Class 20 – SOLAECE Course

# ECG in channelopathies without structural heart disease: LQTS, SQTS, J-wave syndromes Brugada syndrome, malignant early repolarization/idiopathic VF, and catecholaminergic polymorphic VT

**Author: Andrés Ricardo Pérez Riera, M.D.Ph.D.**

**Laboratory Design of Studies and Scientific Writing - ABC Faculty of Medicine-ABC Foundation - Santo André – São Paulo – Brazil**

**The author does not report any conflict of interest regarding this presentation**

| Main cardiac channelopathy phenotypes |
| --- |
| **A) Without apparent structural heart disease** |
| • Congenital long QT syndrome (LQTS) |
| • Short QT syndrome (SQTS) |
| • Brugada syndrome (BrS) |
| • Idiopathic ventricular fibrillation |
| • Early repolarization syndrome |
| • Catecholaminergic polymorphic ventricular tachycardia (CPVT) |
| • Familial progressive cardiac conduction defect (PCCD): Lenegre disease |
| • Familial atrial fibrillation |
| • Sudden infant death syndrome |
| • Overlapping clinical phenotypes or mixed forms: Brugada syndrome associated with LQT3, Brugada syndrome associated with Progressive Cardiac Conduction Defect, Brugada syndrome associated with sinus node dysfunction Brugada and sick sinus syndrome, Brugada syndrome associated with atrial standstill, SQTS with concomitant Brugada-like ECG pattern |
| **B) With structural heart disease** |
| • Conduction disease with abnormal heart: NKX2-5 mutations (transcription factors), PRKAG2 mutations (pretein kinase subunit), LMNA gene mutations (Lamin A/C), some muscular dystrophies (SCN5A sodium channel mutations). |
| • Arrythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) |

# QT interval

QTc interval is the value corrected according to HR, which represents the period between electric depolarization onset in the ventricles and the end of their repolarization.

The end of T wave is defined as T wave return to the baseline, here called T-P segment.

For a proper medication of the QT interval, we should be certain of not having included the U wave. To that end, it is advisable to perform the measurement in the aVL lead, because it is usually perpendicular to the U wave axis (SAU) (Shamroth 1971). In the cases where there is R-R irregularity, we will conduct the measurement in three consecutive cycles, and then, the mean value is estimated. The normal maximal value that is accepted for the QT interval in males is 446 ms and in females 447 ms $\pm$ 15.

If it exceeds 440 ms in males and 460 ms in females, the QT interval should be considered as prolonged.

Values above 500 ms may cause a tendency to TdP.

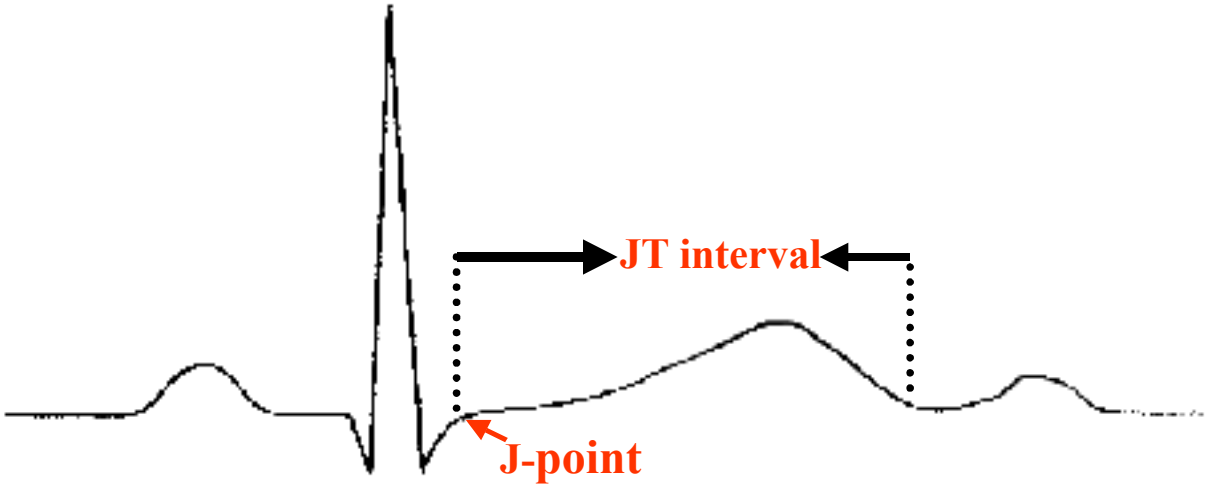
Patients with QTc intervals >600 ms are considered to be in high risk of arrhythmic SCD by TdP. In these cases, if the pharmacological treatment with beta blockers is insufficient to abolish TdP or in patients carriers of severe bronchial asthma or type 1 diabetes mellitus, where they are contraindicated, VATS ("Video-Assisted Thoracoscopic Sympathectomy") should be considered; or pacemaker at higher HR, when inappropriate bradycardia is observed as the main cause for TdP; and in special cases, ICD (Garson 1993).

The QTc interval estimation is performed by applying the Bazett's formula proposed in 1920:

$$QTc = \frac{\text{Measured QT}}{\sqrt{RR}}$$

Besides sex, the age also influences QT interval duration. In those affected with congenital LQTS, the QTc interval may be normal or in borderline values ($\leq$ 450 ms).

# The JT and JTc intervals concept



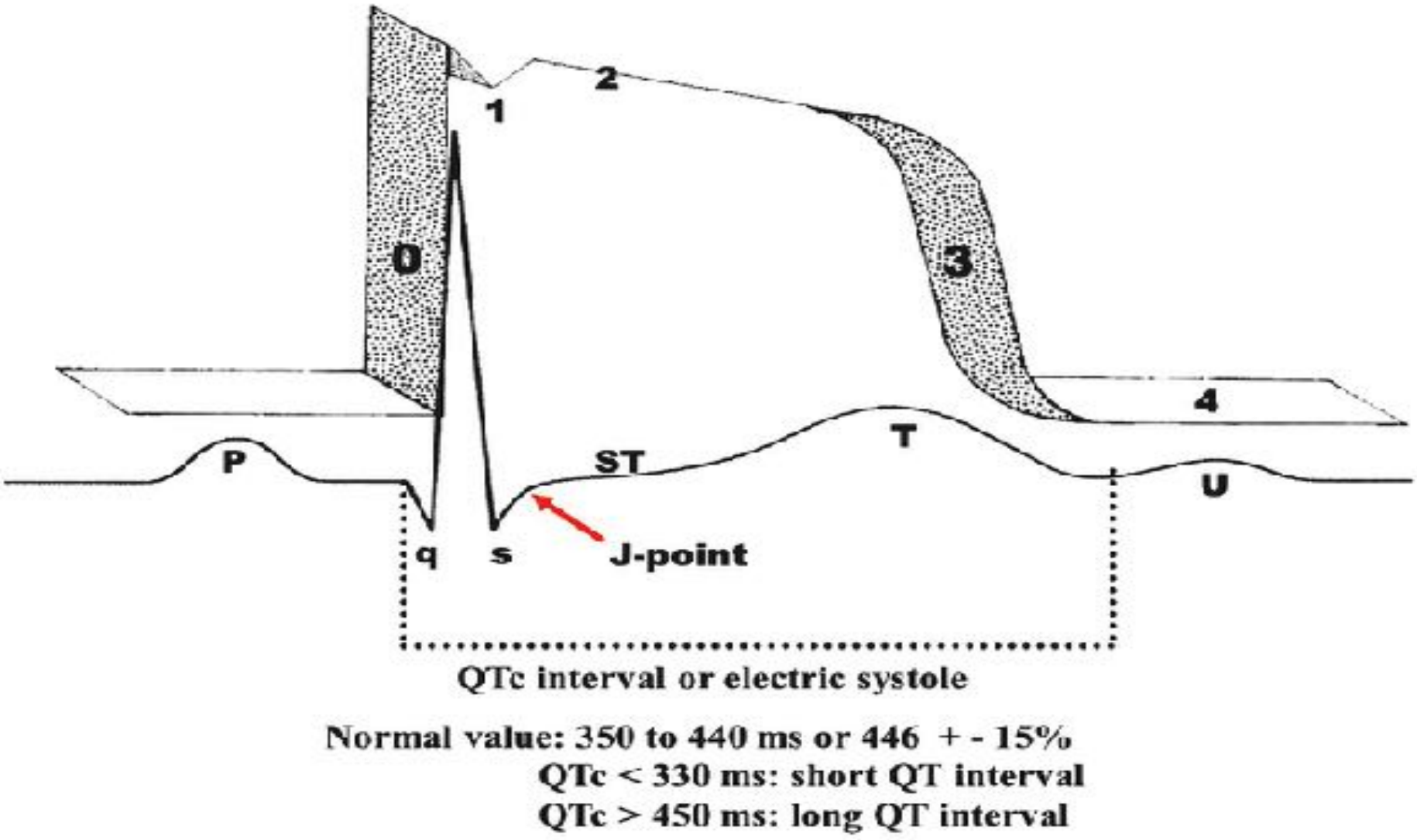

**JT and JTc intervals:** interval that extends from the J point to the end of the T wave.

The QTc interval constitutes the classical measurement of ventricular repolarization; however, the parameter includes ventricular depolarization. Thus, when there is branch block or WPW 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 measurement of JTc may be useful to identify LQTS cases with borderline values, where QTc interval could be normal in rest ECG.

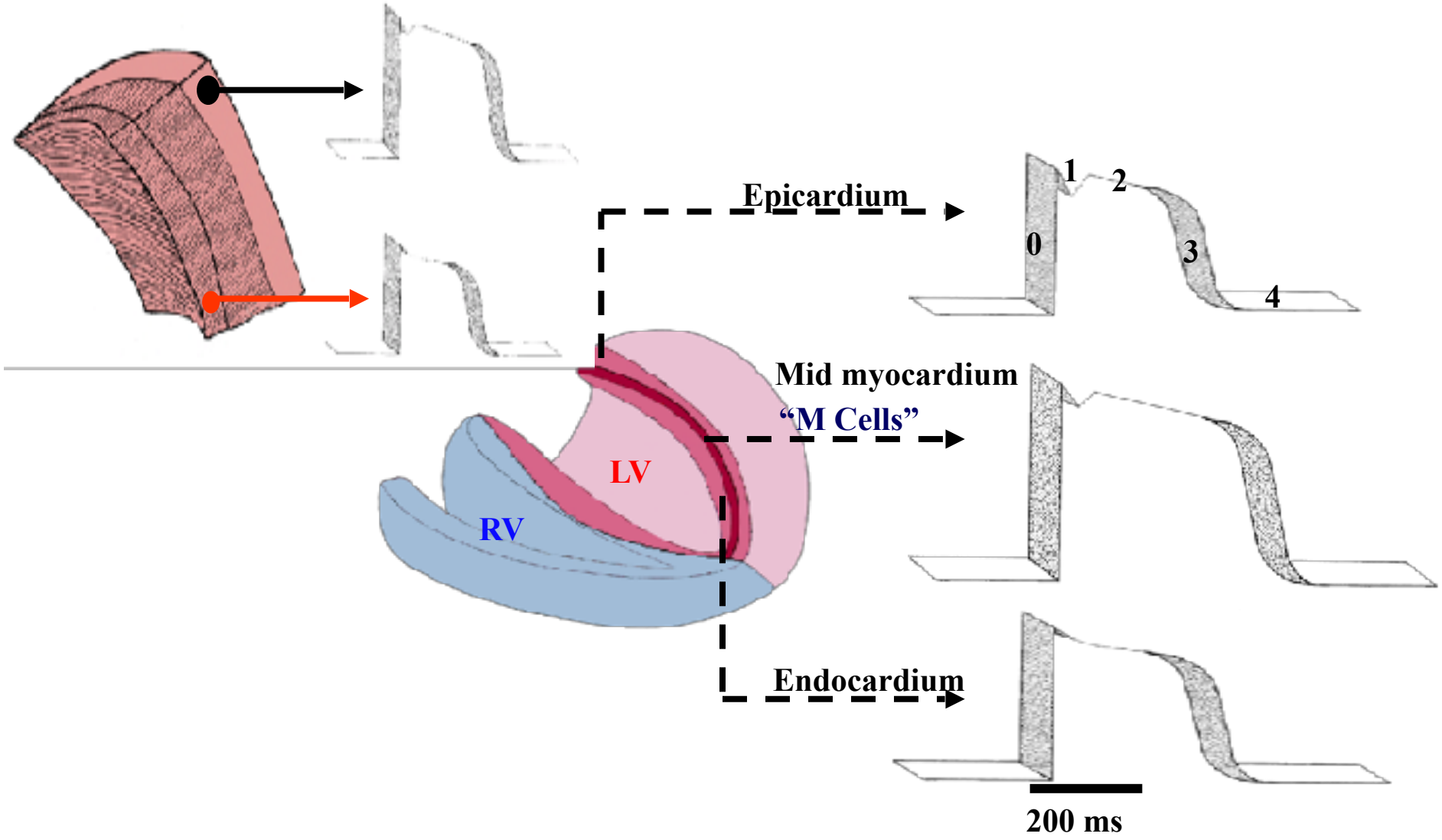
We find an example in patients carriers of tetralogy of Fallot who underwent surgery, and as a consequence of RV ventriculotomy, developed CRBBB. In these cases, JTc interval measurement is more sensitive than the QTc interval to detect prolonged repolarization.

# Action potential and QT interval concept ECG correlation



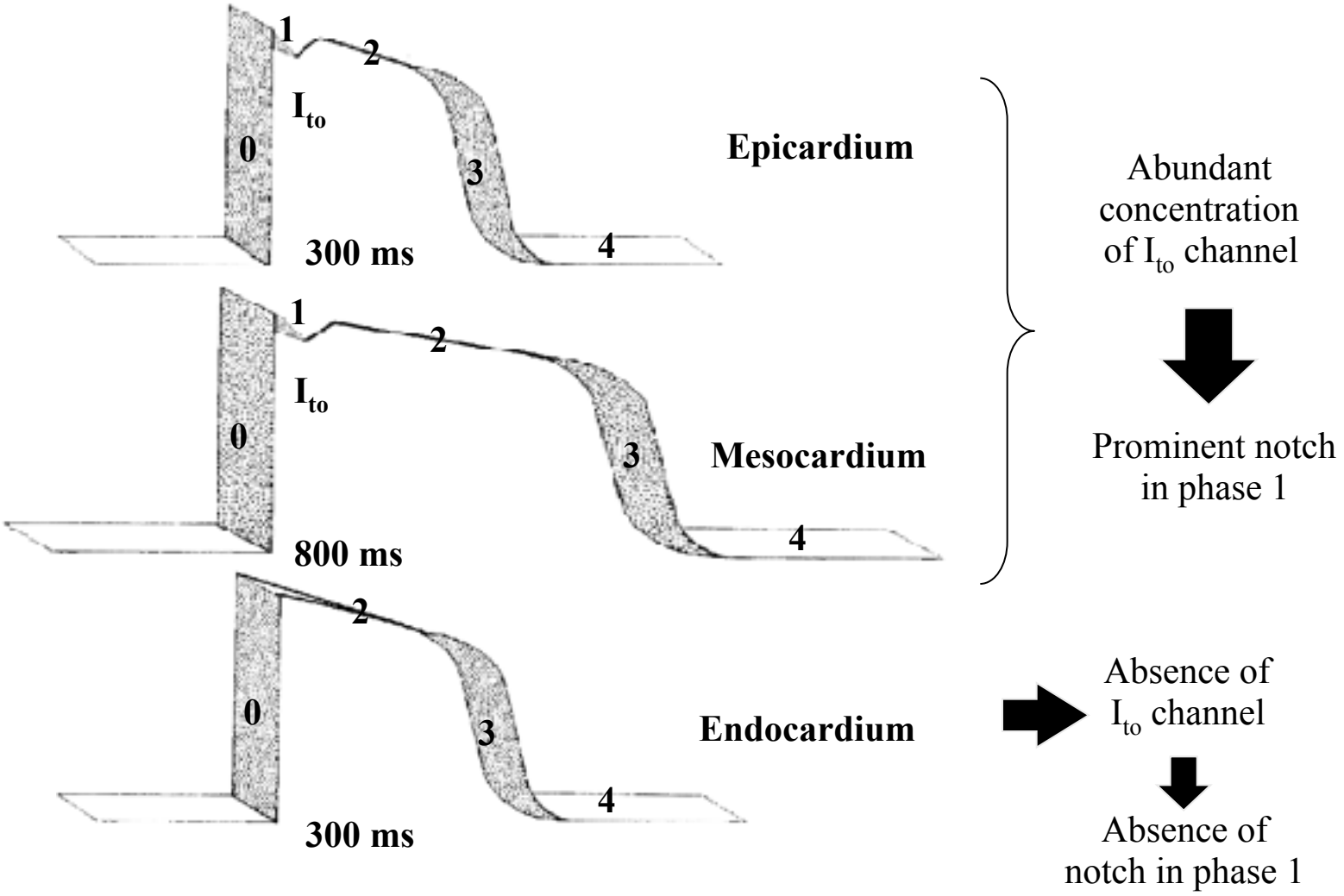

Representation of minimal and maximal normal values of QTc interval and its correlation with action potential. QTc values < 330 ms are considered short QT interval. Values of QTc > 450 ms are considered long QT intervals. Normal values of QTc are between 350 to 440 ms or 446 + - 15%.

