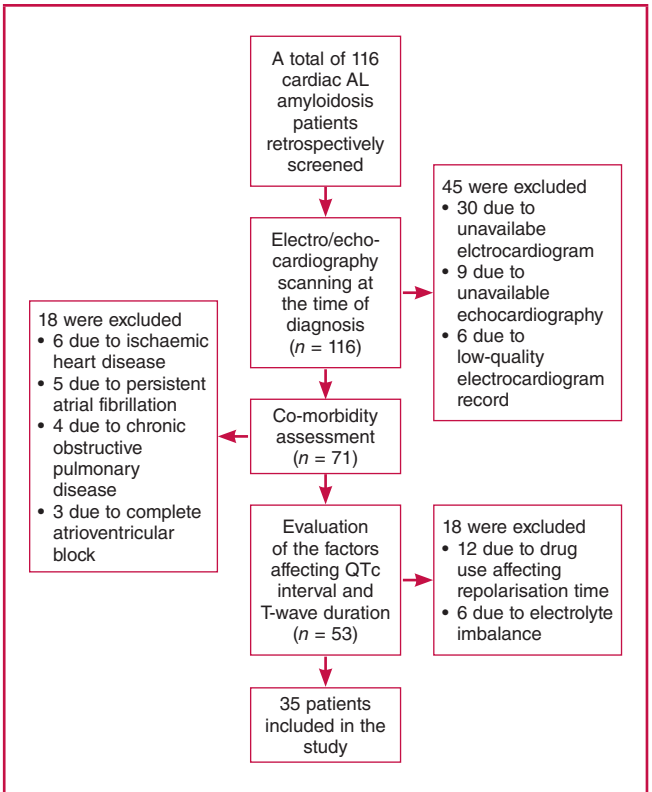

Fig. 1. Flow chart of the exclusion and enrollment of patients.

Table 1. Demographic characteristics of the study population

Variables	*Total*	*Patient group*	*Control group*	p-*value*
Gender, *n* (%)				
Female	42 (60)	20 (57.1)	22 (62.8)	0.625
Male	28 (40)	15 (42.9)	13 (37.2)	
Age, (mean ± SD)	59.39 ± 9.70	60.71 ± 10.62	58.06 ± 8.70	0.257

The mean age of the study population was 59.39 ± 9.70 years (40–88 years), the mean age of the patient group was 60.71 ± 10.62 years, and the mean age of the control group was 58.06 ± 8.70 years. Sixty per cent of the study population (n = 42) were female and 40% (n = 28) were male. Female/male ratios were 1.33 and 1.69 in the patient and control groups, respectively. No significant statistical difference was detected in the demographic features between the groups (Table 1).

When the laboratory data between the groups were compared, it was determined that the mean plasma values of fasting glucose (p = 0.016), creatinine (p = 0.000), calcium (p = 0.048) and NT-proBNP (p = 0.000) were significantly higher, and the mean plasma values of sodium (p = 0.043) and albumin (p = 0.000) were significantly lower in the patient group (Table 2).

Parameters of rate-corrected QT interval (QTc), Tp–Te V2, Tp–Te V3, Tp–Te V4 and Tp–Te V5 were significantly prolonged in the patient group (p = 0.000, 0.002, 0.000, 0.000 and 0.000, respectively). Additionally, analysis of echocardiographic parameters revealed that LVEF and LVEDD were significantly decreased (p = 0.011 and 0.012, respectively), and IVSd was significantly increased in the patient group (p = 0.000) (Table 3).

There was a positive and statistically significant correlation between the values of QTc and Tp–Te V3, Tp–Te V4, Tp–Te V5 and Tp–Te V6. Again, a positive and statistically significant correlation was found between the values of IVSd and Tp–Te V2, Tp–Te V3, Tp–Te V4 and Tp–Te V5 (Fig. 2, Table 4).

