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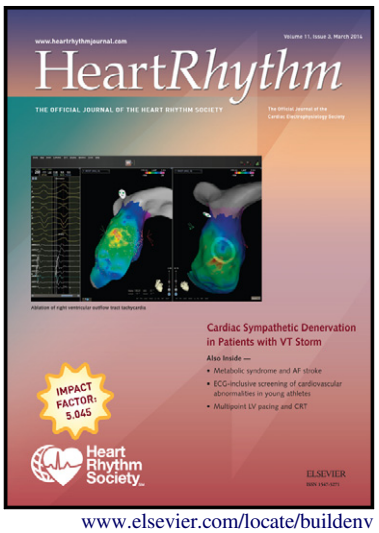

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PQ Segment Depression in Short QT Syndrome Patients: A Novel Marker for Diagnosing Short QT Syndrome?

Short Title: Short QT Syndrome and PQ Segment Depression

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Abbreviations

SQTS	Short QT Syndrome
ECG	Electrocardiogram
PQD	PQ segment depression

BACKGROUND: Patients with a short QT syndrome (SQTS) have an increased risk for atrial, ventricular tachyarrhythmias and/or sudden cardiac death. PQ segment depression (PQD) is related to atrial fibrillation and carries a poor prognosis in the setting of acute inferior myocardial infarction and is a well defined ECG marker of acute pericarditis.

OBJECTİVES: The aim of this study was to evaluate the prevalence of PQD in SQTS and to analyze the association with atrial arrhythmias.

METHODS: Digitalized 12-lead ECGs of SQTS patients were evaluated for PQD in all leads and for QT intervals in lead II and V5. PQD was defined as ≥ 0.05 mV (0.5 mm) depression from the isoelectric line.

RESULTS: A total of 760 leads from 64 SQTS patients [mean age 36 ± 18 years, 48 males (75%)] were analyzed. PQD was seen in 265 (35%) leads from 52 (81%) patients and was more frequent in leads II, V3, aVF, V4, and I [n=43 (67%), n=30 (47%), n=27 (42%), n=25 (39%), n=25 (39%), respectively]. Nine of 64 patients (14%) presented with atrial tachyarrhythmias and all of them had PQD.

CONCLUSIONS: Fifty-two of 64 patients (81%) with SQTS reveal PQD. As PQD is rarely observed in healthy subjects, this ECG stigma may constitute a novel marker for SQTS in addition to a short QT interval.

Keywords: PQ depression, short QT syndrome, sudden cardiac death, ECG

Introduction:

Short-QT-syndrome (SQTS) is a recently described highly arrhythmogenic cardiac channelopathy characterized by shortened QTc-interval, reduced atrial and ventricular effective refractory periods, and atrial and/or ventricular arrhythmias with an increased risk for familial sudden cardiac death[1]. Although the hallmark of the disease is a short QT interval on ECG, a universally accepted diagnostic cut-off value of short QT interval has not been defined. SQTS was initially recognized in patients with QTc interval of 300 ms or less. However, in subsequent studies, patients with similar clinical presentations and slightly or moderately shortened QT intervals (≤ 340-360 ms) were described[2-5]. Moreover, impaired QT adaptation to heart rate changes makes the correction formulas like Bazett or Fredericia inappropriate or of limited value in SQTS patients with heart rates above 100/min or below 60/min [4, 6, 7]. Poor performance of correction formulas, in addition to lack of universal diagnostic cut-off value for a SQTS, makes it difficult to establish a diagnosis in cases of borderline shortened QT intervals. Apart from a short QT interval, the ECG pattern of the ST segment, the T wave (tall and symmetrical T waves with a short interval between the QRS offset and the onset of T wave), an abnormal J point-Tpeak interval, Tpeak-Tend/QTc intervals or frequent clear demarcation of the U-wave (especially in precordial leads), as well as the lack of adaptation of the QT interval during exercise were previously reported to be helpful to establish the diagnosis of SQTS[8-10].