# Action potential of ventricular contractile cells in wall thickness: epicardium, mesocardium and endocardium: heterogeneity

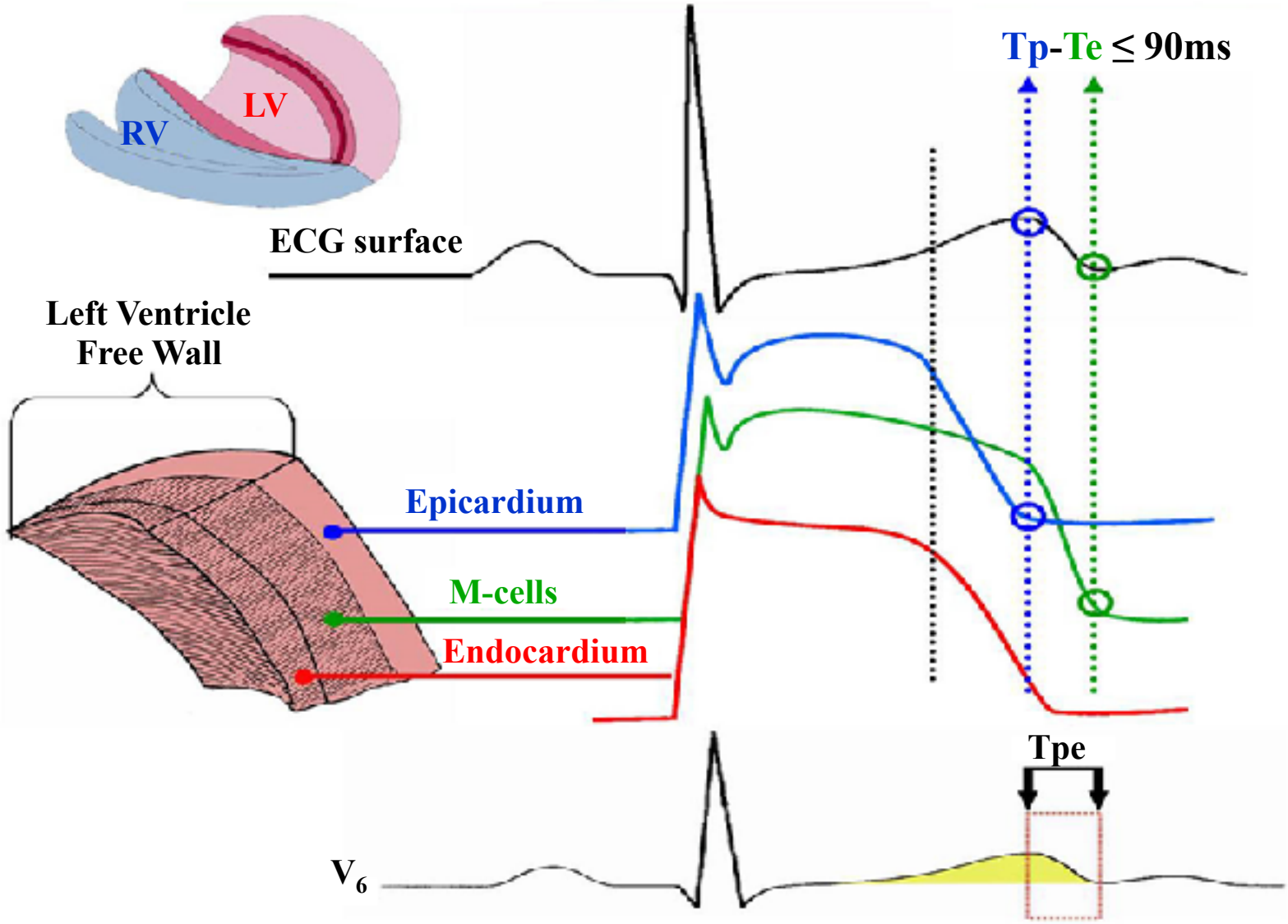



Outline of action potential in ventricular wall thickness. Differences in epi, meso and endocardium action potential profile and duration. The heterogeneous character of action potential is clearly observed in the 3 areas.

# Epicardium, mesocardium and endocardium: heterogeneity in ventricular wall thickness

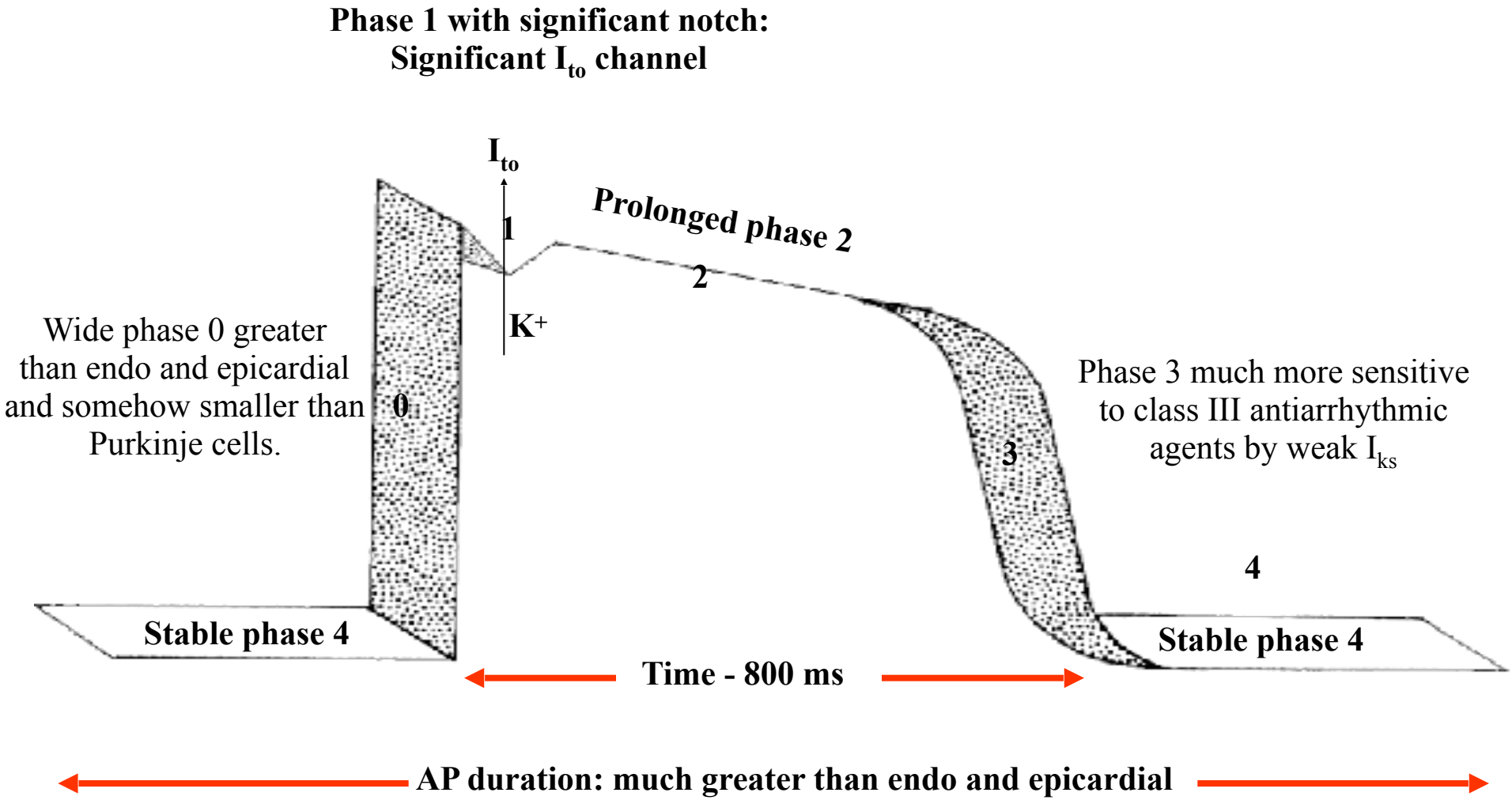



Outline of action potential in ventricular wall thickness. Differences in epi, meso and endocardium action potential profile and duration. The heterogeneous character of action potential is clearly observed in the 3 areas.




Representation of the Tpeak/Tend interval (Tpe).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 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 > 92ms in women and > 94ms in men (measurement in V5).

# Characteristics of action potential of “M” cells of the ventricular mid-myocardium




Features of M cells action potential, essential in electrogenesis of long QT syndrome (LQTS).

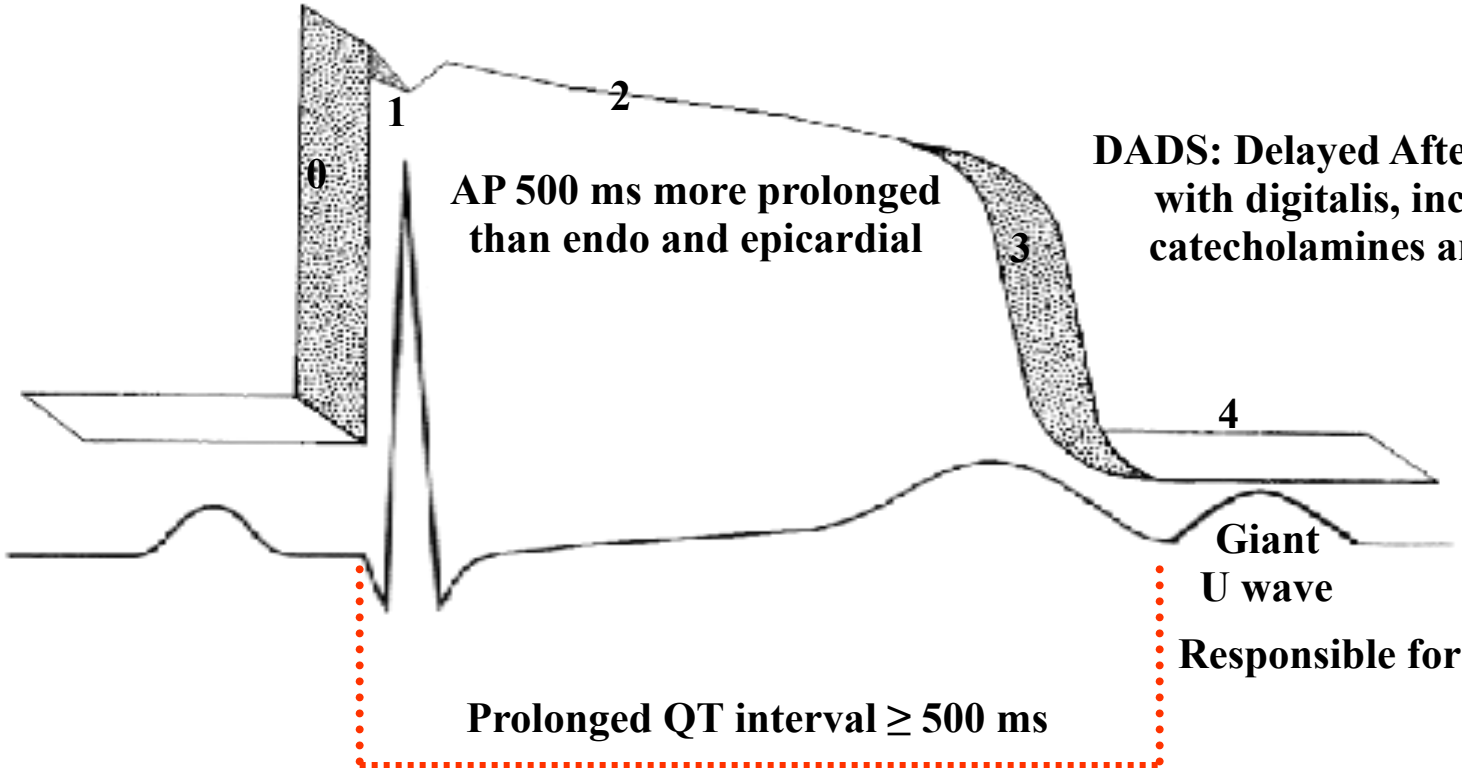
# Characteristics of "M" cells

1) **Location:** central or mid-myocardium; deep epicardial portion of LV lateral and anterior wall, and throughout the RV outflow tract.
2) **Histology:** cannot be differentiated from endocardial and epicardial cells.
3) **Action Potential:** more prolonged: ≥ 800 ms, phase 0 wider than endocardial and epicardial cells, and smaller than Purkinje; phase 1 with significant notch by abundance of $I_{to}$ channel; prolonged phase 2; phase 3 more sensitive to class III antiarrhythmic agents by having a weaker slow delayed outward rectifying potassium channel ($I_{ks}$) and phase 4 is stable (non-automatic cell).
4) Responsible for QTc interval prolongation in LQTS.
5) Responsible for numerous alterations in T waves, known as "enigmatic" T waves, observed in LQTS.
6) Responsible for prominent U waves of LQTS (QU), decisive in the genesis of Torsade de Pointes (TdP).
7) Greater increase in AP duration during low heart rates (bradyarrythmia), before the use of class III antiarrhythmic agents (d-sotalol), quinidine, erythromycin, ATX-II, and anthopleurin A.
8) They are responsible for early after depolarizations (EADs) or in phase 3: bradycardia-dependent.
9) They are responsible for triggering TdP (subendocardial focus by "M" cells and Purkinje cells).
10) They are responsible for the Delayed After Depolarizations (DADs) with digitalis, increase of Ca2+, catecholamines and $\alpha 1$ agonists. They induce changes in AP duration. In this aspect, they are different from epicardial and endocardial cells, and are similar to Purkinje. The ion substrate for these differences is caused by a weaker slow outward K+ channel at the end of AP phase 3 ("delayed rectifier current"): IKs that determines a more prolonged AP.

