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Short QT diagnosis and follow up

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Short QT syndrome

Introduction

Congenital short QT syndrome (SQTS) is an hereditary, congenital, familial or sporadic orphan channelopathy, which is part of the so-called ion channel defects or channelopathies with dominant autosomal or sporadic and, genetically heterogeneous both from the genotypic and phenotypic point of view, which affects the electric system of the heart, and where the hallmark of the disease is a very short QT/QTc interval on the electrocardiogram in potassium genetic forms and relatively short QT/QTc in calcium forms. A universally accepted diagnostic cutoff value of a short QT interval has not been defined (QTc interval ≤ 340–360 ms?). Characteristically, the heart rate is not significantly modified with heart rate changes, and sometimes the T waves have great voltage, narrow base, which resemble T wave in "desert tent" of mild hyperkalemia. The entity is clinically characterized by a large set of signs and symptoms, such as syncope, sudden cardiac death and palpitations dizziness and high tendency to appearance of episodes of paroxysmal runs of atrial fibrillation.

From the structural point of view, the heart is normal and electrophysiologically, there is significant shortening of refractory periods of atria and ventricles, being inducible (sustained VF) by programmed stimulation. A few families have been identified, with several types existing: to date mutations in eight genes have been reported to associate with SQTS: **HERG or KCNH2 (SQT1), KCNQ1 (SQT2), KCNJ2 (SQT3), CACNA1C (SQT4), CACNB2b (SQT5)** ***CACNA2D1*** **(SQT6), SCN5A(SQT7) and SLC4A3 (SQT8)** based on the chronology of their discovery.

The main features of congenital SQTS are:

- *Absence of structural heart disease*
- *Familial clinical-electrocardiographic entity*
- *Autosomal dominant inheritance or sporadic, and genetically heterogeneous*
- *Constant and uniform very short QT and QTc intervals (QTc interval ≤3340 ms)*
- *Positive family history for sudden cardiac death (SCD)*
- *Manifested by syncope, sudden death, dizziness and high tendency to appearance of episodes of paroxysmal runs of atrial fibrillation (AF)*
- *The response to exercise testing is a slight reduction of the QT interval during the increase in heart rate.*
- *Short refractory periods and tendency for inducible AF and VF were seen in electrophysiology studies (EPSs).*
- *Autopsy did not reveal any structural heart disease*

Electrocardiographic and electrophysiological features

The study of ECG abnormalities in channelopathies showed characteristic phenotypic traits, which in combination with information derived from molecular genetics, have allowed using the ECG as a prognostic tool as well as a diagnostic test. The assessment of genotype-phenotype correlations in inherited arrhythmogenic diseases has allowed to advance the idea of the ECG as an inheritable trait. Such heritable quantitative traits are potentially related to the risk of sudden death in the general population, which is known to have a familial predisposition.

Lower boundaries of the QT interval in the normal population, and successive cutoffs used to define a short QT

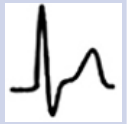
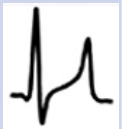
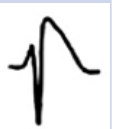
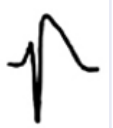
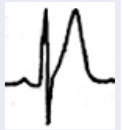
Author	QT interval	QT_C interval
Lower normal limit of the QT interval		
Moss 1993, Luo S 1994	330 ms (children 310 ms)	360-380 ms
Vincent 1992		360 ms (M) – 370 ms (F)
Definition of "short QT"		
Gussak 2000, Gaita 2003	< 300 ms	< 300 ms
Schimpf 2005	< 320 ms	< 320 ms
Giustetto 2006		≤340 ms
Campuzano 2018 and International guidelines		≤340 ms

Gollob score system - QTc in milliseconds	Score
< 370	1
< 350	2
< 330	3
J point – T peak interval	
< 120	1
Clinical history	
Sudden cardiac arrest	2
Polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history	
1st or 2nd degree relative with SQTS	2
1st or 2nd degree relative with sudden death	1
Sudden infant death syndrome	1
Genotype	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

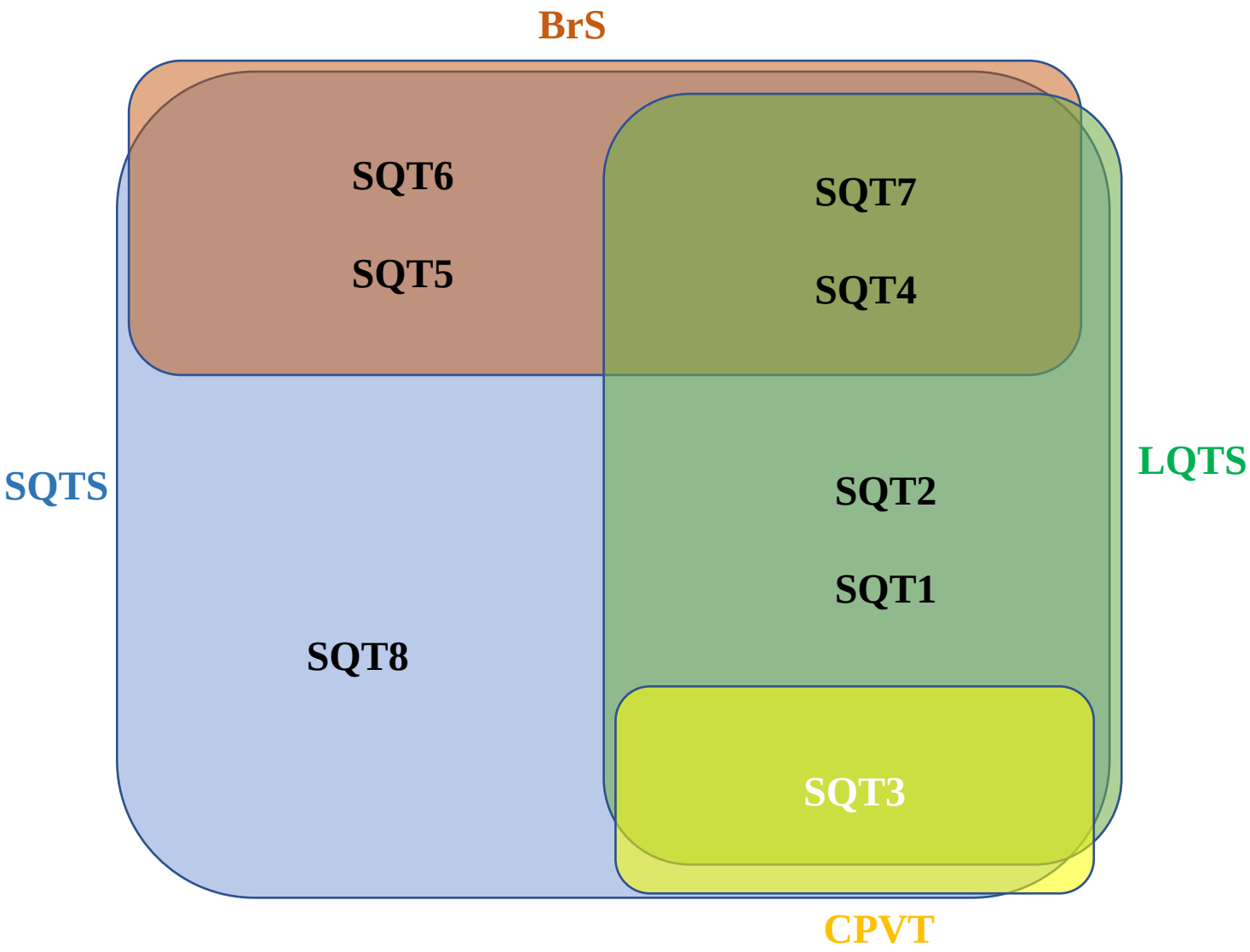
Interpretation: High-probability: ≥ 4 points; Intermediate probability: 3 points; Low probability: ≤ 2 points.

Difference of T waves morphologies in the potassium congenital SQTS variants

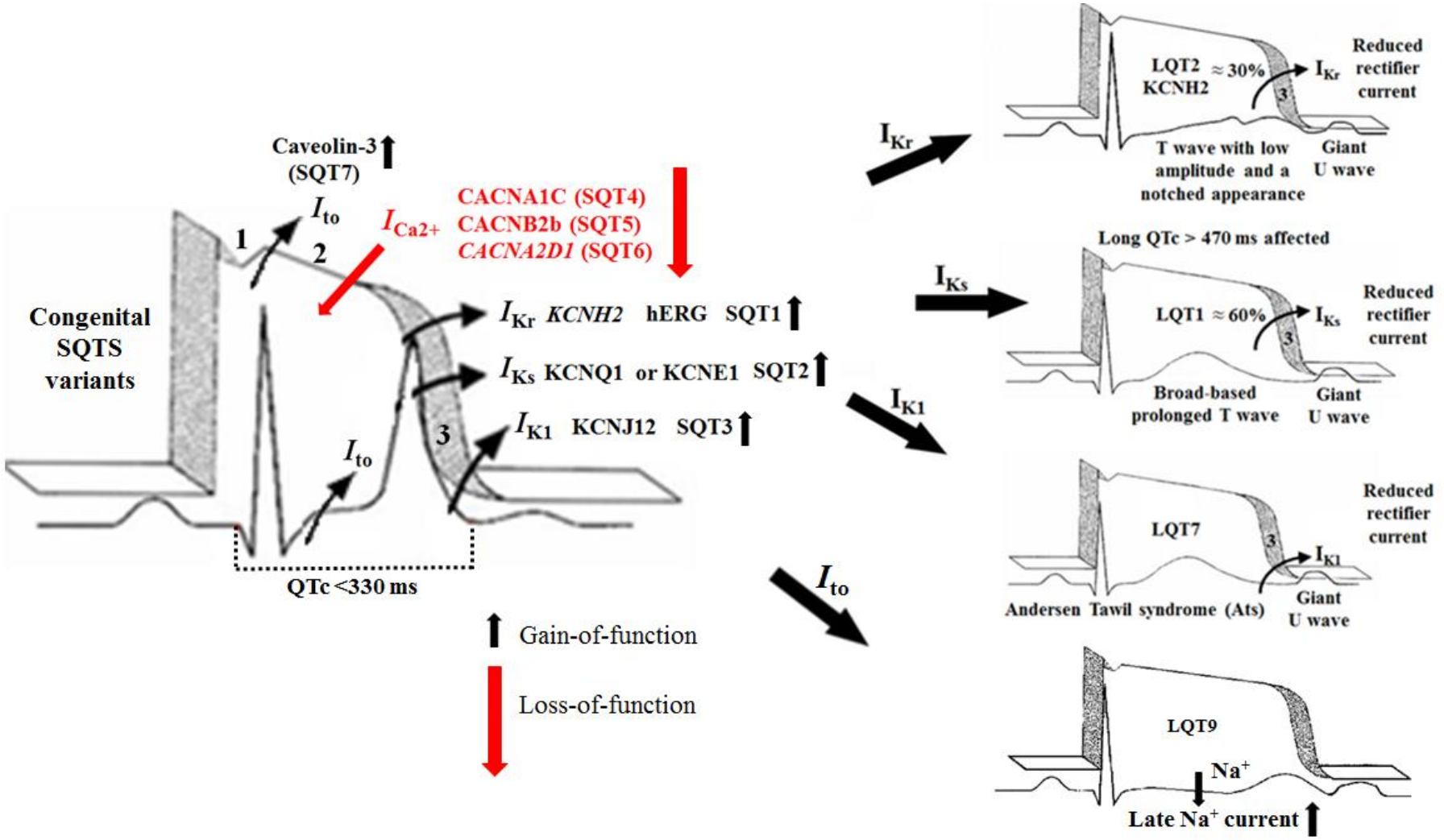
SQT1: The T waves in the precordial leads appear often tall, narrow and symmetrical, with a relatively prolonged Tpeak-Tend interval. The proposed diagnostic scoring scheme that has been put forward by Gollob et al,142 has not been accepted unanimously.143,144 In analogy to the Schwartz score for the LQTS the score uses a number of clinical criteria with a gradual score for the QTc interval and a significant role for clinical and genetic criteria.

Gene	Channel	Protein	Phenotype	Author/Year
KCNQ1 SQT1	I_{ks}	K^+ voltage-gated channel subfamily Q member 1 (Kv7.1 or Kv1.9). OMIM: #609620. Locus: 7q36.1	SQTS (270 ms) 	Brugada R et al. Circulation. 2004 Jan 6;109(1):30-5
KCNH2 SQT2	I_{kr}	K^+ voltage-gated channel subfamily H member 2 (hERG or Kv11.1). OMIM: #609621. Locus: 11p15.5-p15.4	SQTS (290 ms) 	Bellocq C, et al. Circulation. 2004;109:2394
KCNJ2 SQT3	I_{k1}	K^+ voltage-gated channel subfamily J member 2 (Kv2.1 or Kir2.1). OMIM: #609622. Locus: 17q23	SQTS (317 ms) 	Priori SG et al. Circ Res. 2005 Apr 15;96(7):800-7
CACNA2D1 SQT4	I_{CaL}	Ca^{2+} voltage-gated channel auxiliary subunit α2/δ1. OMIM: #600919. Locus: 11q23-q24	BrS + SQT Interval (350 ms) 	Antzelevitch C et al. Circulation 2007;115:442
CACNA1C SQT5	I_{CaL}	Ca^{2+} voltage-gated channel subunit Alpha1 C (Cav1.2). OMIM: #600003. Locus: 10p12.33-p12.31	BrS + SQT Interval (353 ms) 	Antzelevitch C et al. Circulation 2007;115:442
CACNB2C SQT6	I_{CaL}	Ca^{2+} voltage-gated channel auxiliary subunit Beta 2 (CavB2). OMIM: # 114204. Locus: 7q21.11	BrS + SQT Interval (329 ms) 	Templin C et al. Eur Heart J. 2011;32(9):1077-88
SCN5A SQT7	I_{Na}	Na^+ channel voltage-gated type V α subunit (Nav1.5)	BrS + SQT Interval 	Refsgaard L et al. Eur J Hum Genet. 2012;20:905–8
SLC4A3 SQT8	Cl^- / $HCO3^-$	Solute carrier family 4 member 3	SQTS (400 ms) 	Thorsen K et al. Nat Commun. 2017;8:1696

Overlapping phenotype in short QT syndrome



LQTS, long QT syndrome; BrS, Brugada Syndrome; CPVT, Catecholaminergic Polymorphic Ventricular Tachycardia



The figure shows the representation of monophasic action potentials and ECGs of the four congenital SQTS potassium channels variants and their respective counterpart LQTS variants (mirror image):