Discussion

Although malignant ventricular arrhythmias have previously been suspected as the cause of sudden death in cardiac AL amyloidosis, studies have demonstrated that receiving an implantable cardiac defibrillator (ICD) did not have a positive effect on mortality.[20,21] This supports the notion that complex pathological conditions are present beyond the predictions. Valid data suggest that patients may develop electromechanical dissociation or that the defibrillation threshold is higher, which causes the refractoriness to ICD therapy.[9]

Table 3. Comparison of the electrocardiographic and echocardiographic parameters between the groups

Variables	*Patient group (mean ± SD)*	*Control group (mean ± SD)*	p-*value*
QTc (ms)	44791 ± 30.11	412.60 ± 22.26	0.000
Tp–Te V1 (ms)	7948 ± 16.81	71.62 ± 9.33	0.051
Tp–Te V2 (ms)	8724 ± 15.84	77.12 ± 9.09	0.002
Tp–Te V3 (ms)	91.70 ± 15.10	77.43 ± 9.27	0.000
Tp–Te V4 (ms)	91.97 ± 13.77	77.63 ± 8.91	0.000
Tp–Te V5 (ms)	87.89 ± 12.79	77.20 ± 8.75	0.000
Tp–Te V6 (ms)	81.42 ± 15.45	75.50 ± 8.40	0.060
LVEF (%)	58.87 ± 8.60	65.11 ± 3.66	0.011
LVEDD (cm)	4.21 ± 0.56	4.54 ± 0.35	0.012
LVESD (cm)	2.91 ± 0.50	2.88 ± 0.32	0.856
IVSd (cm)	1.66 ± 0.20	1.04 ± 0.07	0.000

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSd, interventricular septum thickness at end-diastole.

Although ventricular tachycardia was found in 26.7% of patients in a study in which 232 patients with AL amyloidosis with cardiac involvement were examined, development of sudden death was found at a similar rate in groups with and without ventricular tachycardia (36.4 and 35.4%, respectively).[22] In a prospective study with a limited number of cardiac AL amyloidosis patients, implantable loop recorders demonstrated that the majority of deaths were associated with bradycardia and complete atrioventricular block, followed by pulseless electrical activity.[23]

Tp–Te represents the interval between the peak and the end of the T wave on electrocardiogram, and it is the index of global dispersion of repolarisation.[24-26] It is a relatively new electrocardiographic parameter and is not reviewed by clinicians in daily practice routines. This may be due to studies with contradictory results, under-recognition and a lack of consensus.

There is an opinion that the Tp–Te interval does not carry an additional benefit for a clinician who uses the ECG and vectorcardiogram, since action potential prolongation extends the routinely screened QT distance as well as the Tp–Te.[26] However, in a prospective study including 1 384 patients with myocardial infarction, Erikssen *et al.* examined the prognostic effect of the Tp–Te interval and demonstrated that, although QT was a significant predictor of mortality when Tp–Te and QT were evaluated together, only Tp–Te remained significant. They revealed that this prognostic significance for postmyocardial infarction at one year was due to the terminal part of the QT, which is the Tp–Te interval.[27]

Table 2. Comparison of the laboratory parameters between the groups

Variables	*Patient group (mean ± SD)*	*Control group (mean ± SD)*	p-*value*
Fasting glucose (mg/dl) (mmol/l)	111.45 ± 33.00 6.19 ± 1.83	95.25 ± 16.61 5.28 ± 0.92	0.016
Creatinine (mg/dl)	1.94 ± 1.58	1.00 ± 1.16	0.000
Sodium (mmol/l)	139.65 ± 3.81	141.59 ± 1.86	0.043
Potassium (mmol/l)	4.17 ± 0.52	4.37 ± 0.26	0.070
Albumin (g/dl)	3.62 ± 1.17	4.35 ± 0.25	0.000
Calcium (mg/dl)	9.13 ± 1.04	9.08 ± 0.28	0.048
Phosphorus (mg/dl)	3.82 ± 0.78	3.48 ± 0.51	0.075
NT-proBNP (pg/ml)	9316.38 ± 9300.48	79.85 ± 31.38	0.000