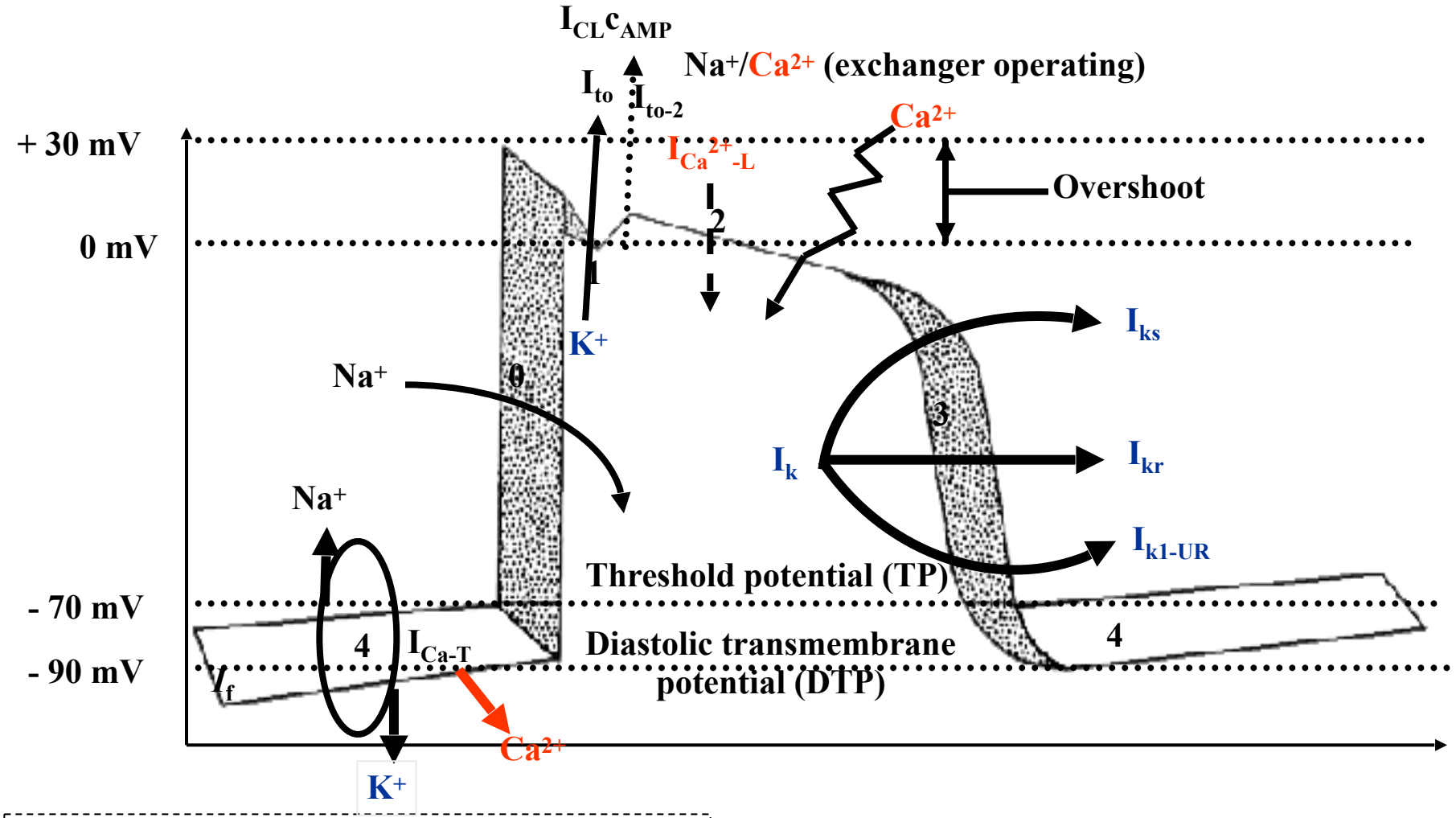
# “M” cell action potential and ECG with long QT interval

**EADs: Early After Depolarizations with class III antiarrhythmics agents.**

**Important AP prolongation with bradycardia and class III antiarrhythmic agents.**



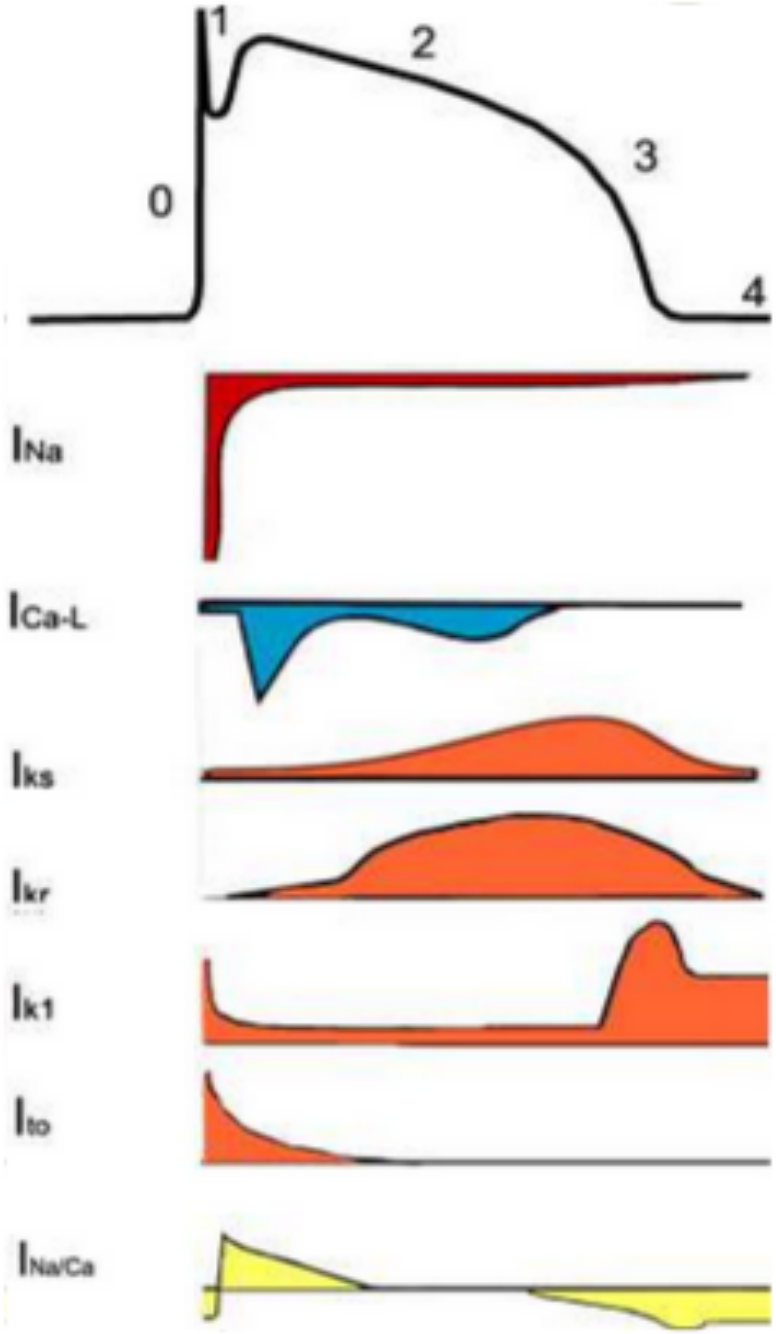
# Outline of electrophysiological characteristics of rapid Purkinje cells and its main channels




1) **Much Greater Dromotropism: 4000 mm/s.**
2) **Greater cell size and diameter.**
3) **Underdeveloped T system.**
4) **Very developed GAP junctions.**
5) **More negative DTP (close to -90 mV).**

6) **Phase 0:** wider, faster and overshoot
7) **Phase 1:** with prominent notch.
8) **Longer AP:** greater refractory period.
9) **Phase 4:** slightly ascending: automatic cells.

# The action potential (AP) and schematic of the currents involved in creating it




The duration of the AP (APD) increases with decreasing repolarization; e.g., by loss-of-function mutations in the repolarizing potassium channels or gain-of-function mutations in genes coding for depolarizing $Na^+$ and $Ca^{2+}$ channels.

The red current represents the sodium current (INa), which is formed by the $Na^+$-channel.

The blue current represents the long-lasting calcium current ($I_{Ca\text{-}L}$), which is formed by the long-lasting $Ca^{2+}$ channel.

The orange currents represent the potassium currents ($I_K$), which are formed by the K1-channels: Kv4.3 conducts the $I_{to}$ -current,
Kv11.1 conducts the $I_{Kr}$-current, Kv7.1 conducts the $I_{Ks}$-current, and Kir2.1 conducts the $I_{K1}$-current.

The yellow current represents the $Na^+/Ca^{2+}$ exchange current which is formed by the $Na^+/Ca^{2+}$-exchange channel.

# Congenital Long QT Syndrome

**Concept**: Rare syndrome, heredofamilial and autosomal (there are isolated non-familial sporadic cases), genetically heterogeneous, caused by mutations in the genes encoding potassium or sodium sarcolemmal channels (channelopathies), causing their dysfunction and thus, prolonging ventricular repolarization, which in turn predisposes the appearance of a special modality of polymorphic or atypical malignant ventricular tachycardia, known as Torsade de Pointes (TdP) that may cause syncope and possibly, degenerate into VF and sudden cardiac death (SCD) (Ackerman 1998).

**History**: Unexplained syncope, syncope during exercise in pediatric patients should be considered malignant until the contrary is proved, dizziness, palpitations or chest pain, SCD in children or young adults.

1) Very fast VT or TdP with hypotension; 2) AF or atrial flutter with high rate of ventricular response in WPW; 3) AV block; 4) Sinus arrest.

**Triggers**:

1. Exercise, especially swimming in LQT1 variant
2. Emotion or stress and noises: LQT2
3. Events during sleep or at rest: LQT3.

**Family background:** early sudden death in first degree family members. Unexplained early sudden death.

**ECG**: Long QT interval and Torsade de Pointes (TdP), T wave with notches, low HR for the age, family history of dizziness or deafness.

How should we proceed to read the ECG in suspicion of LQTS?

1. Do not perform the measurement of intervals and waves by the computerized method.
2. Conduct an independent review of ECG.
3. The measurement of the QT interval should be made by an experienced cardiologist.
4. The general cardiologist, before the suspicion of LQTS, should refer the patient to a colleague familiar with this for cardiological evaluation.

# Genetic basis of Romano-Ward syndrome: types, chromosomal locus, mutation, and ion channel affected (in red color the main variants)

| Type of LQTS | Chromosomal Locus | Genetic Mutation | Ion Channel Affected |
|---|---|---|---|
| LQT1 (60%) | 11p15.5 | KVLQT1 (KCNQ1) (heterozygote) | Slow outward potassium rectifier channel ($I_{Ks}$) |
| LQT2 (35%) | 7q35-36 | HERG | Rapid outward potassium rectifier channel ($I_{Kr}$) |
| LQT3 (< 1%) | 3p21-24 | SCN5A | Rapid sodium channel ($INa^{+}$) |
| LQT4 | 4q25-27 | ? | ? |
| LQT5 | 21q22.1-22.2 | KCNE1 (heterozygote) Jervell and Lange-Nielsen syndrome. | Slow outward potassium rectifier channel ($I_{Ks}$) |
| LQT6 | 21q22.1-22.2 | MiRP1 | Rapid outward potassium rectifier channel ($I_{Kr}$) |
| LQT7 | 17 | KCNJ2 | Associated to Andersen-Tawil syndrome (ATS1) ($I_{K1}$) |
| LQT8 Timothy's Syndrome | 12p13.3 | CACNA1C Cav1.2 | LTCC: L-type Calcium Channel |
| LQT9 | 3p25 | CAV3 | Late inward $Na^{+}$ current in phase 2 |
| LQT10 | 11q23 | SCN4B | Prolonged Na+ influx |
| LQT11 | 7q21-q22 | AKAP9 | $I_{ks}$ |

# Jervell and Lange-Nielsen Syndrome Genetic Basis

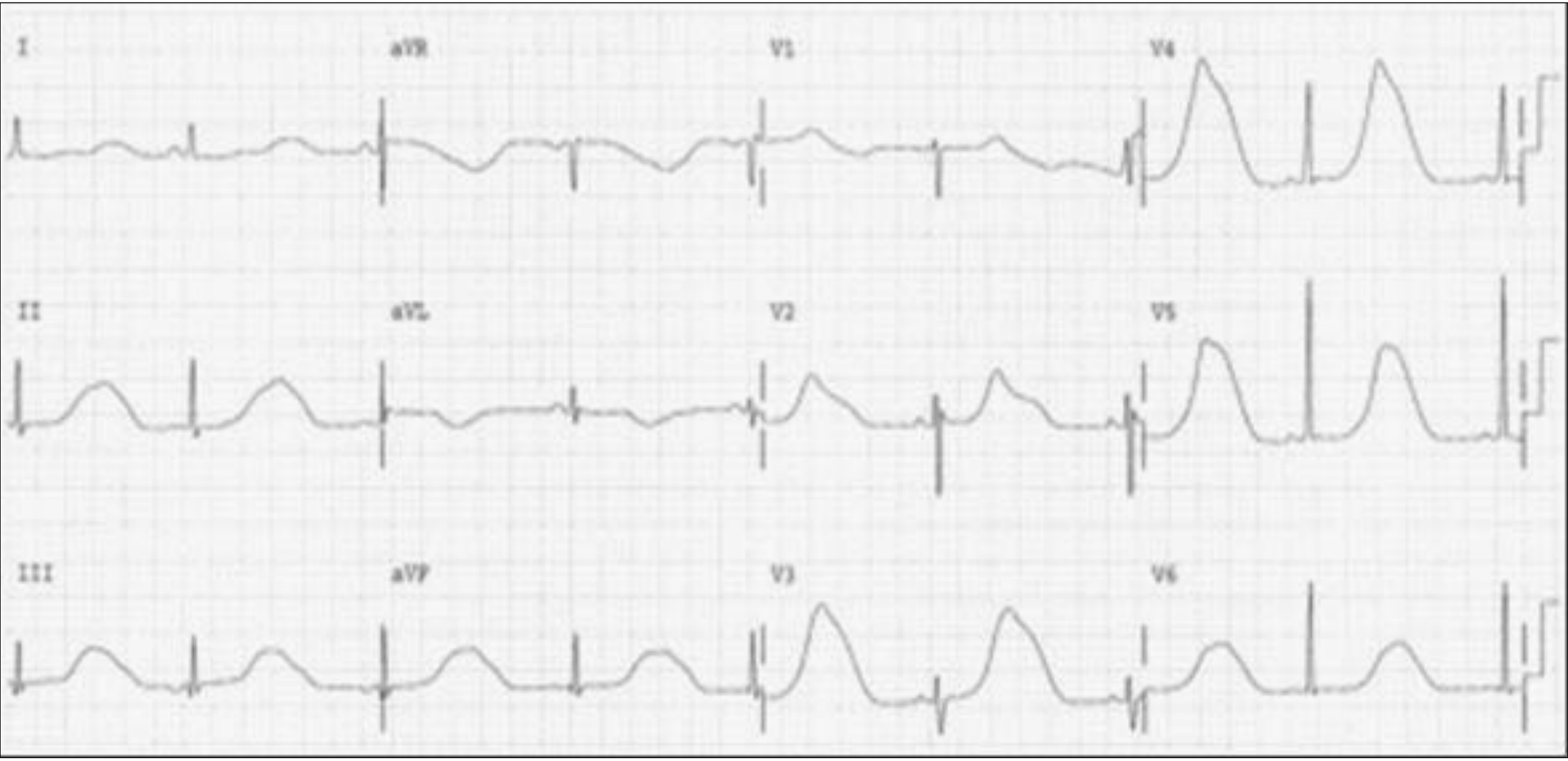
| Type of LQTS | Chromosomal Locus | Genetic Mutation | Affected Ion Channel |
|---|---|---|---|
| JLN1 **(LQT1) (90%)** | 11p15.5 (LQT1) | KVLQT1 (KCNQ1) (homozygote) | Slow outward potassium rectifier channel ($I_{Ks}$) |
| JLN2 **(LQT5) (10%)** | 21q22.1-22.2 (LQT5) | KCNE1 (homozygote) | Slow outward potassium rectifier channel ($I_{Ks}$) |

The diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) is definitively established in individuals with all of the following:

- Congenital sensorineural deafness
- Long QT interval (> 500 ms, average 550 ms), often manifest as syncope, most often elicited by emotion or exercise.
- Presence of biallelic pathogenic variants in either *KCNQ1* or *KCNE1 (LQT1 and LQT5).*
- **Hearing loss:** Deafness is congenital, bilateral, profound, and sensorineural.
- QTc prolongation in JLNS, particularly when severe, appears to be associated with increased risk for death in infancy (SIDS)

Prevalence of Jervell and Lange-Nielsen syndrome in children aged 4 to 15 years in England, Wales, and Ireland is between 1.6 and 6 per million.

# ECG example of Jervell and Lange-Nielsen syndrome with giant T waves ("Himalayan")




Marked QT interval prolongation and TU complexes with remarkable great width in patient with Jervell-Lange-Nielsen syndrome. The diagnosis of such syndrome, the recessive autosomal form of long QT syndrome, associated with congenital deafness, was confirmed by the identification of 2 different mutations in the KCNQ1 (KvLQT1) gene of potassium channel, which results in A341V and K362R; one was a de novo mutation and the other one inherited from his father. In the peripartum period, there is increased risk of arrhythmia in this syndrome. Marked QT prolongation is characteristic, but the T waves of remarkable great width that are shown here are unusual (Darbar 2005).