Beside these markers of shortened ventricular repolarization, ECG markers of atrial repolarization abnormalities may improve the diagnostic value in differentiating patients with a SQTS. The greater abbreviation of the action potential of the pectinate muscle as compared to the cristae terminalis generates a spatial dispersion of repolarization in atria, which may cause a PQ depression on ECG due to a voltage gradient[11]. A heterogeneous shortening of atrial repolarization and a reduced wavelength lead clinically to an increased incidence of atrial fibrillation/flutter in patients with a congenital SQTS[5]. However, the impact of spatial repolarization dispersion on the PQ segment has not been established in SQTS.

PQ segment depression (PQD) is a well defined electrocardiographic marker of acute pericarditis. It is related to injury like currents and is present in the acute phase in up to 82% of patients[12]. Furthermore, it is a powerful tool in the differential diagnosis of patients with STEMI [12-16]. PQD is also associated with extensive atrial myocardial damage, atrial fibrillation and poor prognosis in patients with an acute inferior myocardial infarction[17]; Finally, it has been observed during ablation of the left upper pulmonary vein or in patients with atrial tumors[18, 19].

The aim of this study was to evaluate the prevalence of PQD in SQTS, the value of PQD as an additional diagnostic ECG marker of SQTS.

Methods:

Study Population:

This multicenter study population consisted of 64 patients (48 males, age 36 ± 18 years, range 5-88 years) diagnosed with SQTS from a European SQTS registry[5]. In this registry, the SQTS was diagnosed: (1) if the patient had a QTc interval of 360 ms or less (in lead II or V5), with history of sudden death or aborted sudden death or syncope of arrhythmic origin; or (2) if subjects had a very short QT interval (QTc < 340 ms) (even if they were asymptomatic); or (3) if the patient had a short QT interval (QTc interval ≤ 360 ms, in lead II or V5) with a family history of SQTS.

To best of our knowledge, there is not any large scale study reporting about an abnormal or physiological PQ segment deviation in healthy subjects. Hence, we included age- and sex-matched 117 subjects as a control group without any known structural structural heart disease or channelopathy; to evaluate the presence and frequency of PQD in normal population and to avoid the bias and hypothesis driven false positive results due to the measurements performed in a single group.

ECG Measurements

All resting 12-lead ECGs (paper speed 25 or 50 mm/s, gain 10 mm/mV) of SQTS patients were scanned and analyzed for PQD in all leads and for QT-intervals in lead II and V5. All measurements were performed after 4-fold

magnification of the ECGs (using Adobe Acrobat 8 Professional; Adobe Systems Incorporated, San Jose, CA).

PQ segment depression was defined as ≥ 0.05 mV (0.5 mm) depression from the isoelectric line. The TP segment (the isoelectric interval between the end of T wave and the next P wave) was used as baseline for the examinations[20 21]. If no clear-cut TP segment could be defined or in case of drifting, non-parallel TP and PQ baselines, the beat with less drifting baseline has been chosen for measurement and if it was not possible at all, the vertical distance from the beginning of P wave to the dip of PQ segment was measured (Figure 1).

In lead aVR, PQ segment elevation (≥ 0.05 mV) was accepted as equal to PQD in other leads. The ECGs of each patient were examined separately by three investigators blinded to the clinical information. In case of disagreement, decision was made by majority vote. The quantitative measurements were made by a single investigator. For intra-observer reliability analysis of quantitative measurements, a sample of 20 patients was re-analysed. The intra-observer correlation co-efficient was between 0.82 and 0.98; and variability was <16% in all leads.

The end of T wave was defined by a standard tangential method and the QT-interval was corrected for the heart rate according to Bazett's formula.