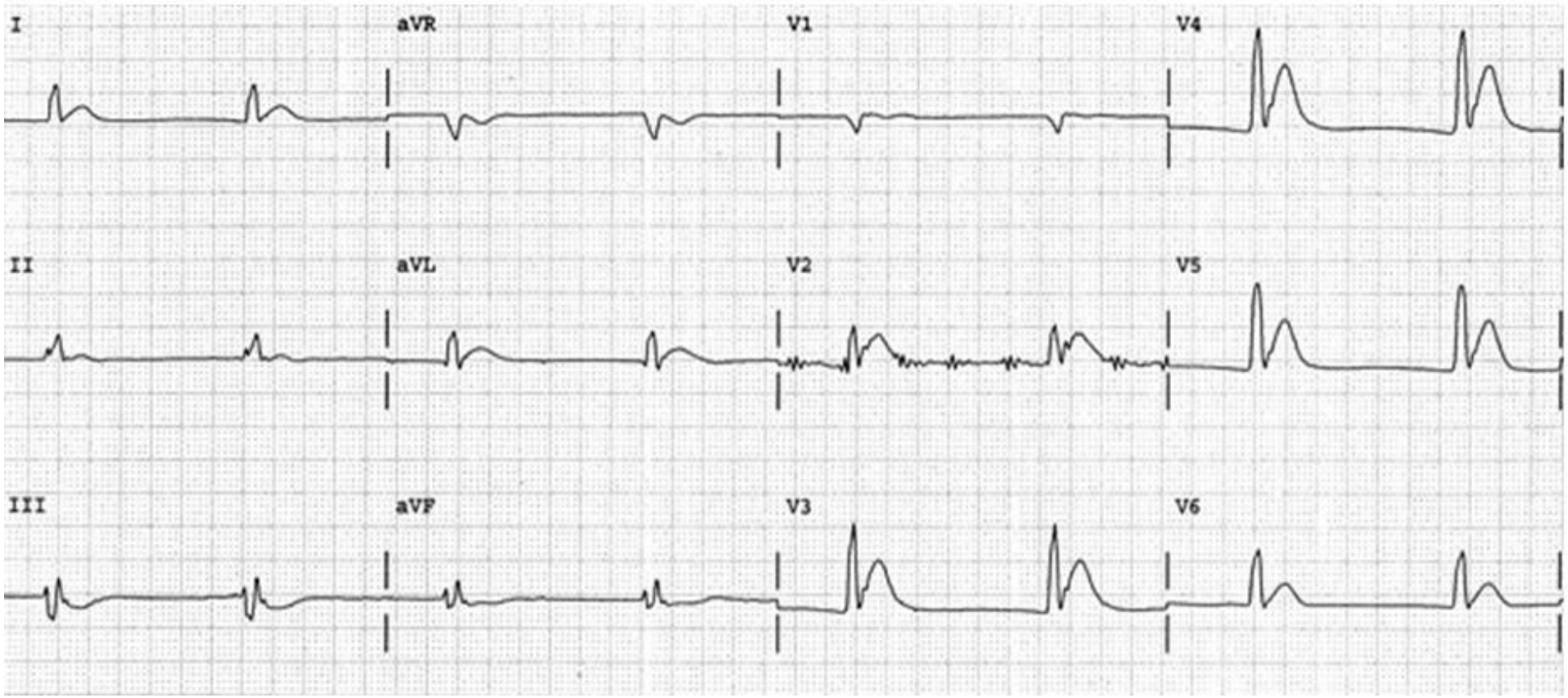
- Congenital SQT1: I_{Kr}: LQT2
- Congenital SQT2: I_{Ks}: LQT1
- Congenital SQT3: I_{K1} LQT7 or Andersen-Tawil Syndrome
- Congenital SQT7: I_{to} LQT9 Caviolin-3

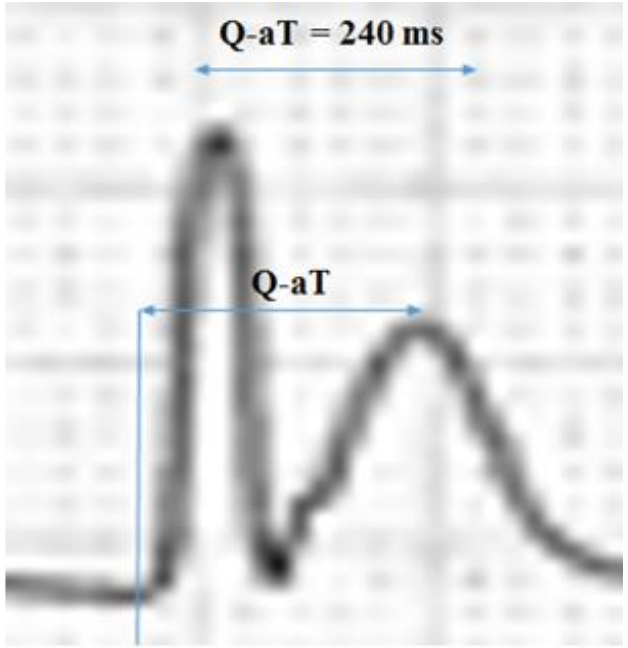
And the three calcium channel variants: CACNA1C (SQT4), CACNB2b (SQT5), and *CACNA2D1* (SQT6).

Acquired and other genetic causes of short QT/QTc interval

Hyperkalemia (mild elevations of K^+<6.5 mEq/L), consequence of narrow-based, peaked T waves. T waves with short duration, ≈150 to 250 msec.
Hypercalcemia
Hyperthermia
Acidosis
Effect of catecholamines
Toxicity and digitalis effect. PR prolongation is a commonly present. Additionally, characteristic sagging, “coved,” or “scooped” appearance of the asymmetric and downsloping ST depression, which resembles a reversed check mark.
Autonomic tone alterations
In response to atropine
Dysautonomia of Chronic Fatigue Syndrome with QTc mean values of 371 a 384 ms.
Selective K^+_{ATP} channel activation.* ATP-dependent potassium channel openers such as pinacidil and levcromakalim have long been known to shorten action potential duration and to be profibrillatory in non-clinical models.
Activation of K_{Ach} caused by strong parasympathetic stimuli to the heart.
Klinefelter syndrome (KS). It is a sex chromosomal aneuploidy (47,XXY) affecting 1/660 males. QTc was shortest among testosterone treated males with KS, while untreated and thus hypogonadal KS had QTc interval comparable to controls.
Rufinamide, a recently approved anticonvulsant, illustrates the current regulatory approach to drugs that shorten QT interval.

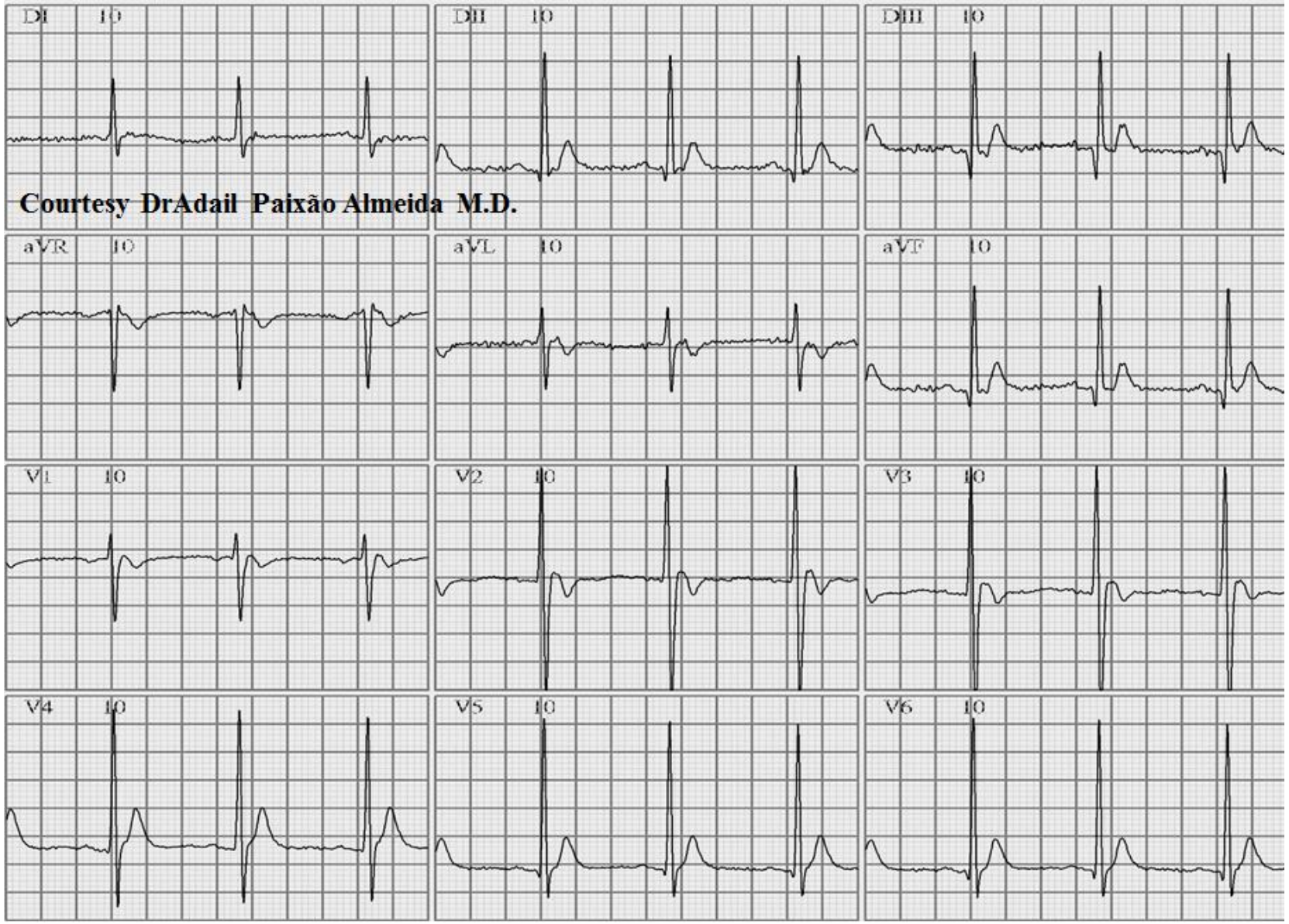
For the diagnosis of SQTS, especially with borderline shortened QT intervals, acquired causes of short QT interval should be excluded.





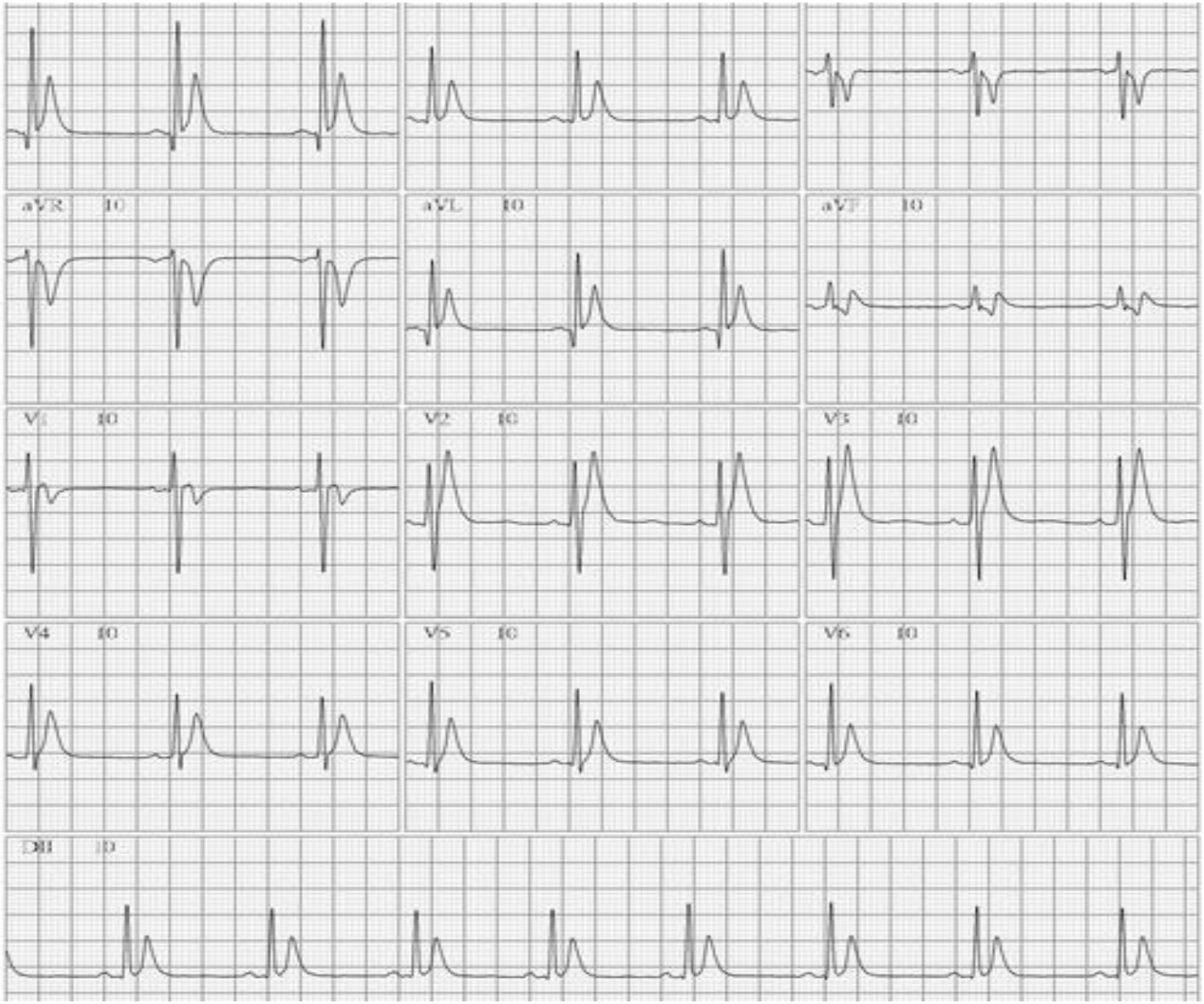
12-lead ECG of a patient with severe hypercalcemia showing marked shortening of the QT interval (QTc =260ms) and Q-aT values < 270 ms (Pfeiffer 2007).

Name: VTC; **Gender**: M; **Ethnic group**: Caucasian; **Age**: 44 y/o (from Bahia/ Brazil, February 12/1968);**Weight**: 84 Kg; **Height**: 1.79 m; **Date**: April 19/2012; **Drugs in use**: None. This is the ECG of the proband, index case or propositus.