# Diagnostic Criteria of Long QT Syndrome (Modified from Schwartz et al. [1993])

| | Points |
|---|---|
| **ECG findings** | |
| QTc ≥ 480 ms | 3 |
| QTc between 460-470 ms | 2 |
| QTc = 450 (males) | 1 |
| Torsade de Pointes | 2 |
| T-wave alternans | 2 |
| Notched T-wave in three leads | 1 |
| Low heart rate for age | 0.5 |
| **Clinical history** | |
| Syncope with stress | 2 |
| Syncope without stress | 1 |
| Congenital deafness | 0.5 |
| **Family history** | |
| Family members with definite LQTS | 1 |
| Unexplained SCD below 30 years old, among immediate family members | 0.5 |

Low probability of LQTS is defined by an LQTS score ≤ 1 point; an intermediate probability of LQTS is defined by an LQTS score of 2 to 3 points; ≥ 4 points, high probability of LQTS.

# Classification of long QT syndromes (LQTS)

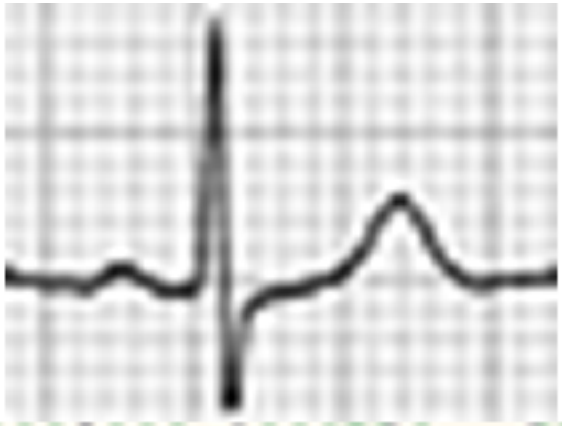
**A) Heredofamilial, congenital, "idiopathic" or adrenergico-dependent:**

- ✓ Rare syndrome (sensorineural deafness) of recessive autosomal Jervell-Lange-Nielsen. 0.25% to 1% of deaf and mute individuals. One each 300,000 individuals.
- ✓ Common Romano-Ward syndrome, without deafness, dominant autosomal.
- ✓ Nonfamilial, acquired, sporadic.

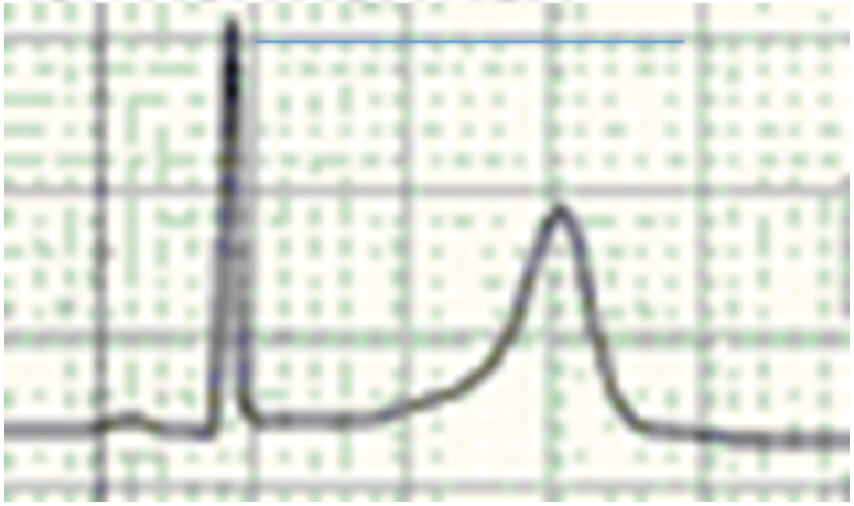
**B) Acquired, secondary or iatrogenic forms**

- ✓ By severe bradyarrhythmias;
- ✓ By electrolytic alterations;
- ✓ By effect of different drugs;
- ✓ By toxins e.g.: organophosphorate compounds;
- ✓ By cocaine;
- ✓ By subarachnoid hemorrhage and effusions;
- ✓ By liquid protein diets;
- ✓ By myocardial ischemia;
- ✓ By autonomic neuropathy;
- ✓ By mitral valve prolapse;
- ✓ By hypothyroidism;
- ✓ By Beri-Beri;
- ✓ By HIV.

# Characteristics of LQT1 variant or kvLQT1 defect



**Normal (QT = 390 ms)**

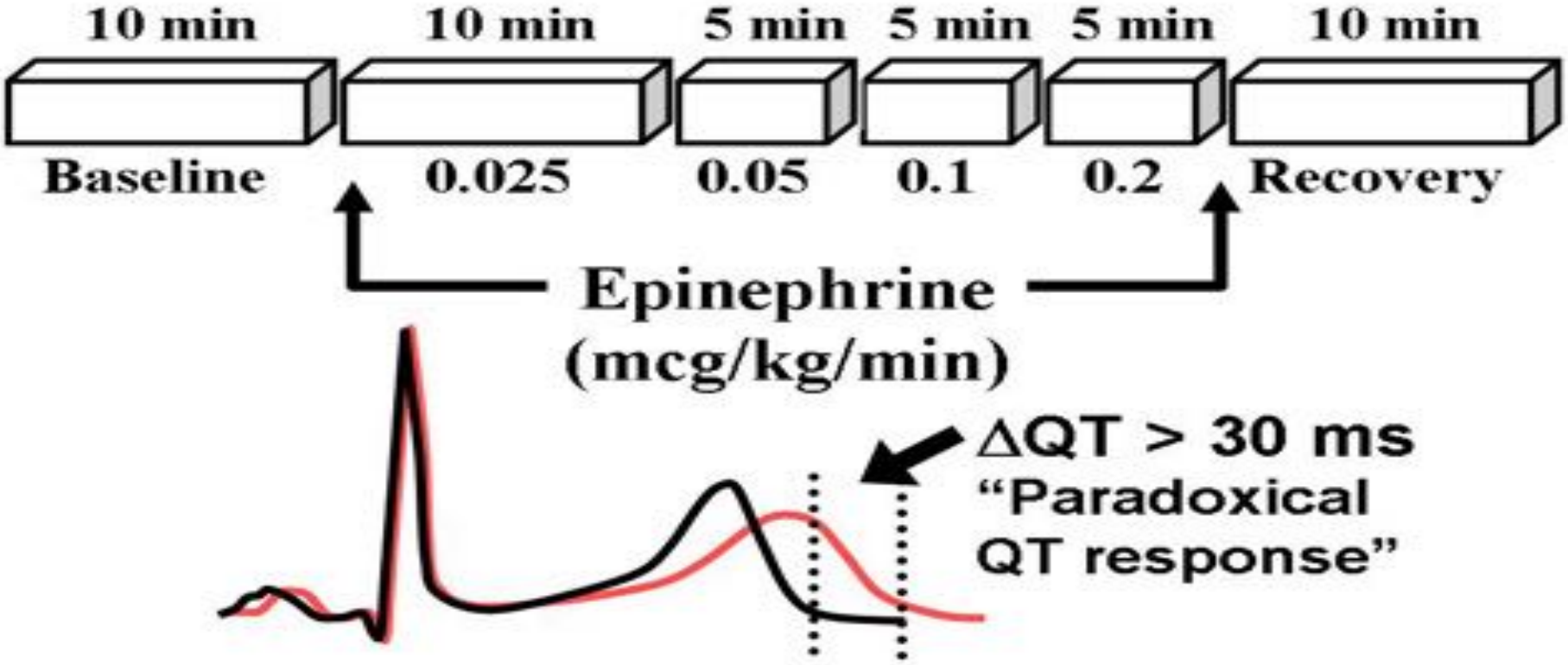


**LQT1 60% of total**

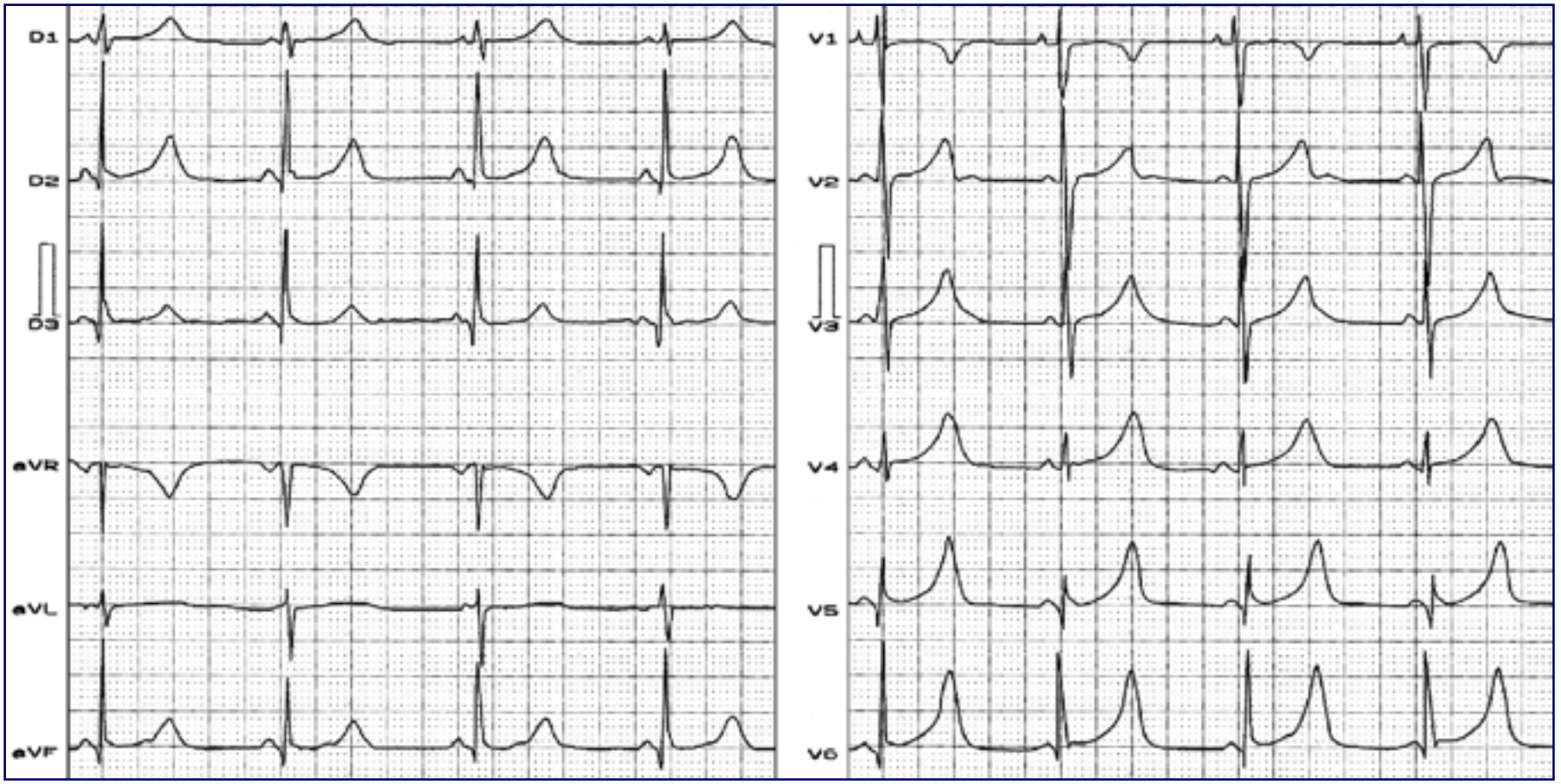
**Events triggers:** *Exercise, especially swimming*

- Broad-based prolonged T waves (QT = 580 ms).
- Moderate HR dependence of QT interval.
- Short arm of chromosome 11.

- Mutation: 11p15.5.
- Affected channel in TAP: $I_{ks}$ delayed rectifier potassium current.
- Single variant with high % of events during exercise or swimming.

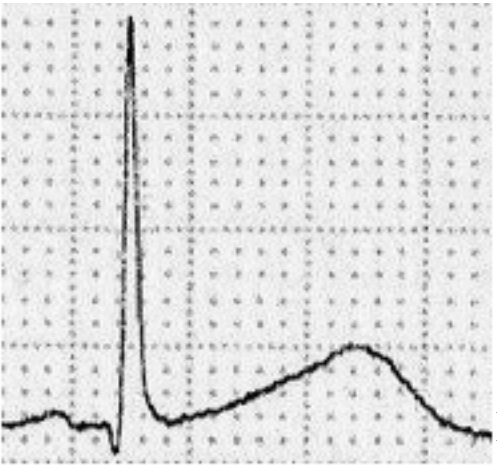



The Mayo Epinephrine QT Stress Test (Mayo Clinic Proceedings 2002) and demonstrated that paradoxical lengthening of the absolute QT interval during low-dose epinephrine infusion has 75% positive predictive value and 96% negative predictive value with respect to LQT1. This clinical diagnostic test is now used in heart rhythm centers throughout the world in an effort to unmask patients with concealed LQT1.

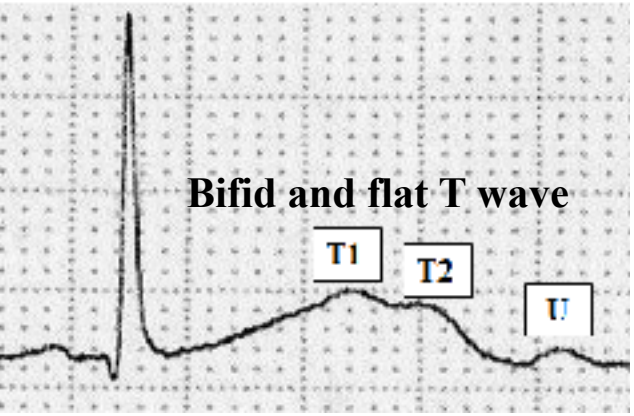



ECG from a patient with a LQT1. Typical wide-based T-waves with a large amplitude are observed.