Statistical Analysis:

Numerical variables were presented as mean ± standard deviation (SD) and when the distributions were skewed, as the median and interquartile range; categorical variables are presented as absolute numbers and percentages. The differences in mean values between groups were analyzed with Student's *t*-test for independent samples. When distribution of variable is skewed the Mann-Whitney U-test is used for comparison of 2 groups and the Kruskal-Wallis test is used for comparison of 3 groups. The categorical variables were analyzed with Pearson's chi-square test. P values < 0.05 were considered significant. The receiver operating characteristics (ROC) curve was obtained for the various PQ depression cut-off values, as a predictor of atrial fibrillation/flutter. Youden's index was calculated (YI = sensitivity + specificity –1) for each coordinate point of the ROC curve to determine the cut-off value, which has the maximum sensitivity and specificity pair. Statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows version 16.0 (SPSS, Chicago, IL, USA).

Results:

Demographic, Clinical and Genetic Data

Sixty-four patients with SQTS and 117 subjects without any structural heart disease or channelopathy were included in the study. Of the 64 patients, 48 (75%) were males and the median age was 30 years (interquartile range: 23 to 44 years). Patients and controls demographic, clinical, genetic and ECG data are summarized in table 1. Thirty (47%) patients had symptoms including 18 (28%) patients with cardiac arrest (5 patients deceased), 5 (8%) patients with syncope (1 with presyncope), 9 (14%) patients with atrial fibrillation/flutter and 15 (23%) patients with ventricular premature contractions. Three of 9 patients had atrial fibrillation/flutter before 35 years of age. Initial presentation was cardiac arrest in 15 patients, syncope in 4 patients and palpitations in 5 patients.

Genetic screening was performed in 46 patients: 13 (20%) patients were identified with a gain-of-function mutation in KCNH2 (HERG) and 2(3%) patients with loss-of-function in cardiac L-type calcium channel (CACNB2b).

Electrocardiography

760 leads of 64 SQTS patients and 1404 leads of 117 controls were analyzed (8 leads of two SQTS patients were missing). QTc intervals were shown in table 1. PQD was seen in 52/64 (81%) patients and in 265/760 (35%) leads of patients (Fig. 2). PQD was seen only in 28/117 (24%) subjects and in 73/1404 (5.1%) leads of healthy subjects ($p<0.0001$). PQD was most often found in both the

anterior and inferior leads in patients. Lead II was the most common (67%) and lead aVL was the rarest (3%) lead for PQD (Fig. 3). PQD was also most frequent in inferior leads [n=18 (15.8%) in lead II; n=9 (7.7%) in lead aVF] in healthy subjects. PQ segment elevation in aVR was found in 36% (n=23) of the patients and 6.8% (n=8) in controls. PQD was rare in other leads in control group (<10%). PQD was more prominent in the inferior leads in patients and healthy controls, especially in lead II (Fig. 2). PQD was also more prevalent in all leads in SQTS patients compared to controls ($p=0.05$ for aVL, $p<0.001$ for other leads).

QTc (II) and QTc (V5) were not significantly different between patients with PQD in any lead and without PQD in any lead in patients (Table 2).

As PQD is related to atrial repolarization, the relationship between PQD and atrial arrhythmias was evaluated: patients with PQD in any lead vs. patients without any PQD; or presence of PQD in every lead separately.

There was no significant association between the prevalence of PQD and atrial arrhythmias. However, all of 9 patients with atrial fibrillation/flutter had PQD at least in one lead. We also conducted quantitative measurements of PQ depression and found that the patients with atrial arrhythmias had significantly more prominent PQ depression in leads II, III and aVF, i.e. inferior leads. (0.44 mm vs 0.78 mm, p:0.01; 0.17 mm vs. 0.48 mm, p:0.005 ; 0.28 mm vs. 0.66 mm, p:0.004, respectively). The cut-off values for atrial arrhythmias in leads II, III, aVF were 0.66 mm, 0.59 mm, 0.42 mm, respectively (sensitivity 67%, 67%,

89%; specificity 80%, 82%, 65%, respectively). There was no significant difference in quantitative PQ depression in any other leads. Quantitative measurements of PQ depression were similar in all leads between patients with and without syncope or cardiac arrest (data not shown).

There was also no significant difference between patients with and without PQD in any lead in terms of gender, age, QT intervals, cardiac arrest, and syncope (Table 3).

