Short QT interval in oligosymptomatic teenager boy

Mario Heñin, MD
Argentina

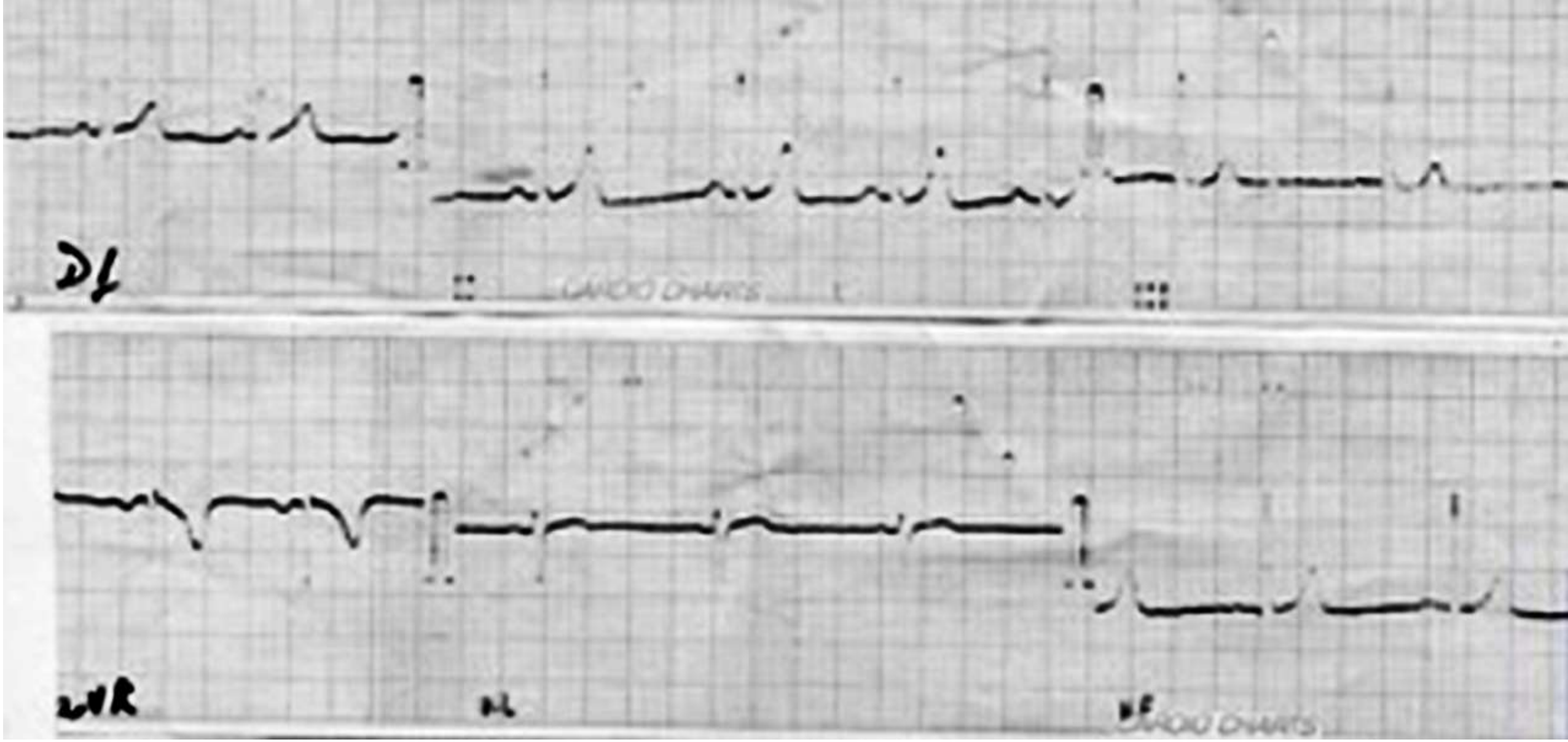
English

Dear friends, I share with you a case that I saw last week. He is a boy who just turned 12 years old these days. He frequently plays soccer, and also rides bicycle. Asymptomatic until a few weeks ago, when his father noted that "does not perform" physically (??) as before. When questioned, the child answered that he "gets tired" when he plays (??). Doubtful presence of palpitations, and of some sporadic dizziness during the effort.
Without family history of sudden death, syncope, or other heart diseases.
Physical examination: Blood pressure: 105/70 mmHg; pulses all present, heart rate about 72-78 bpm, with sinus phasic respiratory arrhythmia.
Auscultation: Normophonetic first and second heart sounds (S1-S2), systolic murmur barely audible, 1/6 in mesocardium and pulmonary focus suggestive of innocent murmur in nature.
ECG (see slides 3-5): Sinus rhythm, normal PR interval duration, short QT interval (II 350ms in II and 320 ms, in V6 early repolarization pattern in anterior wall.
Echocardiogram: normal.
Holter (see slides 7 and 8): I am struck by the short QT interval and the image "in spoon" at the beginning of the ST segment, with persistent depression. Only 2 isolated supraventricular premature contraction were recorded.
He complained of dyspnea coinciding with the efforts, sinus tachycardia and nothing else.
What do you think?
I wait for your valuable considerations.
Thank you, hugs,
Mario Heñin MD from Argentina

Spanish

Queridos amigos: Comparto con Uds un caso que he visto la semana pasada.
Es un niño que justamente cumplió 12 años en estos días.
Juega fútbol de manera intensa, además de bicicleta.
Asintomático hasta hace pocas semanas, en que el padre nota que el niño "no rinde" fisicamente (sic) como antes. Al interrogarlo el niño responde que "se cansa" cuando juega(sic). Dudosa presencia de palpitaciones, y de algún mareo esporádico durante el esfuerzo. Es un niño algo retraído para expresarse y tímido.
No hay ningún antecedente familiar de muerte súbita, ni síncopes, ni de otras cardiopatías.
Examen:
TA 105/70.Pulsos todos presentes, unos 72-78 por minuto , con arritmia sinusal respiratoria.
Auscultación: R1 y R2 normofonéticos. Soplo sistólico apenas audible, 1/6, en mesocardio y F. Pulmonar sugestivo de inocente. Nada más.
ECG (se adjunta):Sinusal, PR normal. QT en D2 350ms y en V6 320 ms. Patrón de repolarización precoz en cara anterior.
Ecocardiograma: totalmente NORMAL, nada destacable a informar. Función ventricular NORMAL.
Holter (se adjunta): me llaman la atención el QT corto y la imagen "en cubeta" de su ST, con infradesnivel persistente.
Se registraron solamente 2 extrasístoles supraventriculares, aisladas.
Refirío "falta de aire" coincidente con los esfuerzos/taquicardia sinusal y nada más.

Qué opinan ustedes?
Espero vuestras valiosas consideraciones.
Gracias, abrazos,
Mario Heñin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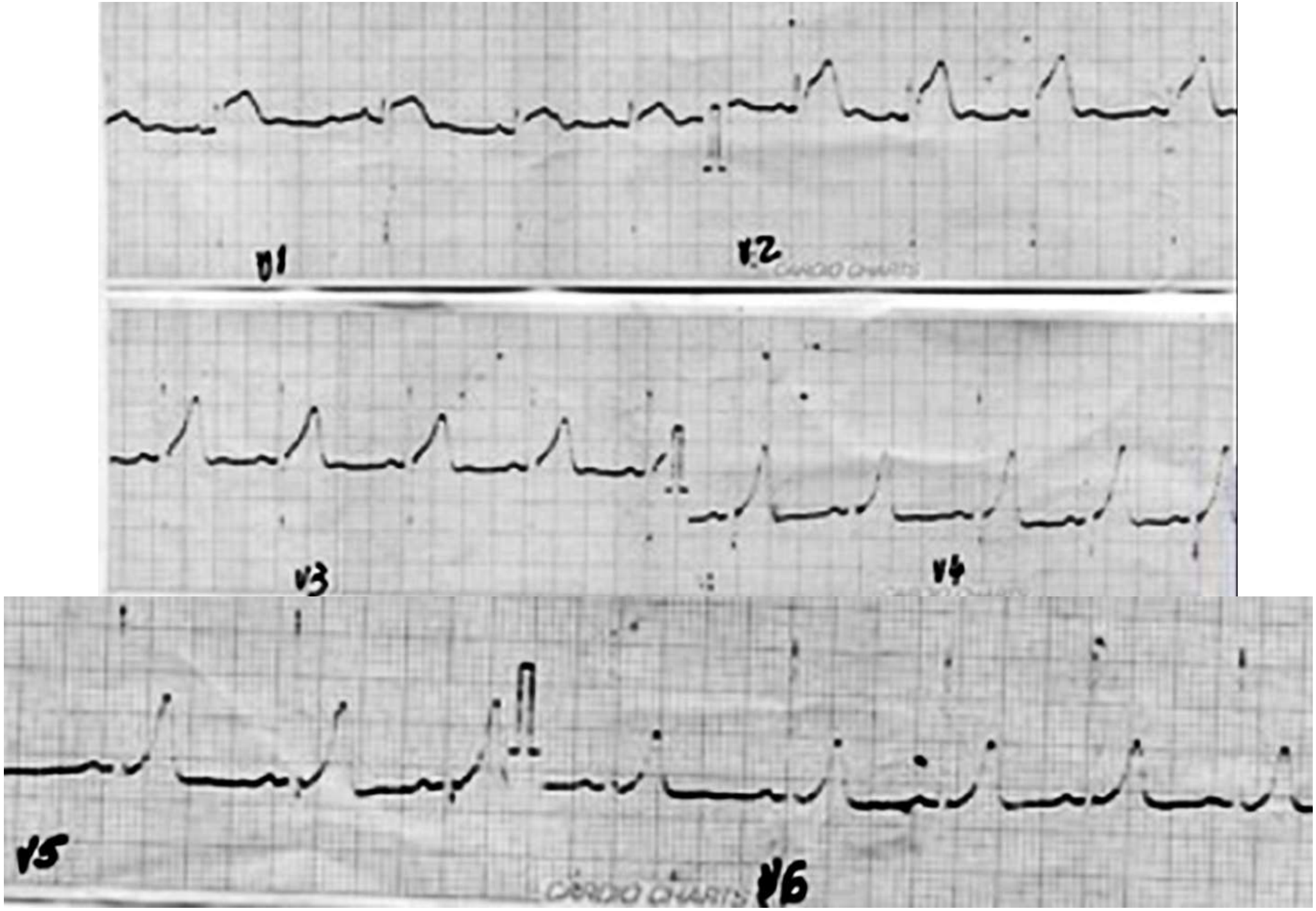
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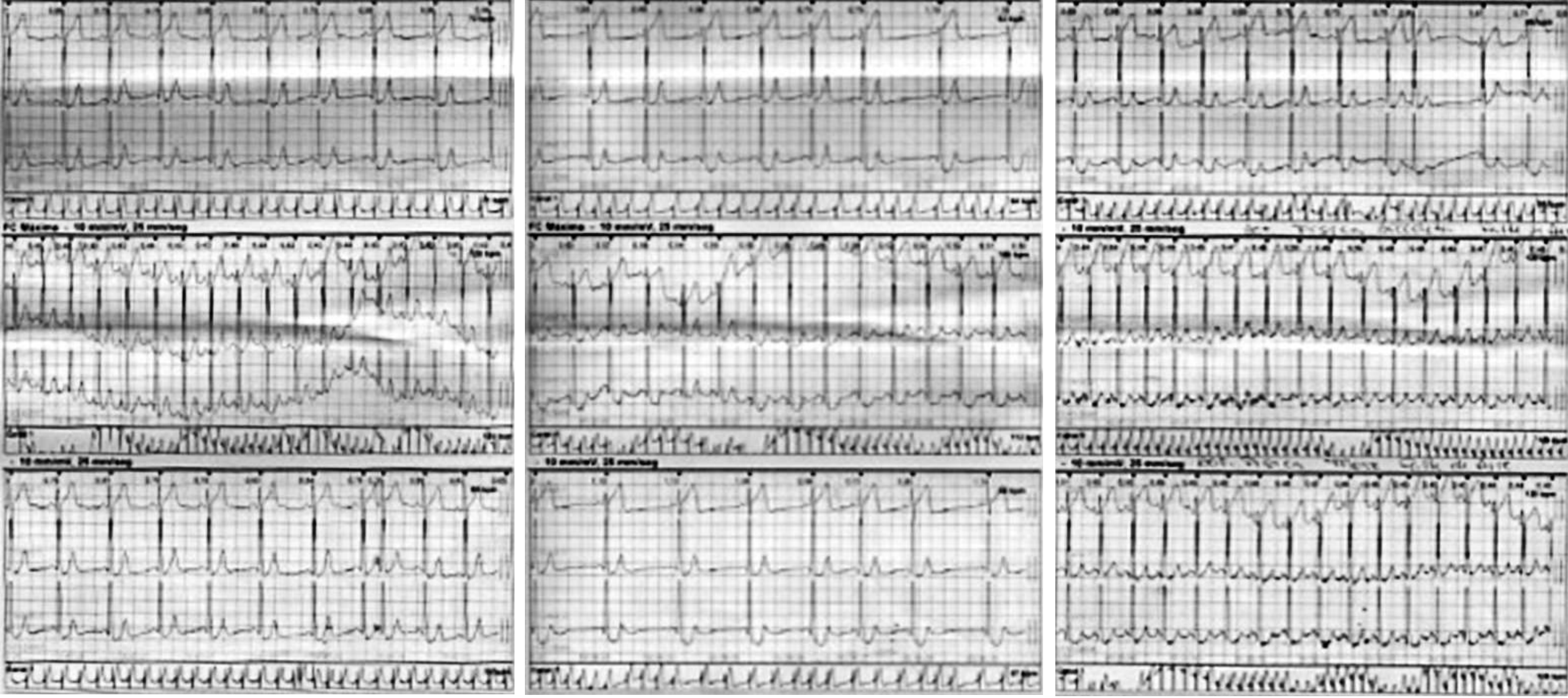


Colleagues' opinion

Querido Mario ; si tiene disnea de esfuerzo seria bueno un eco de esfuerzo para valorar función diastólica. El estudio de la función pulmonar me parece importante. El ECG tiene todo derecho para mi. La imagen de la cara anterior me parece anormal. Podria tener una coagulopatia? Como esta la circulación Pulmonar?
Es un caso interesante- Lo único el ECG y la disnea.
Emilio Marigliano
English
Dear Mario; If he has dyspnea of effort, it would be good to perform an stress echo to assess diastolic function. The study of pulmonary function seems important to me. The ECG has RVH for me. The ECG pattern of the anterior wall seems abnormal. Could it be a coagulopathy? How is the pulmonary circulation?
It is an interesting case.

Muy buen día Dr. Mario. Mi agradecimiento por su labor formativa y por permitir mi acceso al grupo. Le escribo desde San Cristóbal, Venezuela. En cuanto al caso pienso que por los trastornos de repolarización vistos en ECG y Holter y por la pérdida de capacidad funcional del chico debe descartarse origen anómalo de la Coronaria Izquierda. De lograrlo descartaría trastornos tiroideos y luego una RMN cardíaca para descarte de miocardiopatía incipiente. Finalmente estudio genético para descarte de can alopatía.
Muchas gracias Dr. Edgardo. Atento a sus conclusiones y casos para seguir en este interminable proceso formativo.
Leonardo Ramírez Zambrano Venezuela
English
Good morning Dr. Mario. Regarding the case, I think that due to the early repolarization pattern seen in ECG and Holter and the loss of functional capacity of the boy, the anomalous origin of the left coronary should be ruled out. If successful, I would also rule out thyroid disorders and then a cardiac MRI to rule out incipient cardiomyopathy. Finally genetic study to discard channelopathies.
Thank you very much Dr. Edgardo. I am looking forward to their conclusions and cases to continue in this endless formative process.

A propósito... ¿Que medidas de QT consideran normales en el Holter de 24hs? Gracias
Mario Pelegrini
English By the way ... What QT measures do you consider normal in the 24-hour Holter? Thanks

Spanish
Buenas tardes foro, el síndrome QTc corto según Gussak es un síndrome congénito y hereditario, caracterizado con QTc < o igual a 300 mseg. Generalmente no hay más de 40 mseg de variación con los cambios de FC. Ondas T altas, picudas y simétricas (en tienda de campaña). Y un indice J- T peak < 120 mseg. En niños de 1° infancia, adolescentes o adultos jóvenes
Síntomas
a) menores:disnea, palpitaciones, mareos
b) mayores: síncope inexplicado, resucitación de una MS, o TV/FV documentada.
En raras ocasiones taquiarritmias supraventriculares o episodios de FA paroxística.
Historia familiar de MS o síncope en familiares de 1° grado.
No hay cardiopatía estructural demostrada.Descartar hipercalcemia, hiperkalemia, hipertermia, alteraciones autonómicas y drogas como digoxina.
En este caso tiene síntomas (disnea y palpitaciones) y un ECG con QTc (es difícil medir por resolución de la fotografía) aproximadamente 330-340 mseg, y el índice J-T pico es francamente > 120 mseg.Con mucho respeto, en mi celular NO puedo medir exactamente el QT y la FC en todas las dericaciones del ECG ni del holter. Pero las ondas T no las veo altas picudas y simétricas, son asimétricas y de baja amplitud.
Sólo para agregar otras mediciones para SQTS: **Indice Pico T-Te** = pico de onda T -final de onda T, mide la dispersión de repolarización, (existente entre endo-epicardio) causa de reentrada para TV . Valor normal **medido en V5**, 92 y 94 mseg para varones y mujeres respectivamente. En SQTS y otras canalopatías esta prolongado. En niños es más ancho en V3 y se prolonga a medida que disminuye la FC , tiene una mediana de 40 mseg de variación. **Índice Q-aT** = desde inicio QRS hasta pico de onda T, valores < 270 mseg a favor de SQTS.
En este caso para el 1° índice de necesitan otras herramientas para medición , y no es el ojo precisamente.
No creo se trate de un verdadero SQTS.
Pero si las mediciones dan para pensar en SQTS, descartando patología estructural, alteraciones electrolíticas y drogas, Y con diagnóstico electrocardiográfico inequívoco de SQTS, realizaría Ergometría para medir el comportamiento del QTc, eventual EEF para medir períodos refractarios y posible inducción de FA-TV/FV.
Test genético al paciente y a los familiares para descartar canalopatía.
Esperando la opinión de expertos me despido cordialmente.
Dr Juan Carlos Manzzardo
Mendoza -Argentina

English

Good afternoon forum, the short QTc syndrome, according to Gussak, is a congenital and hereditary syndrome, characterized by QTc ≤ 300 ms. Generally there is no more than 40 ms of heart rate (HR) variation. High voltage T waves, peaked and symmetrical (desert tent). And a J-T peak interval <120 ms. The entity is observed in children of 1st childhood, adolescents or young adults.

Symptoms:

a) Younger: dyspnea, palpitations, dizziness

b) Older: unexplained syncope, resuscitation of a SD, or documented VT/VF.

In rare cases supraventricular tachyarrhythmias or episodes of paroxysmal AF.

Family history of SD or syncope in first-degree relatives.

There is no demonstrated structural heart disease. It is necessary rule out hypercalcemia, hyperkalemia, hyperthermia, autonomic alterations and drugs effects or toxicity such as digoxin.

In this case he has symptoms (dyspnea and palpitations) and an ECG with QTc (it is difficult to measure by resolution of the picture) approximately 330-340 ms, and the peak J-T peak is >120 ms. With much respect, from my cell phone I can exactly measure the QT and the HR in all leads of the ECG and the Holter. But I do not see the T waves tall, peaked and symmetrical, they are asymmetric and of low amplitude.

Only to add other measurements for SQTS: Tp-Te peak interval = T-wave peak - end of T wave measures the repolarization dispersion (existing between endo-epicardium) cause of reentry for VT. Normal value measured in V5, 92 and 94 ms for men and women respectively. It is prolonged in SQTS and other channelopathies. In children it is wider in V3 and it lasts longer as the HR decreases, it has a median of 40 ms of variation. Q-aT index = from the beginning of the QRS until T wave peak, values <270 ms in favor of SQTS.

In this case for the 1st index you need other tools for measurement, and it is not the eye precisely.

I do not think it's a true SQTS.

But if the measurements lead to SQTS, discarding structural heart disease, electrolyte imbalance and drugs, and with unequivocal electrocardiographic diagnosis of SQTS, ergometry should be performed to measure the QTc behavior, eventual EPS to measure atrial and ventricular refractory periods and possible induction of AF-VT/VF.

Genetic test to the patient and relatives to rule out channelopathies.