# Characteristics of HERG LQT2 variant



**Normal**

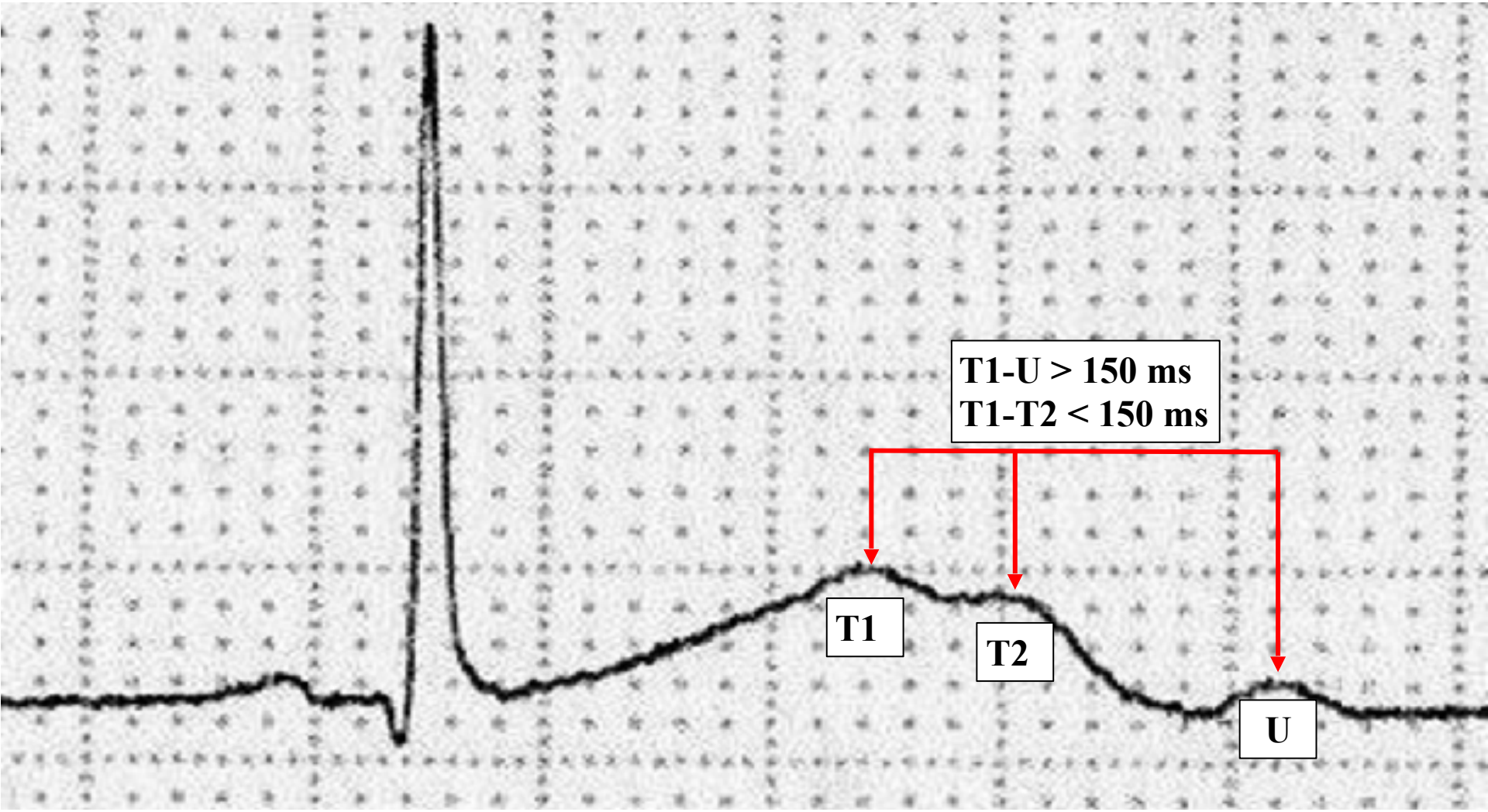



**LQT2 ≈ 35% of total**

**Events triggers:** *Emotion or stress and noises*: LQT2
Auditory arousal

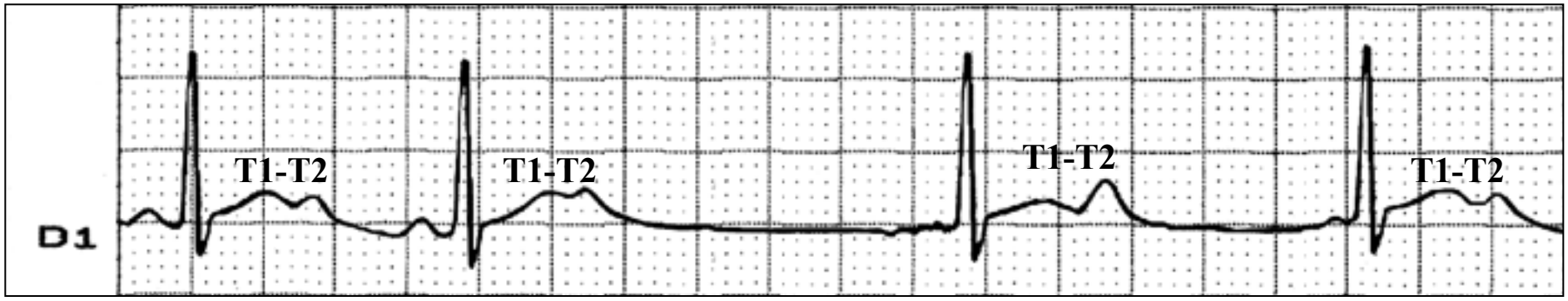
LQT2: OMIN 152437. Mutation: alpha subunit of the rapid delayed rectifier potassium channel (hERG = MiRP1) Current through this channel is known as $I_{Kr}$. This phenotype is also probably caused by a reduction in repolarizing current.

# Differentiation between bimodal T waves of LQT2 from T-U interval




Characteristics of HERG LQT2 variant (Lepeschkin 1969; 1972)

# Bimodal T wave (T1-T2 pseudo U-wave dependent on bradyarrhythmic pause

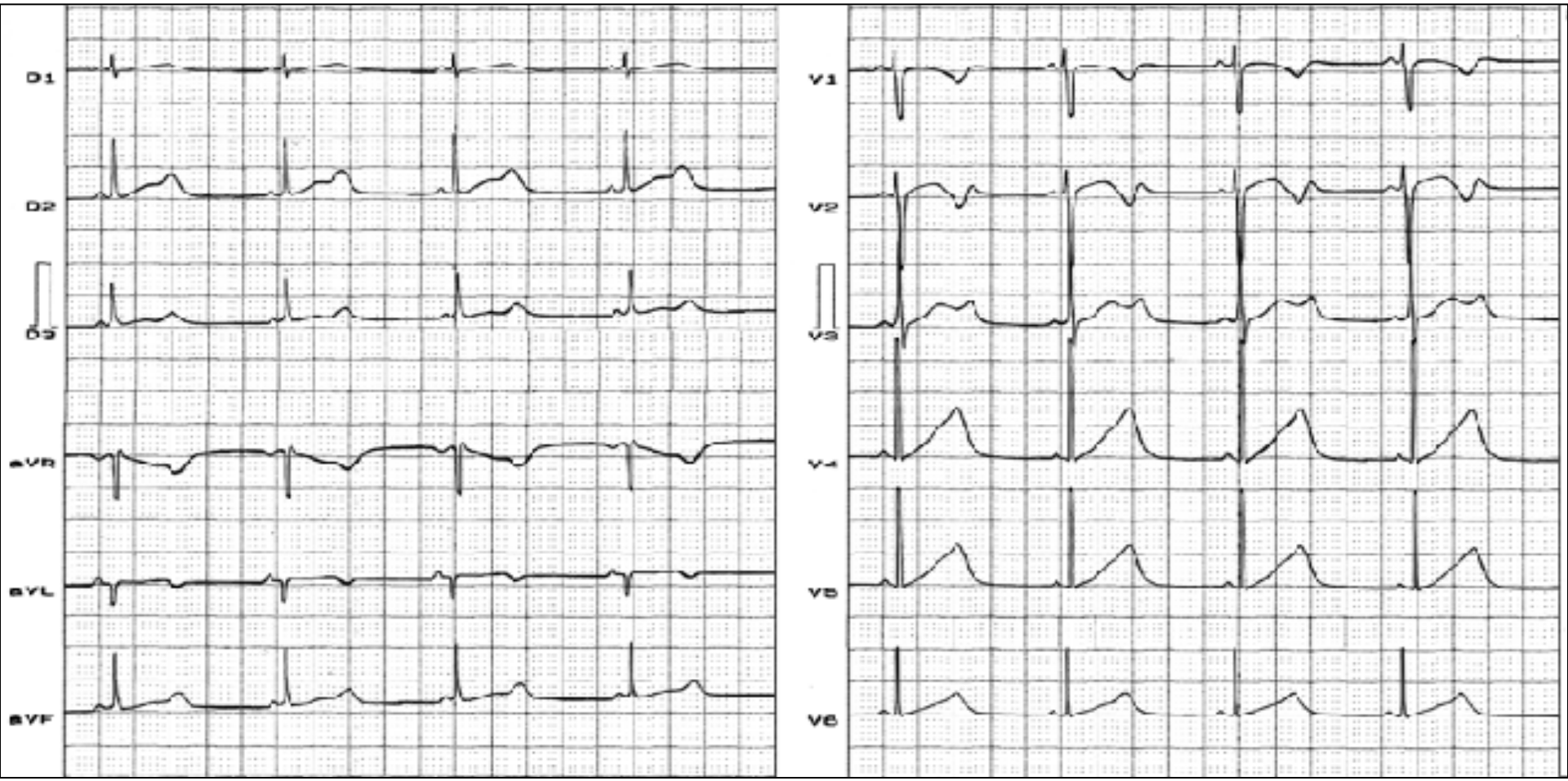



Prominent U wave that increases voltage in pauses (Roden 1999).

**Congenital long QT syndrome with high-risk:**

- Congenital deafness (Jervell-Lange-Nielsen syndrome).
- Recurrent syncope due to malignant ventricular tachyarrhythmia.
- Family history of sudden death.
- QTc > 500 ms.
- 2:1 atrioventricular block.
- T wave electric alternans.
- LQTS3 genotype.

**Name:** D.S.F**Age:** 11 years old **Sex:** Fem. **Weight:** 38 kg**Height:** 1.45 m**Race:** white**Date:** 09/18/2001
**Medication in use:** Propanol 240 mg.

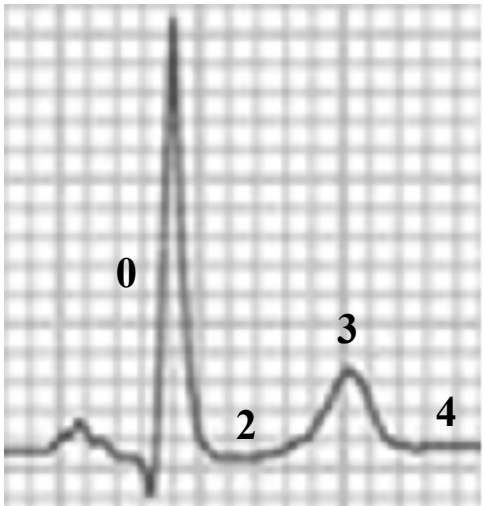



**Clinical diagnosis:** heredofamilial long QT syndrome without deafness. Tracing performed moments after episode of syncope. Marked increase of T-U wave is observed.
**ECG diagnosis:** sinus rhythm, HR: 63 bpm, long QT interval 500 ms (normal maximal value: 430 ms); very evident prominent U waves in DII and V3.

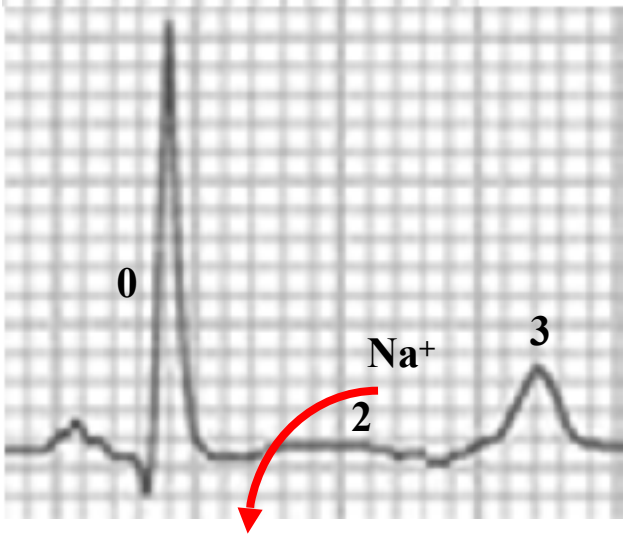
ECG of a heredo-familial long QT syndrome case without deafness. Tracing performed moments after syncope episode. Marked T-U wave increase observed.

# Characteristics of LQT3 variant, SCN5A mutation

Long QT interval by ST segment prolongation.
Delayed appearance of T wave, significant dependence on heart rate of QT interval, affected gene: SCN5A, p21-24 mutation in chromosome 3, TAP phase: plateau, dome or phase 2 by persistent sodium inflow.




**Normal**



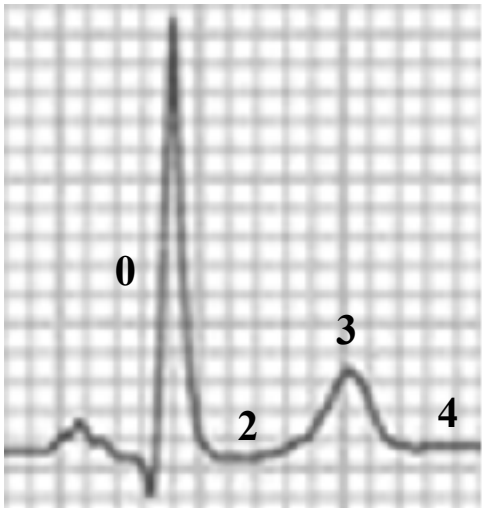

**≈ 1% of total**

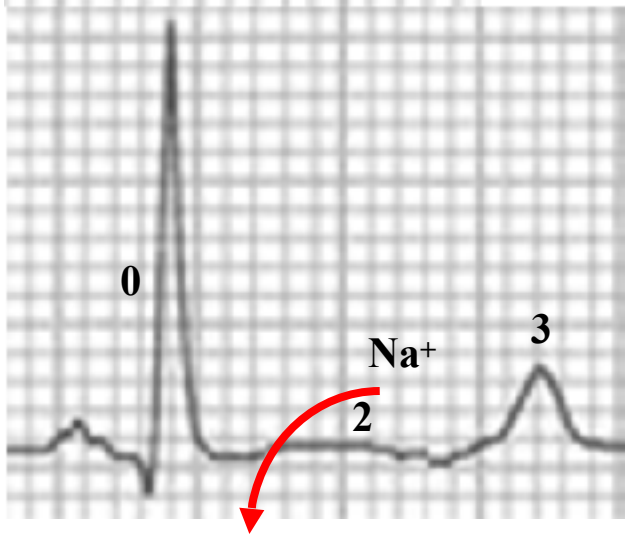
**Delayed appearance of T wave**

**≈ 80% of events during sleeping or at rest**

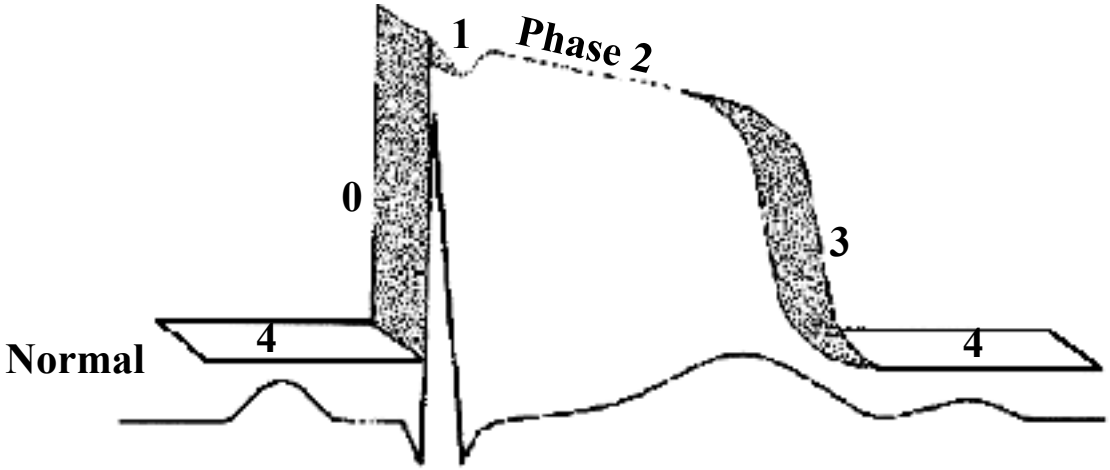
Male sex has higher risk This is the mirror image of Brugada syndrome

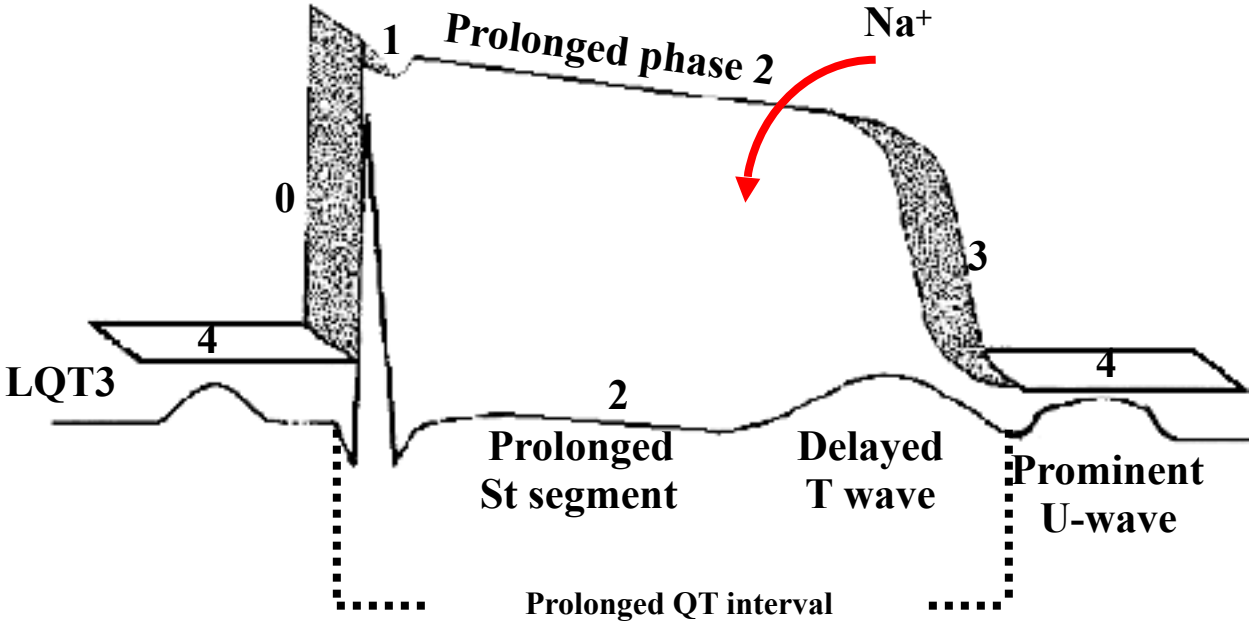
# Normal ECG and action potential versus LQT3 ECG and action potential