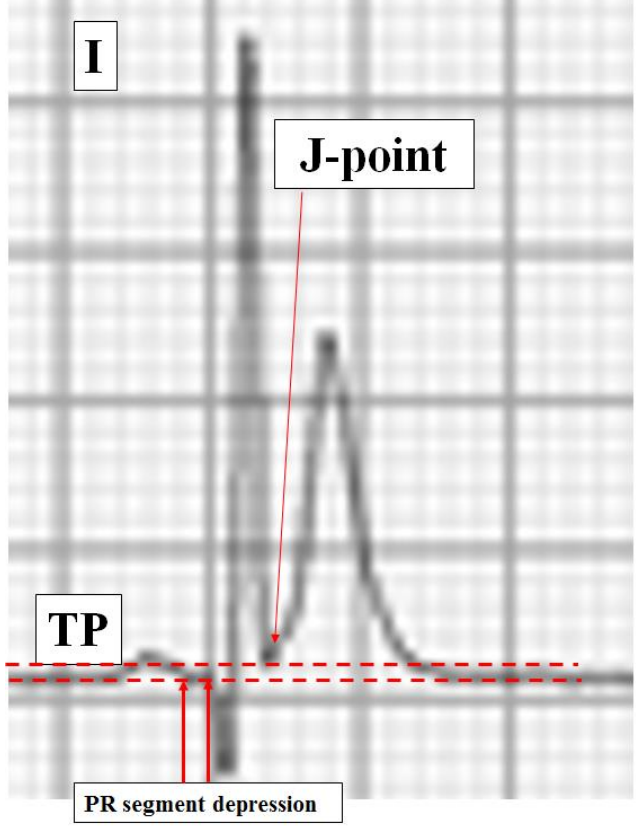
ECG diagnosis: sinus rhythm, heart rate (HR) = 83 bpm; SÂP + 60º, PR interval duration: 120 ms, QRS duration: 60 ms. SÂQRS: +65º and to the left, ST segment with minimal duration, SÂT +63º and backward. QT = 220 ms; QTc = 353 ms (proband)

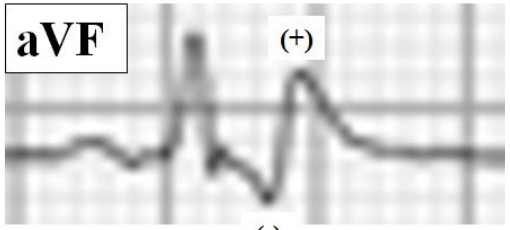
Name: MTC; **Sex**: F; **Age**: 54 y/o; **Date**: March 20, 2014; **Ethnic group**: Caucasian. ECG of one sister of the proband.



Clinical diagnosis: Congenital short QT syndrome with mutation in Caveolin-3 (SQT7).

ECG diagnosis: Sinus rhythm, HR = 68 bpm; P wave: ; SÂP + 32º, PR interval duration: 120 ms, PR segment depression (>0.5 mm) in II and V5, absence of ST segment, positive-negative T wave or “minus-plus T wave sign” in aVF, and QT = 280 ms; QTc = 295 ms.





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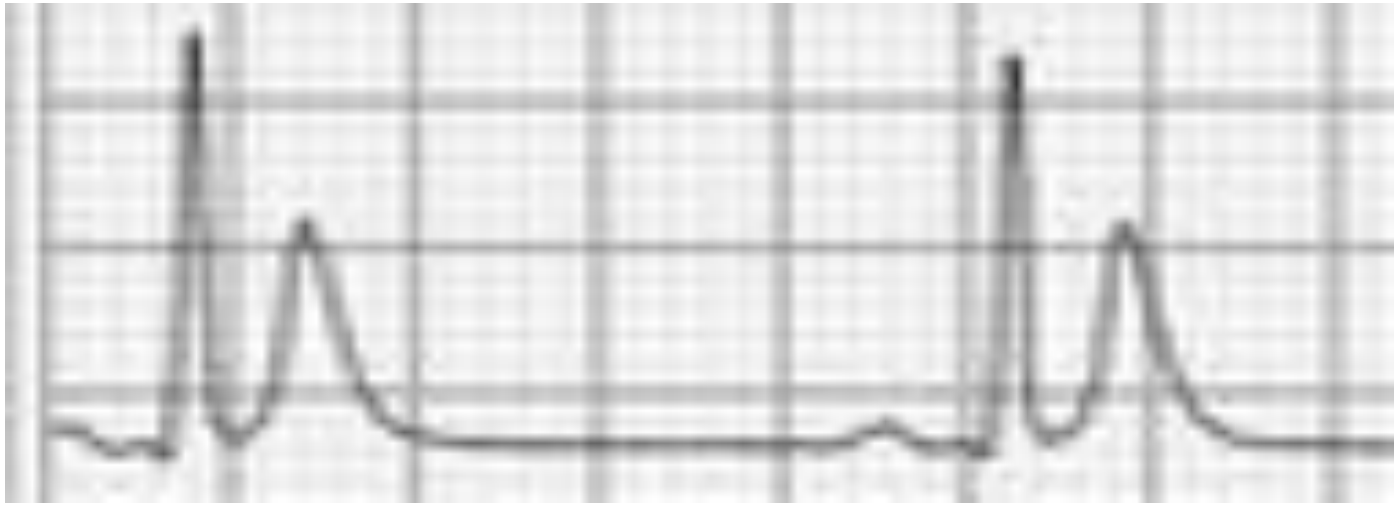
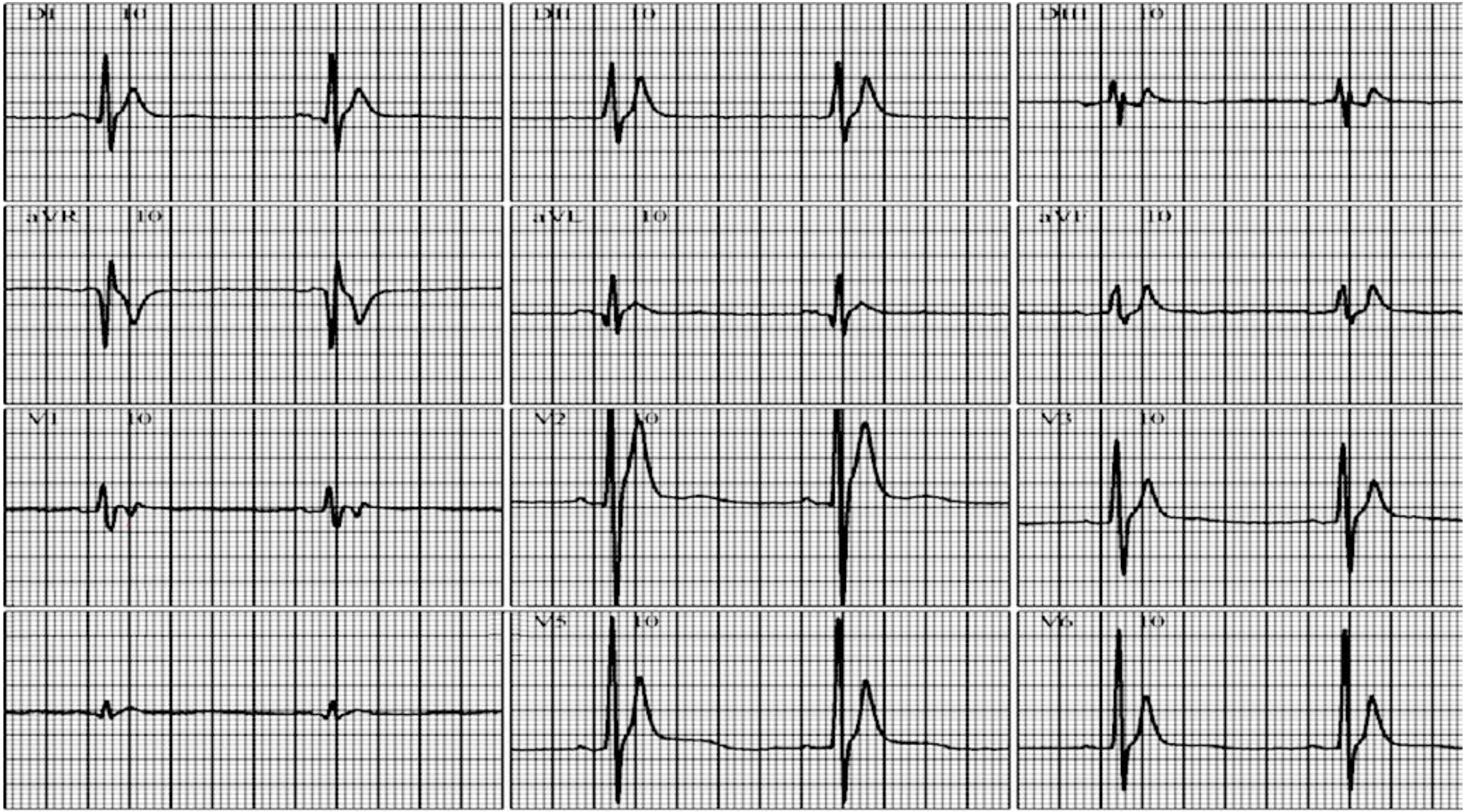
Minus-plus T wave sign



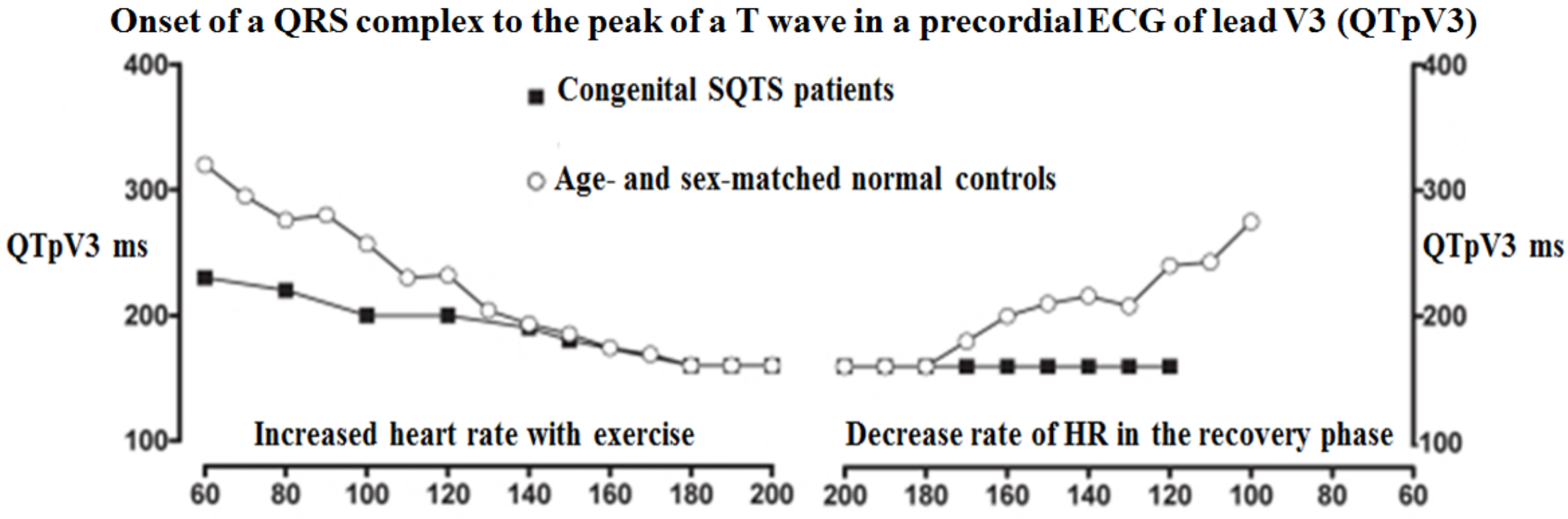
Name: WTC; **Gender**: Male; **Ethnic group**: Caucasian; **Age**: 23 y/o (from Bahia, Brazil, March 21, 1989); **Weight**: 68 Kg; **Height**: 1.72 m; **Date**: April 24/2012; **Drugs in use**: None. It belongs to 23 y/o son of the proband.



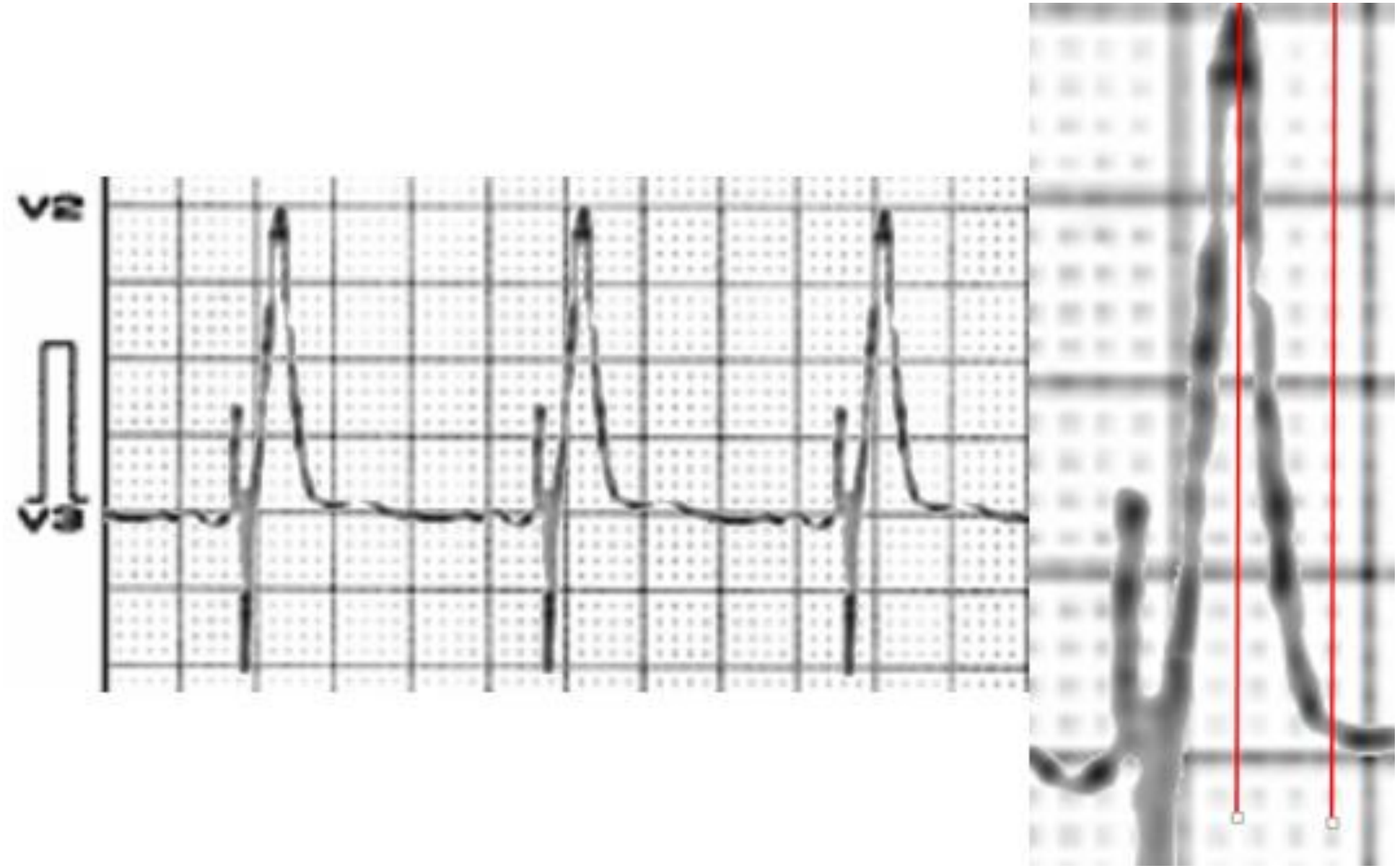
ECG diagnosis: HR = 60 bpm; QT = 280 ms; QTc = 280 ms. We observe a very short QT interval and unlike the father (proband), additionally tall with narrow-based T wave.