I am looking forward to the opinion of experts. Cordially,

Dr Juan Carlos Manzzardo

Mendoza -Argentina

En relación al caso clínico (siempre interesante) del chico de 12 años sin clínica aparente, me llama la atención las anomalías en la repolarización de la cara anteroseptal (supradesnivel convexo de V1 - V3) sin embargo por los cientos de papers y los varios consensos no existiría "repolarización precóz en este cara" (debe ser inferior/inferolateral o en todas las derivaciones y siempre debe tener las ondas notch o slur EXCEPTO DE V1 - V3) (1).
En relación a la sospecha de "TEP" los criterios clínicos y score como el de Wells u otros ayudarán a categorizar (leve-moderada-alta) la sospecha y junto con biomarcadores como el dímero D y NT - ProBNP sustentar someter al paciente a una angioTAC. De todos modos parece que el score es bajo, y en el ECG como criterios sensibles no observo taquicardia sinusal o criterios específicos como el patrón S1Q3T3 , bloqueo de rama derecha de alto grado o signos de sobrecarga sistólica del VD (eje a la derecha/BRD/R alta en cara anteroseptal/inversión asimétrica de la onda T en cara anteroseptal).
En relación al QT creo que la medición siempre se debe realizar con un ECG basal y en el que nos presenta el colega esta conservado (midiéndolo a vuelo de pájaro). Otro diagnostico diferencial en relación a anomalías de la repolarización en dicha cara es el Brugada, pero no veo ninguna de las 3 patentes o 2 patentes segun los varios consensos. Saludos Cordiales.
Diego Villalba Paredes, Quito - Ecuador.

English

In relation to the clinical case (always interesting) of the 12-year-old boy without apparent clinical symptoms, I am struck by the anomalies in the repolarization of the anteroseptal wall (convex elevation from V1-V3), however, by the hundreds of papers and the various consensuses there would be no "repolarization on this wall" (it must be inferior / inferolateral or in all leads and it should always have notching or slurring waves EXCEPT FROM V1 - V3) (1).
In relation to the suspicion of “acute pulmonary embolism" the clinical criteria and score such as Wells or others will help to categorize (mild-moderate-high) the suspicion and together with biomarkers such as D-dimer and NT-ProBNP to support subjecting the patient to a angioTAC. Anyway it seems that the score is low, and in the ECG as sensitive criteria I do not see sinus tachycardia or specific criteria such as the S1Q3T3 pattern, high-degree right bundle branch block or signs of RV systolic overload (right axis / RBBB / high R anteroseptal wall / T wave asymmetric inversion in anteroseptal wall).
In relation to the QT I believe that the measurement should always be done with a basal ECG and in which the colleague presents us is preserved (measured as a bird's eye). Another differential diagnosis in relation to repolarization anomalies in that wall is the Brugada, but I do not see any of the 3 patents or 2 patents according to the various consensuses. Best regards.

Estimados colegas. El trazado en un niño de 12 años, me sugiere hipertrofia ventricular izquierda: r pequeña y S profunda en V1 y V2 con T positivas, asociado a R relativamente alta en V6 y sin S. Las alteraciones del STT en el esfuerzo son compatibles con miocardiopatia hipertrofica o insuficiencia coronaria de etiología a estudiar.
En conclusión: MCPH difusa e incipiente como primer diagnostico a descartar.
Gerardo Nau

English

Dear colleagues. The tracing in a 12-year-old boy suggests left ventricular hypertrophy: small r and deep S in V1 and V2 with positive T wave, associated with R relatively high in V6 and without S. The alterations of ST-T in the effort are compatible with hypertrophic cardiomyopathy or coronary insufficiency of etiology to be studied.
In conclusion: diffuse and incipient MCPH as the first diagnosis to be discarded.

Final comments by

Andrés Ricardo **Pérez-Riera,** M.D. Ph.D.
Laboratorio de Escrita Científica da Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil
https://ekgvcg.wordpress.com

Raimundo **Barbosa-Barros**, MD
Centro Coronariano do Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza – CE-Brazil

Luiz Carlos **de Abreu**, PhD
Visiting Scientist Department of Environmental Health, Harvard T.H. Chan School of Public Health

This patient is not a child. This is an adolescent. Adolescence begins with the onset of physiologically normal puberty, and ends when an adult identity and behavior are accepted. This period of development corresponds roughly to the period between the ages of **10 and 19 years**, which is consistent with the World Health Organization's definition of adolescence.

The normal ECG between eight to sixteen years old has:

Heart rate: equal to adults: 60 bpm to 100 bpm.

Rhythm: sinus.

P wave: SAP: between 0° and 90°. Values beyond +75° are only observed in young asthenic individuals. Duration: up to 90 ms up to 12 years old and 100 ms since this age up to sixteen. Voltage: maximal limit 2.5 mm. Polarity: similar to the previous age group.

PR interval: up to 180 ms (0.18 s) for teenagers for rates between 80 and 120 bpm.

SAQRS in frontal & horizontal planes: FP: average +55°. It may vary between +120° and +25°. HP: slightly intermediary posterior or possibly anterior: R/S ratio in V_2 lower, equal or greater than 1.

QRS duration: average 70 ms. Normal maximal limit 90 ms up to 12 years old and 100 ms up to 16 years.

R/S ratio in precordial leads: adult progression of R/S ratio in precordial leads, i.e. progressive increase of voltage of R wave up to V_5 and concomitant decrease of S wave up to V_6.

QRS complexes voltage in precordial leads: V_1: average voltage of R wave 6 mm. Maximal 16 mm. Average depth of S wave 15 mm. Maximal 25 mm. ; **V_5:** average voltage of R wave 20 mm. Maximal 34 mm. Average depth of q wave 1.5 mm. Maximal up to 4 mm. Average depth of S wave 5 mm. Maximal 16 mm.; **V_6:** average voltage of R wave 14 mm. Maximal 24 mm. Average depth of q wave 1.5 mm. Maximal up to 4 mm. Average depth of S wave 1 mm. Maximal 4 mm. In teenagers, the Sokolow index may possibly be recorded, and modified with values greater than 60 mm: S wave of V_2 + R wave of V_5 with values greater than 60 mm in absence of LVH (**Bayés de Luna 1998**). The phenomenon is explained by a greater proximity of the LV with the chest wall, due to a narrower chest, which approaches the exploring electrode. This makes the diagnosis of LVH just by the criterion of voltage, more difficult in these age ranges (**Walker 1961**).

ST segment/T wave: The ST segment is isoelectric and horizontal at the same level as the PR and TP intervals. An elevation of 1 mm may be admitted in the limb leads and 2 mm in left precordial leads. The voltage of the maximal T wave in V_5 is 14 mm and in V_6 of 9 mm. In the FP, SAT is between 0° and 90°. In the HP, SAT may be both posterior and anterior, and after 10 years of age, it progressively becomes more anterior.

QRS/T angle: smaller than 60^0.

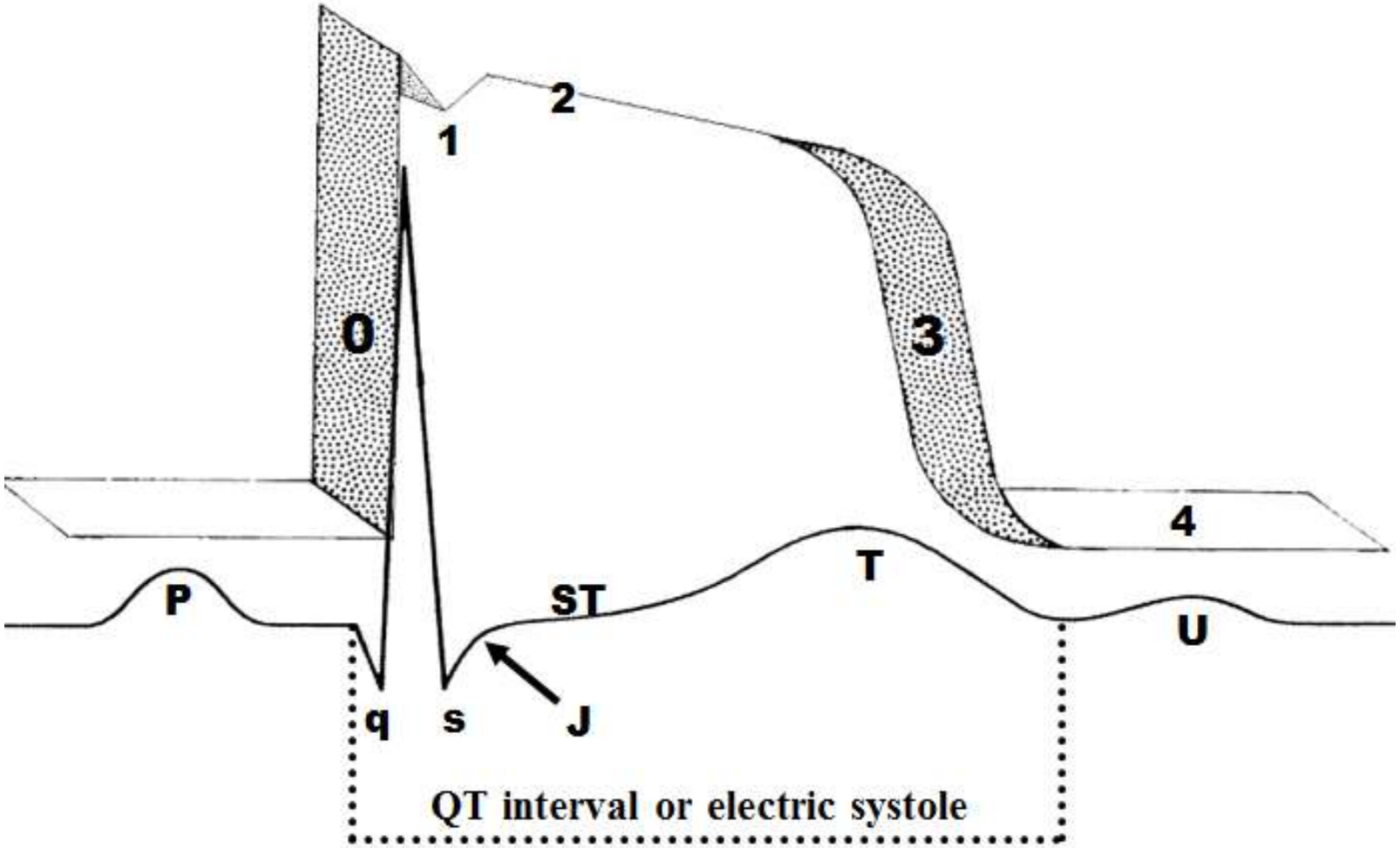
QTc interval duration: maximal value of 440 ms. Minimal value: 320-330ms? (Polemic see next slide)

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 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

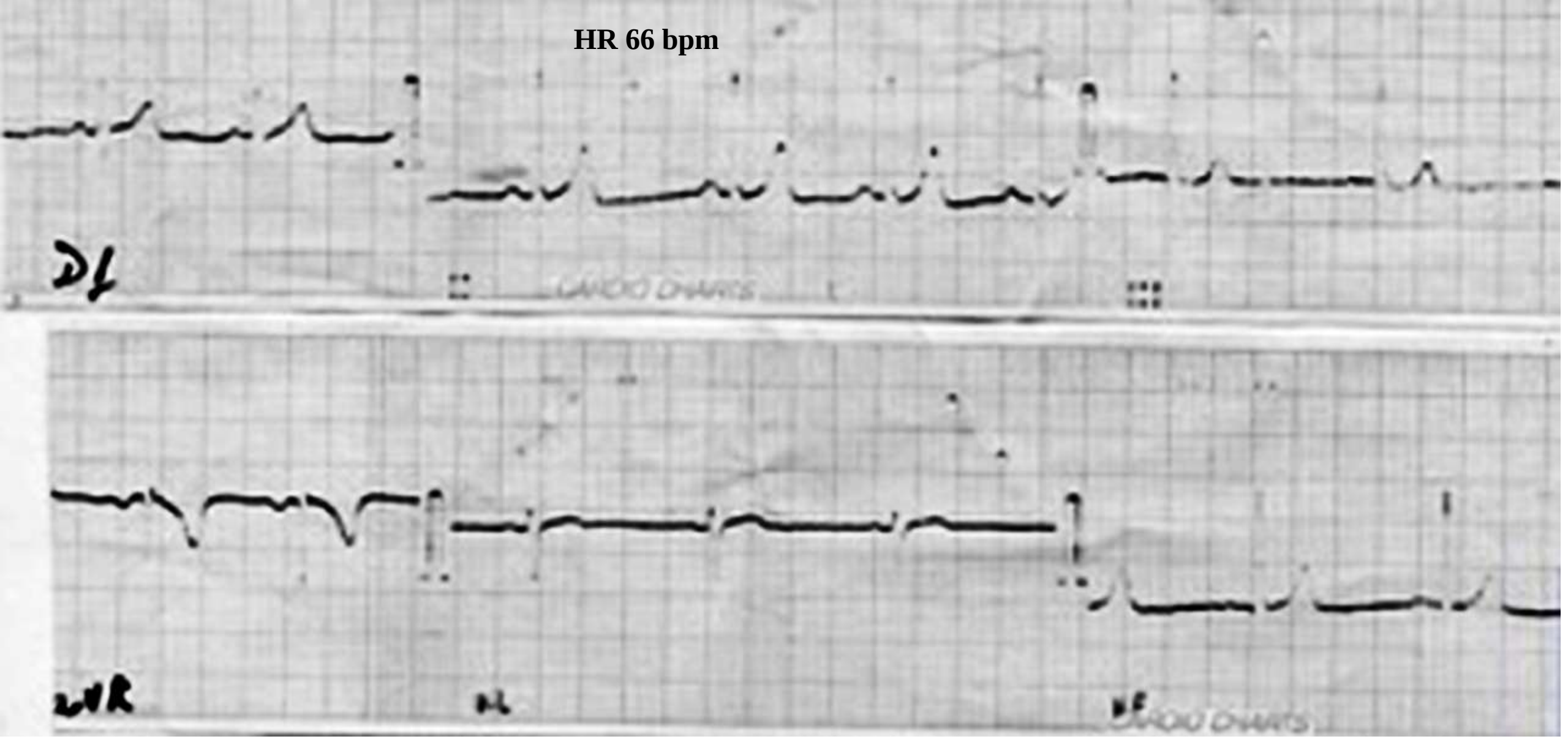
According to Viskin (**Viskin 2009**), males with QTc <330 ms and females with QTc <340 ms should be diagnosed with SQTS even if they are asymptomatic since this values are very rare in a healthy population. In addition, QTc intervals shorter than 360 and 370 ms (males and females respectively) should only be considered diagnostic of SQTS when supported by symptoms or positive family history because they overlap with a healthy population. Currently, SQTS is usually defined as QT_c ≤330 ms, or QTc interval <360 ms and one or more of the following: history of cardiac arrest or syncope, family history of sudden cardiac death (SCD) at age ≤ 40 or a family history of SQTS (**Priori 2013**). Population-based and genetic studies show that QTc interval <330 ms is extremely rare (**Kobza 2009**). Data from over 10,000 adults suggest that, in the healthy population, the prevalence of QT_c <340 ms is approximately 0.5 % (with 95 % confidence interval) (**Anttonen 2007**).

The European SQTS registry considers SQTS if patients had a QTc interval of ≤ 360 (in leads II or V5) with history of sudden death or aborted sudden death or syncope of arrhythmic origin; if patients had a very short QT interval (QTc interval of 340 ms) (even if they were asymptomatic); or if patients had a short QT interval (QTc interval 360 ms, in leads II or V5) with a family history of SQTS.
Giusstetto et al (**Giustetto 2006**) refer that SQTS patients exhibited a QT <320 ms and a QTc <340 ms.

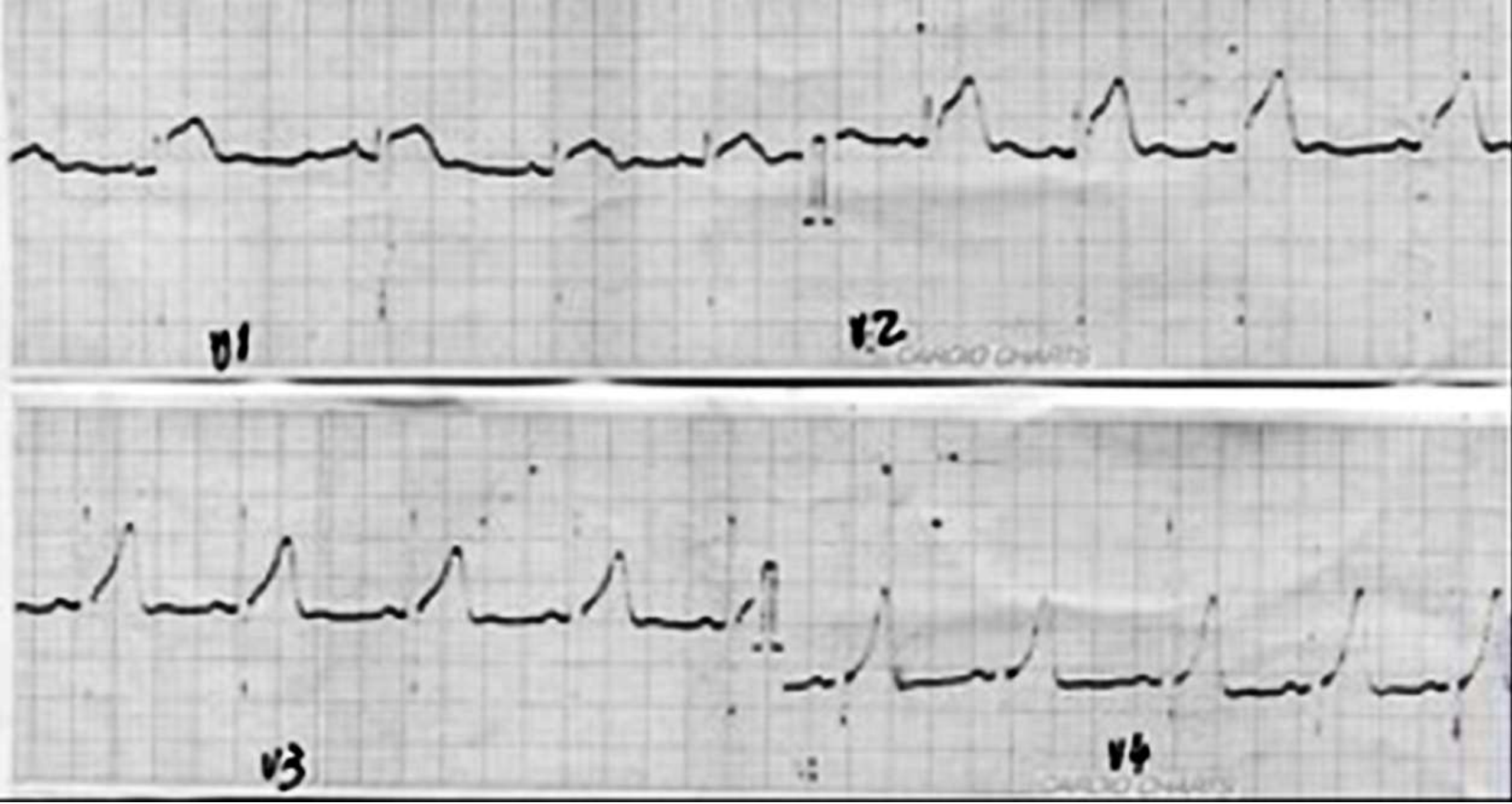


Representation of minimal and maximal normal values of QTc interval and its correlation with monophasic action potential. QTc values <330 ms are considered short QT interval. Values of QTc >450 ms are considered long QT intervals. Normal values of QTc are between 350 to 440 ms or 446±15%. QTc intervals are considered very long with values of QTc ≥ 470 ms for men and ≥ 480 ms for females. LQTS even if asymptomatic.