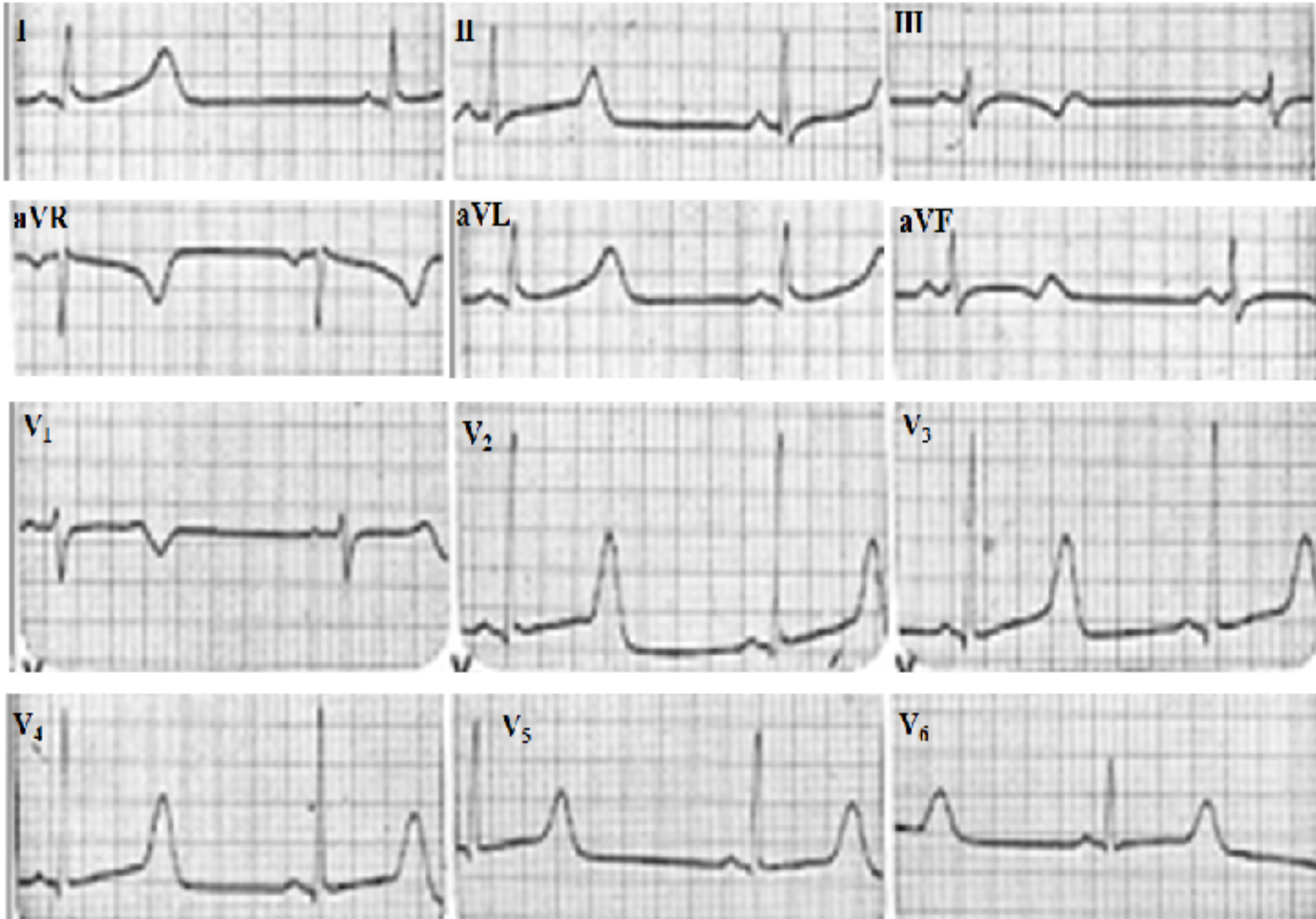

Delayed appearance of T wave

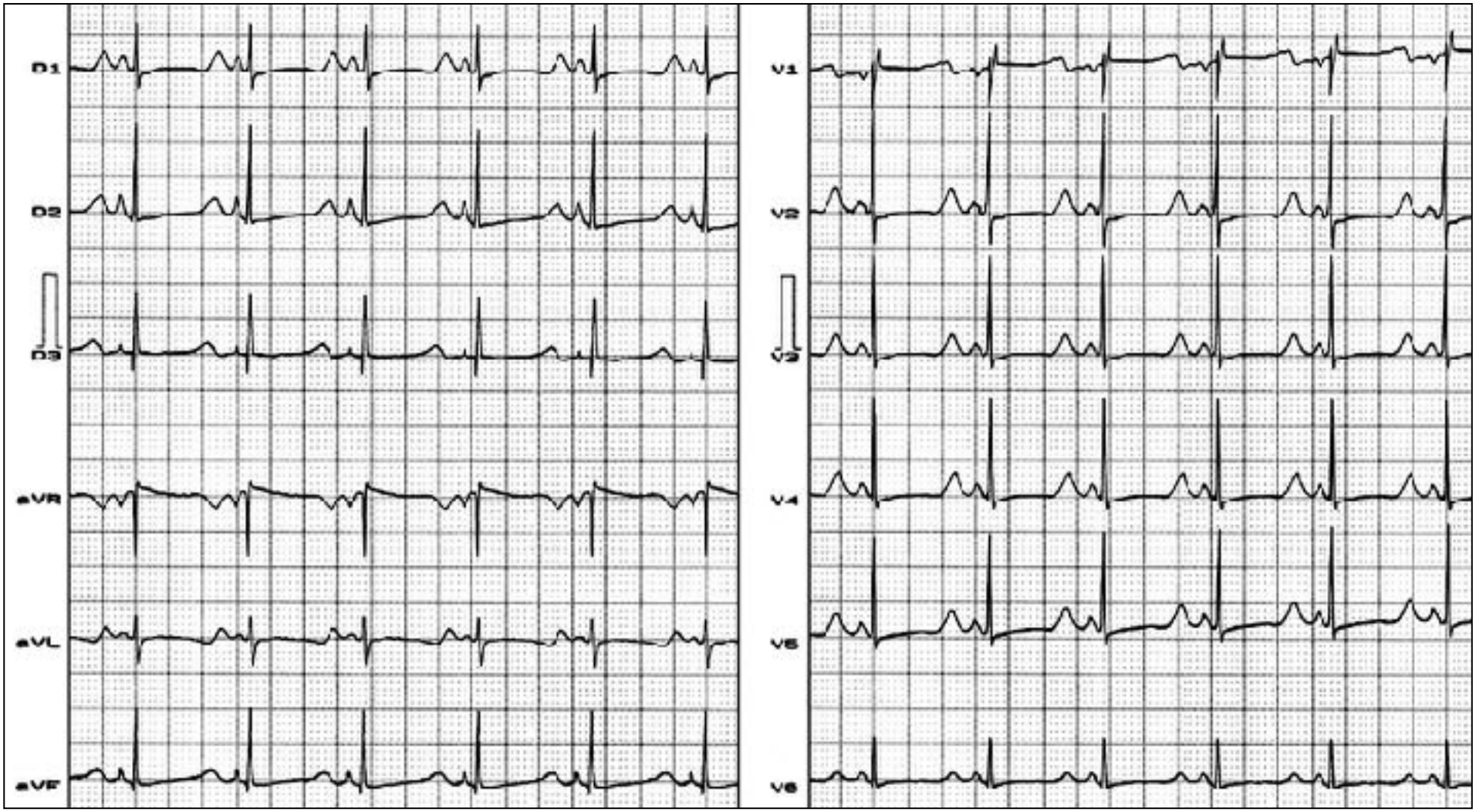



Characteristics of LQT3 variant, SCN5A mutation

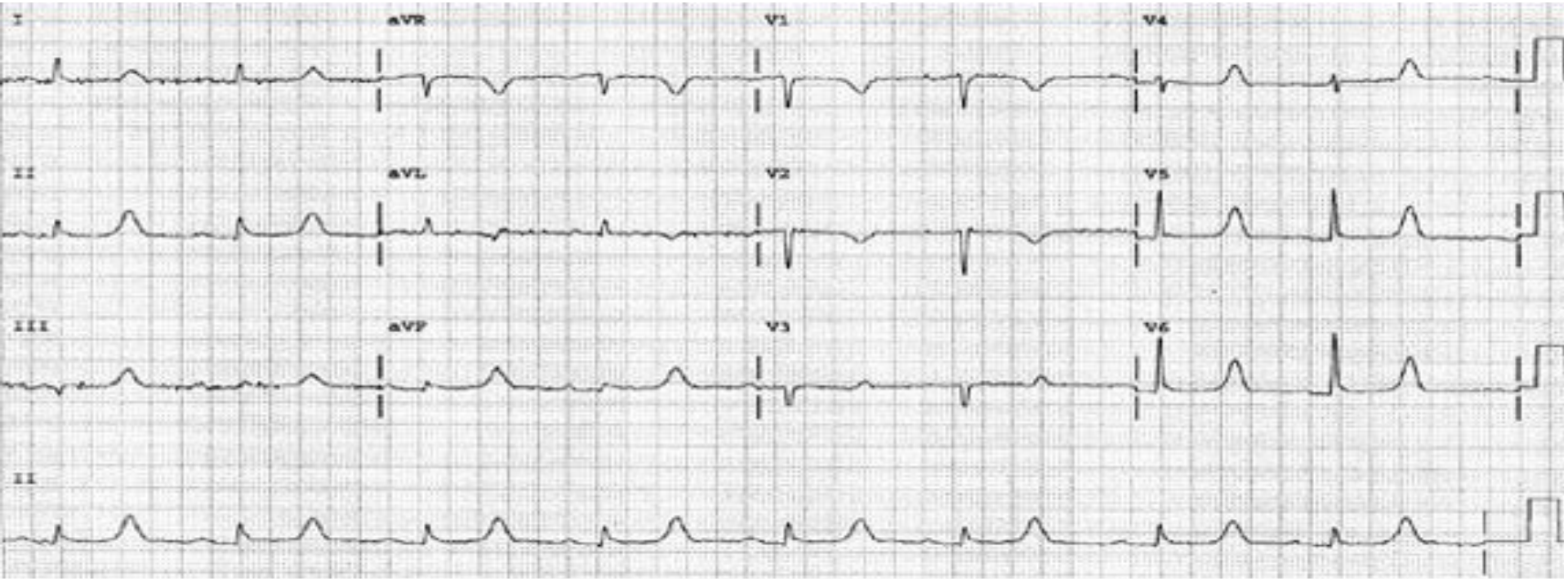
# LQT3 ECG



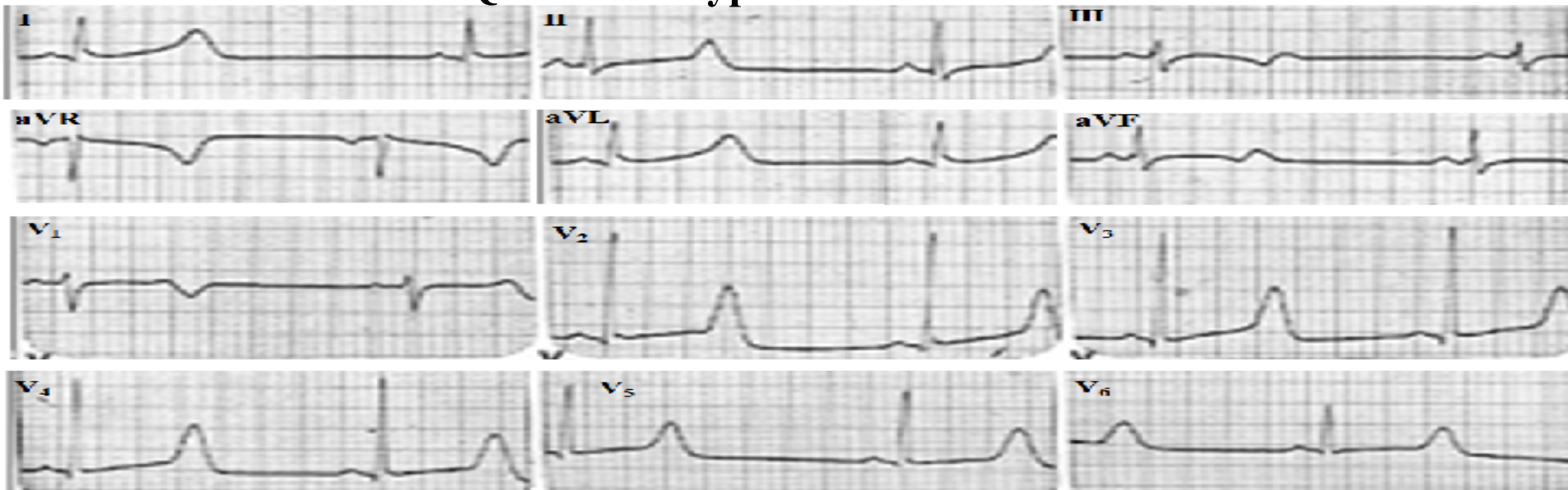



This ECG belongs to a new born with LQT3 variant. Clear ST segment prolongation and delayed appearance of T wave. Affected gene: SCN5A, p21-24 mutation in chromosome 3, AP phase: plateau, dome or phase 2 by persistent sodium inflow.