Reduced heart rate-adaptation of QT interval during increasing and decelerated heart rates

The QT interval, an index of ventricular repolarization, is heart rate (HR) dependent, in other words the QT interval shortens with exercise. Some of this shortening is due to an increase in HR, and some is due to other effects of exercise, probably mostly neuroendocrine effects. In normal hearts, two-thirds of exercise-induced QT interval shortening are due to an increase in HR, and one-third to other effects. Changes in plasma catecholamine levels on exercise are not closely related to changes in the QT interval on exercise (Davey 1999).
Both exaggerated or lower rate dependence of repolarization are arrhythmogenic. Adaptation of the QT-interval to changes in HR reflects on the body-surface ECG the adaptation of action potential duration (APD) at the cellular level. The initial fast phase of APD adaptation has been shown to modulate the arrhythmia substrate. Whether the slow phase is potentially, proarrhythmic remains unclear.
Patients with congenital SQTS have less variation of the QT interval in relation to the change in HR. Treadmill testing show a lack of adaptation of the QT interval, in congenital SQTS. Relative lack of adaptation of the QT interval (onset of a QRS complex to the peak of a T wave in a precordial ECG of lead V3) (QTpV3) to accelerated HR during exercise and lack of adaptation of the QT interval during decelerated HR in the recovery phase when compared with age- and sex-matched normal controls.

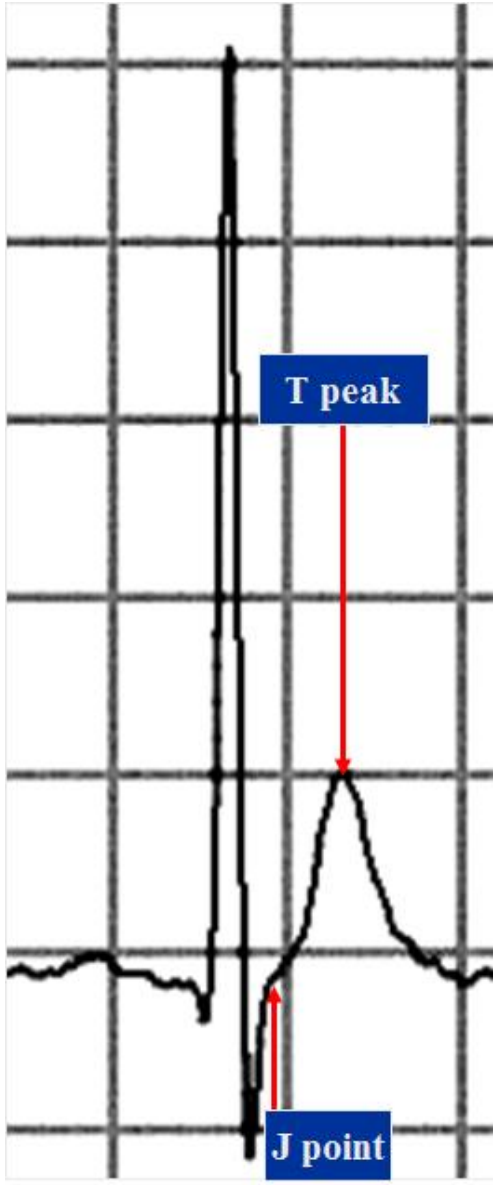


Absent or minimal ST segment: “hypercalcemic-like phenotype”

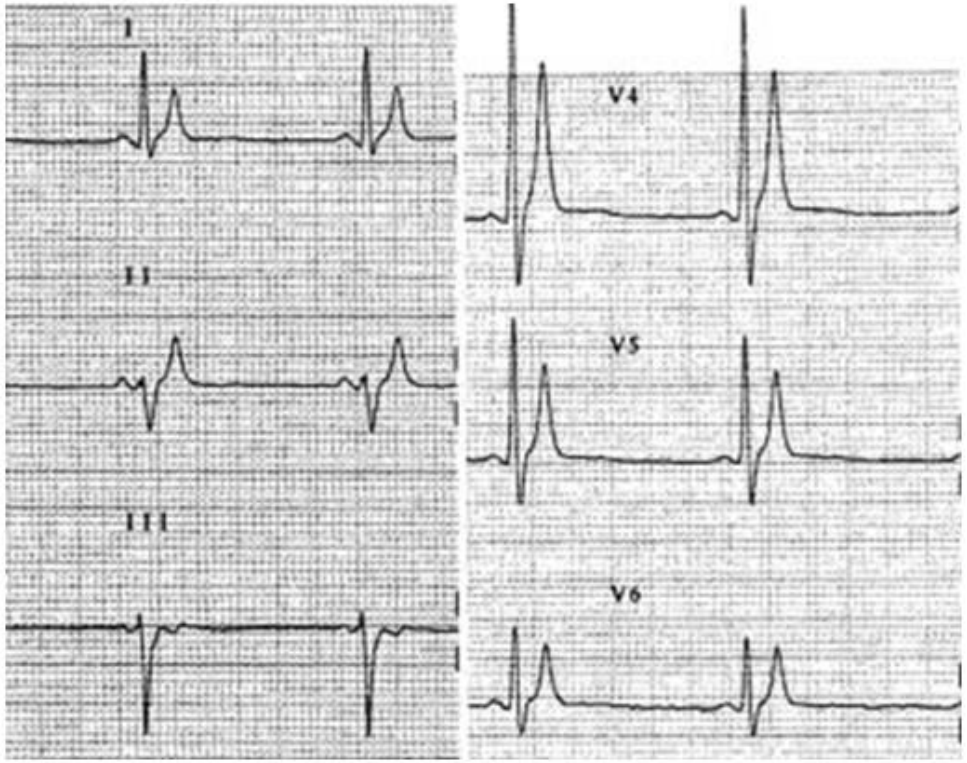


Short J point-T peak interval <120 ms

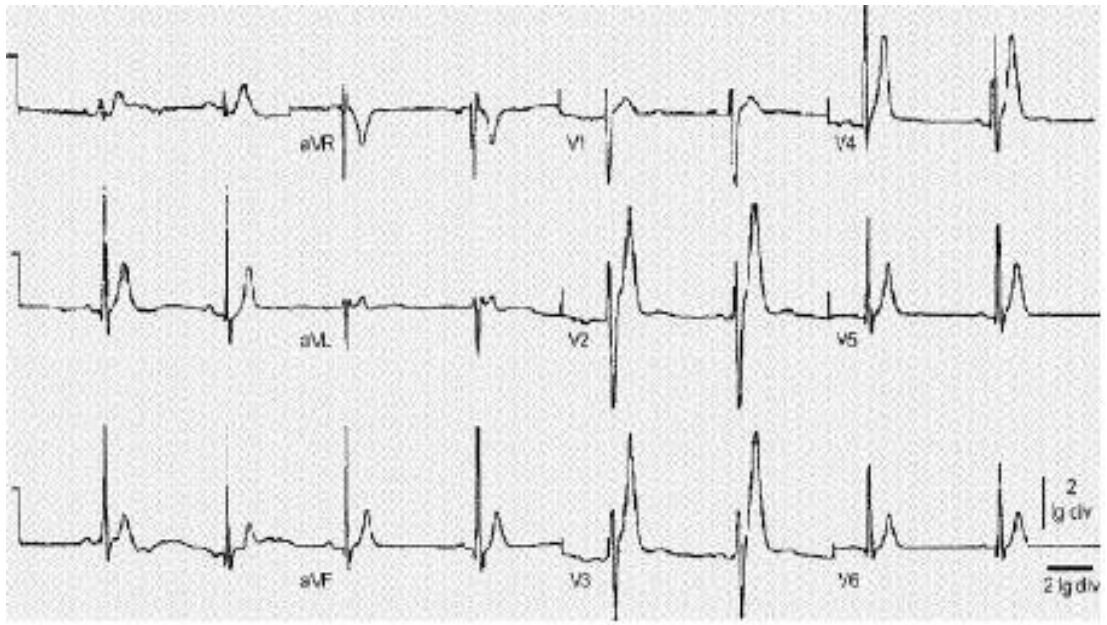
The J point-T peak interval is the distance from the J point to the T peak. Values <120 ms are useful for the diagnosis of congenital SQTS.



J point-T peak interval <120 ms: considered a criteria for diagnosis in the Gollob score; value = 1 point.

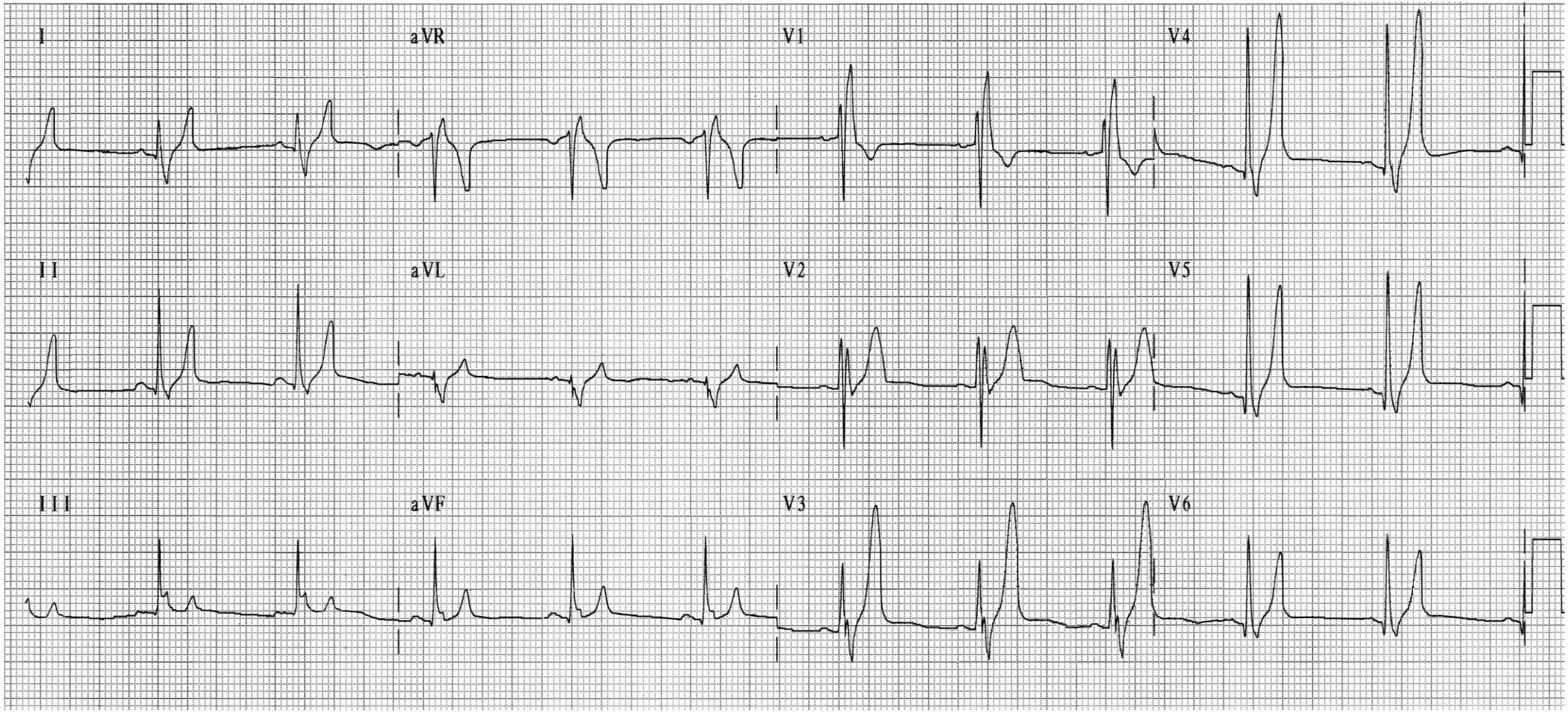


Twelve-lead ECG showing typical SQT1 features: tall, narrow and peaked T waves, QT 280 ms. Reproduced with permission from Gaita.



Electrocardiogram of a patient with short QT syndrome. Check the tall peaked T waves. Reprinted, with permission, from Brugada.