HR 66 bpm



HR 66bpm, QT II = 290 ms. QTc Bazett formula: QTc= QT/ raiz cuadrada del RR = 304 ms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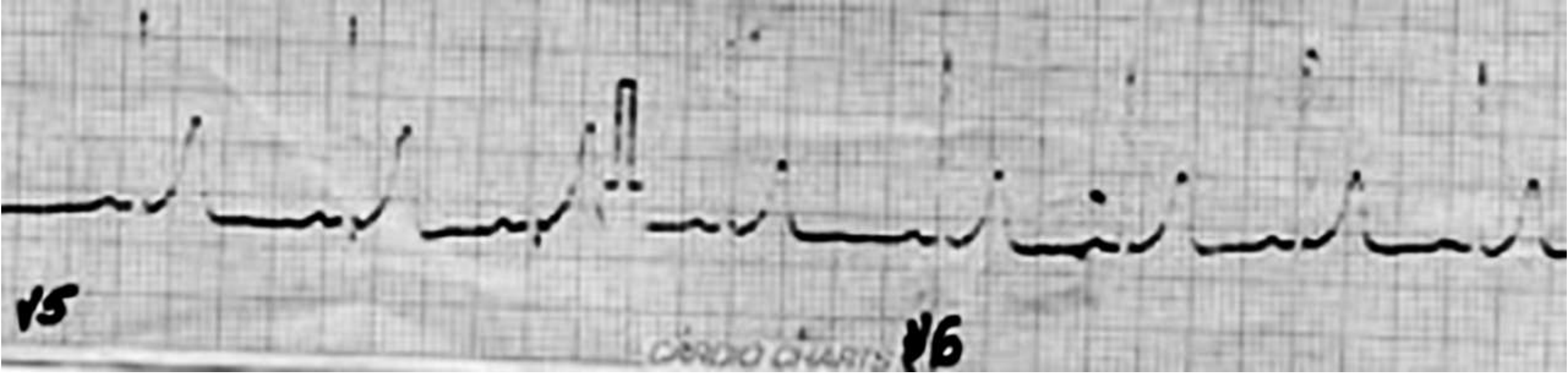
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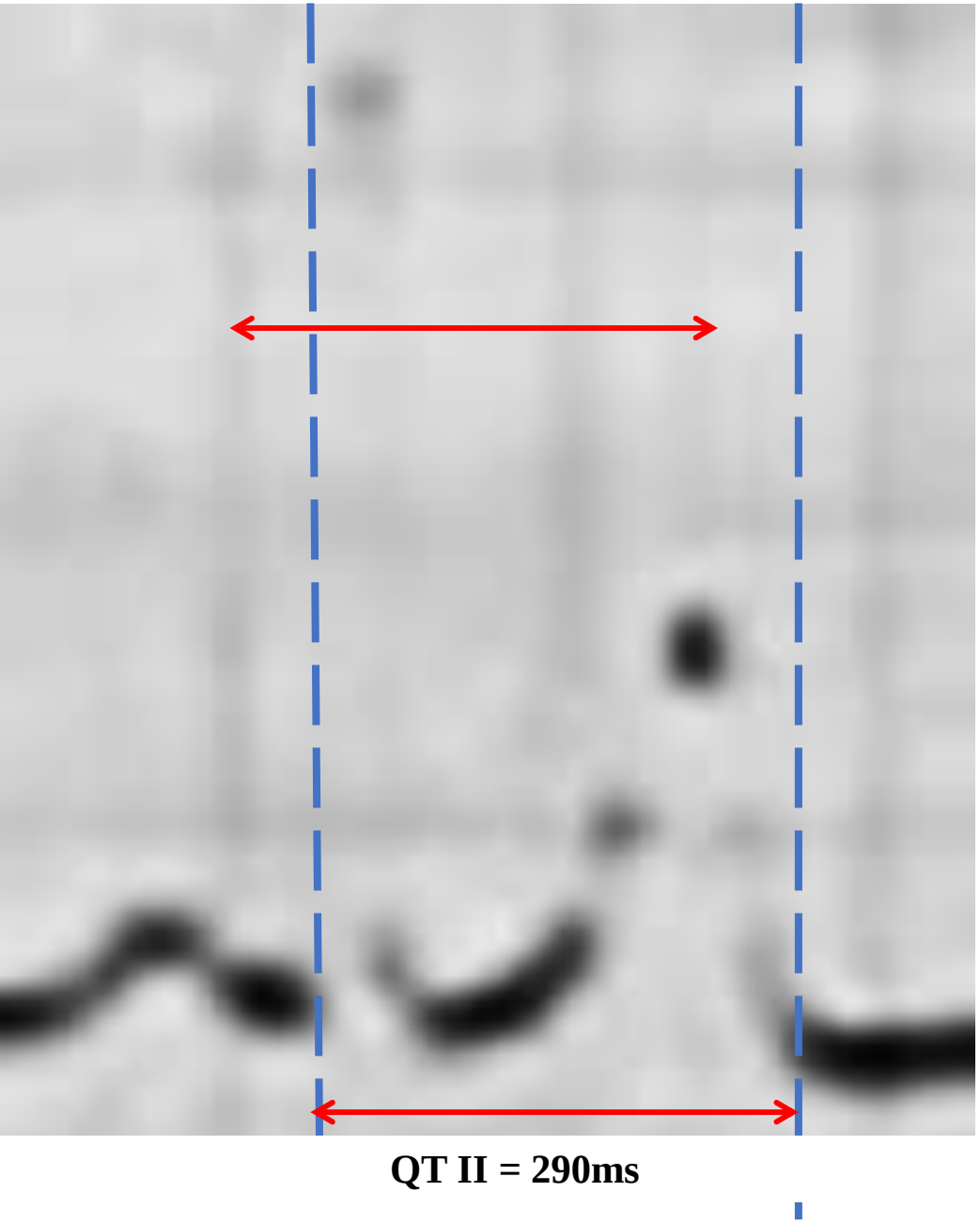
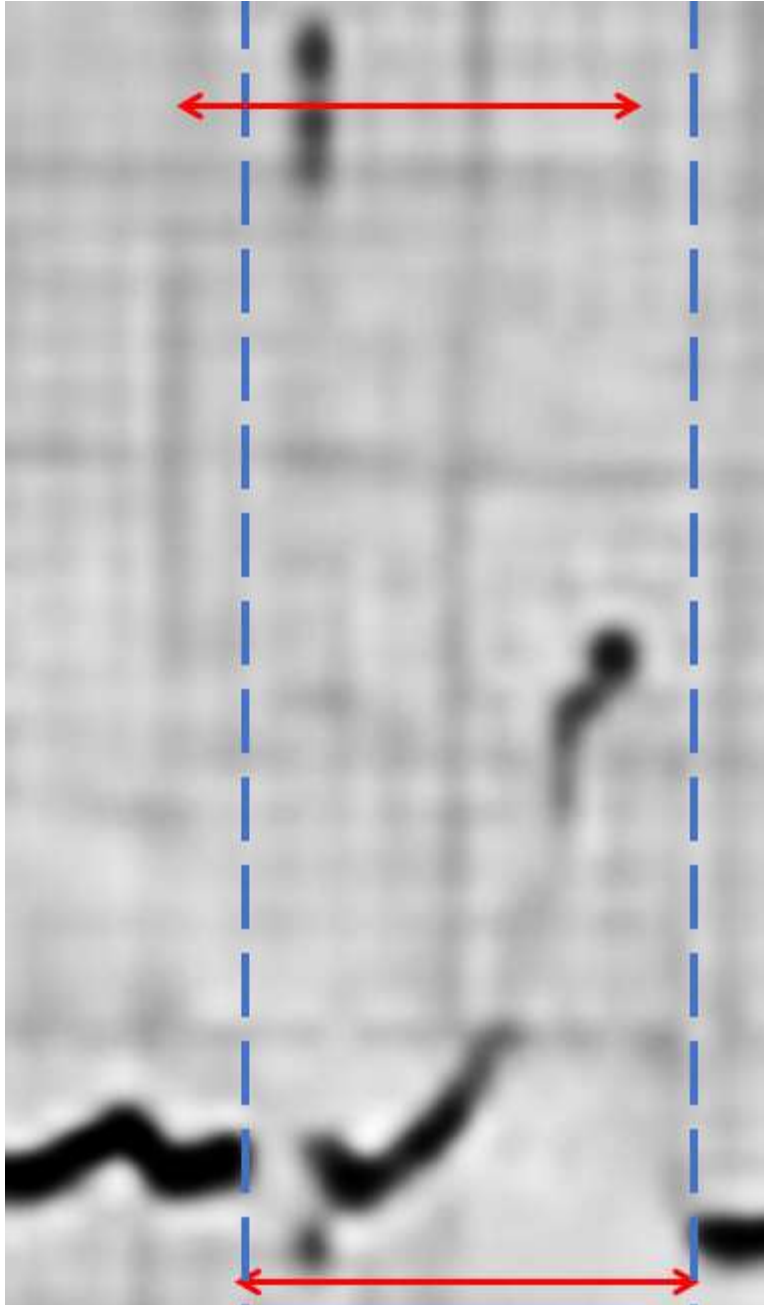
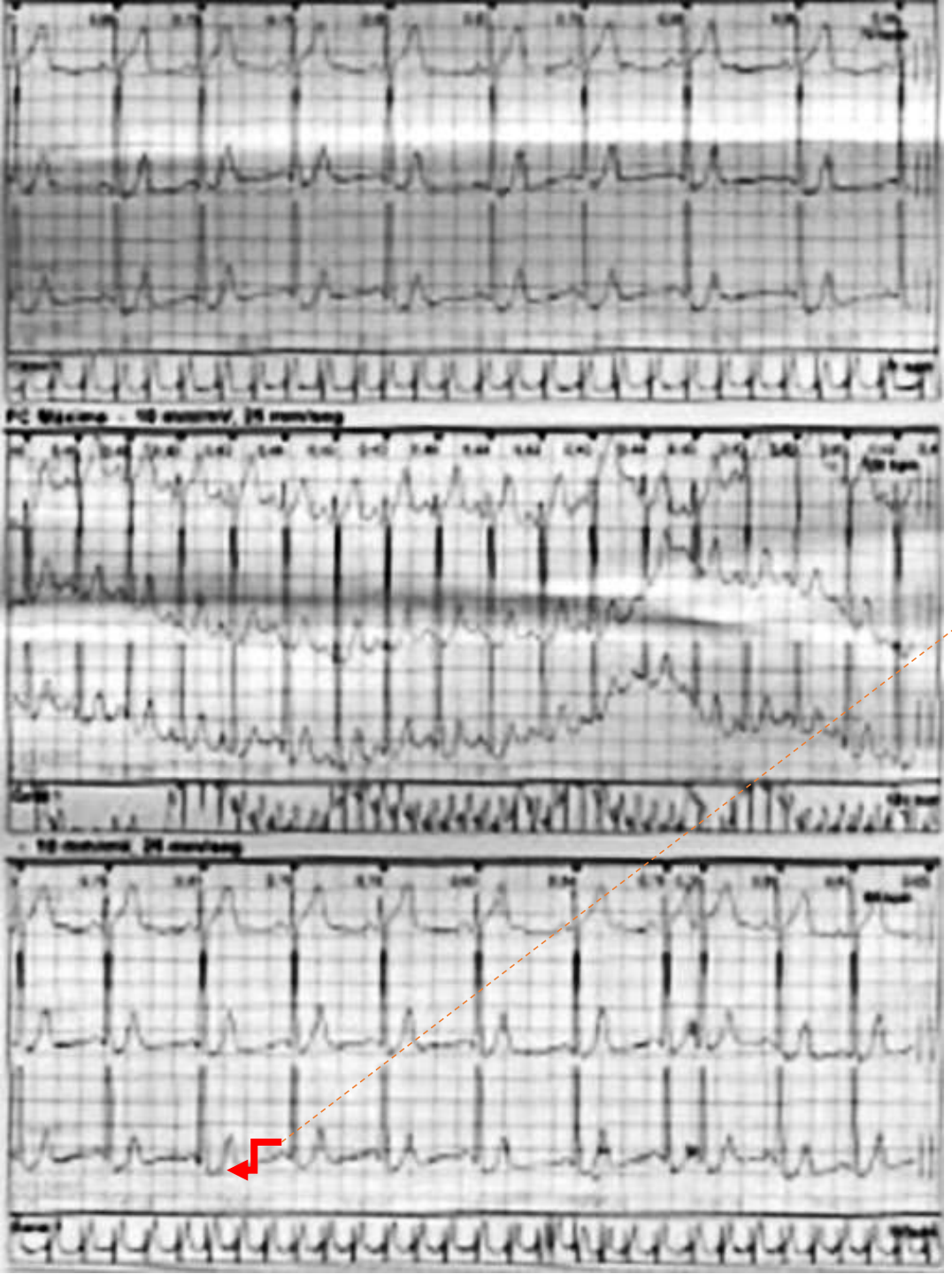


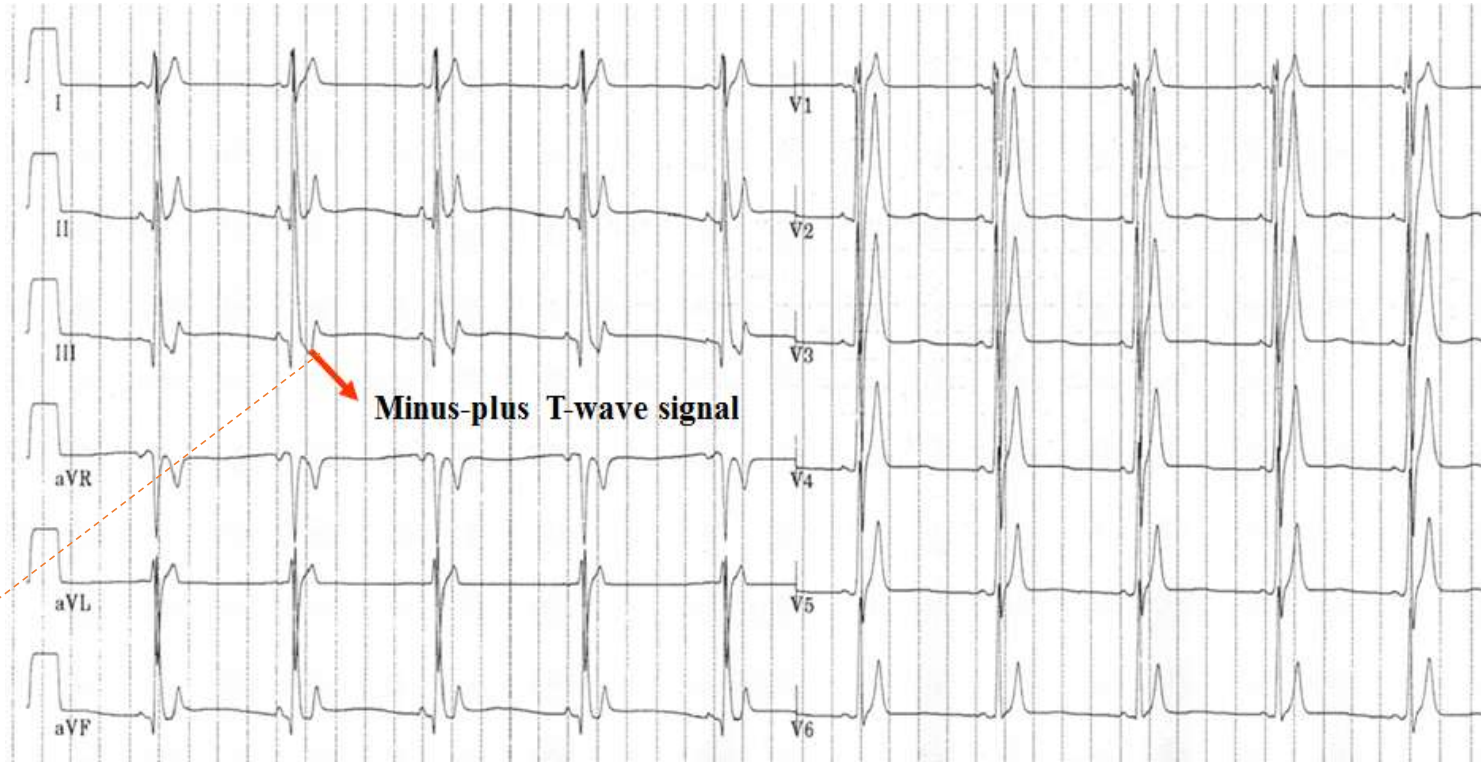
QT II = 290ms



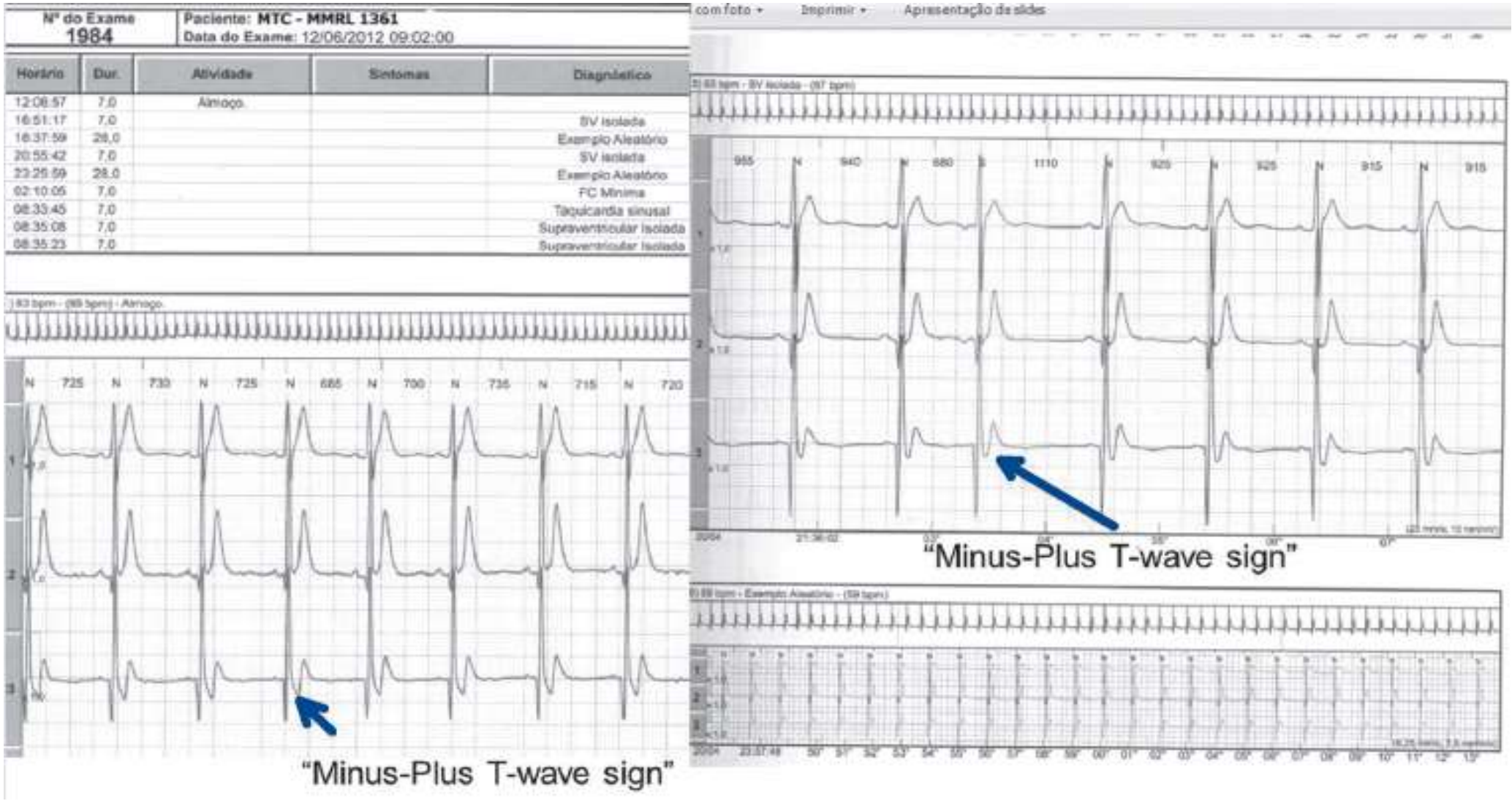
QT- V_5 = 319ms

Minus-plus T wave signal?





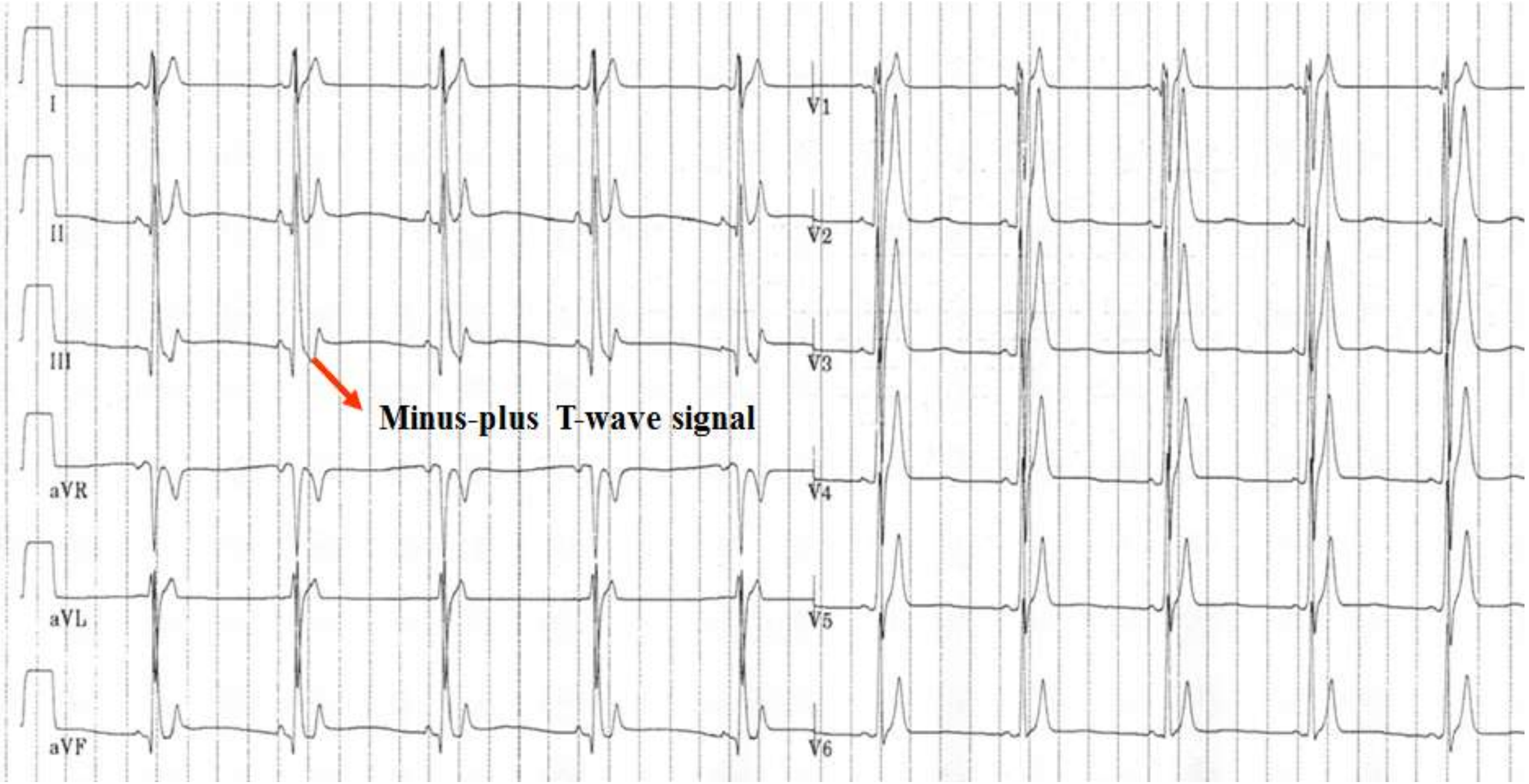
We observed for the first time this signal in SQT1 variant The minus-plus T wave signal or biphasic negative-positive T wave without ST segment observed in III in a patient with SQT1 variant showing by Schimpf et al (**Schimpf 2005**). See next slide.