# Hypocalcemia ECG



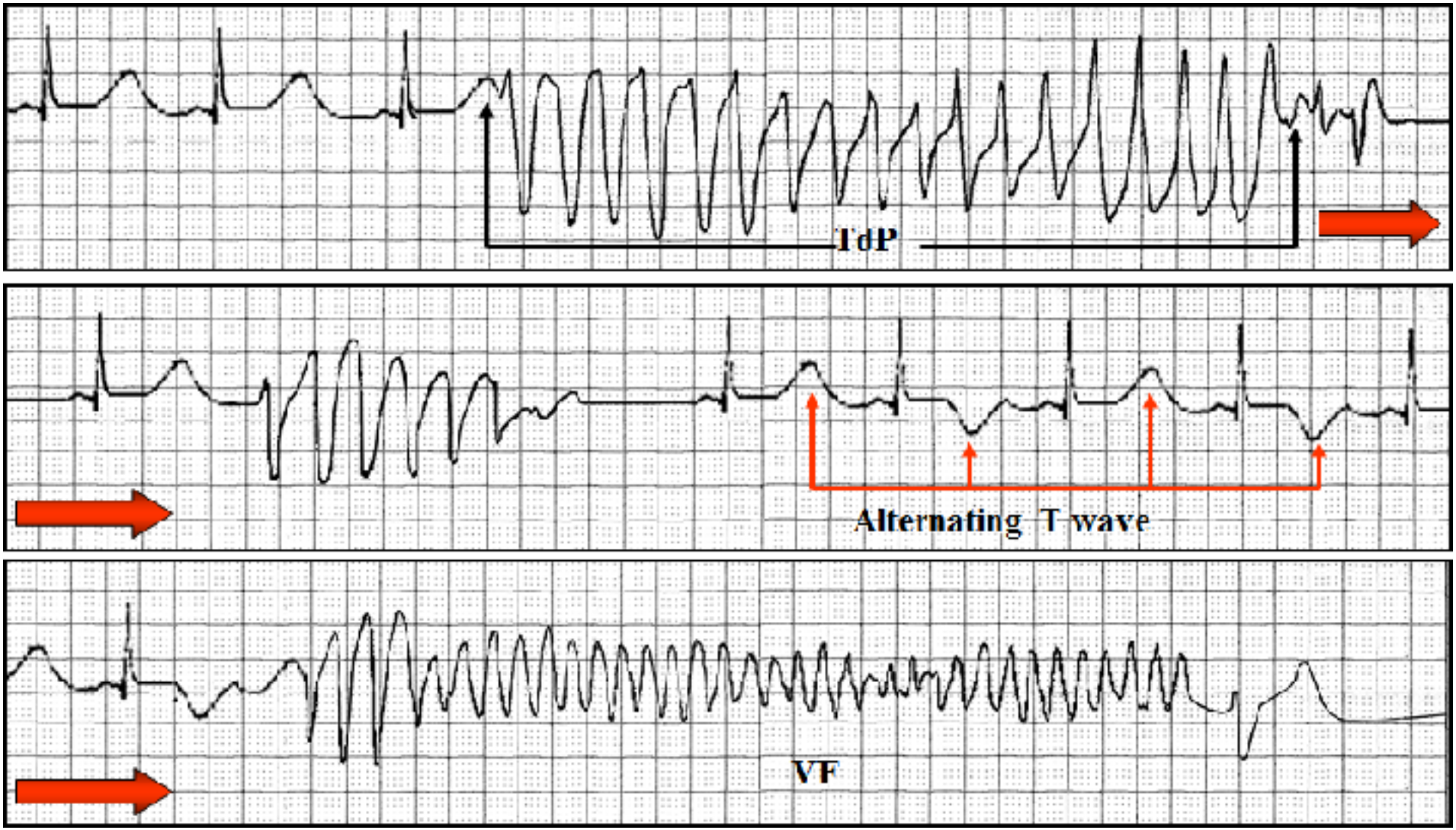

# LQT3 ECG: hypocalcemic-like ECG



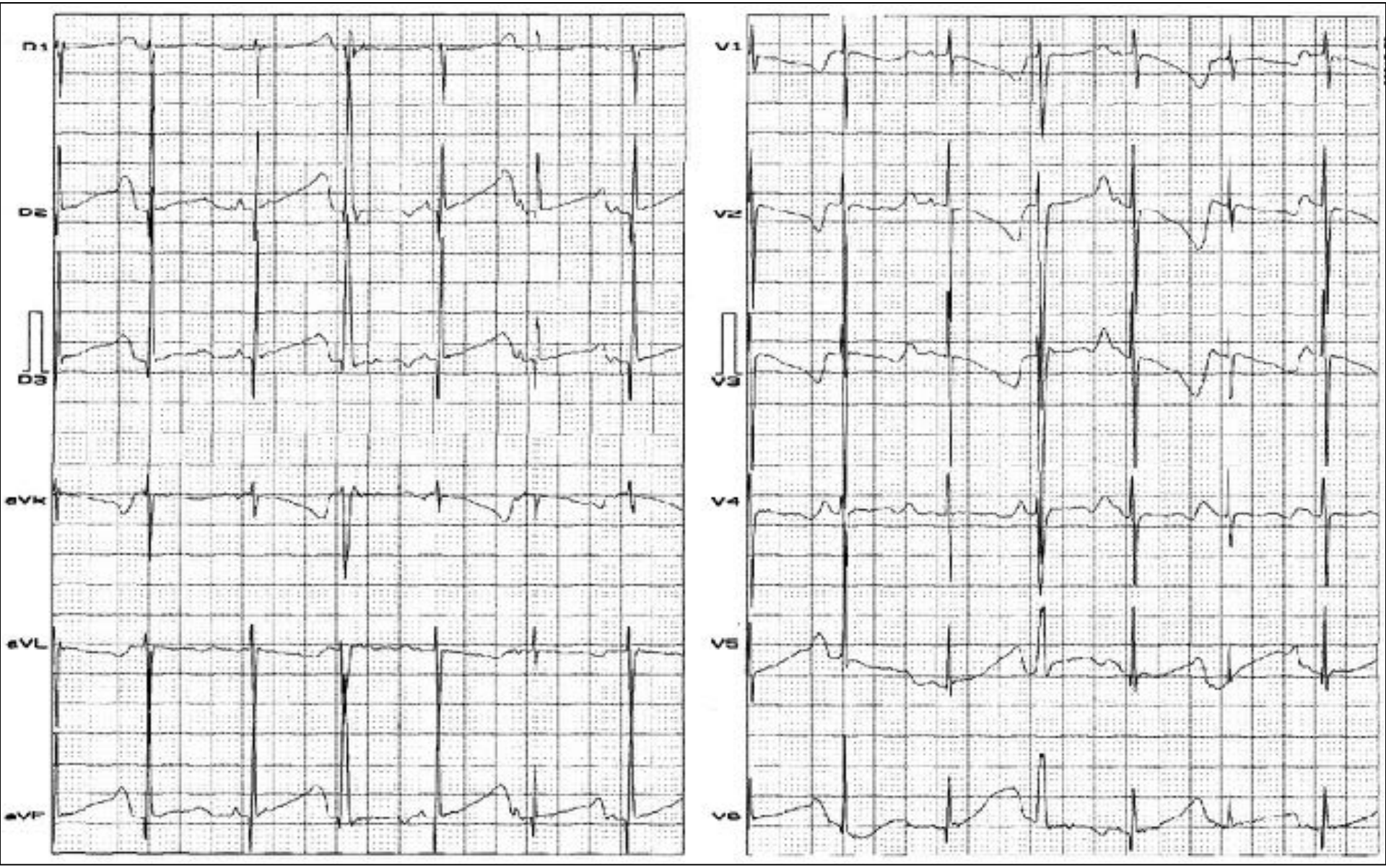
# T-Wave Alternans

**6 y/o Caucasian female**

**Diagnosis: Congenital LQTS - QT: 670 ms**



# Microvolt T wave alternans




Long QT syndrome, LQT3 variant. Long QT interval and microvolt T wave alternans, 1:1 sequence. QTc interval: >500 ms, very long ST segment.

# Torsades de Pointes (TdP)

**Concept:** atypical or helicoidal PVT, associated to long QT interval (generally > 600 ms) or increase in U wave width, with possible typical 180º rotation of QRS axis around the baseline, with phasic variation of polarity and width of QRS complexes, and that may be suppressed by establishing a higher HR.
**Electrophysiological mechanism:** onset of EADs by triggered activity and maintained by reentry secondary to repolarization dispersion, where heterogeneous response of ventricular myocardium thickness cells stands out, especially the so-called M cells of the mid and deep myocardium.
**Cardinal sign:** polymorphic QRS. Rotation of QRS apices of up to $180^0$ along the baseline: swinging pattern of Marriot.
**Usual duration:** from 5 to 20 complexes.
**Heart rate:** from 150 to 300 bpm (usually 200 to 250 bpm).

# Characteristics of TdP

**Clinical repercussions:** asymptomatic, presyncope, syncope or degeneration into VF with cardiorespiratory arrest.
**Onset:** by extrasystole of long, delayed or telediastolic coupling; however, with R on T phenomenon. Frequent after pauses by "long-short" sequence or in bradyarrhythmias, complete atrioventricular (AV) block and sudden PR interval prolongation.
**End:** spontaneous or rarely, it degenerates into VF.
**Most common causes:** severe bradyarrhythmia, hypopotasemia, drugs.
**Effective measures:** β-blockers, bretylium tosylate, diphenylhydantoin, association of β-blockers and diphenylhydantoin or β-blockers associated to permanent pacemaker.
In refractory cases, left sympathectomy or implantable cardioverter defibrillators.

# Classification of polymorphic or atypical ventricular tachycardias

➢ **Torsade de pointes (TdP): in patients with long QT interval**
- Acquired or iatrogenic long QT syndrome;
- Heredofamilial, congenital or idiopathic forms;
- Sporadic or nonfamilial forms.

➢ **Non QT prolongation or true polymorphic ventricular tachycardias**
- With structural heart disease
  - ✓ Associated to chronic coronary artery disease and prior myocardial damage;
  - ✓ Associated to Acute Myocardial Ischemia or infarction;
  - ✓ Associated to Prinzmetal variant angina;
  - ✓ Associated to severe ventricular dysfunction.
- Without structural heart disease
  - ✓ Brugada disease;
  - ✓ Genuine idiopathic ventricular fibrillation (GIVF);
  - ✓ Variant of short coupling of TdP sensitive to Verapamil or "Leenhardt type";
  - ✓ CPVT.
- Others
  - ✓ Alternating or pleomorphic ventricular tachycardia.
  - ✓ Bidirectional ventricular tachycardia.

➢ **Pseudo polymorphic ventricular tachycardia**
- MVT with frequent captures or fusions.

In general, all are triggered in association with what is called "long-short" sequence.

❑ **Acquired, secondary, pause-dependent or of bradycardia:** they occur after critical decrease of HR and are associated to significant increase of QT-U interval;

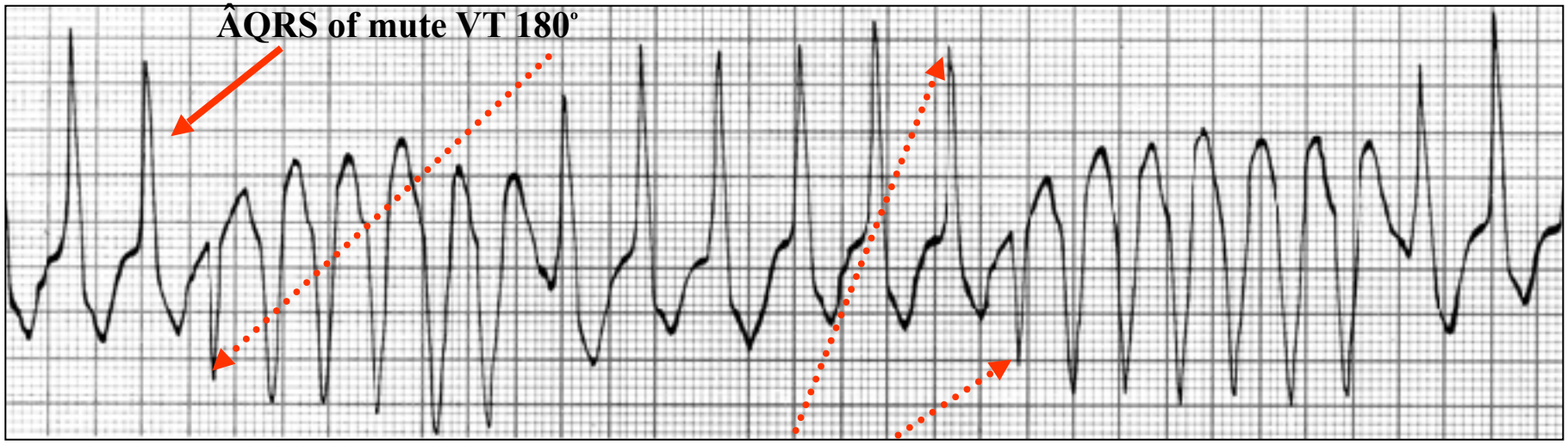
❑ **Congenital, heredofamilial or adrenergico-dependent:** they occur by physical and/or psychological stress;

❑ **Intermediary:** they mix characteristics of the abovementioned ones.

# Differential diagnosis between Torsade de Pointes and true polymorphic VT

| | TdP | True PVT |
|---|---|---|
| Related to sinus bradycardia | Yes | No |
| Events that precede pauses: “pause-dependent” onset of arrhythmia or “long-short” sequences | Yes | No |
| HR: | 200-250/bpm. | Between 260 and 352 bpm in Brugada disease. |
| Associated electrolytic anomalies | Frequent | No |
| Coupling of initial PVC | Delayed or telediastolic: 600 ms | Short or protodiastolic: 240 ms |
| QTc | Long, in average 600 ms | Normal. |
| U wave: | Prominent | Normal voltage |
| Treatment | Correction of electrolytic disorders and suspension of drug with potential to prolong QTc interval. Magnesium, isoproterenol or pacemaker provide specific antiarrhythmic treatment. Pacemaker. Stellectomy. ICD. | ICD: Brugada disease, GIVF and Verapamil + ICD: in “Leenhardt type”.<br><br>Beta blocker: CPVT or ICD. |

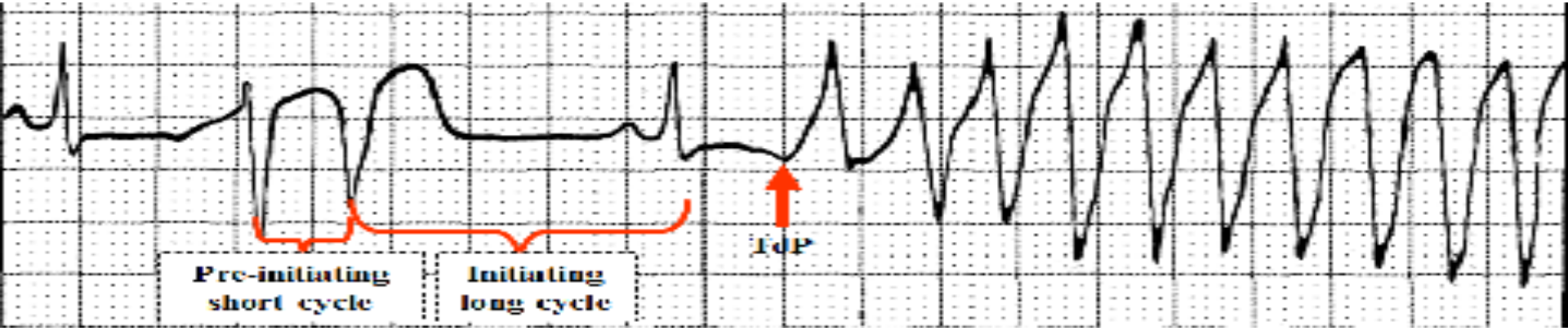
# Typical example of Torsade de Pointes (TdP)




**“Swinging pattern” of QRS ends of 180° sinusoid quality in the change of QRS form**

TdP is characterized by:

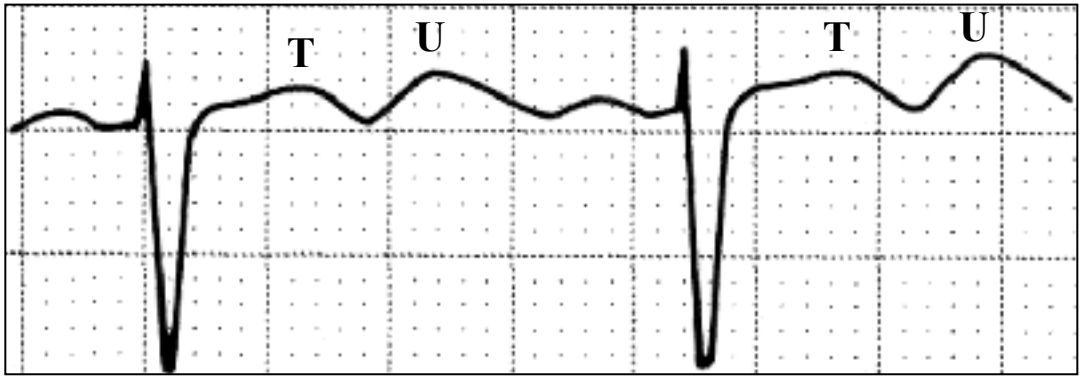
1) Being associated to acquired or congenital long QT interval.
2) The possibility of suppression after higher HR.
3) Onset**:** by PVC of long, delayed or telediastolic coupling.
4) Frequent after pauses by “long-short” sequence or in bradyarrhythmias, complete AV block and sudden PR interval prolongation. TdP that started by intoxication with quinidine. The cycle interrupted by TdP is longer than the prior cycle.



# Acquired LQTS

## 1) Hypopotasemia causing LQTS

**T/U ratio ≤ 1 in II and/or $V_3$**




**U wave > 0.5 mm in II or > 1 mm in $V_3$**

**Characteristics of long QT syndrome in hypopotasemia**

- ✓ Gradual ST segment depression:
  - Depression ≥ 0.5 mm in II or from $V_1$ through $V_3$
- ✓ Decrease T wave amplitude (flat T)
- ✓ Possible T wave inversion
- ✓ Prominent U wave
- ✓ QTc interval prolongation
- ✓ Digitalis action enhancement.