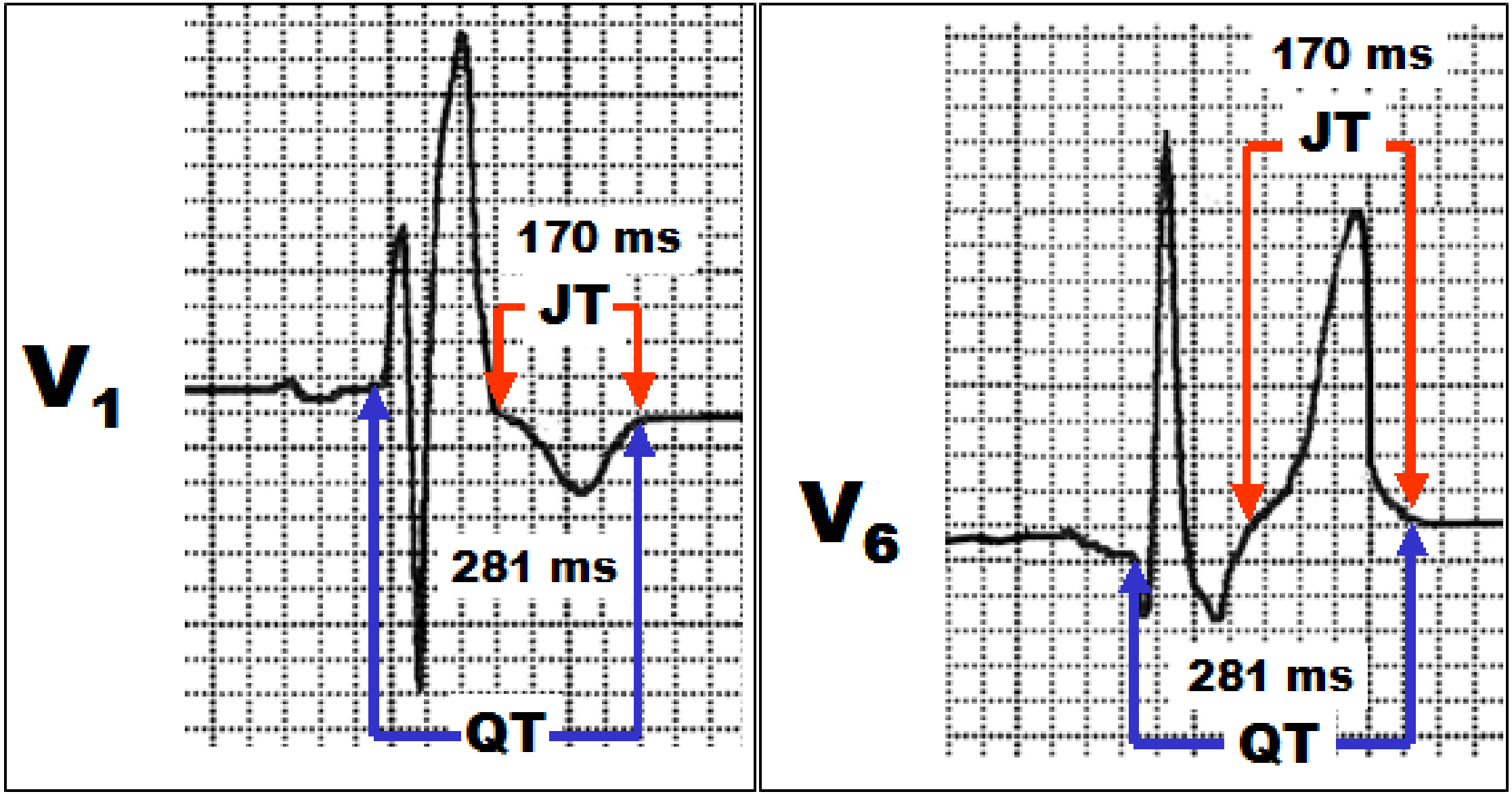
Name: JSVB; **Age**: 27; **Sex**: Male; **Race**: White; **Weight**: 67 Kg; **Height**: 1.72 m; **Date**: 06/24/2004; **Medication in use**: none.



Rhythm: sinus; HR: 65 bpm; P wave: SAP axis: +54º in the FP and to the front in the HP; duration: 80 ms; voltage: 1 mm; PR interval: 134 ms; QRS: SÂQRS: +106º in the FP and to the front in the HP; QRS duration (QRSD): 120 ms; QRS morphology: triphasic rSR' pattern in V1 and broad S wave in left leads I, aVL V5 and V6 (right terminal forces); intrinsic deflection in V1 >50 ms.

T wave morphology: tall T wave from V3 through V5 with narrow base and a tendency to be symmetrical (the patient does not have serum potassium increase); SAT: +42º in the FP and discretely heading to the front and below in the HP; QT/QTc interval: 302/315: short for this rate (the inferior limit for a 67 bpm heart rate in men is 324 ms.

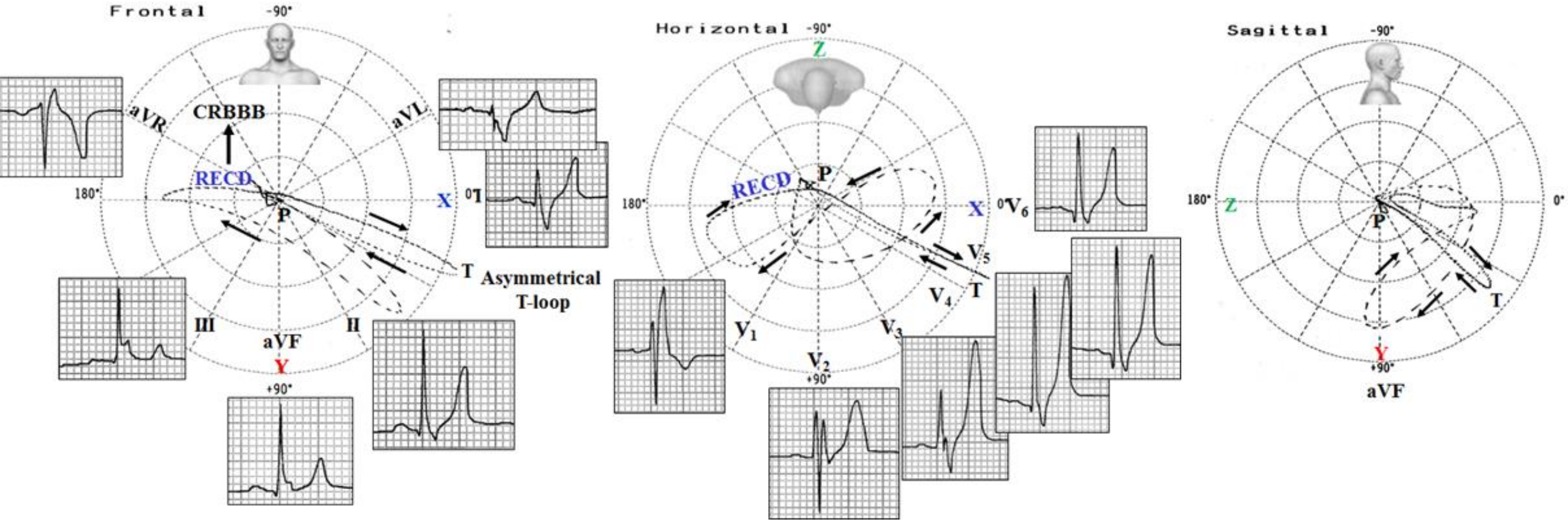
Characteristics of JT and QT intervals in congenital short QT syndrome



JT/JTc interval: 182/199 ms: extremely short (QT-QRSD = JT. 302-120 = 182 ms). (The inferior limit for a 67 bpm heart rate in men is 224 ms).

Conclusion: 1) CRBBB; 2) Increase of QRS duration; 3) Short QT interval with no use of drugs, electrolytic disorders or any associated pathophysiological state; 4) Very short JT interval; 5) Probable early repolarization pattern.

ECG/VCG correlation



FP - QRS loop duration 120 ms. Right End Conduction Delay (RECD) located on the top right quadrant near the aVR lead. Asymmetrical T-loop SÂT +20º.

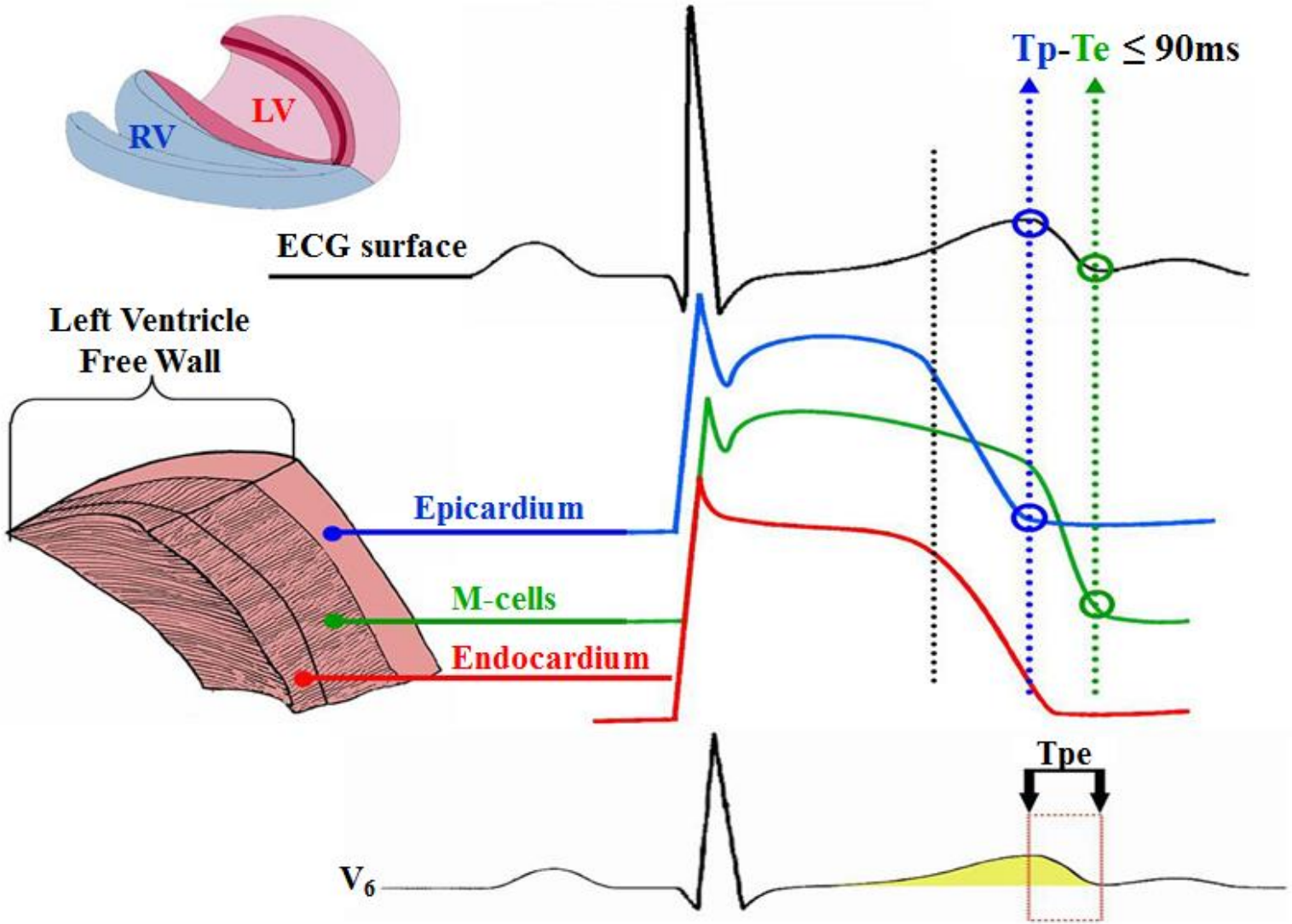
HP – Triphasic QRS pattern in V1-V2 and broad final S-wave in V5-V6: CRBBB. VCG Grishman-type of CRBBB: afferent loop behind the X line; triphasic rSR' pattern; short QT interval; tall T waves with narrow base from V_3 through V_5.

RSP – Asymmetrical T loop heading down and to the front.

Note: The VCG is conclusive that the T wave is not symmetrical because the efferent limb has tears very close to one another; on the other hand, the afferent limb has tears more separated from each other.

VII) Prolongation of T peak/Tend interval (Tpe)

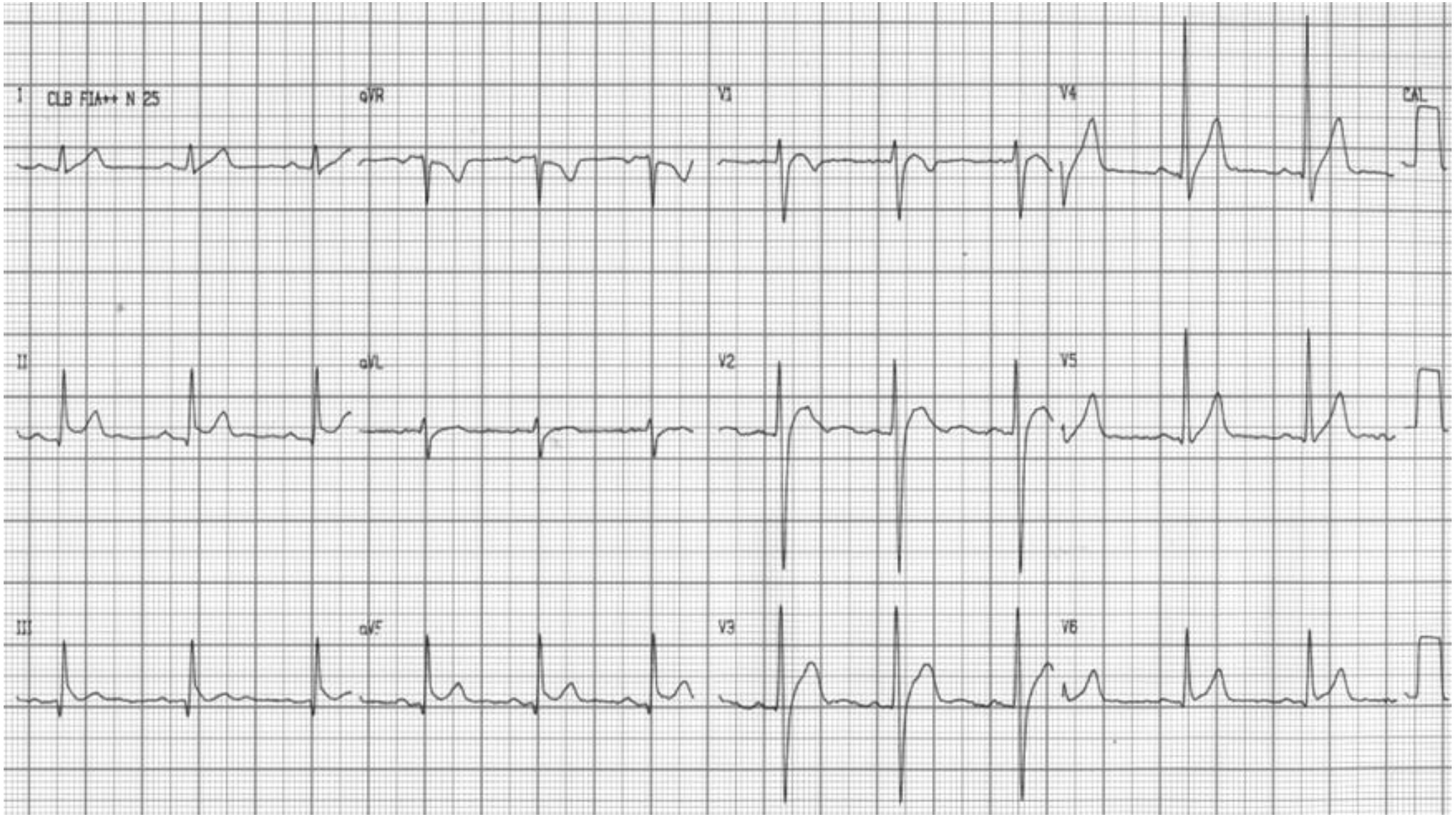
The possible substrate for the development of ventricular tachyarrhythmias may be a significant transmural dispersion of the repolarization due to a heterogeneous abbreviation of the action potential duration. Normally T peak/Tend interval is 94 ms in men and 92 in women when measured in the V5 lead. In SQTS this parameter is prolonged >92 ms in women and >94 ms in men with the measurement in V5. In SQT1 patients the T waves in the precordial leads, appear often tall, narrow and symmetrical, with a relatively prolonged Tpeak-Tend interval.