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

“Minus-plus T wave signal” (**Pérez-Riera 2005,2013**): 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 genetypic/phenotypic relationship?

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



The minus-plus T wave signal or biphasic negative-positive T wave without ST segment observed in III in a patient with SQT1 variant (**Schimpf 2005 case**).

Congenital and acquired causes of short QT interval

A) Congenital/familial causes of short QT interval

1. **Congenital, hereditary or familial short QT syndrome (SQTS) SQTS** appears to have an autosomal dominant pattern of inheritance and high penetrance, some affected individuals have a family history of SQTS or related atrial fibrillation, syncope and/or sudden cardiac death. Other cases of SQTS are sporadic and occur in people with no apparent family history of related heart problems. The clinical profile of SQTS consists of: family history of SCD, personal history of palpitations, syncope, dizziness, resuscitated SCD, history of AF and documented VF. It is important to emphasize that SQTS is symptomatic from early age (new-born) to old age. Therefore, it is possible that SQTS accounts for some of the sudden infant death syndrome(SIDS) cases and for some cases of AF, especially lone AF.
   - I. **Congenital SQT1:** it is associated with gain-of-function mutation in KCNH2, affecting the rapid potassium rectifier channel Ikr / HERG (KCNH2) (**Brugada R 2004**). The mutation causes gain on function of the channel Ikr, and heterogeneous shortening in action potential and refractoriness reducing channel activity. The QTc value in SQT1 is 286±6 ms. SQT1 is the mirror image of LQT2 (Gain in function mutation versus decrease in channel function).

   - II. **Congenital SQT2:** Gain-of-function mutation in the KCNQ1 gene in slow potassium rectifier channel Iks. KCNQ1 (Iks) (**Bellocq 2004**). The mutation causes gain in Ikr channel. The QTc value in SQT2 was 302 ms. SQT2 is the mirror image of LQT1.

   - III. **Congenital SQT3:** It occurs secondary to gain-of-function mutations in KCNJ2, leading to an increase in the outward IK1 current and an acceleration of the final phase of repolarization. Gain of function by mutation IK1 iKCNQI (Iks) KCNJ2(Ik1) (**Priori 2005**). The QTc mean value in SQT3 is between 315-330 ms. SQT3 is the mirror image of LQT7 or Andersen-Tawil Syndrome.

   - IV. **Congenital SQT4:** mutation in CACNB2b (ICa) (**Antzelevitch 2007**). The QTc mean value in SQT4 is between 331-370 ms. The mutation causes channel loss of function.

V. **Congenital SQT5:** mutation in CACNAIC2b (ICa) (**Antzelevitch2007**). The QTc mean value in SQT5 is between 346-360 ms. The mutation causes channel loss of function. Observation: Calcium channel mutation often produces a combined SQTS/BrS phenotype.

VI. **Congenital SQT6:** mutation in CANA2DI(ICa) (**Templin 2011**). The QTc mean value in SQT5 is 329 ms. The mutation causes channel loss of function.

VII. **Congenital SQT7:** mutation in SCN5A? (**Hong 2012**). The mutation causes channel loss of function.

2. **Idiopathic ventricular fibrillation:** "Short" QTc values are commonly seen in male patients with idiopathic VF. However, "short" QTc values not rare among healthy adults, especially at slow heart rates (**Viskin 2004**). **Idiopathic Ventricular Fibrillation:** "Short" QTc values are commonly seen in male patients with idiopathic VF. However, "short" QTc values are not rare among healthy adults, especially at slow heart rates. Viskin et al demonstrated that male patients with idiopathic VF had shorter QT intervals (371± 22 ms) and suggested gender-specific cutoff values (QTc interval of 360 ms for men; QTc interval of 370 ms for women) for a short QT interval.

3. **Brugada Syndrome type 3:** It is caused by heterozygous mutation in the gene encoding the α-1C subunit of the L-type voltage-dependent calcium channel (CACNA1C; 114205) on chromosome 12p13. Antzelevitch et al (**Antzelevitch 2007**) reported two probands with BrS who also had shortened QT intervals. One was a 41-year-old man of Turkish descent who presented with AF and a QTc of 346 ms. Ajmaline administration led to further elevation of the ST segments on right precordial leads, and monomorphic VT. The patient had a brother who died of cardiac arrest at 45 years of age, and two daughters with short QTc intervals (360 and 373 ms, respectively). The other proband was a 44-year-old man of European descent who had STSE in V1, saddleback STSE in V2, a prominent J wave in III, and a short QTc of 360 ms. He was also diagnosed with facioscapulohumeral muscular dystrophy. His mother had 2 syncopal episodes at age 48 that resulted in SCD; his father, 2 sibs, and 3 children declined examination but reportedly did not exhibit the Brugada phenotype.

4. **Early repolarization syndrome** (**Bjerregaard 2010**): Early repolarization pattern (ERP) is defined as an elevation of the QRS-ST junction (J-point) of at least 1.0 mm from baseline in the inferior or lateral lead in at least 2 contiguous leads, manifest as QRS slurring or notching, is a common ECG finding that is generally considered to be benign but may be associated with VF. Patients with ERP and J-point elevations >2.0 mm, with unexplained events or a family history of unexplained SCD. Patients with ERP were more likely to be males, to have experienced symptoms during sleep, and to have a shorter QTc interval than those without ERP. It is not necessary the presence of STSE for the diagnosis of ERP (**Pérez 2012**). ERP (41 mm) in the inferior/lateral leads occurs in 1%–13% of the general population and in 15%–70% of IVF cases (**Haruta 2011**). In children it is even more prevalent. Male sex is strongly associated with ERP (70% vs 30%). The prevalence of the ERP declines in males from early adulthood until middle age, which suggests a hormonal influence (**Noseworthy 2011**). The ERP is more common in young physically active individuals, athletes, and African-Americans (**Junttila 2011**). There is an increased prevalence of ERP in Asians (**Haruta 2011**). The ERP is associated with vagotony, hypothermia and hypercalcemia. Bradycardia, prolonged QRS duration, short QT interval, and LVH with positive Sokolow-Lyon index are associated with ERP (**McIntyre 2012**). There also is some overlap between the BrS and ERS, since an ERP in the inferior or lateral leads is found in 13% of the BrS patients (**Sarkozy 2009**). ERP is observed in patients with SQTS, and many patients with an ERP or ERS have a relatively short QT interval (**Watanabe 2010**). The magnitude of the J-point elevation may have prognostic significance. Either slurred or notched J-point elevation ≥2 mm is rare in the general population but appears to be associated with an increased risk (**Tikkanen 2009**). Furthermore, J-point elevation in IVF patients is of greater amplitude and ECG lead distribution compared to those with an established cause of cardiac arrest (**Derval 2011**). Transient changes in the presence and amplitude of J-point elevation have a higher risk for VF (**Haissaguerre 2008**). A horizontal or descending STE following J-point elevation is associated with a worse outcome in the general population (**Pérez-Riera 2012**). This observation distinguishes IVF patients from matched controls and is a key aid in clinical decision making (**Rosso 2012**). The clinical implications of the observation of an ERP in the ECG of an asymptomatic subject are not clear.

4. The presence of ERP is associated with 3 times the risk of developing VF, but the overall risk is still negligible considering the rarity of VF in the general population (**Sinner 2012**). Because the presence of ERP may increase the vulnerability to SCD during an acute ischemic, a plausible implication stemming from the population studies is that middle-aged subjects with the ERP, especially those with a high amplitude of J-point elevation and horizontal/downsloping ST segment, should target a reduction in their long-term risk for ACS in accordance with current practice guidelines. Electrical storm is relatively common after ICD implantation in patients with the ERS (**Haissaguerre 2009**). Case series evidence supports the acute use of isoproterenol for suppression of recurrent VF and quinidine for long-term suppression. Recently, Zhang et al. observed using the intact human heart mapping on the epicardial electrophysiological substrate that early repolarization is associated with steep repolarization gradients caused by localized shortening of APD suggesting association of premature ventricular contractions initiation sites with areas of repolarization abnormalities. Conduction abnormalities were not observed (**Zang 2017**). Isoproterenol is typically initiated at 1.0 μg/min, targeting a 20% increase in heart rate or an absolute heart rate 490 bpm, titrated to hemodynamic response and suppression of recurrent ventricular arrhythmia. The abnormal EP substrate in ERS patients has the dromotropic disturbance, including delayed activation, conduction block, or fractionated electrograms; marked abbreviation of ventricular repolarization in areas with J-waves. The APD is significantly shorter than normal. Shortening of APD occurs heterogeneously, leading to steep repolarization gradients compared to normal control. The PVC sites of origin are closely related to the abnormal EP substrate with J-waves and steep repolarization gradients.

5. **Congenital lactase deficiency**: homozygous or compound heterozygous mutation in the LCT gene (603202) on chromosome 2q21. Severe rare recessive disorders that are relatively common in Finland. Gastrointestinal disorder characterized by watery diarrhea in neonate/infants fed with breast milk or other lactose-containing formulas (**Fazeli 2015**).

6. **Dilated Cardiomyopathy with short QT interval suggests primary carnitine deficiency** (**Perin 2017**).

7. **Familial primary hyperparathyroidism** (**Pepe 2013**).

8. **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 (**Jørgensen 2015**).

B) Acquired causes of short QT interval

Acidosis in patients with chronic kidney disease. pH is related to QTd and QTc. QT intervals are decreased after treatment of acidosis in Chronic Kidney Disease [**Yenigun 2016**].

- Dysautonomia of chronic fatigue syndrome with QTc mean values of 371 a 384 ms (**Naschitz 2006**).
- Toxicity and digitalis effect: Digoxin effect refers to the presence on the ECG of: shortened QT interval [**Iribarren 2013**], downsloping ST depression with a characteristic "Salvador Dali sagging" appearance; flattened, inverted, or biphasic T waves. 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 (**Cheng 2004; Garberoglio 2007**).
- Activation of K_{Ach} caused by strong parasympathetic stimuli to the heart.
- In response to atropine
- Autonomic tone alteration
- Hyperthermia [**van der Linde 2008**]
- Hyperkalemia (mild elevations of serum potassium <6.5 mEq/L), consequence of narrow-based, peaked T waves. T waves with short duration, approximately 150 to 250 msec.
- Sporadic primary hyperparathyroidism(**Saikawa 1988; Shah 2004**)
- Hypercalcemia of malignancy: Osteolytic hypercalcemia, humoral hypercalcemia of malignancy and ectopic production of calcitriol (by lymphoma) with extreme or severe hypercalcemia(**Douglas 1984; Otero 2000; Nishi 2006: Garner 2014; Durant 2017**)
- Hypercalcemia of granulomatous disease

- Chronic renal failure with aplastic bone disease
- Tertiary hyperparathyroidism
- Infants with congenital adrenal hyperplasia (**Schoelwer 2017**)
- Acute renal failure
- Lithium-associated hypercalcemia (**Meehan 2017**)
- Increased calcium intake
- Pheochromocytoma or response to catecholamine (**Davey 1999**)
- Response to atropine (**Ahnve 1982**)
- Hyperthyroidism
- Vitamin A intoxication
- Thiazides (**Topsakal 2003**)
- Milk-alkali syndrome
- Immobilization-related hypercalcemia (**Uehara 2017**)
- Theophylline
- Rufinamide, a recently approved anticonvulsant, illustrates the current regulatory approach to drugs that shorten QT interval [**Schimpf 2012**].
- 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

Electro-vectorcardiographic aspects of congenital Short QT syndrome

Introduction

Congenital Short QT syndrome (SQTS) is an hereditary, congenital, familial or sporadic orphan entity 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?) (**Giustetto 2011**). Additionally, characteristically, the heart rate is not significantly modified with heart rate changes (**Kobza 2009**), 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 seven genes have been reported to associate with SQTS: HERG or KCNH2 (SQT1),

KCNQ1 (SQT2),

KCNJ2 (SQT3),

CACNA1C (SQT4),

CACNB2b (SQT5)

CACNA2D1 (SQT6) and Caveolin-3 (SQT7).

They have been labeled SQT1-SQT7 based on the chronology of their discovery. Tables next slide

SQT Variant	QTc duration	Gene symbol and effect	Author
SQT 1	260-280 ms	hERG (human ether-a-go-go-related gene KCNH2) (I_{ks})	Brugada R et al. Circulation. 2004 Jan 6;109(1):30-5
SQT 2	290 ms	(I_{k1})	Bellocq C, et al. Circulation. 2004;109:2394
SQT 3	315-320 ms	KCNJ12 (Kir2.2) i	Priori SG et al. Circ Res. 2005 Apr 15;96(7):800-7.
SQT 4	331-370 ms	CACNA1C(I_{Ca}^{2+})	Antzelevitch C et al. Circulation 2007;115:442
SQT 5	346-360 ms	CACNB2b (ICa2+) loss-of-function	Antzelevitch C et al. Circulation 2007;115:442.
SQT 6	329 ms	(I_{Ca}^{2+})	Templin C et al. Eur Heart J. 2011 May;32(9):1077-88.
SQT 7	320 ms	caveolin-3	Barajas-Martinez H. 2015.

SQT Variant	OMIM	Gene name	Locus
SQT 1	#609620	KCNH2	7q36.1
SQT 2	#609621	KCNQ1	11p15.5-p15.4
SQT 3	#609622	KCNJ2	17q23
SQT 4	#600919	CACNA1C	11q23-q24
SQT 5	#600003	CACNB2b	10p12.33-p12.31
SQT 6	# 114204	CACNA2D1	7q21.11
SQT 7	?	CAVE3	?

SQT Variant	OMIM	Gene name	Protein & subunit	Channel affected and functional abnormality
SQT 1	#609620	Potassium voltage-gated channel, subfamily H, member 2	Kv11.1 alpha	Alpha subunit of the rapid component of cardiac delayed rectifier potassium channel (IKr) Gain of function
SQT 2	#609621	Potassium voltage-gated channel, KQT-like subfamily, member 1.	Kv7.2 alpha	Slow delayed rectifier potassium channel. Gain of function
SQT3	#609622	Potassium inwardly-rectifying channel, subfamily J, member 2	Kir2.1 alpha	Inward rectifier current (I_{K1}) Potassium (I_{K1}) cardiac Kir channels. Gain of function.
SQT4	#600919			L-type calcium channel, α-subunit
SQT5	#600003			L-type calcium channel, β-subunit
SQT6	# 114204			L-type calcium channel subunit
SQT7	?			Late I_{to}

The four mutations on potassium channels called SQT1 (I_{ks}), SQT2 (I_{kr}) SQT3 (I_{k1}) and SQT7 are the opposite of long QT syndrome or genetic mirror image of long QT syndrome type 2, type 1, type 7 or Andersen-Tawil syndrome and LQT9 respectively, because they exert opposite gain-of-function effects on the delayed rectifier potassium current (I_{Kr} and I_{Ks}) and cardiac inwardly rectifying K^+ current**(I_{K1})** in contrast to the loss-of-function of potassium channels in the long QT syndromes.

Initial outward potassium channel in phase 1 of action potential

Phase 1: This phase presents a significant notch in epicardial and midmyocardial cells, and it is mediated by the I_{TO} channel. It is responsible for the Osborn wave of hypothermia and by the J point elevation in Brugada syndrome and early repolarization syndromes. Phase 1 coincides with the J point in surface ECG, and it occurs close to 0 mV. The I_{to1} channel is voltage-dependent. Thus, its activation occurs in the range between –30 mV and +10 mV. In phase 1 a discrete and declining inflow of Na^+ is still observed, as well as slow "in crescendo" onset of K^+ outflow through the so-called I_{to1} channel, transient outward current, or 4-aminopyridine-sensitive outward current. The I_{to1} channel is also found in atrial cells.

Ito channel subtypes

I. I_{to1}, $I_{A,}$ transient outward K^+ current activated during phase 1, or channel sensitive Ito 4 aminopyridine (4-AP): Activated by voltage, modulated by neurotransmitters & blocked by 4- aminopyridine (4AP) quinidine & flecainidine, known as I_{to1}, with the two varieties: $I_{to\text{-}fast}$ that activates and inactivates quickly, and the $I_{to\text{-}s}$ (slow) or $I_{to\text{-}slow}$ that activates and inactivates slowly. During phase 1, even being polyionic, it occurs mainly by the early transient outflow of the K^+ cation, or transient outward K^+ current, by a channel known as $\boldsymbol{I_{to}}$, $\boldsymbol{I_{to1}}$, $\boldsymbol{I_{to\text{-}fast}}$, $\boldsymbol{I_{to\text{-}f}}$, or $\boldsymbol{I_{toA}}$. This channel is voltage-dependent (i.e. controlled by voltage), and its activation occurs in a range from -10 mV and +30 mV. It has a rapid activation and inactivation kinetics, and is blocked among others by (sensitive to) 4-aminopyridine, and manifests at the end of ventricular depolarization, and the onset of ventricular repolarization, which corresponds in surface ECG to the J point (from the word Junction), located between the end of the QRS complex and the onset of the ST segment.

II. I_{to2} or $I_{Cl.Ca}$, channel of Cl^- activated by Ca^{2+}- slow transient outward K+ current or 4-aminopyridine-resistant transient outward current – transported by Cl^- anions: modulated by the percentage of intracellular Ca^{++}. Known as I_{to2} and characterized by being smaller, activated more slowly & inactivated more quickly. Its ion base could be conditioned predominantly by Cl^- outflow by the so-called $I_{Cl}{}^-$ channel. This channel is magnified by adrenergic stimulation. A new class of antiarrhythmic agent was described- classified as class V, which selectively blocks the Cl^- channel (I_{Cl}). Its representative is anilidine.

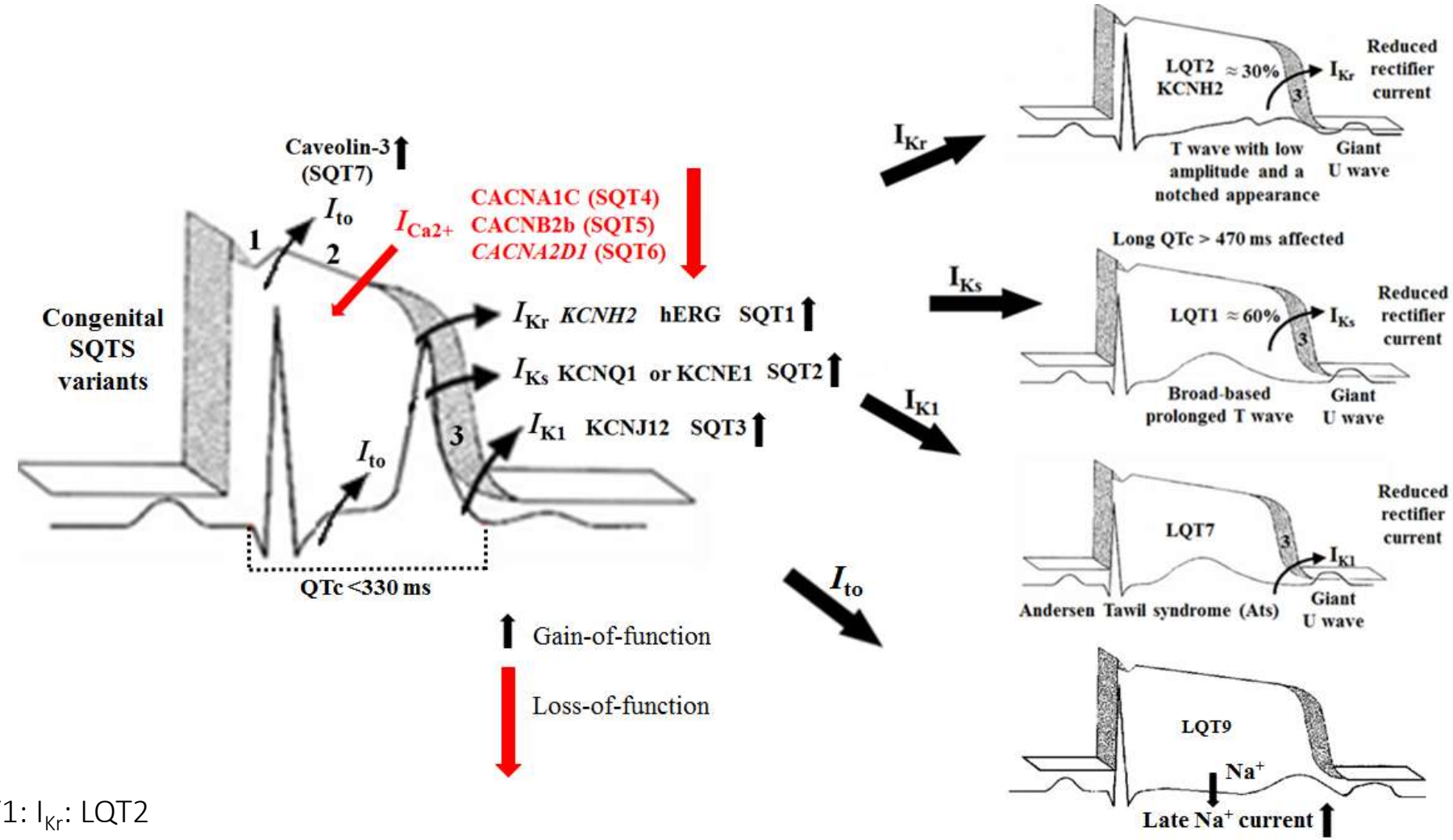
The table shows the characteristics of I_{to1} and I_{to2} currents

Cation		α subunit protein	Cation		α subunit protein	Cation
K^+	Transient rapid outflow I_{to1} current	pore-forming protein isoforms Kv4.3/4.2K_V4.2 and Kv4.3Presumable clone.	K^+	Transient rapid outflow I_{to1} current	pore-forming protein isoforms Kv4.3/4.2K_V4.2 and Kv4.3 Presumable clone.	K^+
K^+	Transient slow outflow I_{to2} current	Pore-forming protein isoforms Kv1.4.	K^+	Transient slow outflow I_{to2} current	Pore-forming protein isoforms Kv1.4.	K^+

III. ICLcAMP or time-independent Cl^- channel regulated by cAMP/adenylate cyclase. $\boldsymbol{I_{Cl\ AMPc}}$ or time-independent chloride (Cl^-) channel, cAMP-activated Cl^- current. The channel is activated by the increase of intracellular concentration of AMPc. It is involved in cell volume, bloodvolume regulation, and regulation of osmolarity and type 1 response to cell chemical stimuli (**Carpenter 1997**). The channel depolarizes slightly the resting potential, and significantly shortens AP duration, and antagonizes AP prolongation mediated by β-stimulation.