Discussion:

SQTS is a recently recognized cardiac channelopathy with an increased risk of life-threatening ventricular tachyarrhythmias and sudden cardiac death[1]. The major hallmark of the disease is a short QT interval. However, there is no clear cut-off value of short QT interval. Additional ECG markers like short or absent ST segment with tall, narrow, peaked, symmetrical T waves, presence of delineated U waves in precordial leads, or additional intervals like Tpeak-Tend, Tpeak-Tend/QTc, Jpoint-Tpeak may be helpful to ensure the diagnosis especially in patients with borderline QTc intervals (QTc 340-370 ms). In the present study, we conducted an analysis of ECGs of SQTS patients from European SQTS registry and observed that PQD is very frequent in SQTS patients.

The patients with QTc interval less than 320 ms were diagnosed with SQTS in early reports[1, 6, 22, 23]. Thereafter, Bjerregaard and coworkers[24] proposed QTc < 350 ms as a short QT interval (<88% of the mean predicted value) and < 320 ms as a very short QT interval (<80% of the mean predicted value) based on Rataharju's ECG analyses of 14379 healthy individuals[25]. Viskin et al demonstrated that male patients with idiopathic ventricular fibrillation had shorter QT intervals (371±22 ms) and suggested gender specific cut-off values (QTc < 360 ms for males, QTc < 370 ms for females) for short QT interval[2]. In several population based studies, the lower limit of QT intervals were identified between 332-380 ms for males and 344-390 ms for females[26-31]. It has also been

shown that very short QT intervals (<300 ms) are very rare and a moderately shortened QT interval (<340 ms) does not always indicate an increased risk of sudden death[7, 26, 31, 32]. Nevertheless, there is still no clear consensus for the diagnostic cut-off value of QTc interval. In our patient population the mean QTc (II) and (V5) intervals were 320.9 ± 29.4 ms (range 242-368 ms) and 322.1 ± 27.9 ms (range 248-364 ms), respectively, though 18 patients had QTc (II)-interval longer than 340 ms. Moreover, contrary to population based studies with short QT interval subjects, cardiac arrest was the initial presentation in 18 of 65 patients. For the diagnosis of SQTS, especially with borderline shortened QT intervals, underlying conditions (hyperkalemia, hypercalcemia, hyperthermia, acidosis and digitalis overdose) should be excluded, other ECG patterns (T wave morphology, PQD, or presence of prominent U wave) should also be taken into consideration and genetic screening should be initiated[33, 34].

The mutations of cardiac ion channels (gain of function of K channels - KCNH2, KCNQ1, KCNJ2) and loss of function of cardiac L-type Ca channels (CACNA1C, CACNB2b, CACNA2D1) operating in phase 2 and 3 of the cardiac action potential are responsible for the abbreviation of action potential duration [23, 35-38]. These mutations lead to heterogenous abbreviation of the action potential duration (preferentially more on epi- and endocardial layers), to a shortened QT interval and also to peaked T wave, and ST segment elevation on the ECG[11, 39]. Antzelevitch et al proposed the heterogeneous shortening of action potential duration among the three layers of myocardium [increased transmural

dispersion of repolarization (TDR)] and the decreased wavelength of activation as the mechanism of the arrhythmogenicity in SQTS[11, 39].

Similarly, the presence of PQD in SQTS patients may be due to heterogeneous abbreviation of atrial repolarization, which is expected to manifest as a deviation in the voltage of the PQ segment. In both animals and humans, the atria are comprised of diverse cell types whose action potential morphologies differ because of differences in the contribution of outward and inward ion channel currents[40-42]. Atrial cells in the crista terminalis and the pectinate muscle have ion channels with different kinetic properties creating spatial dispersion of action potential duration between the crista terminalis and pectinate muscles as well as between atrial epicardium and endocardium[11]. This spatial dispersion of repolarization and attendant dispersion of refractoriness contributes to the development of arrhythmogenesis in the atria [41, 43]. The SQT1 form of the short QT syndrome has been shown to be associated with mutations in KCNH2, which cause a gain-of-function of I_{Kr}[35]. Using a coronary-perfused canine atrial preparation, Nof et al showed that the I_{Kr} agonist PD-118057 is capable of recapitulating the electrophysiologic and arrhythmic manifestations of SQT1 [11]. Abbreviation of action potential duration and effective refractory period together with amplification of spatial dispersion of repolarization predisposed to the development of atrial fibrillation by creating the substrate for reentry. The spatial dispersion of repolarization developed as a consequence of the greater abbreviation of the action potential of the pectinate muscle as compared to the