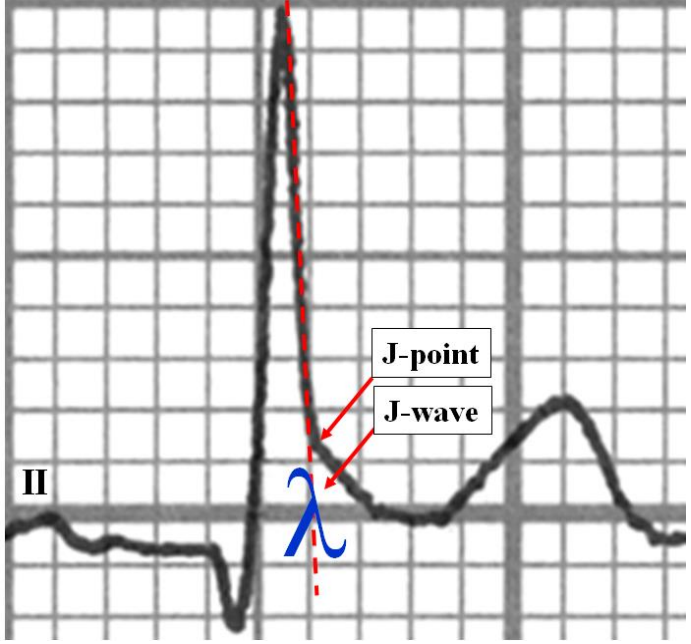
High prevalence of early repolarization. It is associated with arrhythmic events

There is a high prevalence of early repolarization in patients with SQTS. Additionally, early repolarization may be useful in identifying the risk of cardiac events in SQTS.

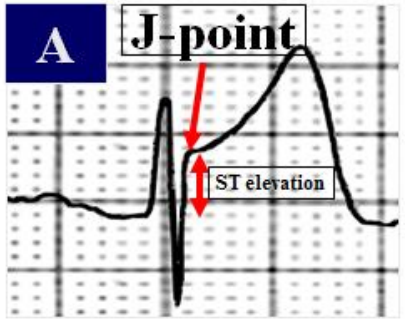
Example of SQTS associated with early repolarization

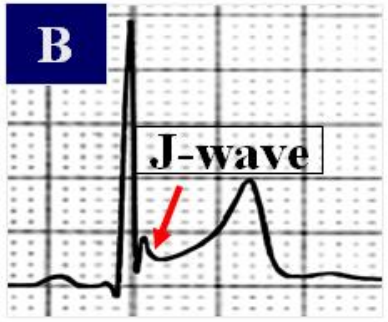


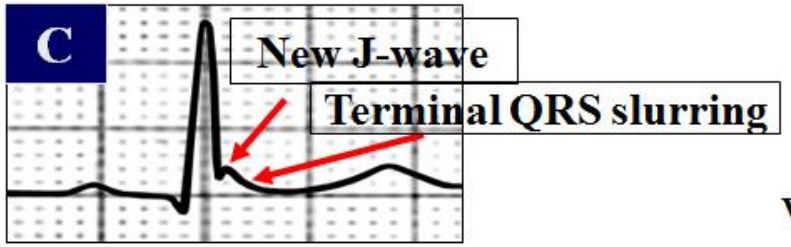
HR = 68 bpm; QT = 340 ms; RR = 880 ms; QTc = 362 ms

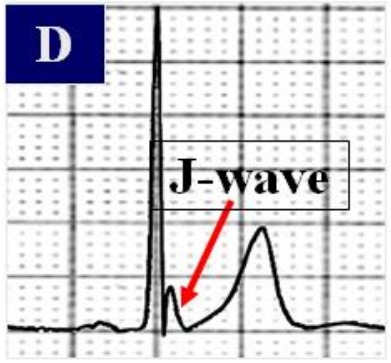


The first point of inflection of the R wave descendent ramp is considered the real J point. In these cases the “tangent line” method is ideal. ST-segment elevation = 0.8 mm. We considered it an atypical C type variant of early repolarization pattern. The lambda aspect is a marker of fatal arrhythmias.









Classic definition of ERP always with ST segment elevation

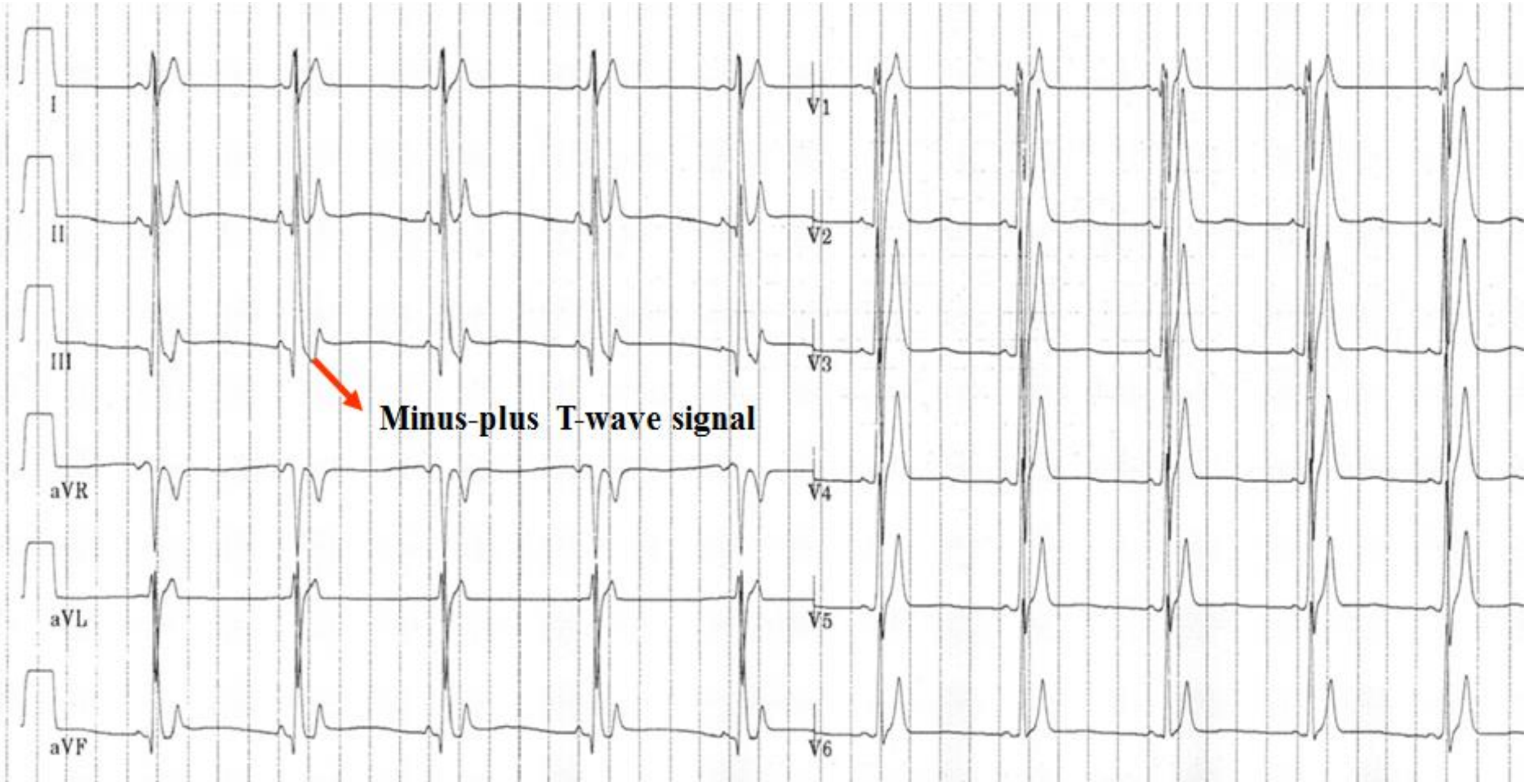
A) ERP with only ST segment elevation

B) ERP with ST segment elevation and J point at the end of J wave.

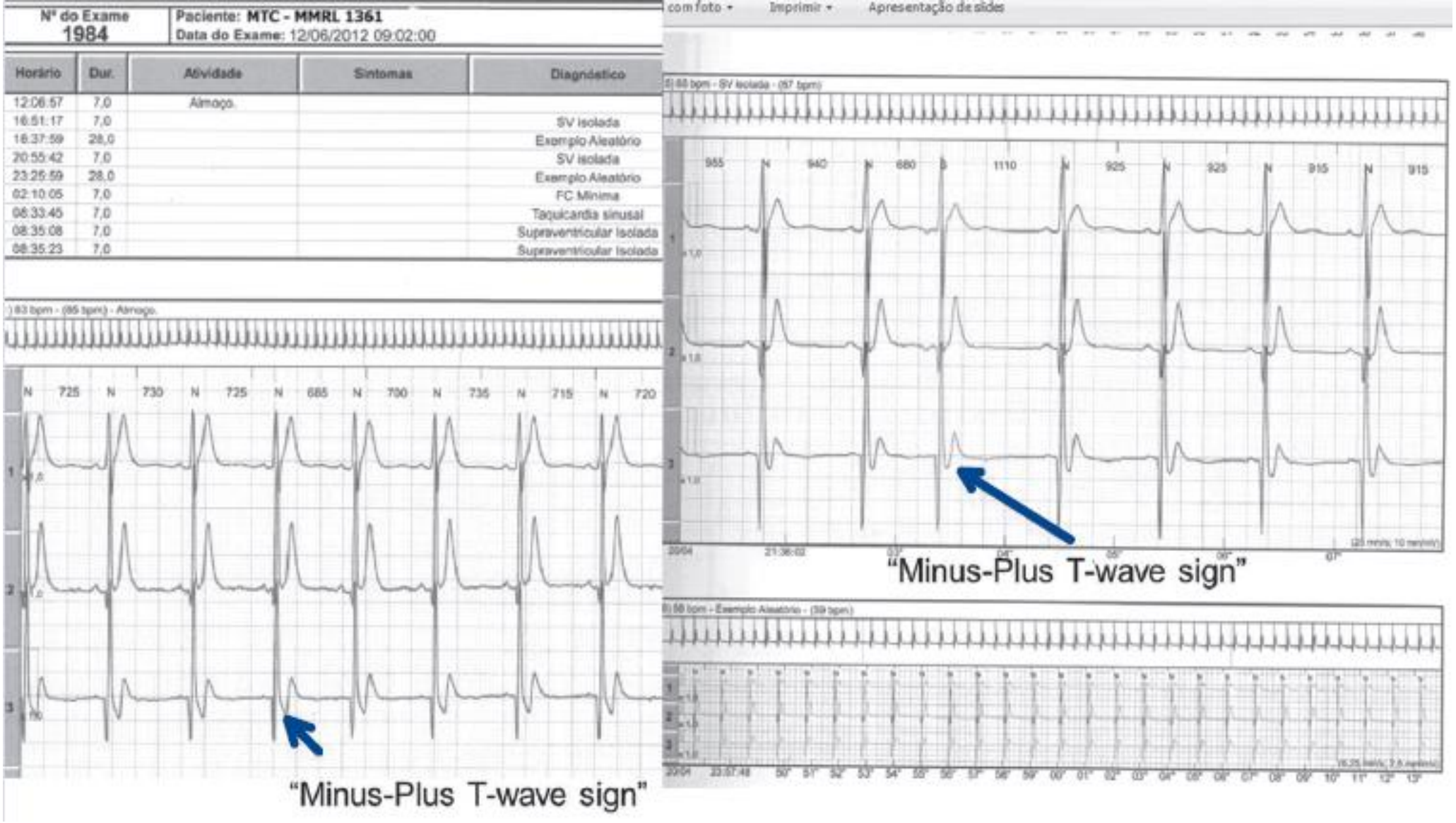
New definition of ERP without ST segment elevation

- J point elevation and terminal QRS slurring without ST segment elevation. The first point of inflection of the R wave descendent ramp is considered the real J point. In these cases the “tangent line” method is ideal.
- J wave without ST segment elevation.

Minus-plus T wave signal (see next ECG and Holter)

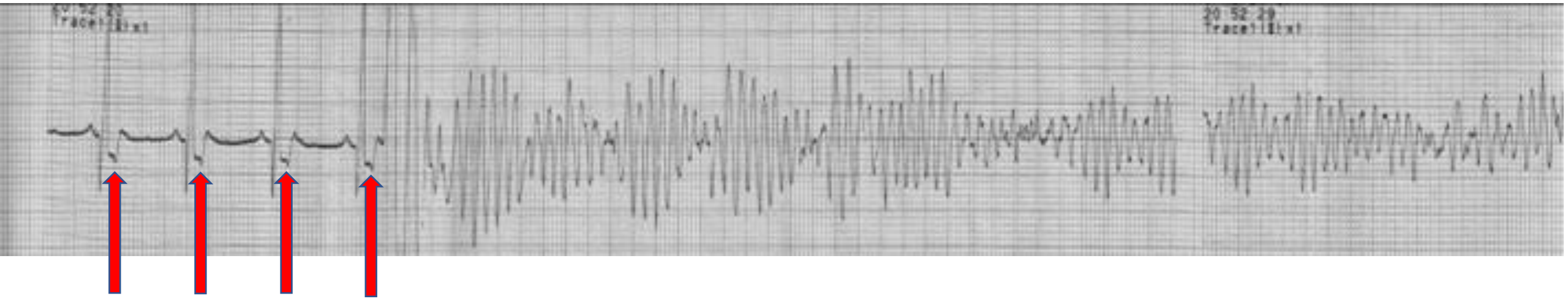


The minus-plus T wave signal or negative-positive T wave without ST segment observed in III in a patient with SQT1 variant.