IV. $I_{Cl\text{-}edema}$ or $I_{Cl}{}^-{}_{\text{-SWELL}}$, swelling-activated chloride channel, swelling-activated, outward rectifying chloride channel. This channel belongs to the category of stretch-activated ion channels. It is inhibited by anthracene-9-carboxylic acid, tamoxifen, or natriuretic peptide precursor B (NPPB), and by diisothiocyanatostilbene-2.2'-disulphonic acid (DDSA) (**Wang 2006**). It shortens AP and causes depolarization. Na^+ outflow through the Na^+/Ca^{2+} exchanger channel operated reversely. Inward Na^+ through the Na^+/Ca^{2+} exchanger channel, operating in a reverse way.

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):

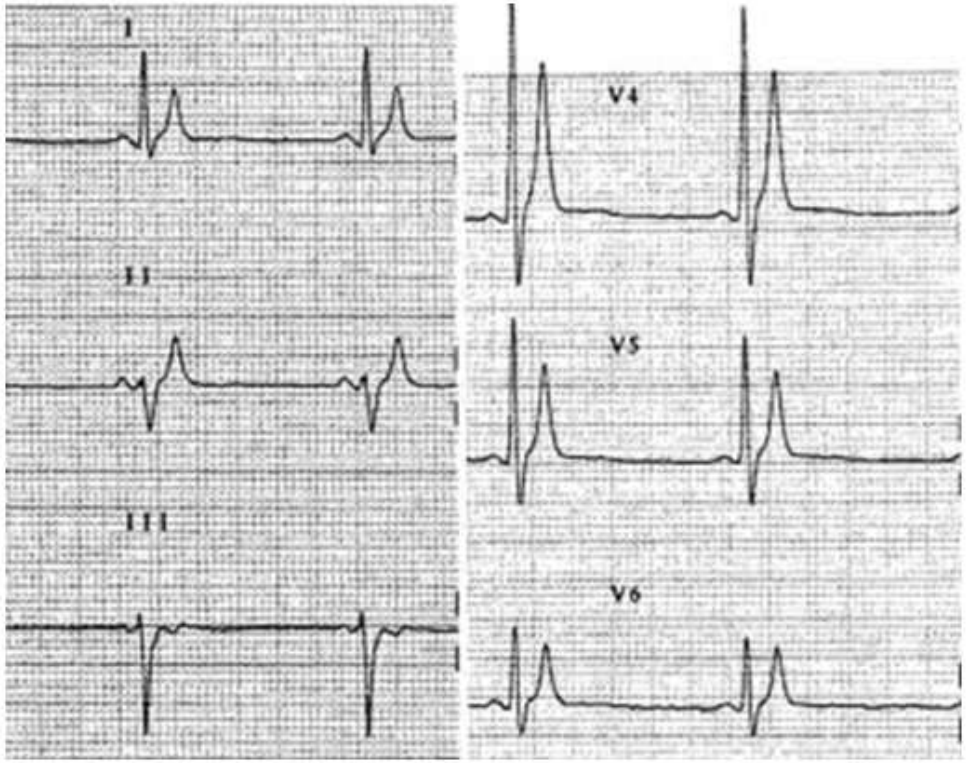


- Congenital SQT1: I_{Kr}: LQT2
- Congenital SQT2: I_{Ks}: LQT1
- Congenital SQT3: I_{K1} LQT7 or Andersen-Tawil Syndrome
- Congenital SQT7: I_{to} LQT9 Caviolin-3 (Umpublished)

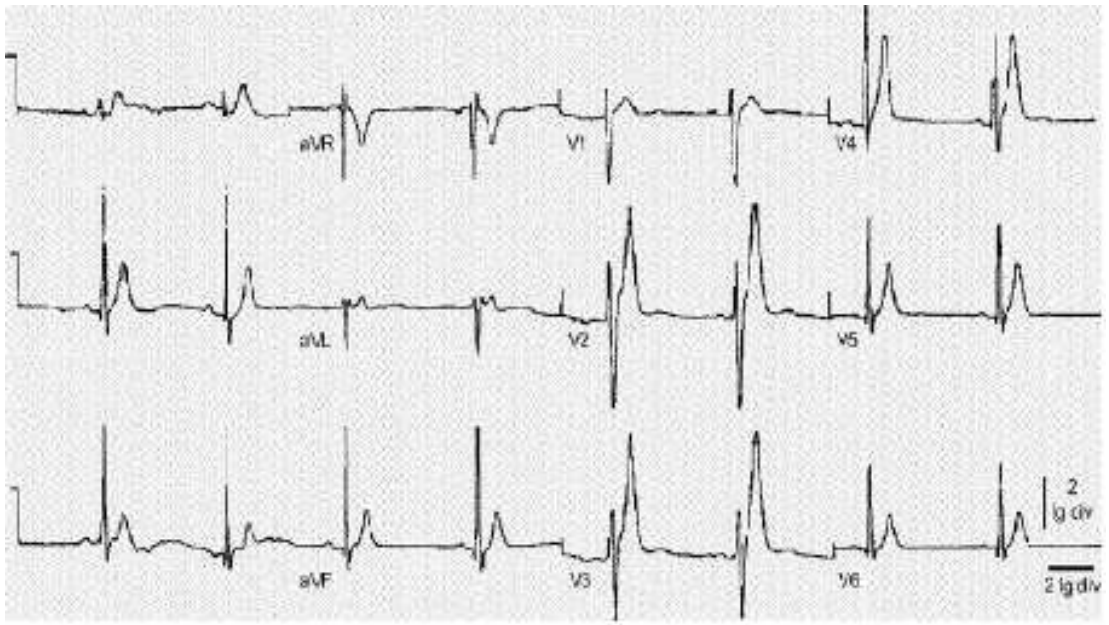
And the three calcium channel variants: CACNA1C (SQT4), CACNB2b (SQT5), and *CACNA2D1* (SQT6).

Short QT syndrome, type-1 phenotype, SQT1 (I_{Ks})

Gussak et al (**Gussak 2000**) reported a brother, sister and their mother who had idiopathic persistently short QT interval, which was associated in the 17-year-old sister with several episodes of paroxysmal AF requiring cardioversion. All 3 patients had QT intervals of less than 80% of predicted value (280 ms, 272 ms, and 260 ms in the sister, brother, and mother, respectively). Similar ECG changes (QT interval, 260 ms) in an unrelated 37-year-old female were associated with SCD. Hong et al (**Hong 2005**) reported that in the family originally studied by Gussak et al, the deceased maternal grandfather also had short QT interval and chronic AF. Programmed electrical stimulation in the mother and two sibs revealed a very short atrial and ventricular refractory period and inducibility of AF/VF. All 3 affected members of the family received ICDs, and treatment with propafenone maintained them free of AF. Gaita et al (**Gaita 2003**) described 2 unrelated 5-generation pedigrees with a strong family history of SCD and an idiopathic very short QT interval on ECG without structural heart disease. Manifestations included syncope, palpitations, and cardiac arrest. SCD occurred in both males and females over 4 generations with father-to-son transmission in both families, suggesting an autosomal dominant mode of inheritance. 6 patients underwent extensive evaluation; all exhibited a QT interval ≤280 ms on ECG and had short atrial and ventricular refractory periods; increased ventricular vulnerability to AF/VF in 3 of 4 patients. SQT1 is caused by a gain of function substitution in the HERG gene (human Ether-a-go-go Related Gene, in Italy or KCNNH2 in the new nomenclature). It is the gene that encodes the pore-forming α-subunit of a voltage-gated K^+ channel. (I_{Kr}) OMIM #609620, SQT1 was first described in January of 2004 by Brugada et al (**Brugada 2004**). The authors identified two different missense mutations in two families resulting in the same amino acid change (N588K) in the S5-P loop region of the cardiac I_{Kr} channel HERG (KCNH2). The mutations dramatically increase IKr, leading to heterogeneous abbreviation of APD and refractoriness, and reduce the affinity of the channels to I_{Kr} blockers. The occurrence of SCD in the first 12 months of life in two patients suggests the possibility of a link between KCNH2 gain of function mutations and SIDS.

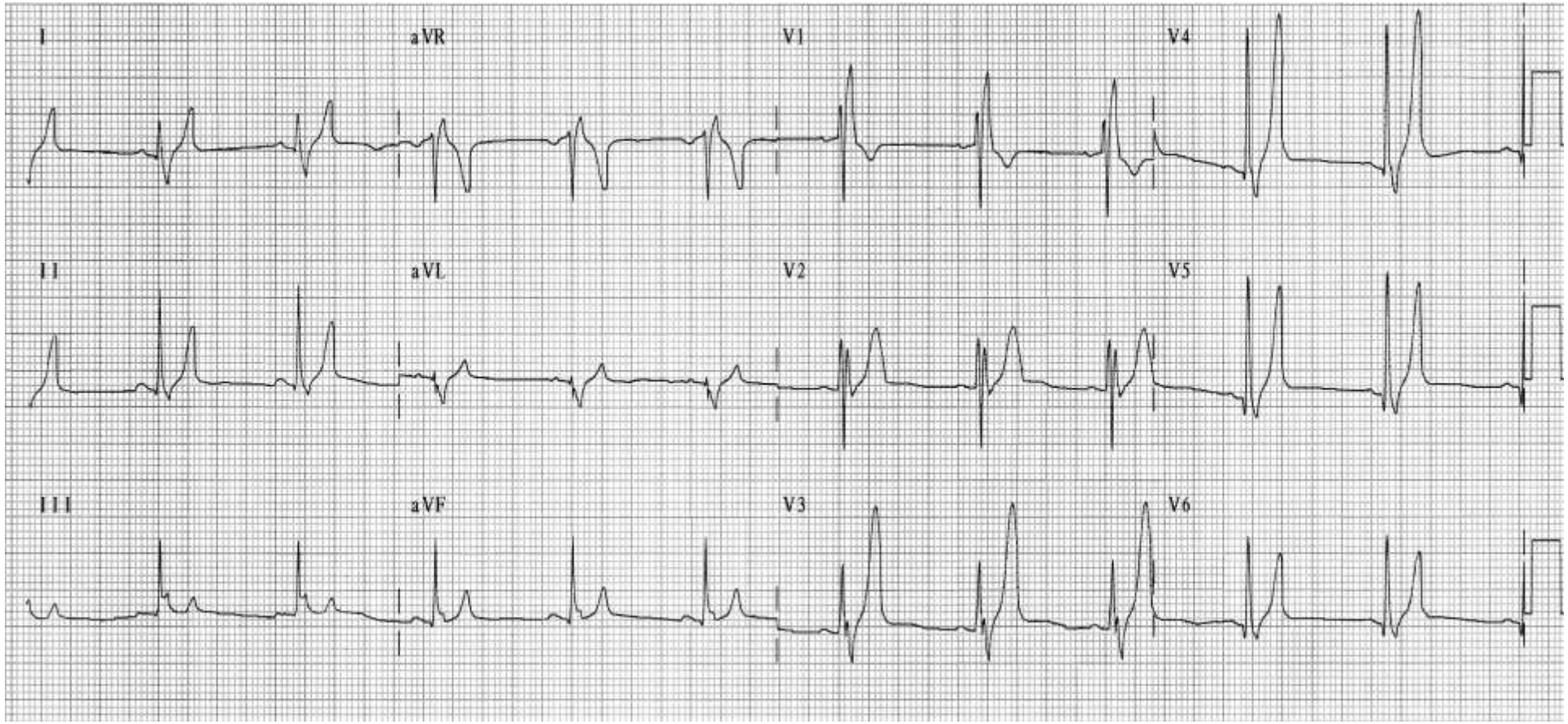


ECG showing typical SQT1 features: tall, narrow and peaked T waves, QT 280 ms. From Gaita (**Gaita 2003**).



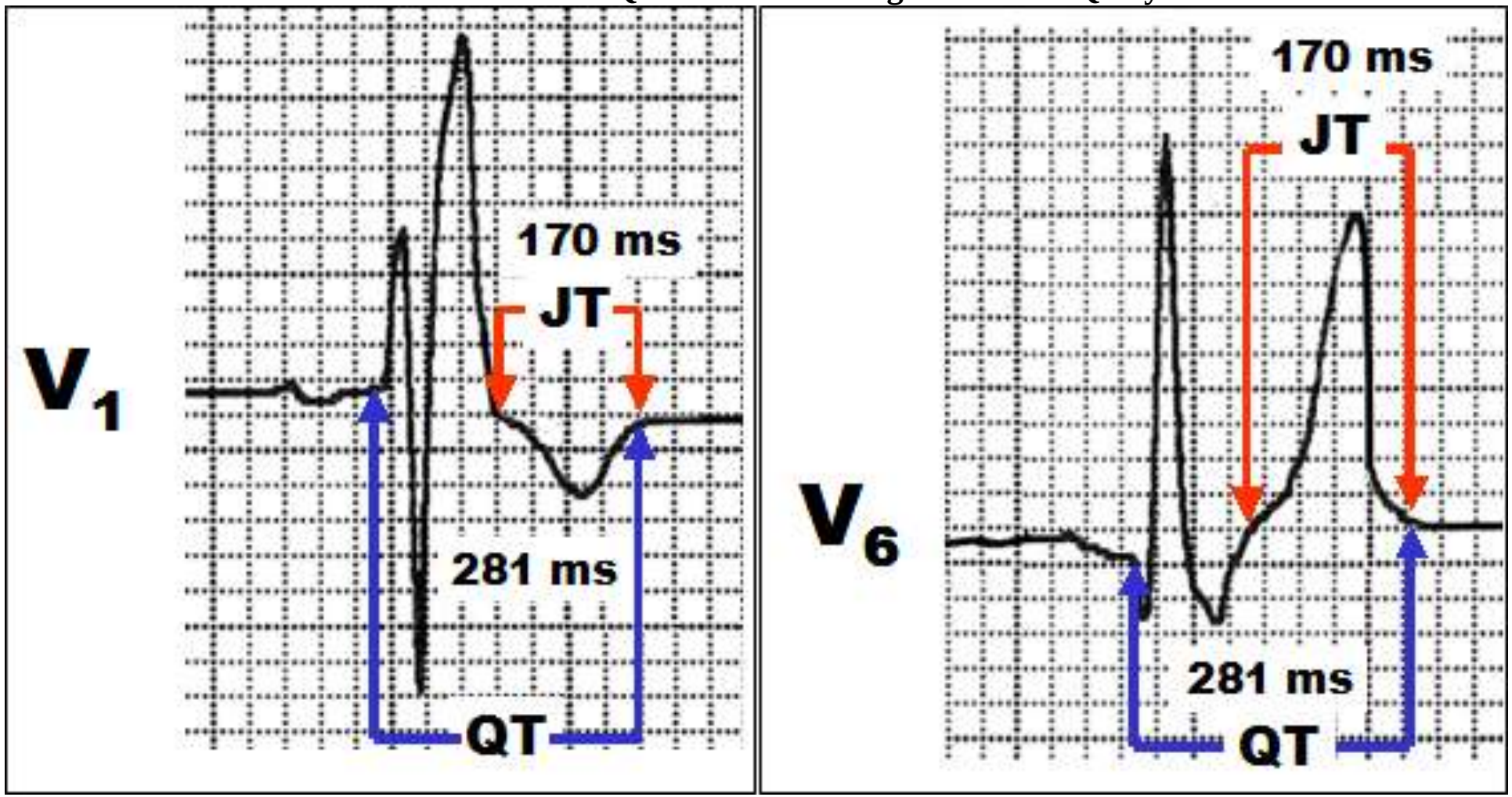
ECG of a patient with SQTS. Check the tall peaked T waves. From Ramón Brugada (**Brugada 2004**).

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



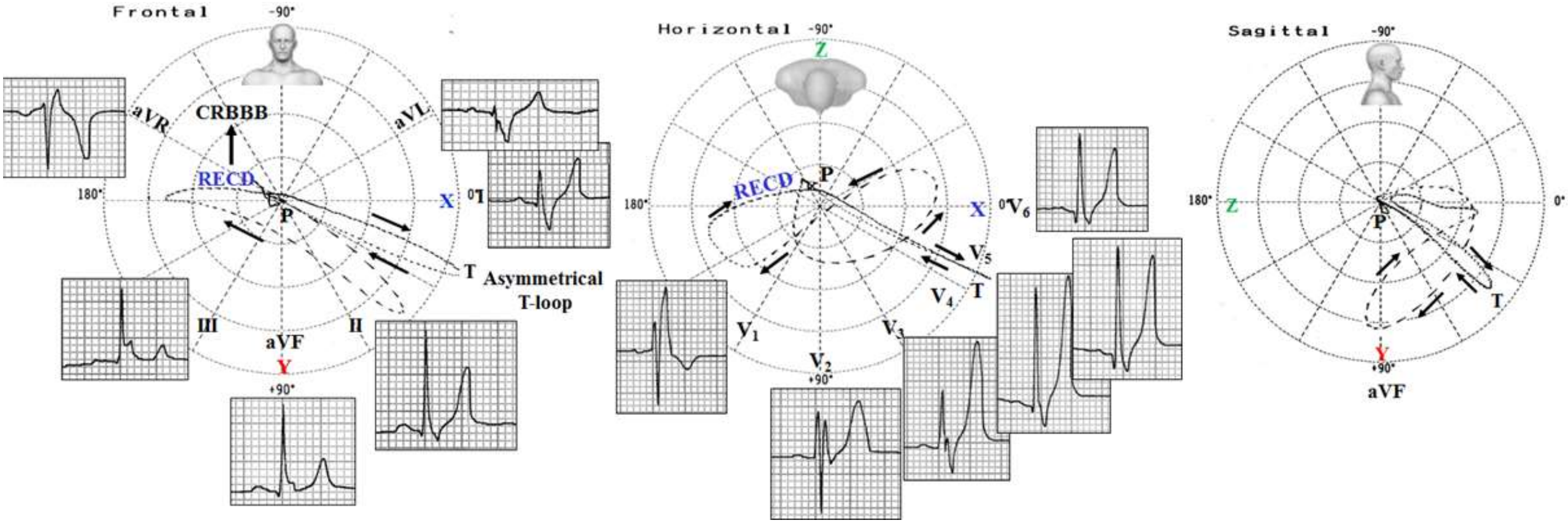
Rhythm: sinus; HR: 65 bpm; P wave: SAP axis: +54º in the FP and to the front in the HP; duration: 80 ms; voltage: 1 mm; PR interval: 134 ms; QRS: SÂQRS: +106º in the FP and to the front in the HP; QRS duration (QRSD): 120 ms; QRS morphology: triphasic rSR' pattern in V1 and broad S wave in left leads 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 (**Sagie 1992**).

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.