cristae terminalis. This heterogeneous action of the I_{Kr} agonist created a voltage gradient at the level of the action potential plateau, giving rise to a depression in the pseudo-ECG. This depression is expected to cause a PQ depression in the body surface ECG [11].

PQD is also seen up to 24% in control group (mostly due to PQD in lead II). One of the possible explanation for this phenomenon in healthy subjects might be simply the augmentation of the atrial T wave in some patients (as it is more prominent and prevalent in lead II). Another plausible explanation could be the increased spatial dispersion in atria in otherwise healthy subjects as in SQTS patients. However, the exact mechanism for PQD in healthy subject, as well as the clinical implications of PQD in healthy subjects (whether PQD is a predictor for atrial arrhtyhmias or other clinical events in the future) remains unknown and requires further studies.

In previous studies, PQD was shown to be a prognostic indicator of atrial fibrillation and poor outcome in several clinical situations[17, 44-47]. In accordance with previous studies, we found that patients with atrial arrhythmias had significantly more pronounced PQ depression in inferior leads, supporting the proposed mechanism of heterogeneous abbreviation of action potentials and consequent spatial repolarization dispersion and voltage gradient presenting as PQD and increased risk of arrhythmias in SQTS.

PQD has also been shown to occur rarely during the left upper pulmonary vein ablation or atrial tumors [18, 19]. In acute pericarditis, likewise, PQD is presented in

about 80% of the patients and it also occurs earlier than ST elevation in course[12] [48]. Proposed mechanism of PQD in these settings is the transient increase in the magnitude (without change in direction) of the atrial repolarization vector due to injury currents [12, 18]. In acute pericarditis, ST elevation and PQD share the same mechanism, which is the injury current due to epimyocarditis. Ventricular epimyocarditis manifests as ST elevation and atrial epimyocarditis manifests as PQD. As in acute pericarditis, PQD is present in 81% of SQTS patients, and more prevalent and prominent in inferior and anterior leads consistent with the direction of the atrial repolarization vector.

Limitations:

Our study has several limitations. The lack of control group consisted of subjects with borderline QT intervals is one of the limitations in the present study. Nevertheless, healthy subjects with borderline QT-interval are extreme rare to constitute a control group and the question whether these subjects are so far asymptomatic SQTS patients or healthy subject with QT interval in very lower physiological border, would remain unanswered. Therefore, we included age- and sex-matched subjects with normal QT intervals without any structural heart disease or channelopathy as a control group to compare the presence and frequency of PQD in healthy subjects with SQTS patients.

Measurement related issues are the other limitations of our study. Tachycardia or drifting baselines may interfere with measurement of the PQD, and also the risks related to manual measurements could not be totally excluded.

Another limitation of the present study is the predefined cut-off value of 0.5 mm. This value was chosen according to previous studies[20, 21, 44-46]. However, this cut-off value was used for definition of PQD in pericarditis or atrial infarction and might not be appropriate to assess the PQD in STQS.

Conclusion:

In this study, we showed a significantly high prevalence (81% of patients) of PQD in SQTS. The association between the degree of PQD in inferior leads and atrial arrhythmias suggests that an augmented TDR and resulting currents in atria may be the operative mechanism. This frequent ECG pattern in SQTS reflecting augmented atrial TDR may constitute a novel marker for SQTS in addition to a short QT interval.

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Tables and Figures:

Table 1. Patients and controls demographical, clinical, genetic and basal ECG data.