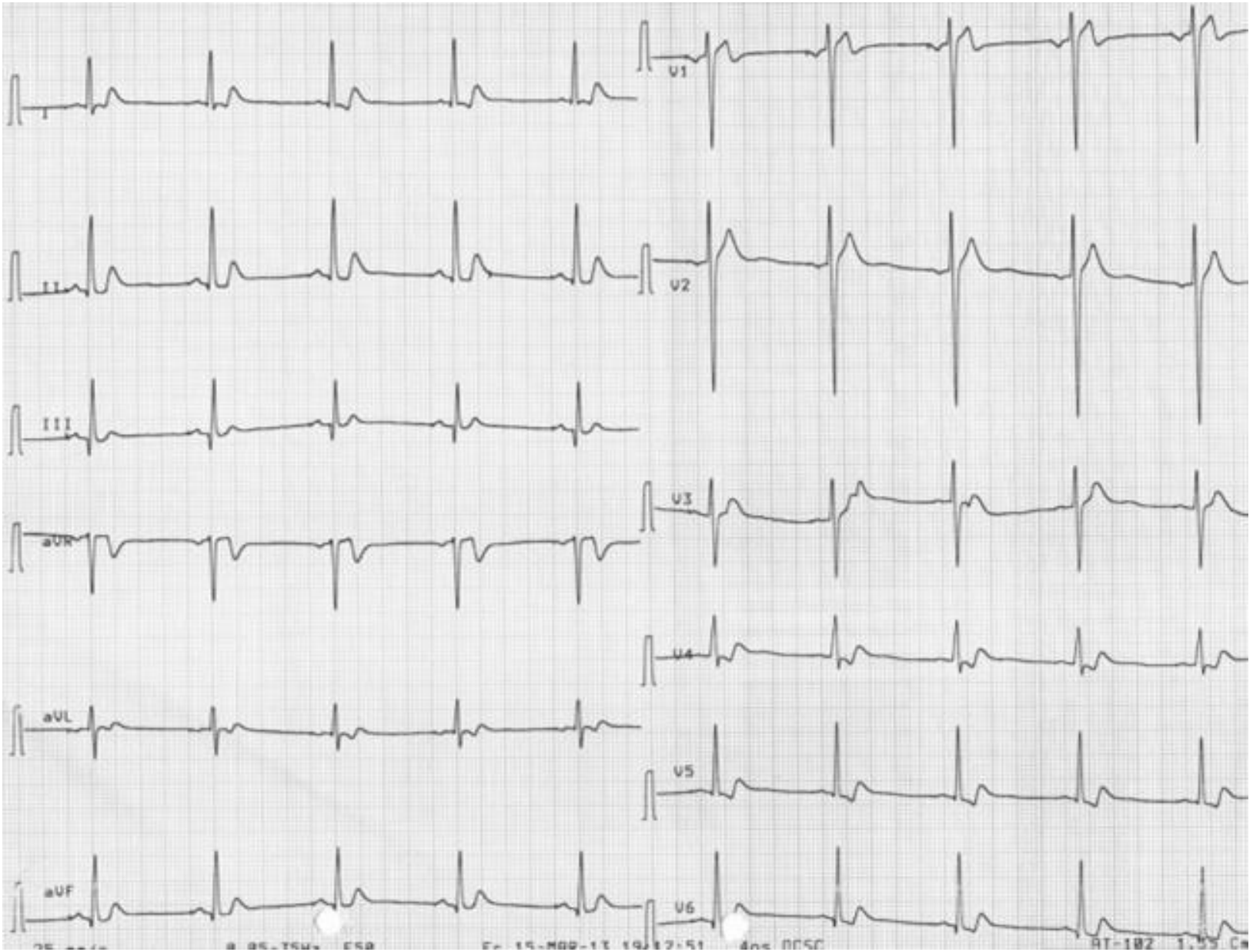
The “minus-plus T wave sign” observed in a Holter recording in a patient from Latin America (Brazil).

“Minus-plus T wave signal”: The initial part of the T wave is recorded immediately after the QRS complex (absence or minimal ST segment) shows a negative initial polarity in some leads (red arrow) that we denominated "minus-plus" T wave signal (negative-positive). Coincidentally, the CAV3 mutation that causes gain-of-function of late I_{to} without affecting other cardiac ion channels corresponds to J point and the initial negative portion of the T wave on the surface ECG. There would be a genotypic/phenotypic relationship?



T-wave minus-plus signal

ECG strip showing an episode of Torsade de pointes degenerate into ventricular fibrillation. The episode was induced after a premature ventricular beat due to R/T phenomenon. The event has very short couplet period with R-on-T phenomenon, which is the superimposition of an ectopic beat on the T wave of a preceding beat. Early observations suggested that R-on-T was likely to initiate sustained ventricular tachyarrhythmias. Note T-wave minus-plus signal (arrows).



The 12-lead surface ECG obtained on the admission showed sinus rhythm with a heart rate of 60 bpm, a QTc of 320 ms

Presence of arrhythmias

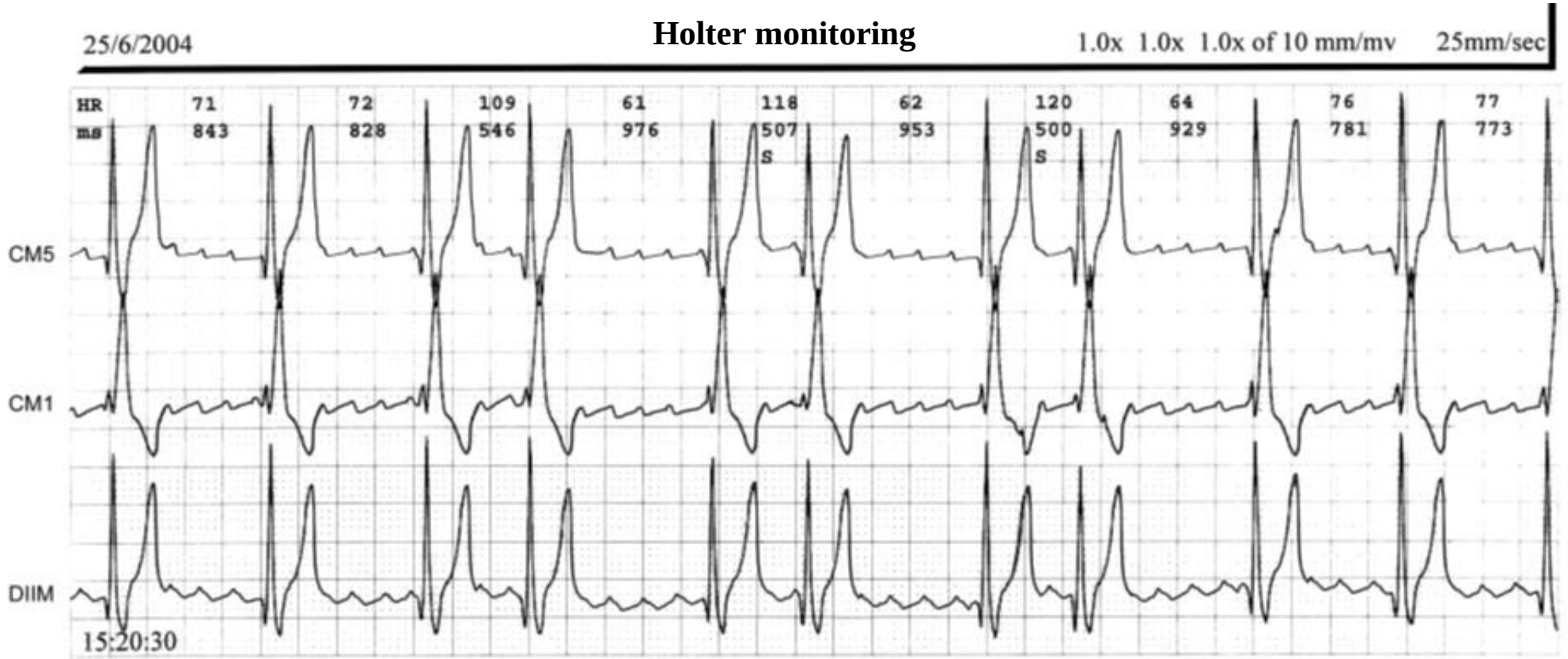
I) Supraventricular arrhythmias

- Paroxysmal atrial fibrillation episodes
- Supraventricular arrhythmias

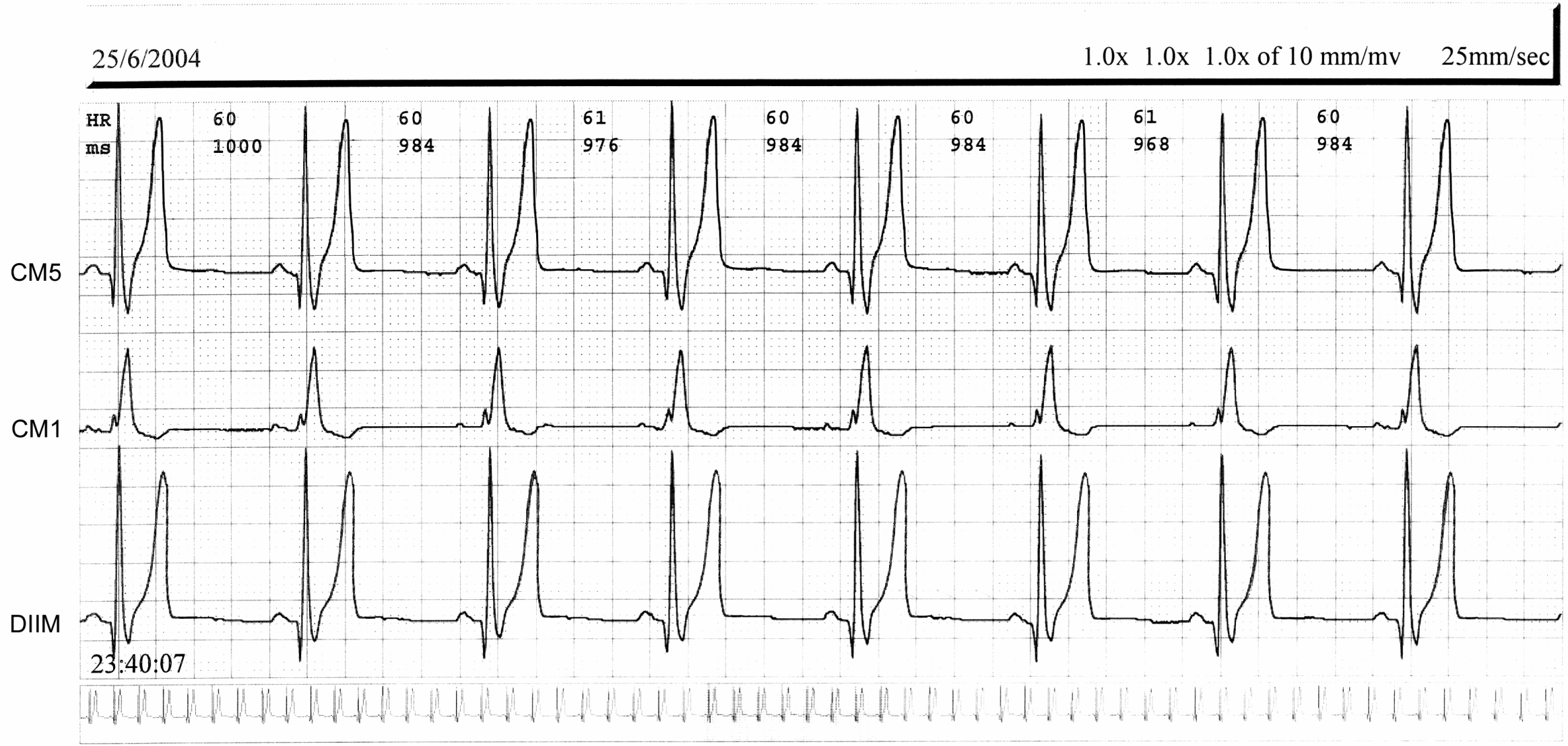
High tendency to paroxysmal atrial fibrillation episodes.

Atrial fibrillation and slow ventricular response.

Patients with hereditary short-QT or long-QT syndromes, representing the very extremes of the QT interval, both seem to have a high prevalence of AF.



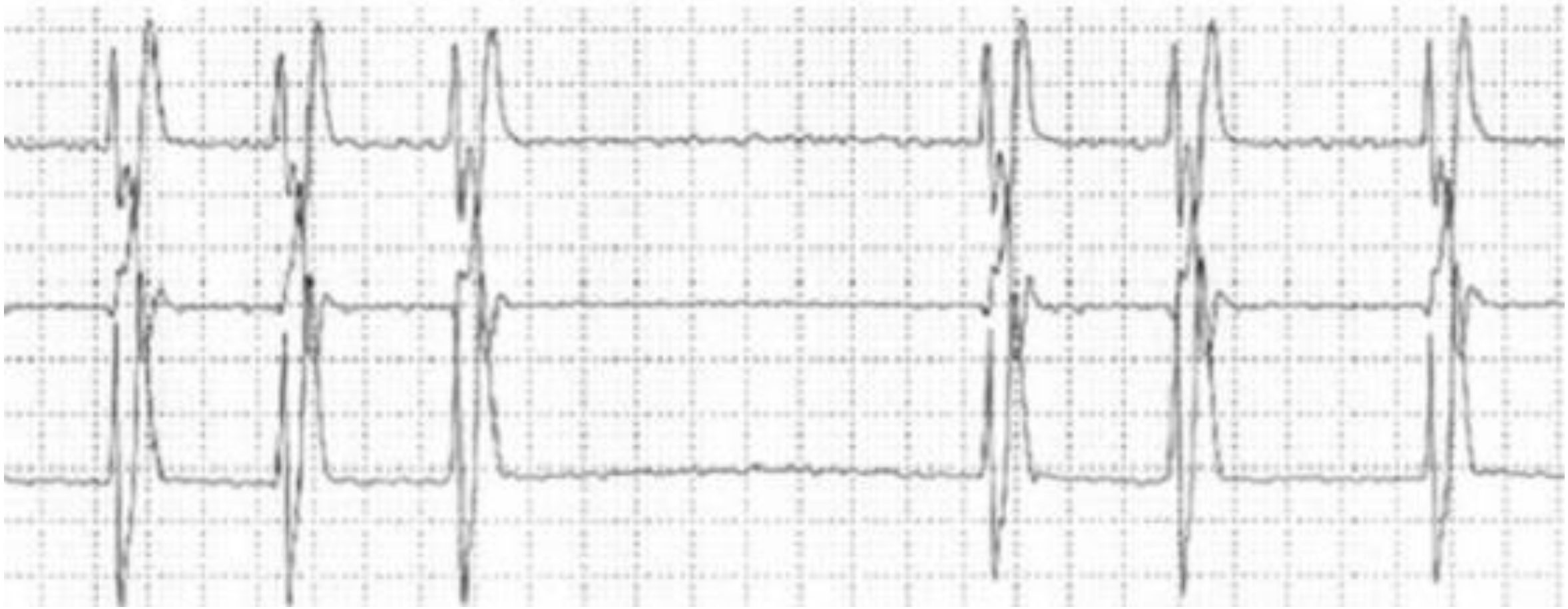
In this tracing we can see a short period of gross atrial fibrillation. The patient described palpitations. Congenital short QT syndrome is associated to a high incidence of paroxysmal atrial fibrillation, the electrophysiological mechanism of which would be caused by very short action potential with heterogeneous shortening of the cardiac potential and refractory period of atrial cardiomyocytes.