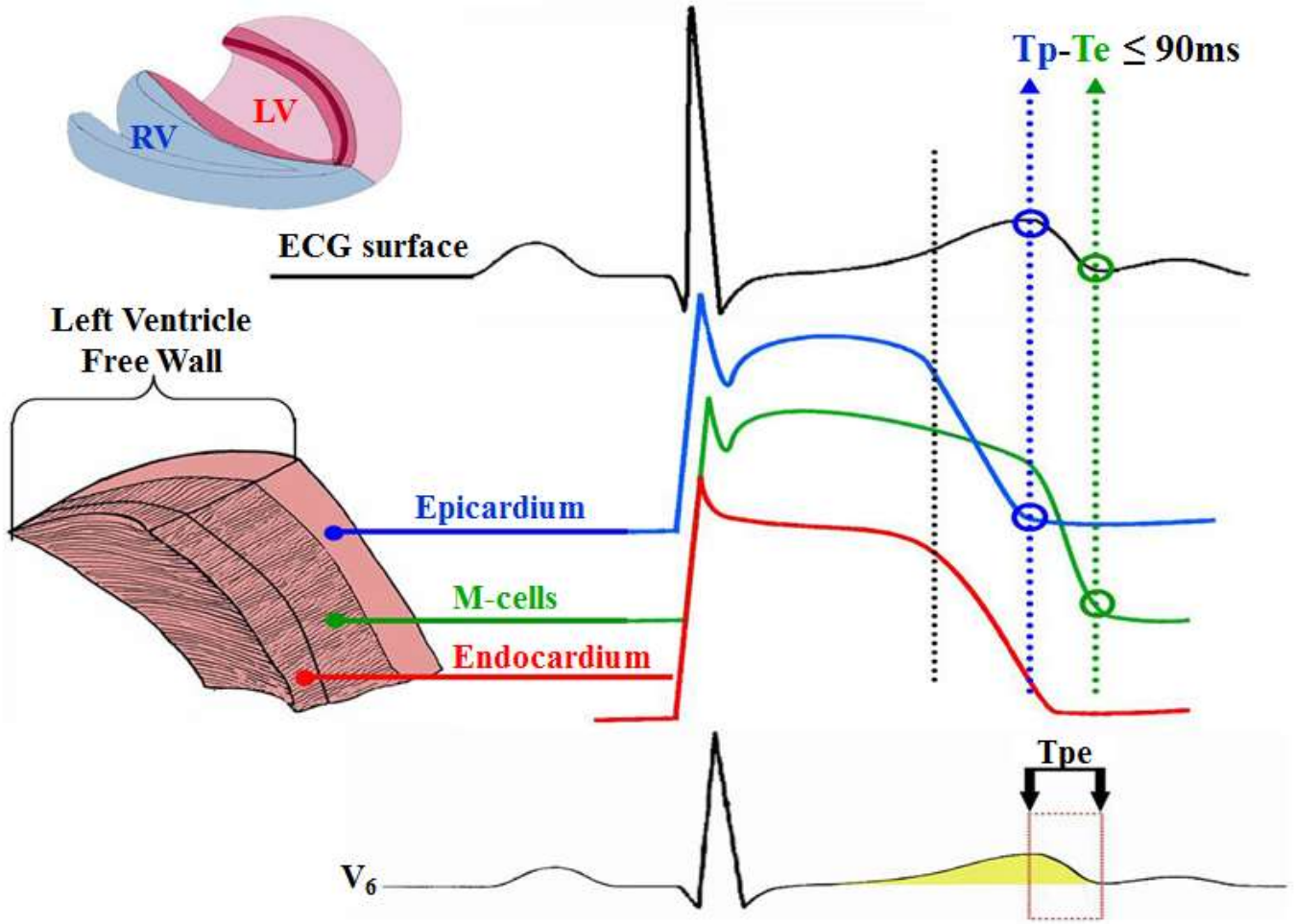
HP – Triphasic QRS pattern in V1-V2 and broad final S-wave in V5-V6: CRBBB. VCG Grishman-type of CRBBB: afferent loop behind the X line; triphasic rSR' pattern; short QT interval; tall T waves with narrow base from V_3 through V_5.

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.

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 (**Gaita 2003**).



Representation of the Tpeak/Tend interval (Tpe or TpTe).This is the interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias. The normal value of the Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V5 lead. In congenital SQTS this parameter is >92 ms in women and >94 ms in men (measurement in V5).

In healthy children and adolescents, TpTe intervals vary between individual leads of ECG, with the longest in lead V3. The TpTe interval is longer in boys and in older children and prolongs as heart rate decelerates. TpTe dispersion varied from 6 to 80 ms (mean 38.6 ms±14.6 ms, median 40 ms) with no gender differences and greater values in older subjects. TpTe/QT and TpTe/JT ratios are higher in boys. TpTe interval should be measured in the precordial leads (**Bieganowska 2013**). In adults, the normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V_5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patients carriers of channelopaties. Interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias.

Amplification of TDR often is secondary to preferential prolongation of the action potential duration (APD) of M cells, whereas in Brugada syndrome, it is thought to be due to selective abbreviation of the APD of the right ventricular epicardium.

These parameters are indicative of augmented transmural dispersion of repolarization (**Anttonen 2008**). However, asymmetrical T waves with a less steep ascending limb followed by a rapid descending limb have been reported as well.

In the short QT syndrome, preferential abbreviation of APD of either endocardium or epicardium appears to be responsible for amplification of TDR.

In catecholaminergic polymorphic ventricular tachycardia, reversal of the direction of activation of the ventricular wall is responsible for the increase in TDR.

Thus, the long QT, short QT, Brugada, and catecholaminergic ventricular tachycardia syndromes are pathologies with different phenotypes and etiologies, however, these syndromes share a common final pathway in their predisposition to sudden cardiac death.

Intravenous administration of nifekalant prolonged effective refractory period at multiple ventricular sites as well as the QT/QTc interval (from 260/300 to 364/419 ms) on the surface ECG in congenital SQTS. Nifekalant also enlarged the transmural ARI dispersion of the ventricular repolarization, which was measured by the difference between the longest endocardial activation-recovery intervals and the shortest epicardial activation-recovery intervals during atrial pacing at 90 bpm, from 73 to 103-105 ms. These values corresponded to the intervals between the peak and end of the T wave on the surface ECG. Nifekalant-induced QT interval prolongation on the surface ECG may not indicate attenuation of the arrhythmogenic potential in the heart of SQTS patients (**Chinushi 2012**).

The T(p-e)/QT ratio

It is an electrocardiographic index of arrhythmogenesis for both congenital and acquired ion channel disease leading to ventricular arrhythmias. In healthy individuals, the T(p-e)/QT ratio has a mean value of approximately 0.21 in the precordial leads and it remains relatively constant between the heart rates from 60 to 100 bpm.

The T(p-e)/QT ratio is significantly greater in the patients at risk for arrhythmic events such as those with LQTS, Brugada syndrome, SQTS, and also in patients with organic heart disease such as acute myocardial infarction (**Gupta 2008**) and left ventricular hypertrophy (**Zhao 2010**) and obstructive sleep apnea (OSA) (**Kilicaslan 2012**).

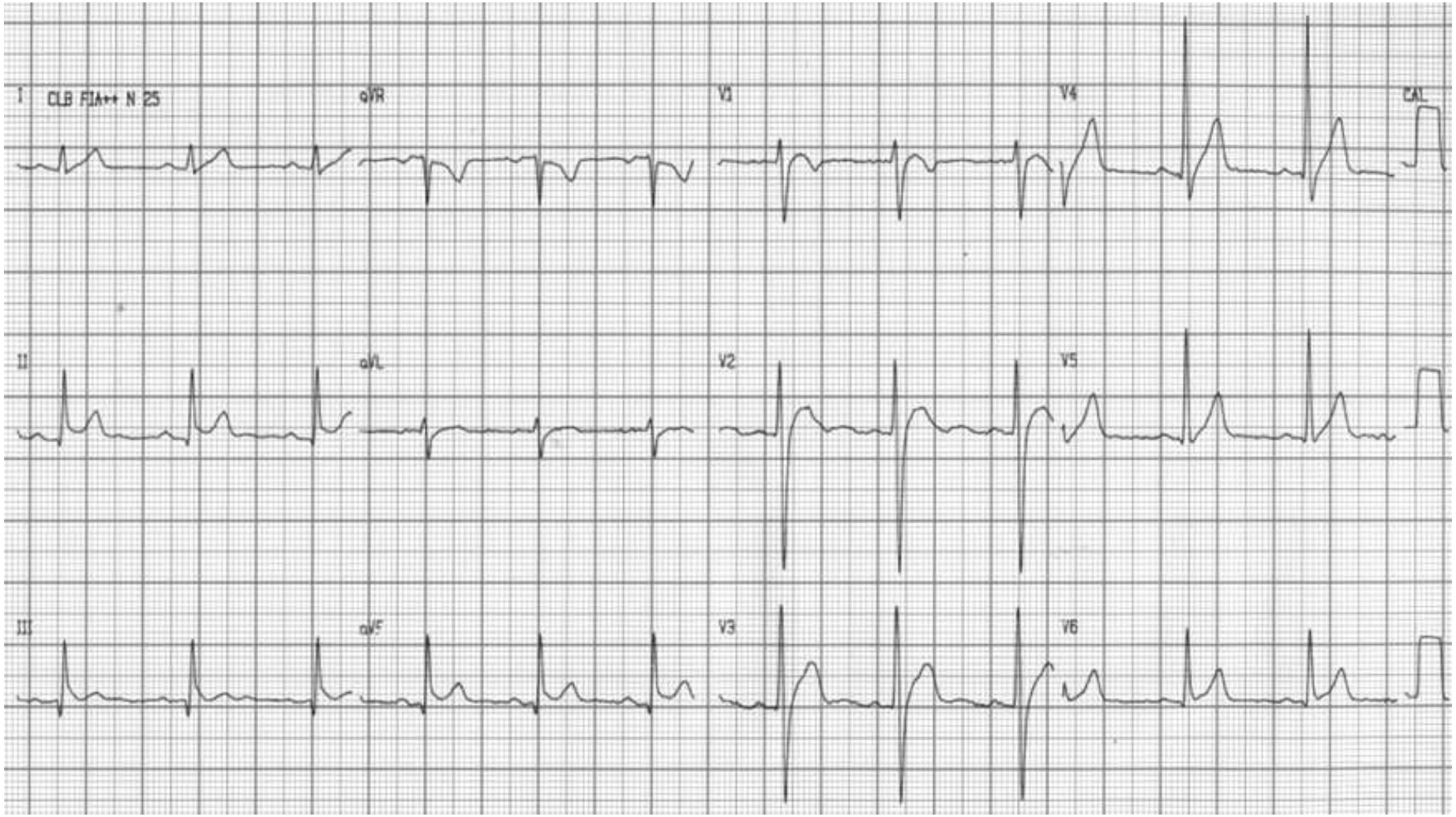
A Tp-e/QT ratio ≥0.29 in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction may serve as a prognostic predictor of adverse outcomes after successful PCI treatment in STEMI patients (**Zhao 2012**).

Functional reentry is the underlying mechanism for arrhythmogenesis associated with an increased T(p-e)/QT ratio

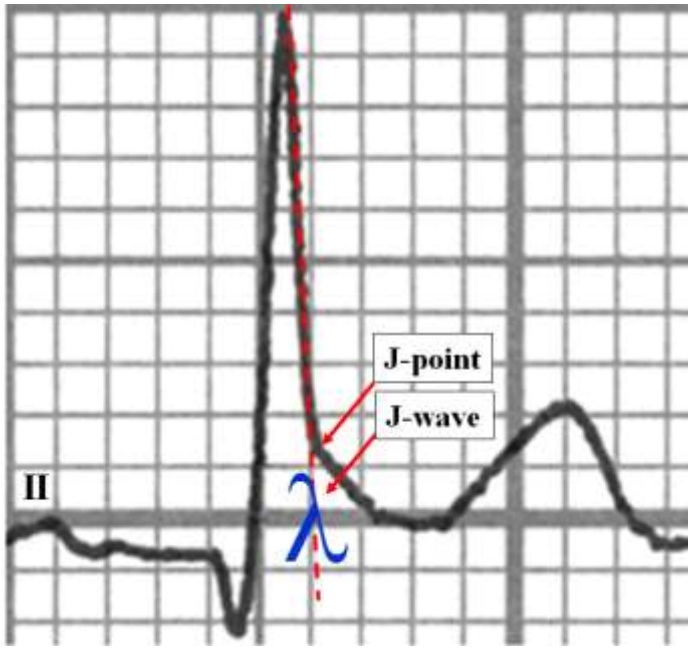
High prevalence of early repolarization. It is associated with arrhythmic events

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 (**Watanabe 2010**).

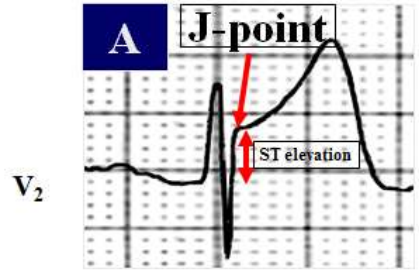
Example of SQTS associated with early repolarization

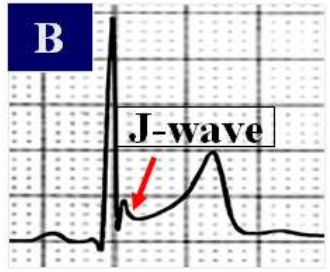


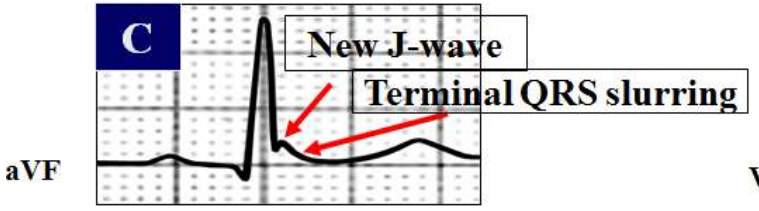
HR = 68 bpm; QT = 340 ms; RR = 880 ms; QTc = 362 ms

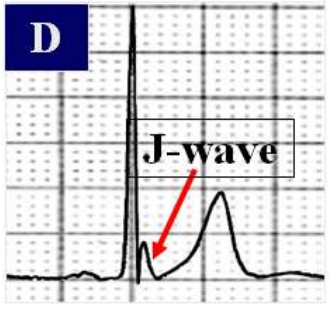


The first point of inflection of the R wave descendent ramp is considered the real J point. In these cases the “tangent line” method is ideal. ST-segment elevation = 0.8 mm. We considered it an atypical C type variant of early repolarization pattern. The lambda aspect is a marker of fatal arrhythmias.









Classic definition of ERP always with ST segment elevation

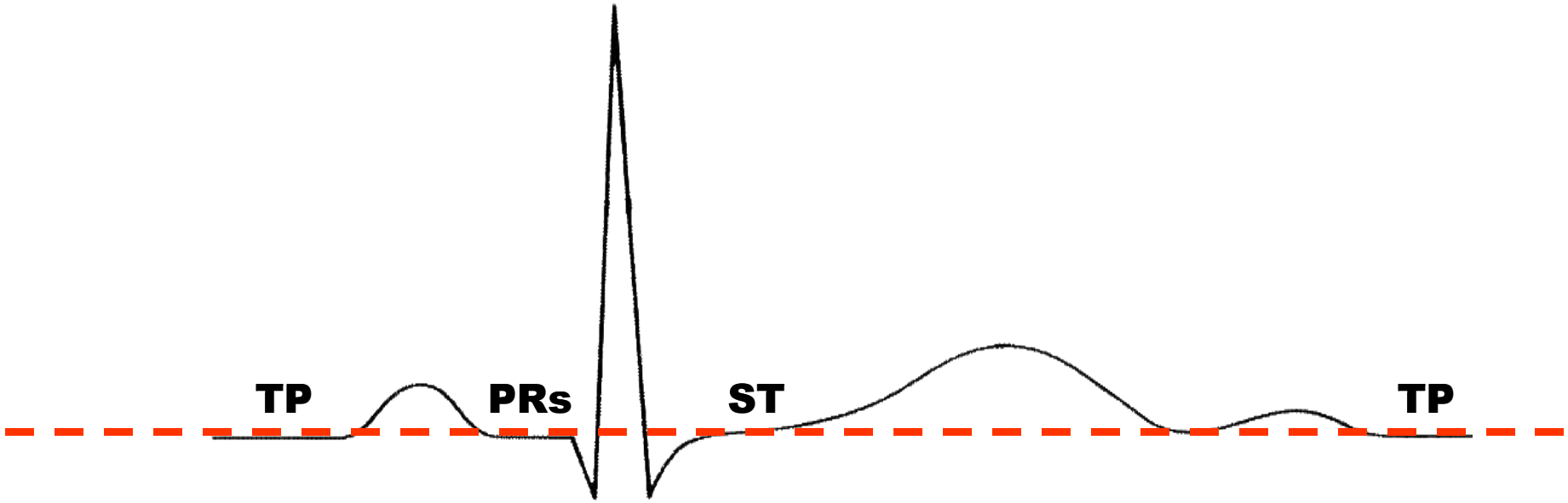
A) ERP with only ST segment elevation

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 (**Pérez 2012**).

Usually, the PR (end of P wave up to QRS complex onset), ST (from the J point or the end of QRS up to the beginning of the T wave) and TP (from the end of the T wave up to the P wave of the following cycle) segments are at the same level. The figure shows a normal ECG and a line of dots pointing out the level of the three segments: PR, ST and TP.



A and B classic definition of ER always with ST segment elevation

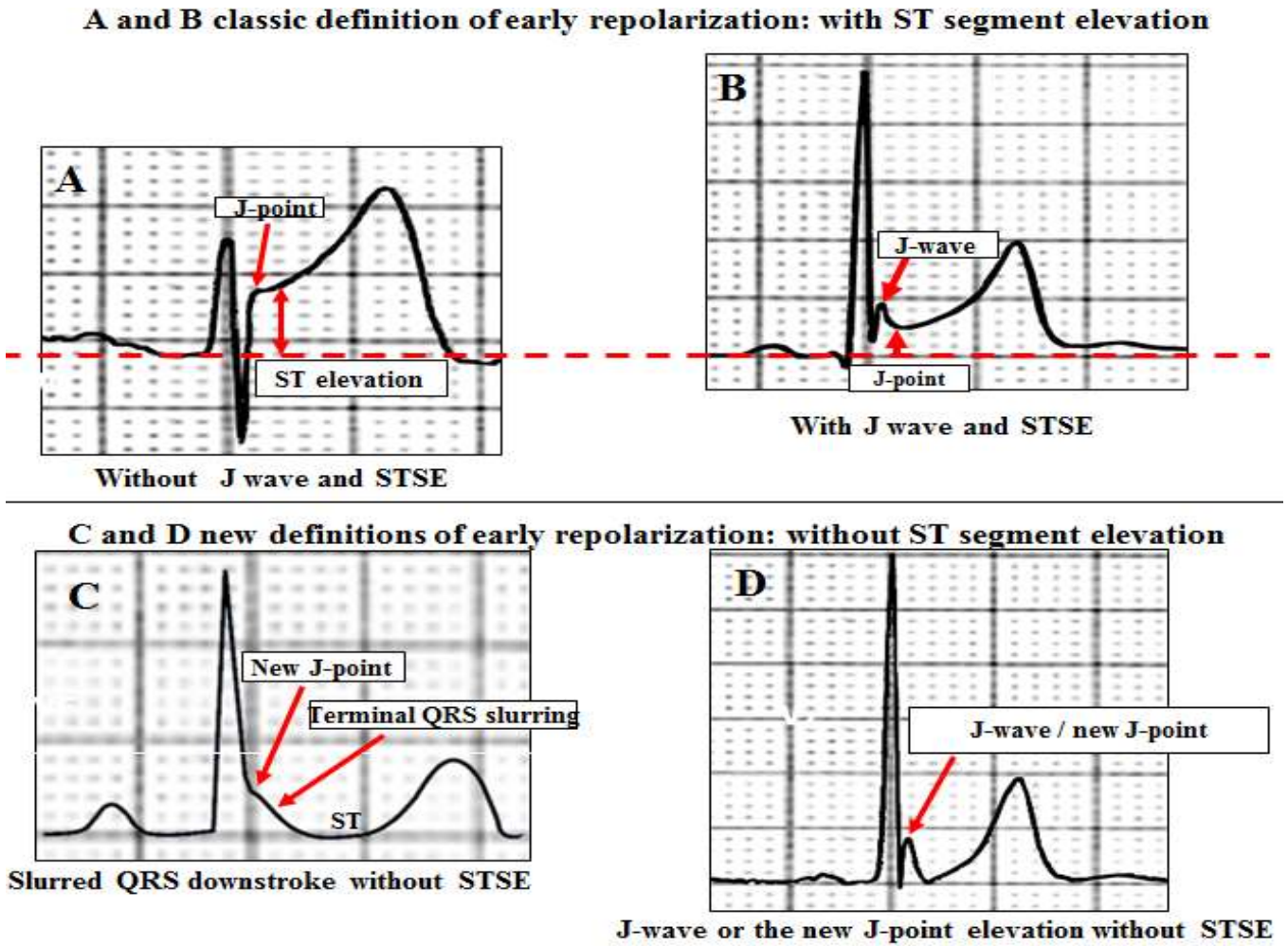
A) ER with only ST segment elevation.