Table 2. QTc-intervals in SQTS patients with and without PQD according to leads

Table 3. QT intervals and clinical events in SQTS patients with PQD in at least one lead and without any PQD

Figure Legends

Figure 1. Measurement of PQ-segment depression with (A) and without (B) clear-cut TP segment (without clear-cut TP segment the vertical distance from the beginning of P wave to the dip of PR segment was measured)

Figure 2. Twelve-Lead electrocardiogram of a patient with a short QT syndrome showing PQ depression (small arrows indicating PQD in leads II, aVF, V3-4).

Figure 3. Distribution of PQD in relation to ECG leads (Values are n (%); PQD is presented in red sections; values under diagrams are median value and interquartile range for PQD in each lead)

Tables:

Table 1. Patients and controls demographical, clinical, genetic and basal ECG data.

	Patients (n=64)	**Controls (n=117)**	**P-value**
Age in years (Median, IQR)	30 (IQR: 21)	36 (IQR: 38)	0.28
Male sex, n (%)	48 (75%)	72 (62%)	0.07
Baseline Heart Rate (mean ± SD)	79±21	72±14	**0.02**
Cardiac arrest, n (%)	18 (28%)	-	
Syncope, n (%)	5 (8%)	-	
Atrial fibrillation/Flutter, n (%)	9 (14%)	-	
ECG Intervals, ms			
QTc (II) (mean ± SD)	320.9 ± 29.4	414.2± 27.7	**0.0001**
Genetic Screening, n (%)	46 (72%)	-	
KCNH2(HERG) Mutation	13 (20%)		
CACNB2b Mutation	2 (3%)		
PQD in any lead, n (%)	52 (81%)	28 (24%)	**0.0001**

IQR: Interquartile Range; Values are n (%) or mean ± SD

Table 2. QTc-intervals in patients with and without PQD according to leads in SQTS patients

Lead	QTc (II)			QTc (V5)		
(PQD)	**PQD (-)**	**PQD (+)**	***p***	**PQD (-)**	**PQD (+)**	***p***
I	322.3±30.0	320.4±28.2	*0.8*	321.5±29.8	324.1±24.9	*0.7*
II	313.9±28.4	325.1±29.0	*0.1*	314.8±26.0	326.2±28.2	*0.1*
III	318.2±26.6	331.4±34.5	*0.1*	319.2±26.5	332.6±29.9	*0.1*
aVR	320.0±26.9	322.4±33.9	*0.7*	321.7±27.8	322.7±28.6	*0.8*
aVL	321.9±28.2	287.7±57.4	*0.1*	322.5±28.1	306.8±15.2	*0.4*
aVF	317.1±26.6	326.0±32.5	*0.2*	316.8±25.3	329.3±30.0	*0.07*
V1	319.2±31.7	325.0±22.6	*0.4*	322.1±29.3	322.0±24.8	*0.9*
V2	324.3±28.2	315.5±30.8	*0.2*	323.7±26.1	319.4±30.8	*0.5*
V3	322.9±29.1	317.3±29.5	*0.4*	322.2±26.1	320.5±29.6	*0.8*
V4	324.6±29.9	316.8±27.7	*0.3*	324.0±26.5	320.3±30.0	*0.6*
V5	322.6±28.7	316.6±31.0	*0.4*	321.7±25.7	322.4±32.8	*0.9*
V6	322.4±27.9	325.4±33.7	*0.5*	320.3±25.9	330.3±33.6	*0.2*