Table 4. Correlation analysis of electrocardiographic and echocardiographic parameters for the patient group

	QTc (ms)		*LVEF (%)*		*IVSd (cm)*	
Variables	r	p	r	p	r	p
Tp–Te V1 (ms)	0.133	0.338	–0.043	0.764	0.259	0.066
Tp–Te V2 (ms)	0.205	0.094	–0.188	0.136	0.298	0.017
Tp–Te V3 (ms)	0.391	0.000	–0.023	0.854	0.479	0.000
Tp–Te V4 (ms)	0.486	0.000	–0.008	0.952	0.583	0.000
Tp–Te V5 (ms)	0.462	0.000	0.026	0.845	0.538	0.000
Tp–Te V6 (ms)	0.304	0.014	0.108	0.403	0.244	0.056

LVEF, left ventricular ejection fraction; IVSd, interventricular septum thickness at end-diastole.

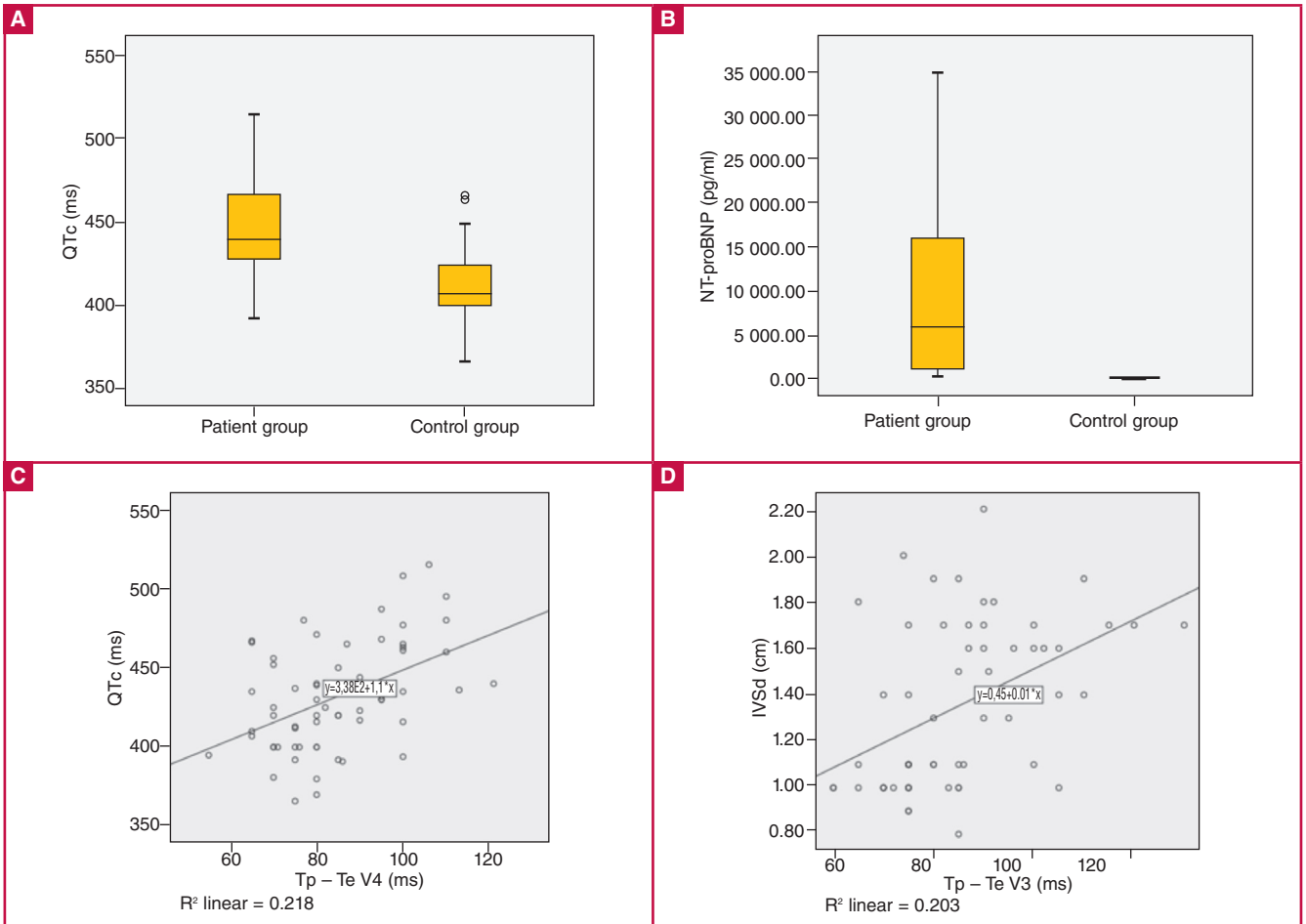

Fig. 2. A. Mean QTc distribution of the groups. B. Mean NT-proBNP (pg/ml) distribution of the groups. C. Correlation between the parameters of QTc and mean Tp–Te V4 in the patient group. D. Correlation between the parameters of IVSd and mean Tp–Te V3 in the patient group. IVSd, interventricular septum thickness at end-diastole.

Furthermore, a meta-analysis published in 2017 that examined the association of Tp–Te interval with arrhythmia and mortality in 155 856 patients from 33 studies revealed strong correlations between prolonged Tp–Te interval and ventricular tachycardia/ventricular fibrillation (VT/VF), sudden cardiac death, cardiovascular death and all-cause mortality ($p < 0.0001$ for each). In addition, the population with the highest risk of VT/VF or death was that with Brugada syndrome [odds ratio (OR) 5.68; $p < 0.01$], followed by patients with hypertension (OR 1.52; $p < 0.0001$), heart failure (OR 1.07; $p < 0.0001$) and ischaemic heart disease (OR 1.06; $p = 0.001$).[28] These results clearly demonstrate that the Tp–Te interval can be used for risk assessment of arrhythmia and death in these diseases and in the general population.