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

C and D New concept of ER without ST segment elevation

C) J-point elevation and terminal QRS slurring without ST segment elevation.

D) J-wave without ST segment elevation.



*SarcK_{ATP} are composed of eight protein subunits (octamer). Four of these are members of the inward-rectifier potassium ion channel family K_{ir}6.x (either K_{ir}6.1or K_{ir}6.2), while the other four are sulfonylurea receptors (SUR1, SUR2A, and SUR2B) (**Inagaki 1995**).

The main features of congenital SQTS are:

- Absence of structural heart disease: "electrical disease"
- Familial clinical-electrocardiographic entity: rarely sporadic
- Autosomal dominant inheritance or sporadic, and genetically heterogeneous
- Constant and uniform very short QT and QTc intervals (QTc interval ≤330 ms)
- Positive family history for sudden cardiac death (SCD), syncope, palpitations (very frequently AF)
- 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 (only detectable with molecular autopsy or postmortem molecular testing: it is a set of molecular techniques used in forensic medicine to attempt to determine the cause of death in unexplained cases, in particular sudden unexplained deaths (for example SCD). About 30% of SCDs in young people are not explained after full conventional autopsy, and are classified as sudden unexplained deaths. The use of a panel of genetic markers for long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia and cardiac channel miopathies elucidated around 40 to 45% of the cases (**Tester 2006**).

Short QT syndrome type-2 phenotype SQT2 (I_{Kr})

It was first reported in 2004 by Bellocq et al **(Bellocq 2004; Hong 2005).** A 70-year-old man who was successfully resuscitated after an episode of ventricular fibrillation. A short QT interval on a subsequent ECG (290 ms) and on every ECG through 3 years of follow-up was noted. He had no prior symptoms and no other physical or physiological abnormalities, and his family history was unremarkable. These authors presented an alternative molecular mechanism for a patient with short QT and ventricular fibrillation: a gain of function mutation in KCNQ1 that enhanced the IKs current. However, there are few and sporadic cases of this variant documented. caused by a gain of function substitution in the KvLQT1 (I_{Ks}) channel. OMIM: #609621.The authors identified a missense mutation in the KCNQ1 gene (607542.0037).

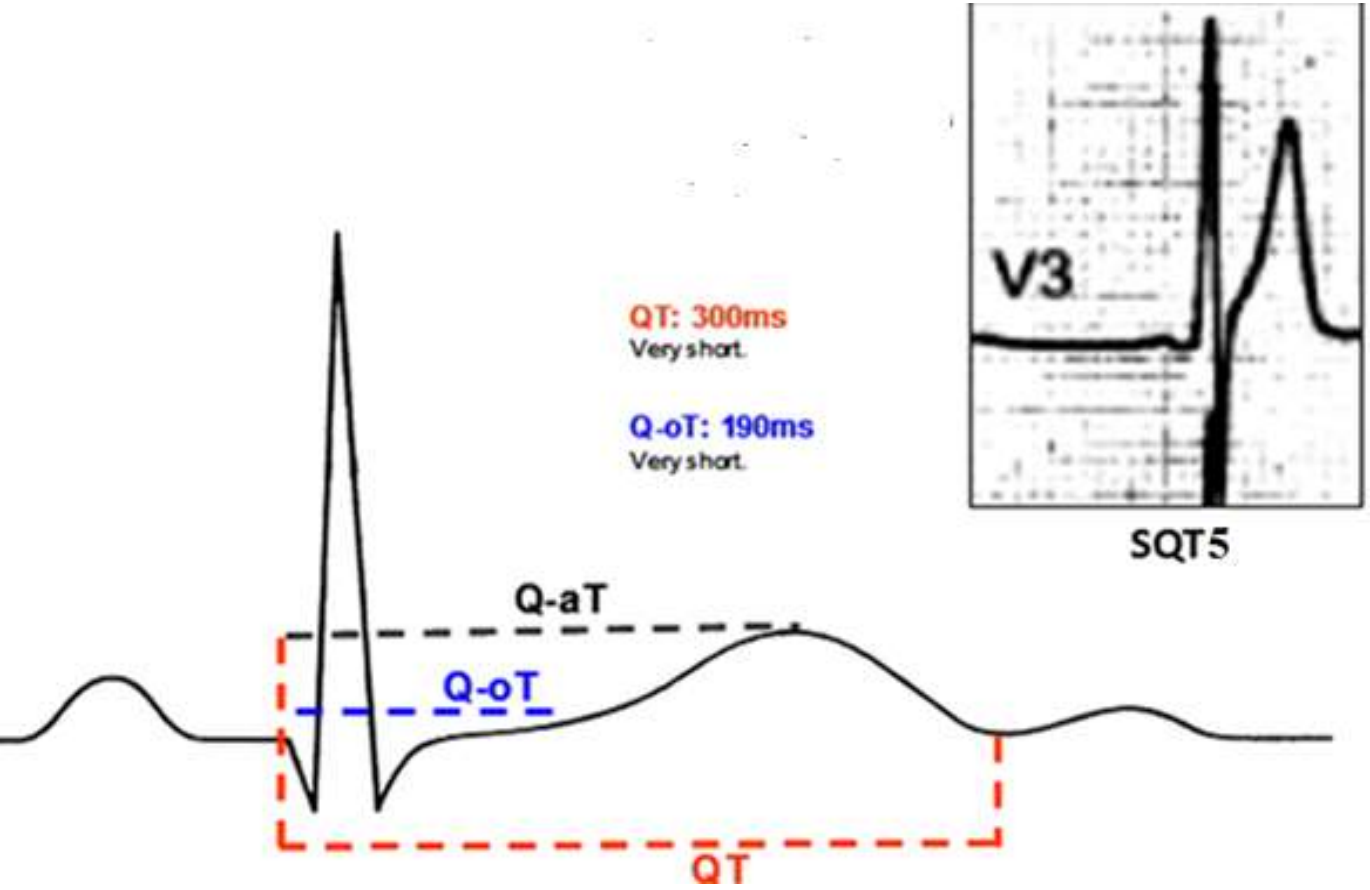
Short QT syndrome, type-3 phenotype, SQT3 (I_{K1})

Priori et al., identified a missense mutation in the KCNJ2 gene (600681.0010). The mutation was not present in the unaffected mother or in the paternal grandparents, indicating that it may have occurred de novo in the father (**Priori 2005**). The affected members of a single family had a G514A substitution in the *KCNJ2* gene that resulted in a change from aspartic acid to asparagine at position 172 (D172N). This is the third variant of the short QT syndrome (SQT3). These mutations were observed in two patients: an asymptomatic 5-year-old girl who was found to have an abnormal ECG on routine clinical evaluation, with a markedly short QT interval (315 ms) and narrow-based and peaked T waves. Her 35-year-old father had a short QT interval (320 ms) and a history of near-syncopal episodes and palpitations since adolescence. ECGs of the proband and her father were characterized by asymmetric T waves with a rather normal ascending ramp and a remarkably rapid descending terminal ramp, a pattern also observed in his father at age 15. The mother and the paternal grandparents had unremarkable ECGs and reported no family histories of sudden death. A genetic defect in the KCNJ2 gene caused a significant increase in the outward Ik1 current leading to an acceleration of the final phase of the repolarization. A study describes a novel heterozygous gain-of-function mutation in the inward rectifier potassium channel gene, KCNJ2, mutation, M301K, associated with SQTS (Hattori 2012). Another mutation described is (E299V) in *KCNJ2*, the gene that encodes the strong inward rectifier K^+ channel protein (Kir2.1) (Deo 2013). Proarrhythmic action potential changes were observed with both loss-of-function and gain-of-function I_{K1} ($K_{ir}2.2$), as associated with Andersen-Tawil syndrome type 1 (ATS OMIM #170390) (LQT7) and short QT syndrome type 3 respectively (**Pérez Riera 2013**).

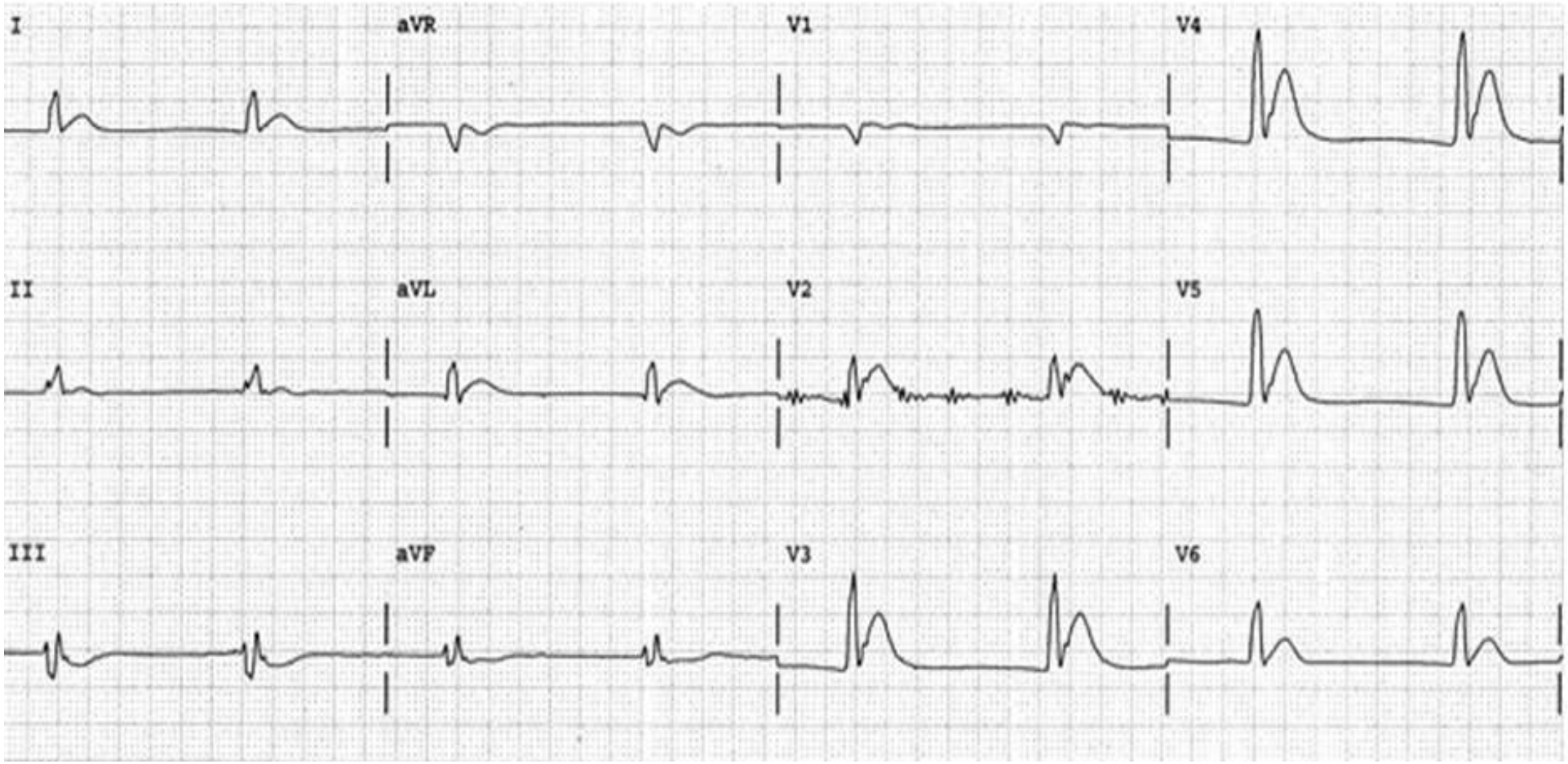
L-type calcium channel (LTCC) mutations related with Short QT syndrome

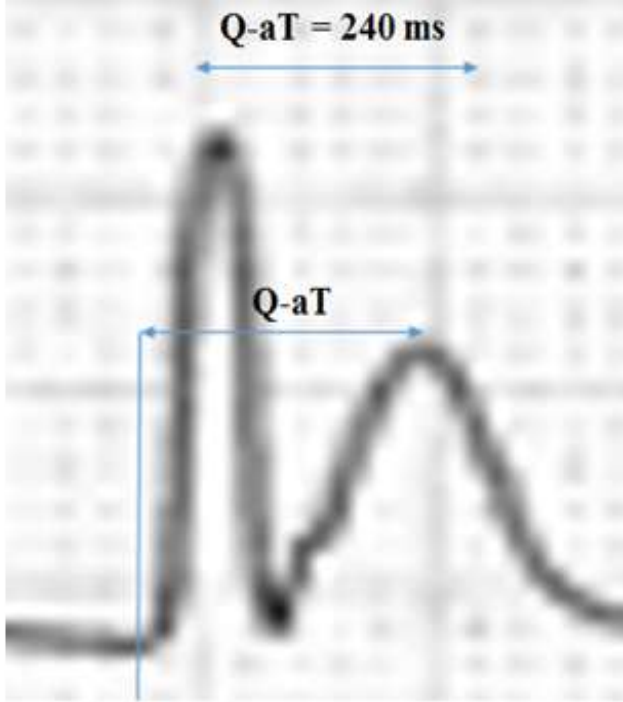
They have been associated with Brugada syndrome (BrS), short QT syndrome, and Timothy syndrome (LQT8). The mutations in the LTCCs are detected in a high percentage of probands with J-wave syndromes associated with inherited cardiac arrhythmias, suggesting that genetic screening of Ca(v) genes may be a valuable diagnostic tool in identifying individuals at risk. CACNA2D1 is a novel BrS susceptibility gene and CACNA1C, CACNB2, and CACNA2D1 are possible novel ERS susceptibility genes (**Burashnikov 2010**). Mutations with loss-of-function in the cardiac L-type calcium channel gene I_{Ca} by a genetic mutation in CACNB2b or *CACNA1C* can result in Brugada Syndrome (BrS) and a shorter than normal QT interval or in an infant BrS phenotype without QT interval because it is accompanied by another genetic mutation leading to a loss of function in I_{Ks}. Calcium channel mutations are SQT4; SQT5 and SQT6 often produce a combined phenotype of SQTS/Brugada syndrome. The Brugada Syndrome phenotype and a family history for sudden cardiac death was associated with QTc ≤ 360 ms (Antzelevitch 2007). In these three cases a mutation in genes encoding the α1- or β2b- subunits of the cardiac L-type calcium channel were identified and specifically a mutation on CACNB2b (S481L) and two mutations on CACNA1C (A39V and G490R). In order to determine the contribution of each mutation to the clinical phenotype, each of the WT and mutated CACNA1C and CACNB2b mutations were expressed in CHO cells. The results of patch-clamp experiments indicate that all the mutations cause a major loss of function in calcium channel activity. The QTc observed in these three cases and in affected family members ranged from 330 to 370 ms, a QTc longer than what was observed in other SQTS families. Accordingly, it seems premature to consider CACNB2b and CACNA1C as SQTS genes, but it is probably more appropriate to define what Antzelevitch et al, observed as a new clinical entity, characterized by overlapping phenotypes. *Mutation on CACNA1C* pathogenic variants have been associated with Timothy syndrome (LQT8), a novel disorder characterized by multiorgan dysfunction including lethal arrhythmias, webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism. In every case, Timothy syndrome results from the identical, de novo Ca(V)1.2 missense mutation G406R. Ca(V)1.2 is expressed in all affected tissues (Splawski 2004).SQT4: Gene symbol: *CACNB2b* (I_{Ca}) Gene name: Calcium channel voltage-dependent, β-2 subunit/ (**Antzelevitch 2007**).

SQT Variant	QTc duration	Gene symbol and effect	Author
SQT 4	331-370ms	CACNA1C	Antzelevitch C et al. Circulation 2007;115:442
SQT 5	346-360 ms	CACNB2b (I_{Ca}) loss-of-function	Antzelevitch C et al. Circulation 2007;115:442.



Mutations in L-type Ca^{2+} channel (*CACNA1C*) or its β2b-subunit (*CACNB2b*) have been reported in BrS patients associated with a shorter than normal QT-interval (>330 ms but <360 ms in male probands), which is to be expected in the presence of decreased calcium inward current. The diseases associated with mutations in *CACNA1C* and *CACNB2b* follow an autosomal dominant pattern of transmission. These mutations (A39V and G490R in *CACNA1C* and S481L in *CACNB2b*) induce a loss of calcium channel function, which in the case of the A39V mutant is most likely caused by defective trafficking to the cell membrane (**Antzelevitch 2007**). Missense mutations in CACNA1C (A39V and G490R) and CACNB2 (S481L) encoding the α-1- and β-2b-subunits of the L-type calcium channel. We observe that these mutations have an extremely short Q-aT interval (240 ms) and absent ST segment, consequently the genotype has an "hypercalcemic-like" phenotype because Q-aT values <270 ms are typical of severe hypercalcemia. See next slide……





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**).

SQT5: Gene symbol: CACNA1C (I_{Ca}). **Gene name:** Calcium channel. Voltage-dependent, L type, α-1C subunit. (**Antzelevitch, 2007**).
SQT 6: Gene symbol: CACNA2D1 (I_{Ca}): **Gene name:** Calcium channel voltage-dependent alpha 2/delta subunit 1 (**Templin 2011**). Additionally, mutation in **CACNA2D1** have been associated with malignant hyperthermia susceptibility (**Robinson 2000**), and early repolarization syndrome (**Burashnikov 2010**).

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

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 (**Napolitano 2014**).

Very Short QTc/QT interval

The QT interval or electric systole: interval that extends between the first recognizable part of QRS complex onset up to the final recognizable portion of the T wave (the latter may be hard to determine accurately). The QT interval represents the time between ventricular electric depolarization onset and electric repolarization end. The QTc interval constitutes the classical measurement of ventricular repolarization; however, the parameter includes ventricular depolarization. Thus, when there is bundle branch block or Wolff-Parkinson-White ventricular preexcitation, the measurement of ventricular repolarization by QTc may be incorrect. In such cases, the measurement of JTc is more accurate than the QTc interval, because it excludes depolarization. The JT and JTc interval extends from the J point to the end of the T wave.

The measurement of JTc may be useful to identify LQTS cases with borderline values, where QTc interval could be normal in rest ECG.

How to measure appropriately the QT interval?

The QT interval should be measured in II or V5. Traditionally, lead II has been used for QT interval measurement because in this lead, the vectors of repolarization usually result in a long single wave rather than discrete T and U waves (Garson 1993).

Several successive beats should be measured, with the maximum interval taken. U waves ≥1 mm that are fused to the precedent T wave should be included include in the measurement. U waves <1 mm and those that are separate from the precedent T wave should be excluded.

Case report

Caucasian 44 asymptomatic man.

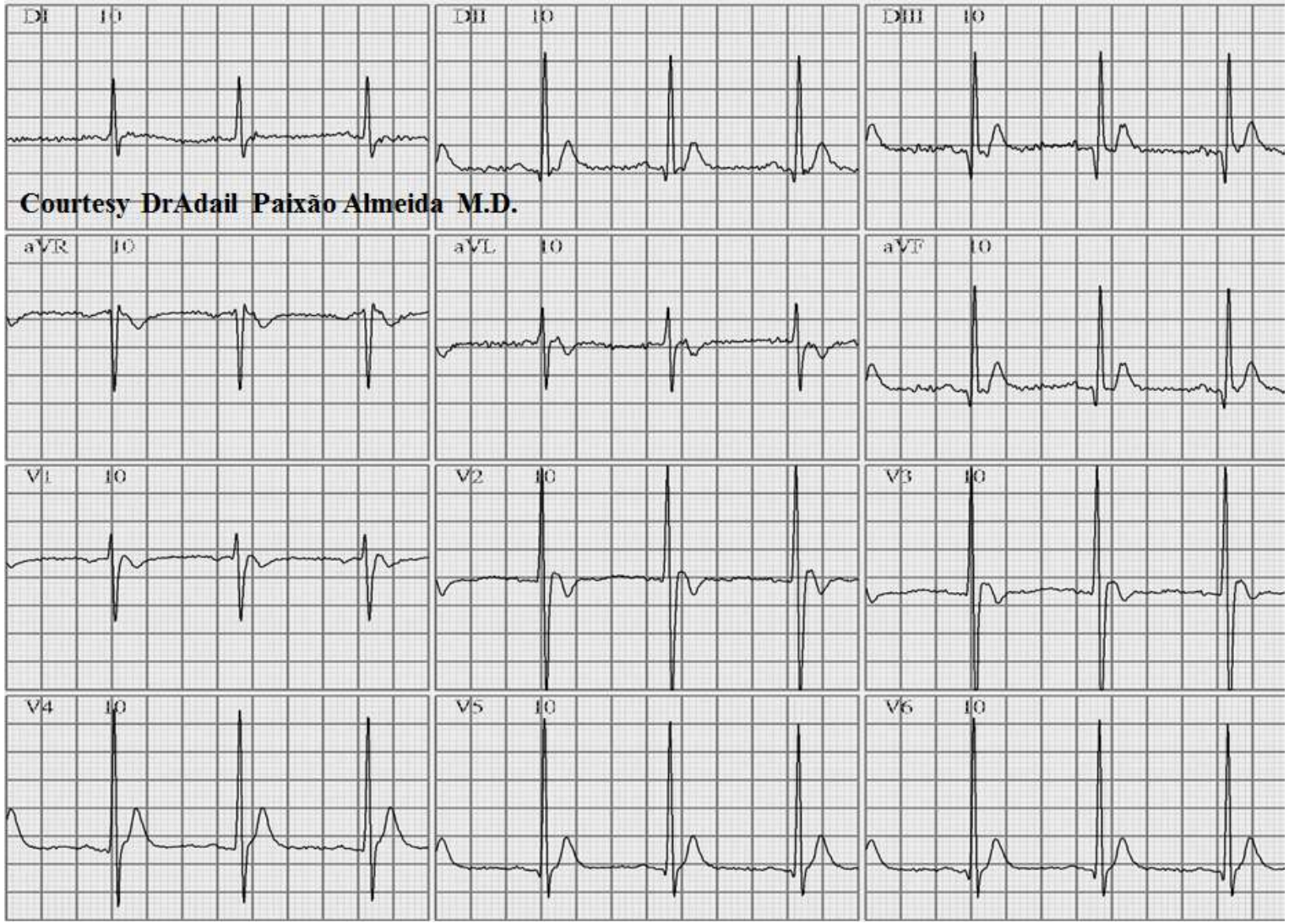
Reason for consultation: patient referred to a cardiologist for risk assessment of prostate biopsy under sedation. Asymptomatic.