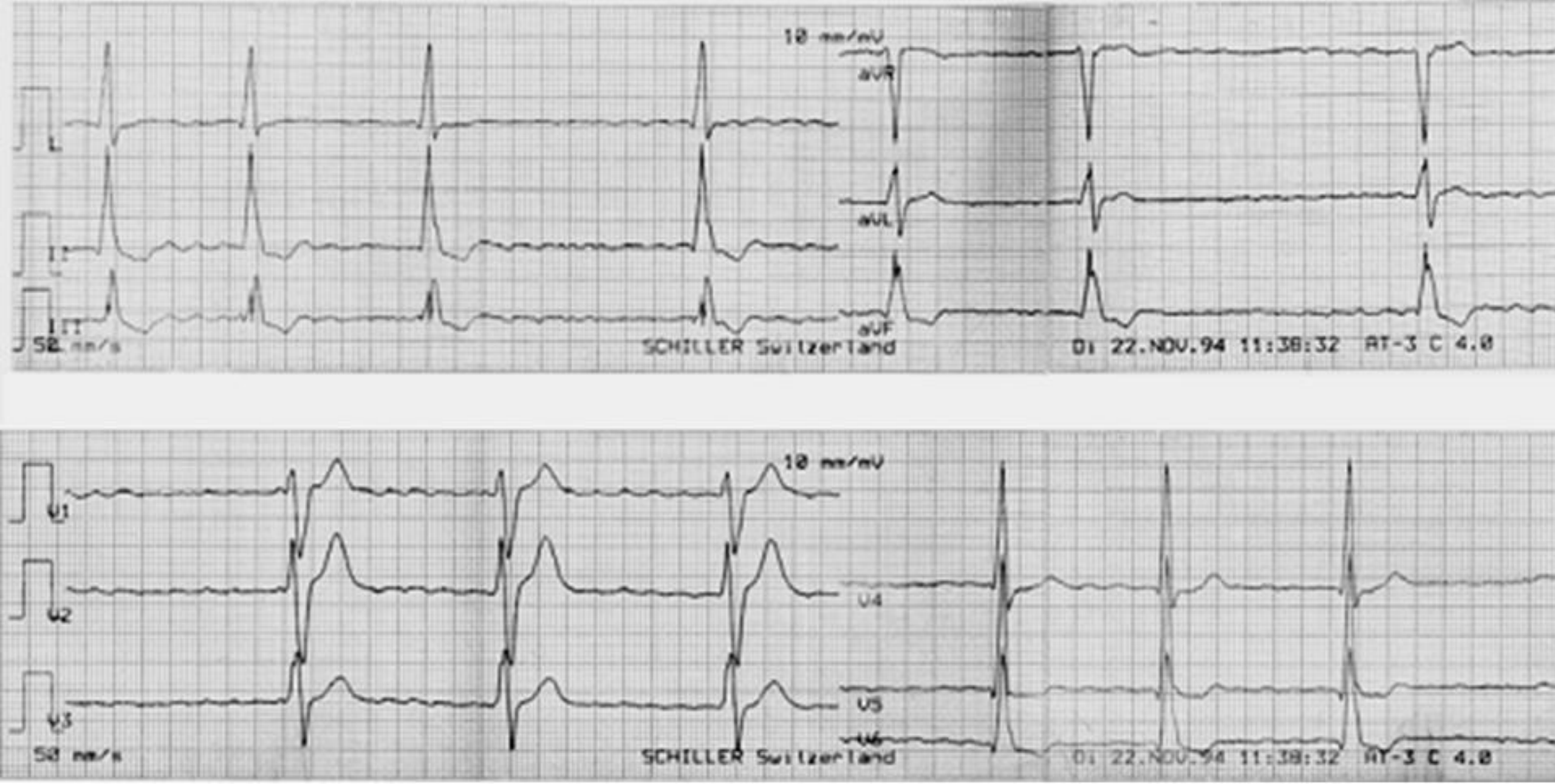
Sinus rhythm, tall/peaked, narrow-based T waves or pseudo symmetrical T-wave in a patient with SQTS. Approximately 8 hours later during the same test, the patient spontaneously reversed into sinus rhythm.

Villafañe et al, present a patient with congenital SQTS with AF and a slow ventricular response. Medical therapy has not been effective in maintaining sinus rhythm. The long-term outcome remains unknown for these children. This condition may present in utero as persistent bradycardia with postnatal ECG showing a very short QT interval.

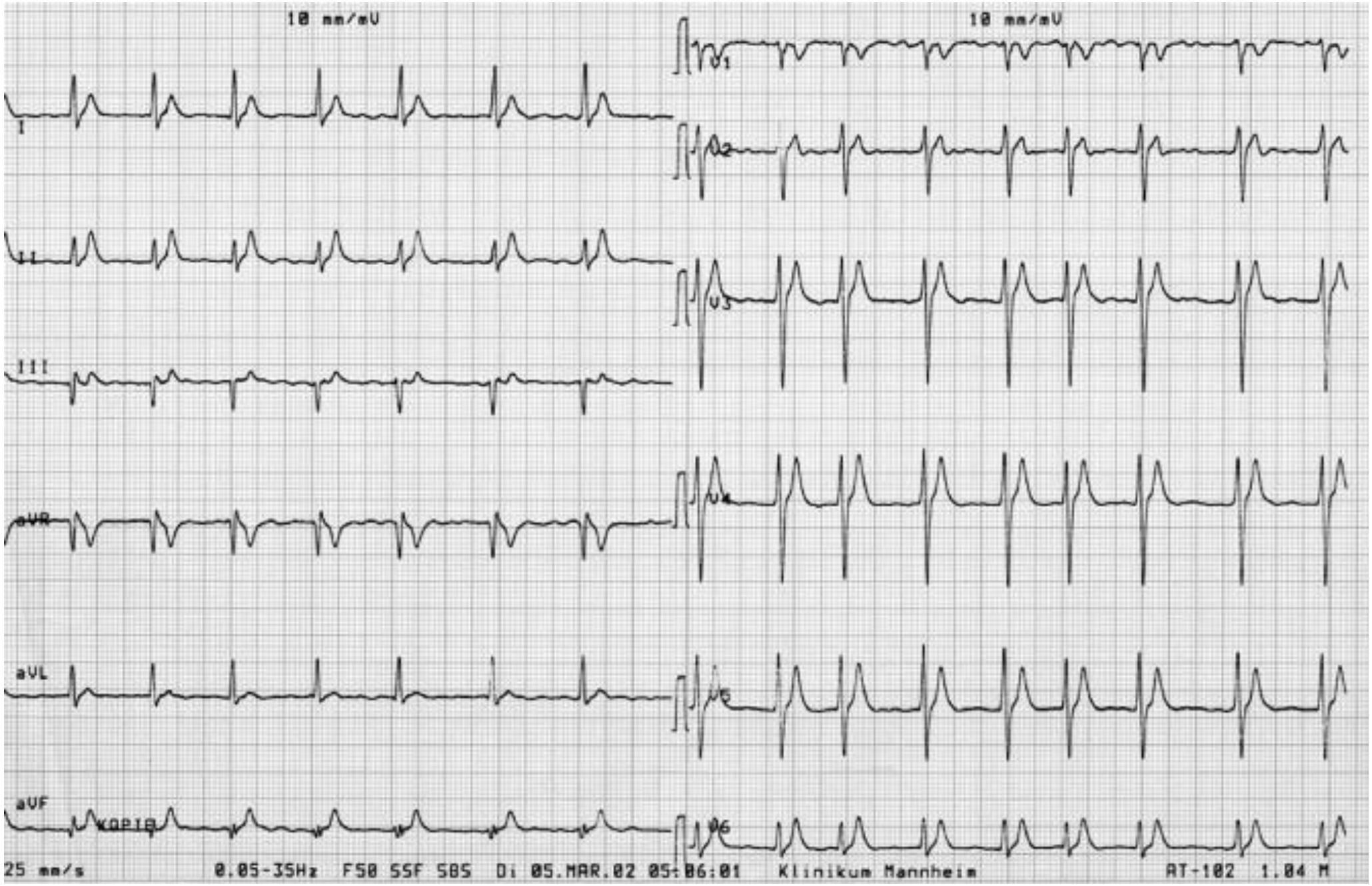
A KCNQ1 mutation (SQT2) causes age-dependent bradycardia and persistent atrial fibrillation. The description of a novel, de novo gain of function mutation in KCNQ1, responsible for atrial fibrillation and SQTS in utero indicates that some of these cases may have a genetic basis and confirms a previous hypothesis that gain of function mutations in KCNQ1 channels can shorten the duration of ventricular and atrial action potentials (Hong 2005). Mutations of KCNQ1 have been identified in patients and a vast majority of the described mutations are linked to the LQTS. Only a few mutations are linked to other pathologies such as AF and the SQTS.



Twelve-lead ECG Holter recording showing atrial fibrillation (heart rate, 120 bpm) with markedly shortened QT interval (QT 200 ms, paper speed 25 mm/s). (*B*) Twelve-lead ECG Holter recording showing atrial fibrillation (heart rate, 60 bpm) with short QT interval (QT 200 ms). (*C*) The flat relationship between heart rate and QT interval indicates lack of adaptation of QT interval to changes in cycle length.



*Presentation named supraventricular tachycardias and Brugada Syndrome from the Brugada Syndrome Consensus Conference held in Lake Placid – NY – September 11-14 2003 by Prof. Martin Borggrefe MD, Ph.D.


10 mm/mV
10 mm/mV
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
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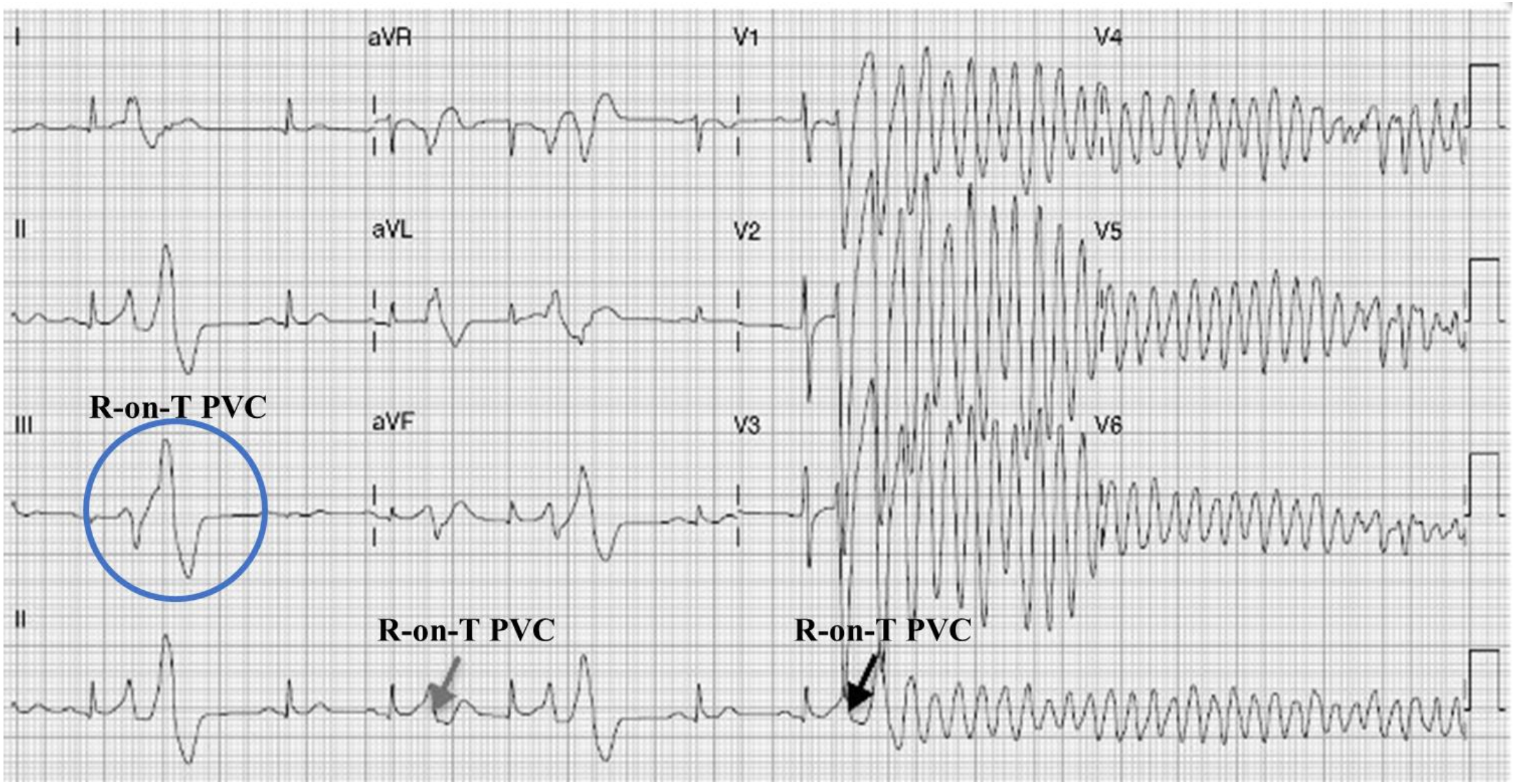
0.05-35Hz FS0 SSF SBS Di 05.MAR.02 05:06:01 Klinikum Mannheim AT-102 1.04 M

Ventricular arrhythmias

- Polymorphic VT with first PVC with very short coupling
- Electrical storm: successive episodes of VF



ECG recorded during a syncopal episode shows sinus rhythm. The tracing shows a shortened QT interval (320 ms) with frequent PVCs causing R-on-T PVCs (grey arrow). One PVC (black arrow) triggers polymorphic VT which caused syncope.

Short QT Syndrome (SQTS) Expert Consensus Recommendations on Short QT Syndrome Diagnosis

Diagnosis

1. SQTS is diagnosed in the presence of a QTc ≤330 ms.
2. SQTS can be diagnosed in the presence of a QTc o360 ms and one or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, survival of a VT/VF episode in the absence of structural heart disease.

Risk factor

In a combined symptomatic and asymptomatic group (QTc o360 ms) QTc was the only risk factor for arrhythmic events.

Treatment

Class I 1. ICD implantation is recommended in symptomatic patients with a diagnosis of SQTS who
a. Are survivors of a cardiac arrest and/or
b. Have documented spontaneous sustained VT with or without syncope.
c. Have strong family history of SCD and evidence for abbreviated QTc in at least some of the victims.

Class IIb 2. ICD implantation may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
3. Quinidine may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. Quinidine seems an effective alternative due to the QT-prolonging action. However, it has been reported that the QTc-prolonging effect of quinidine is particularly prominent in patients with a KCNH2 mutation (SQT1).
4. Sotalol may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. It may be effective in the other subtypes, except SQT1.

Muchas Gracias!!

Muito Obrigado!!

Thank you very much!!