Through a retrospective study, Emet *et al*. found that the Tp–Te interval was significantly prolonged in all precordial leads in sarcoidosis patients with uncertain cardiac involvement, compared to a control group.[29] Considering that prolongation of the Tp–Te interval can predict arrhythmia and mortality even in the general population, these data reveal the necessity of screening and investigating the importance of the Tp–Te interval, especially in multisystemic diseases with cardiac involvement.

There are many studies in the literature highlighting the relationship between QTc prolongation and mortality in cardiac amyloidosis.[11,30,31] In our study, in addition to QTc, significantly prolonged Tp–Te V2–V5 intervals were explored in patients with cardiac AL amyloidosis. A positive and statistically significant correlation was found between QTc values and Tp–Te V3–V6 and between IVSd and Tp–Te V2–V5 parameters. We believe our results are representative since this is the first study that has demonstrated the prolongation of Tp–Te interval in cardiac AL amyloidosis patients.

There are some limitations of our study. Its retrospective design and small sample size are the main limitations. The aim of the study was evaluation of the Tp–Te interval in cardiac AL amyloidosis. The relationship between the development of arrhythmia and Tp–Te prolongation and the prognostic importance of Tp–Te prolongation were not examined.

Conclusion

This study is the first in which prolonged QTc and Tp–Te V2–V5 parameters were determined in cardiac AL amyloidosis patients. The existence of a possible relationship between prolonged Tp–Te and arrhythmias, and the impact on mortality should be investigated through prospective studies with a higher number of cardiac AL amyloidosis patients.

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