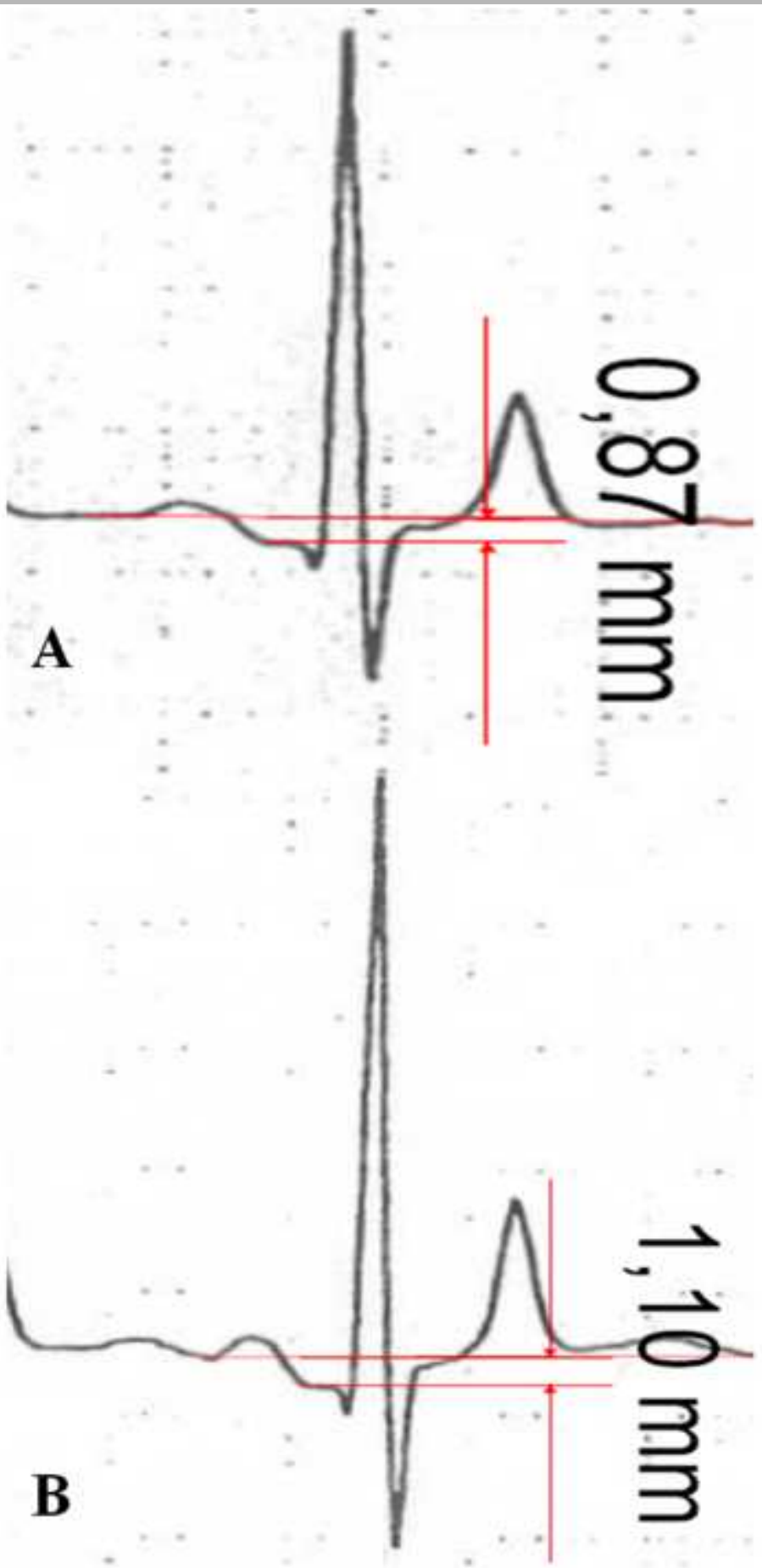
Values are mean ± SD

Table 3. QT intervals and clinical events in SQTS patients with PQD in at least one lead and without any PQD

Variable	PQD (+) in at least one lead (n=52)	PQD (-) (n=12)	P value
Male/ Female gender	37 (71%)/15(29%)	11(92%)/1(8%)	0.2
Age, year	36±17	38±24	0.6
QTc (II), ms	321.1±30.8	319.6±22.7	0.8
QTc (V5), ms	323.4±28.5	315.9±25.0	0.4
Cardiac arrest	17 (32%)	1 (8%)	0.08
Syncope	5 (9%)	0	--
Atrial fibrillation/flutter	9 (17%)	0	--