Personal history: minimal increase of serum prostate specific antigen (PSA test) in recent lab. Checkup. Digital rectal exam performed by urologist.

Family history: strong history of sudden death in first-degree relatives: mother died suddenly aged 62, a sister aged 6 years and a brother 13 years. He has also two asymptomatic sisters with 36 and 41 years old.

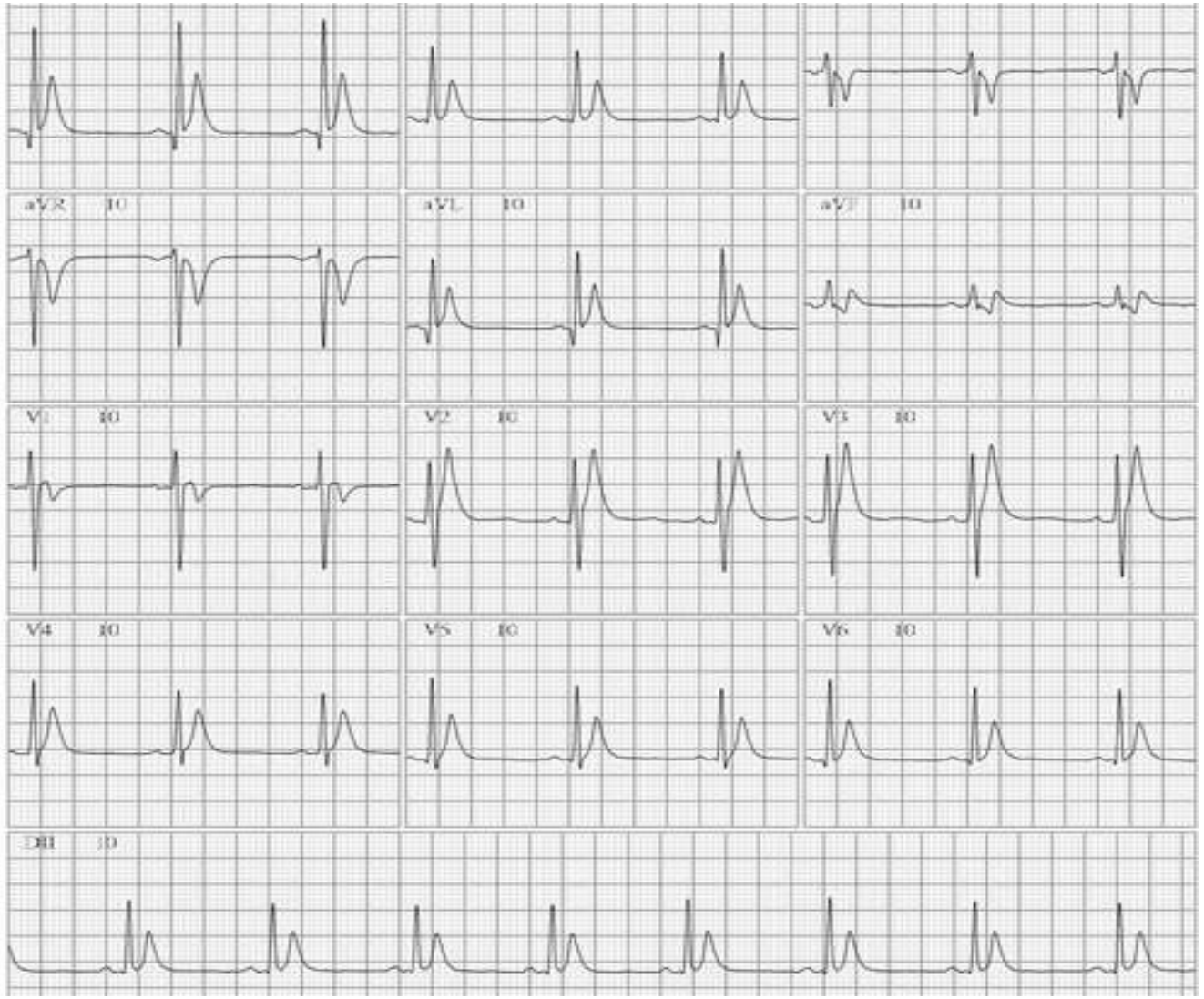
Physical examination: Normal. Nothing to be noted.

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.



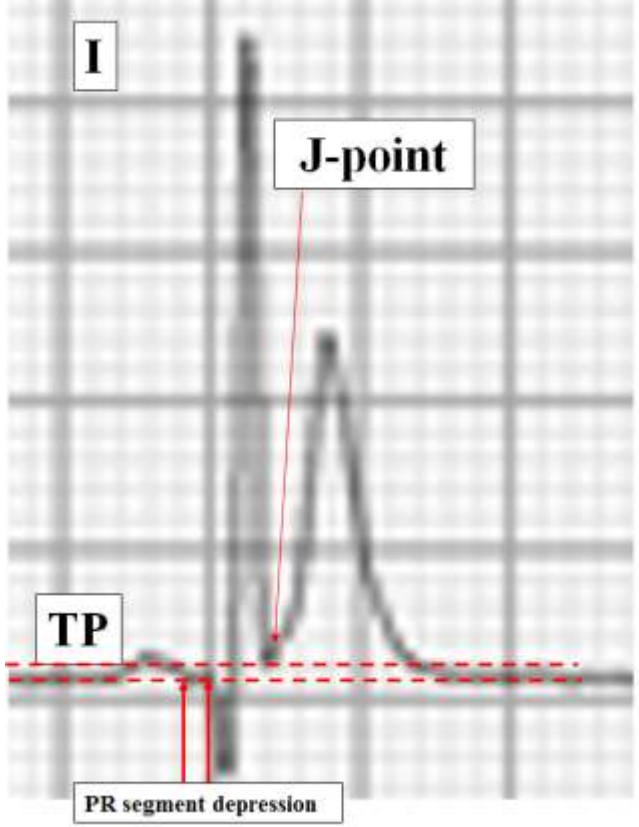
ECG diagnosis: sinus rhythm, heart rate (HR) = 83 bpm; SÂP + 60º, PR interval duration: 120 ms, QRS duration: 60 ms. SÂQRS: +65º and to the left, ST segment with minimal duration, SÂT +63º and backward. QT = 220 ms; QTc = 353 ms (proband)

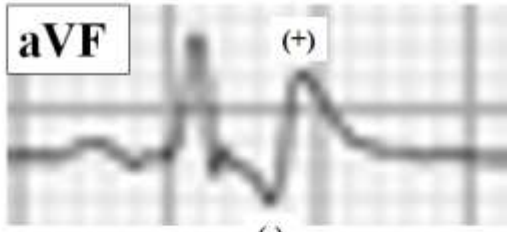
Name: MTC; **Sex**: F; **Age**: 54 y/o; **Date**: March 20, 2014; **Ethnic group**: Caucasian. ECG of one sister of the proband.

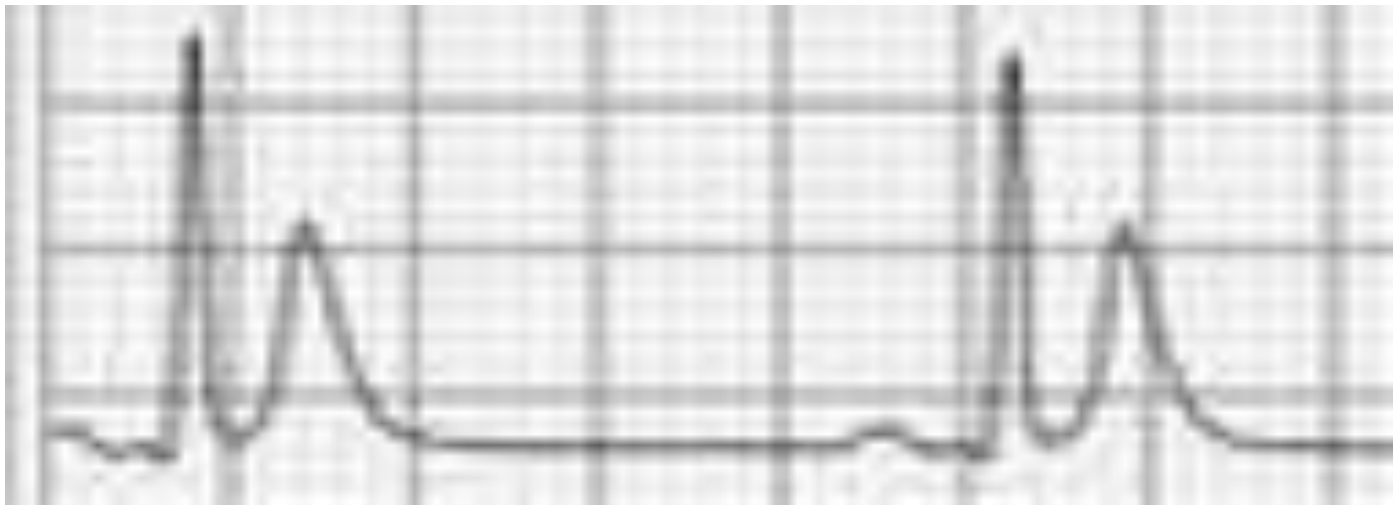


Clinical diagnosis: Congenital short QT syndrome with mutation in Caveolin-3 (SQT7).

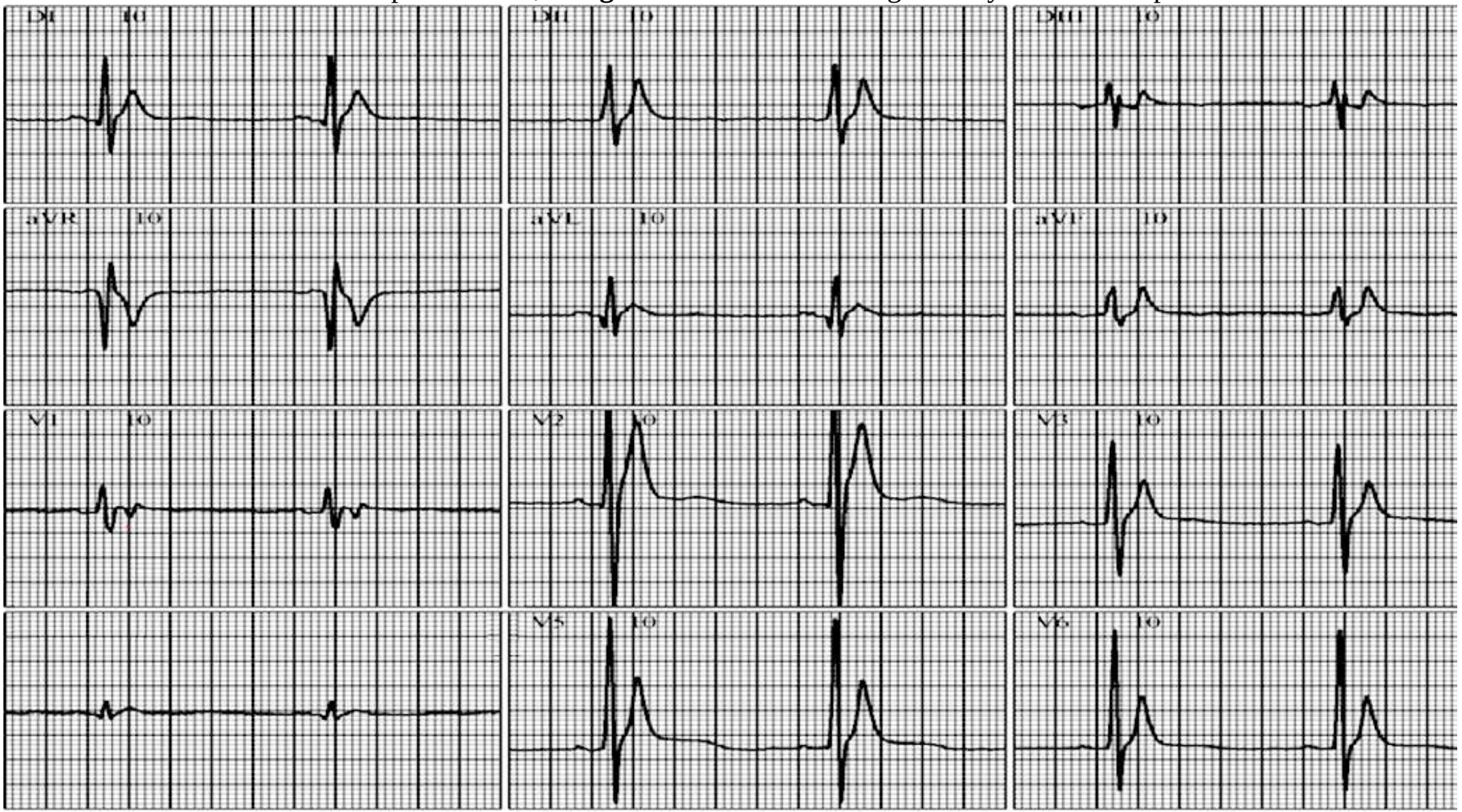
ECG diagnosis: Sinus rhythm, HR = 68 bpm; P wave: ; SÂP + 32º, PR interval duration: 120 ms, PR segment depression (>0.5 mm) in II and V5, absence of ST segment, positive-negative T wave or “minus-plus T wave sign” in aVF, and QT = 280 ms; QTc = 295 ms.


I
J-point
TP
PR segment depression


aVF
(+)
(-)
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.

Approach:

In the present case we have an intermediate probability of SQTS diagnosis because it is diagnosed in the presence of a QTc ≤330 ms (in the present case QTc = 304 ms). The diagnosis of SQTS is still a matter of debate. A major point of discussion in the definition of diagnostic criteria is represented by the cutoff value at the lower end of the QTc that should be used to diagnose the disease. QTc should be calculated avoiding tachycardia and bradycardia to prevent the use Bazett's formula at rates in which its correction is not linear and may lead to underestimation or overestimation of QTc values. For the diagnosis we must follow the Gollob score (**Gollob 2011**). In the present case we only have 3 points,

QTc in miliseconds	Score	The present case
< 370	1	
< 350	2	
< 330	3	3
J point – T peak interval		
< 120	1	0
Clinical history		
Sudden cardiac arrest	2	0
Polymorphic VT or VF	2	0
Unexplained syncope	1	0
Atrial fibrillation	1	0
Family history		
1st or 2nd degree relative with SQTS	2	0
1st or 2nd degree relative with sudden death	1	0
Sudden infant death syndrome	1	0
Genotype		
Genotype positive	2	?
Mutation of undetermined significance in a culprit gene	1	?

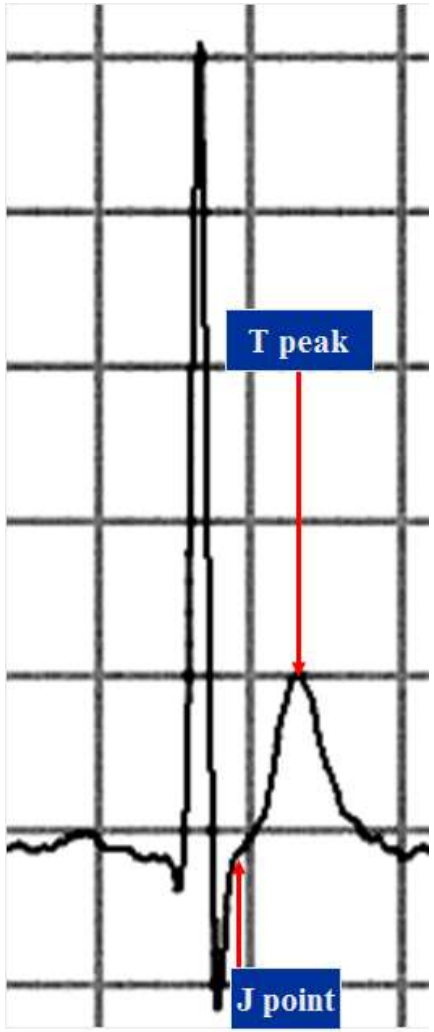
Note: From our point of view, the Gollob score does not mention the characteristics of atrial and ventricular refractory periods. See the next slide. The proposed Gollob score has not been accepted by some experts (**Bjerregaard 2011**)

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.

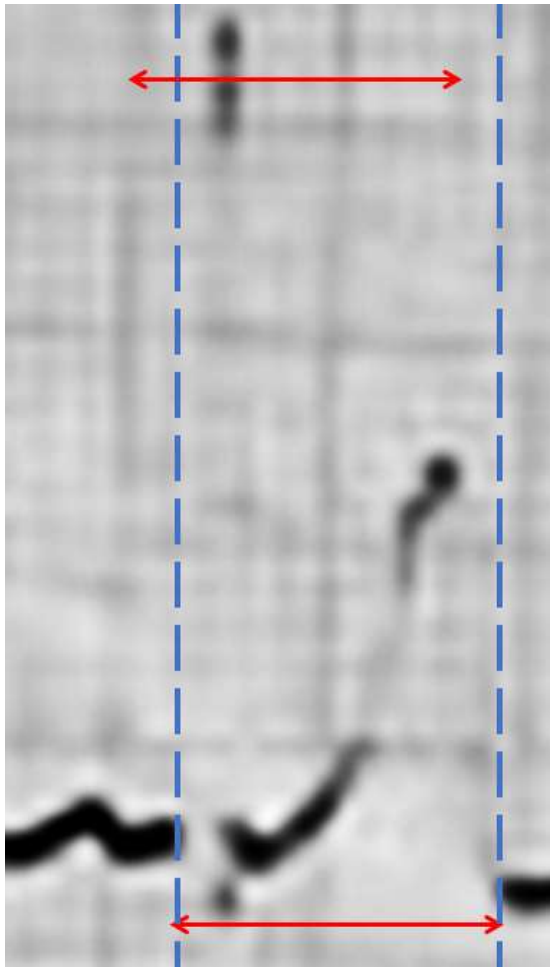
Interpretation: High-probability: ≥ 4 points; Intermediate probability: 3 points; Low probability: ≤ 2 points.

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 (Gollob 2011).



The presente case



QT- V_5 = 319ms

J point-T peak interval <120 ms: considered a criteria for diagnosis in the Gollob score; value = 1 point (Gollob 2011).

The Short QT Syndrome diagnostic criteria is based on a point score system. In the present case, J point-T peak interval > 120 ms.

In my opinion, it is necessary the following steps:

1. To perform genetic study with the intention of excluding some genetic mutations.
2. Electrophysiological study (EPS). Why? Because in case of truly congenital SQTS we will always observe short refractory periods and tendency for inducible AF and VF were seen in EPSs. This fundamental parameter is not considered in the Gollob score.
3. Ajmaline challenge because the possibility of BrS + SQTS overlapping (SQT4 and SQT5).
4. In the present case we do not have Class I criteria for ICD implantation: Class I 1. ICD implantation is recommended in symptomatic patients with a diagnosis of SQTS who
   - Are survivors of a cardiac arrest and/or
   - Have documented spontaneous sustained VT with or without syncope.

   Additionally, we do not have Class IIb criteria for ICD implantation: ICD implantation may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. Quinidine may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD (the present case is oligosymptomatic). If EPS confirms short atrial and ventricular refractory periods and tendency for inducible AF and VF we can use hydroquinidine, because recently, Mazzanti et al. demonstrated for the first time that treatment with hydroquinidine (HQ) was associated with a lower incidence of life-threatening arrhythmic events in SQTS patients. These data point to the importance that quinidine, that in several countries has been removed from the market, remains available worldwide for patients with SQTS. In this study, therapy with HQ has been proven to be safe, with a relatively low rate of side effects (**Mazzanti 2017**). Sotalol is not indicated. This drug may be considered only in asymptomatic patients with a diagnosis of SQTS and a family history of SCD, absent in the present case.
5. If EPS is positive, clinical electrocardiographic screening is recommended in first degree family members.
6. If EPS is negative, it is important rule out hypercalcemia, and other secondary causes of short QT interval.

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