Values are n (%) or mean ± SD

Figure 1



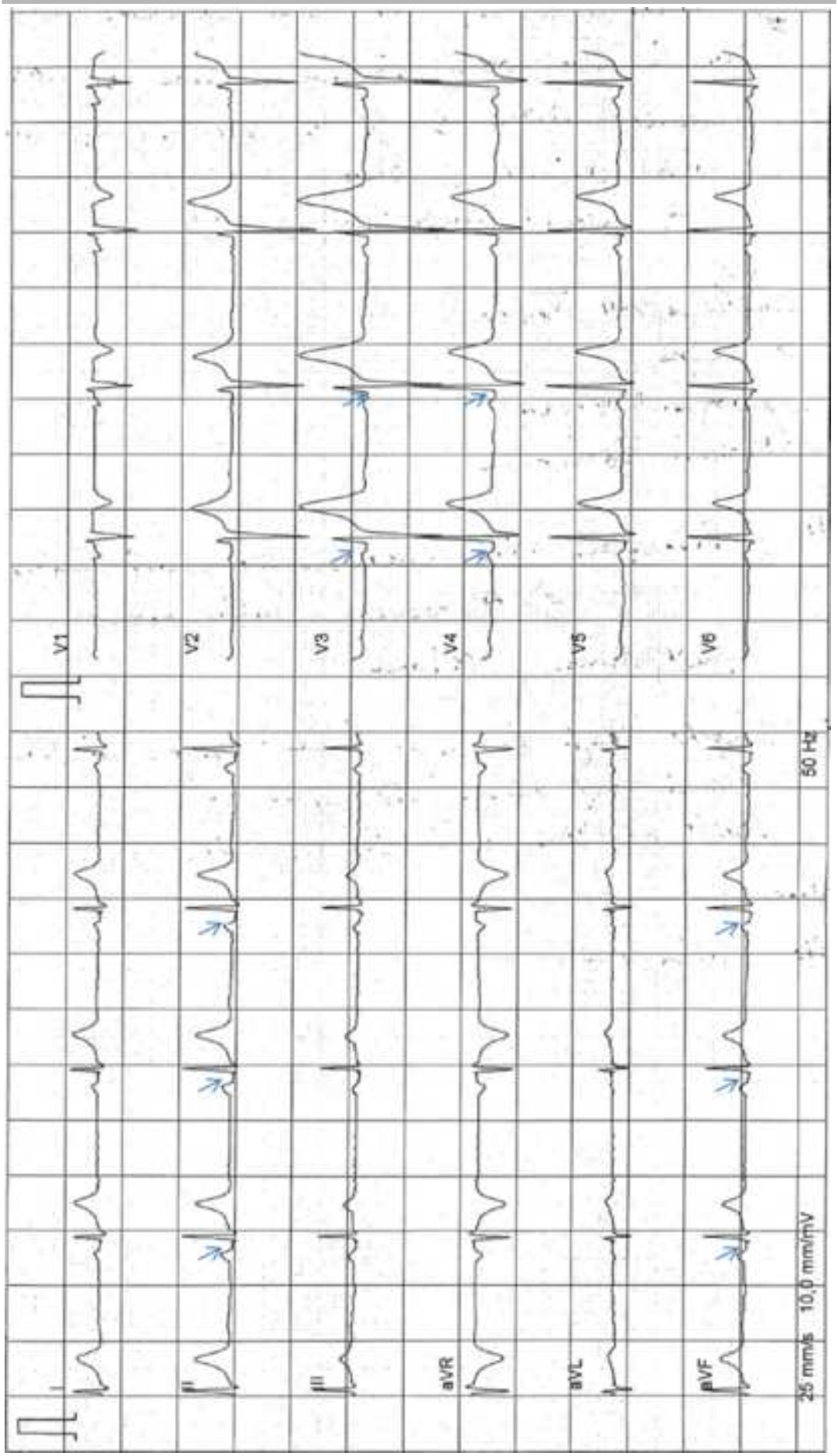


Figure 2

Figure 3