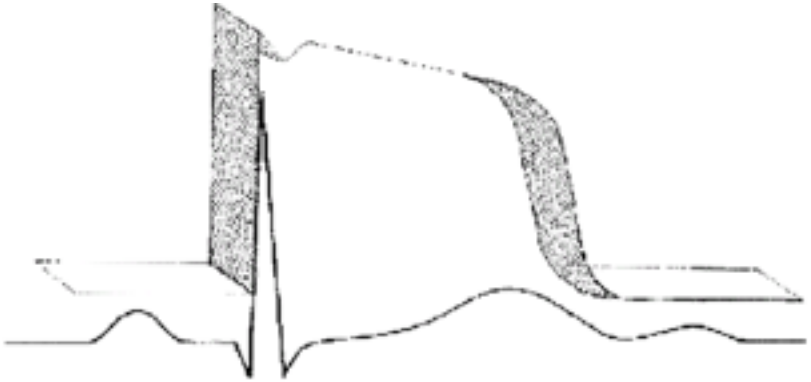
It must be distinguished from hypopotasemia and hypocalcemia, which extends QT interval, but affects flattened T wave and causes prominent U wave.

# 2) Hypocalcemia causing LQTS

Electrolytic alterations

Hypocalcemia < $Ca^{2+}$ < 8.5 mg/dL or < 1.0 mmol/L

**Normal**



**Hypocalcemia and LQTS variant 3**

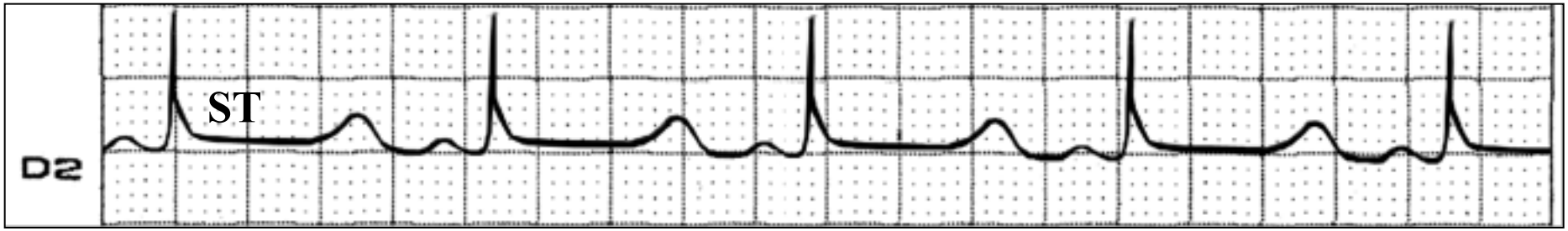
It causes ST segment prolongation but not affecting T wave duration. The phenomenon is more evident in precordial leads.

Characteristics of long QT syndrome in hypocalcemia and comparison with LQT3 genetic variant.

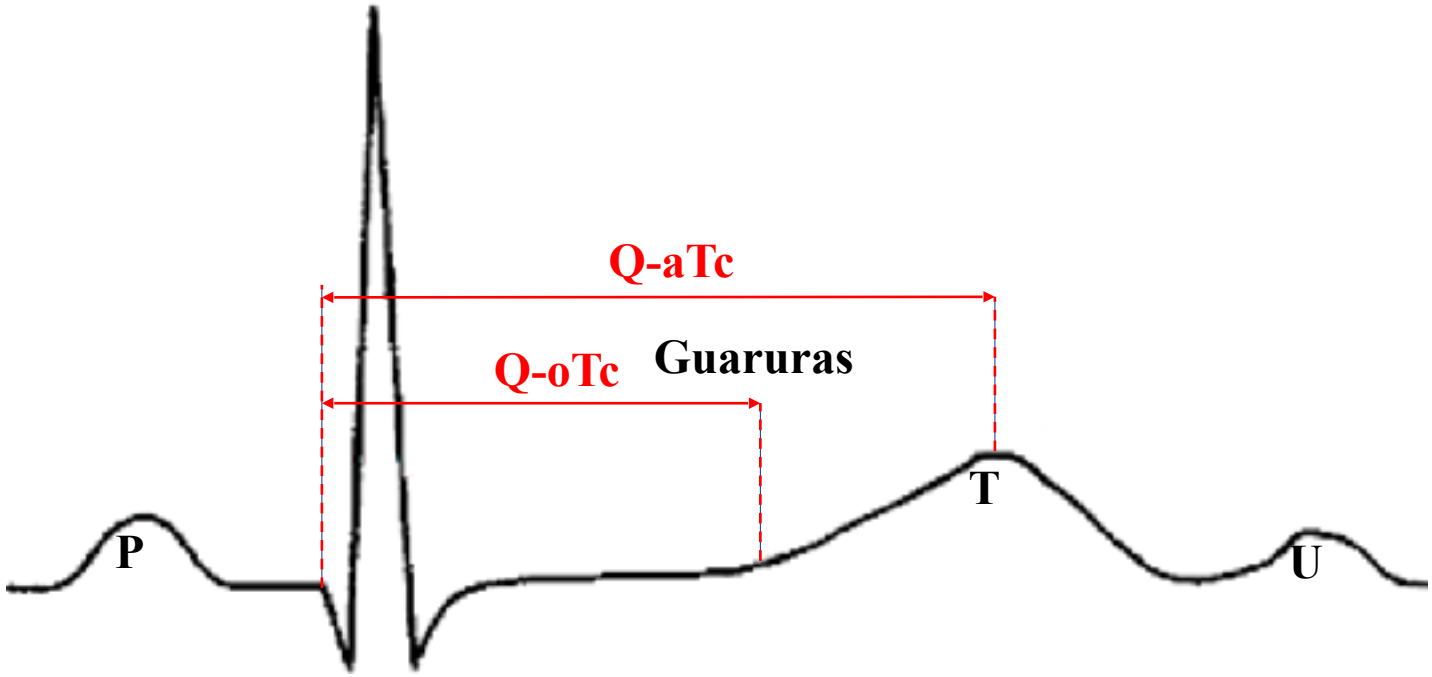
# ECG of hypocalcemia < $Ca^{2+}$

Manifestations usually appear in ECG with levels below 7 mg/dL

**1) Major manifestation:** QT interval prolongation at the expense of ST segment, and normal T wave. This is observed only in hypocalcemia and in hypothermia.

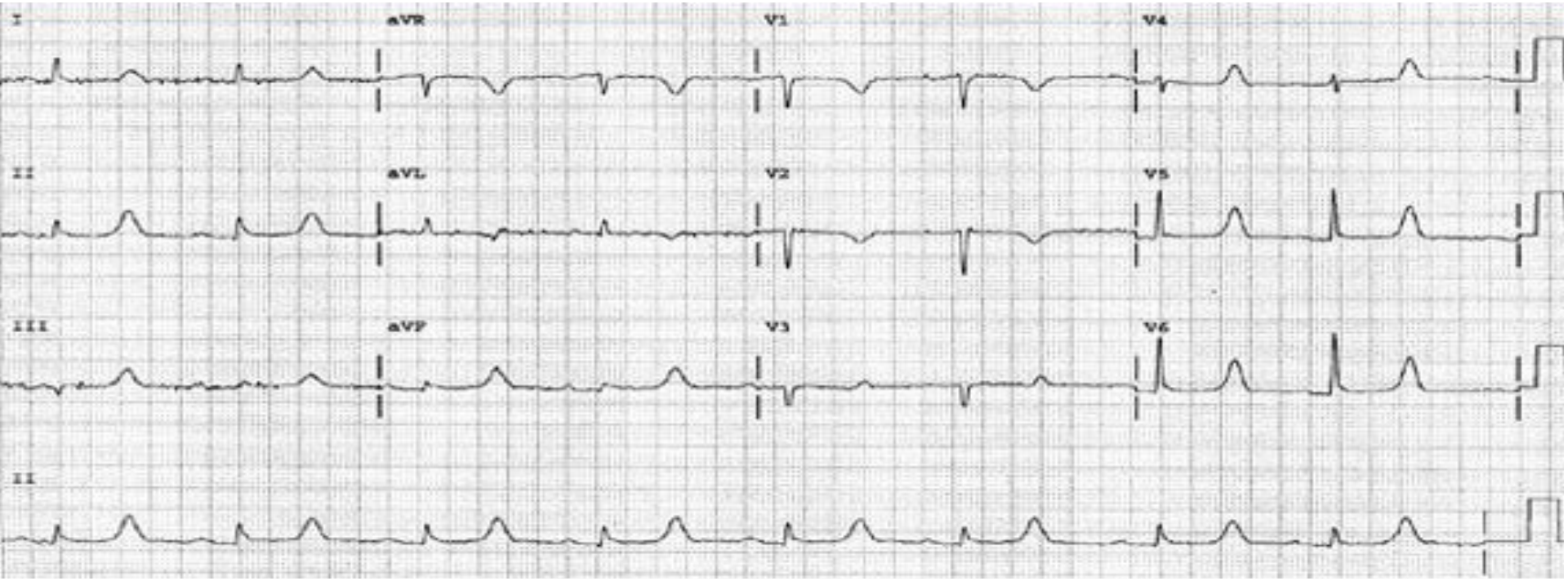



Q-oTc interval prolongation is observed; defined as the interval between QRS complex onset and T wave onset.

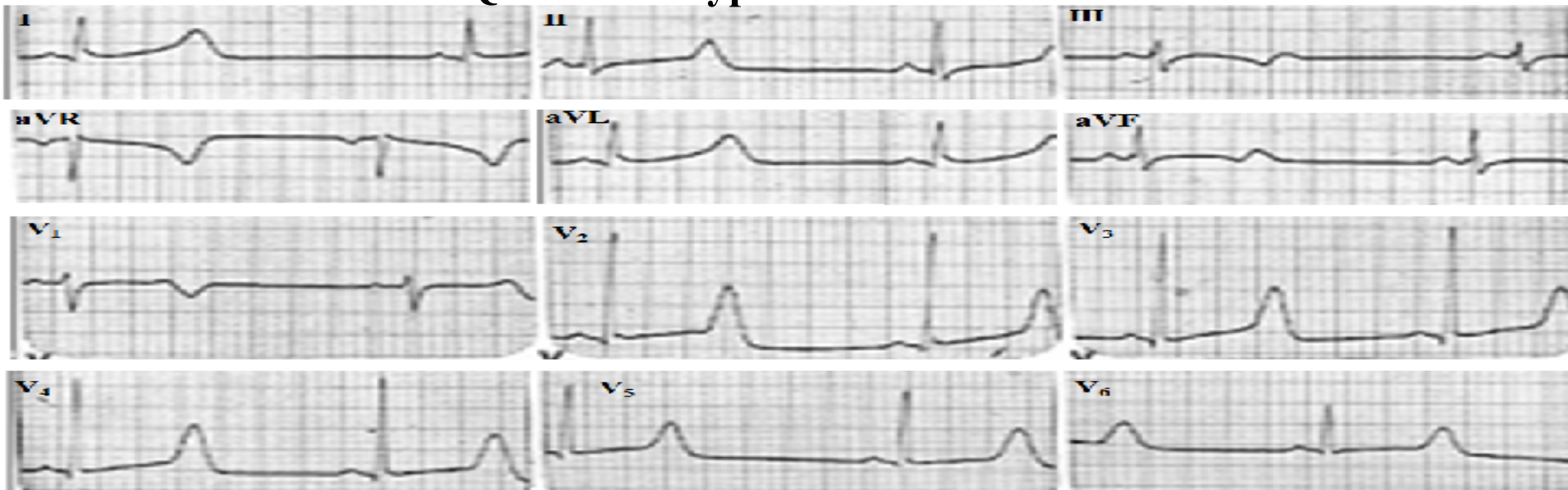



Q-oTc interval prolongation: interval that extends from QRS onset up to T wave onset, corrected by HR.
Q-aTc interval prolongation: interval that extends from QRS onset up to apex T wave corrected by HR.

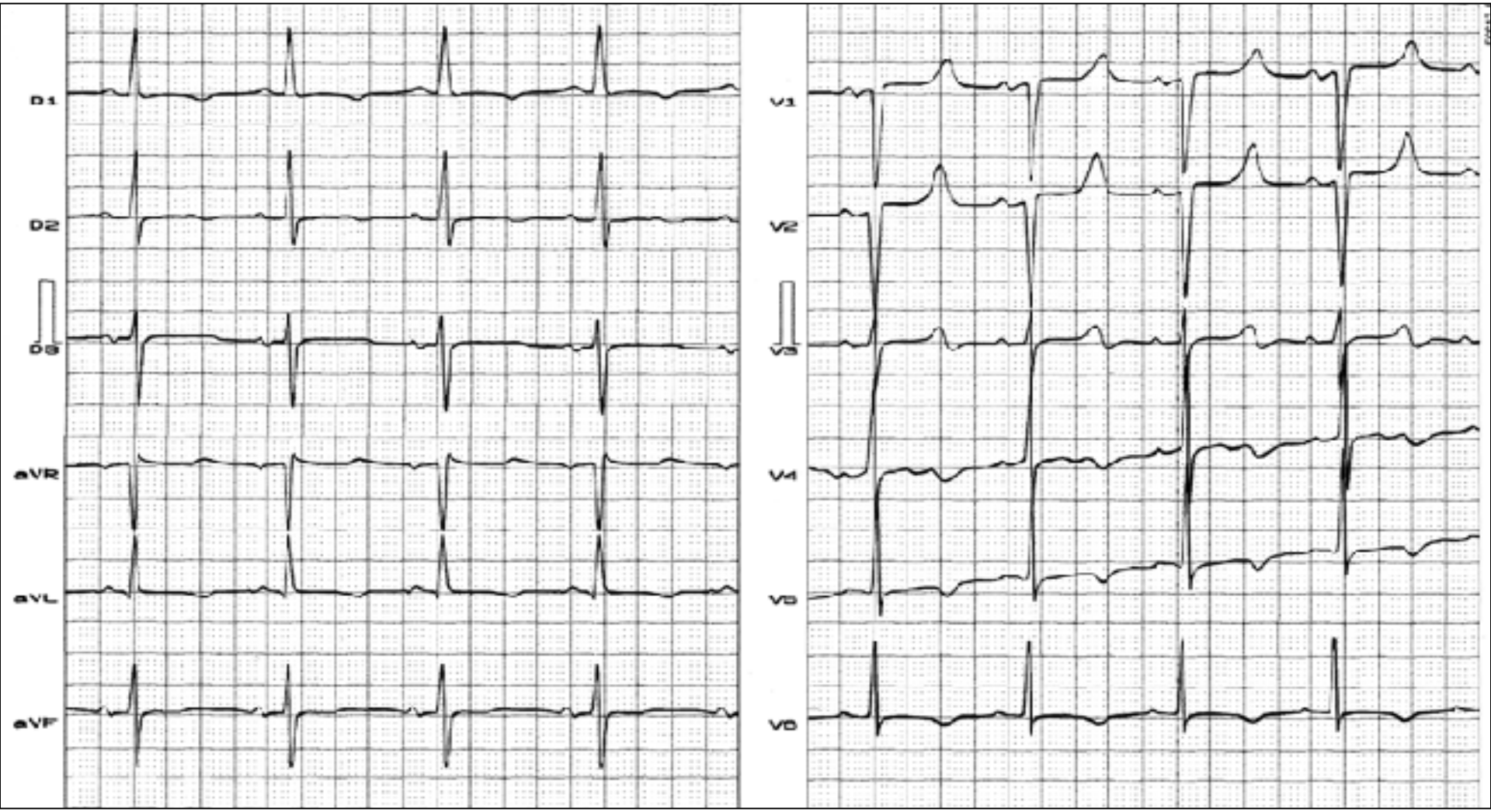
# Hypocalcemia ECG




# LQT3 ECG: hypocalcemic-like ECG



**Name:** AR; **Date:** 08/11/2001; **Sex:** F; **Age:** 53 y/o; **Ethnic group:** Caucasian; **Weight:** 88 Kg; **Height:** 1.60 m; **Biotype:** Endomorph; Complete jejune; nasogastric probe, omeprazole



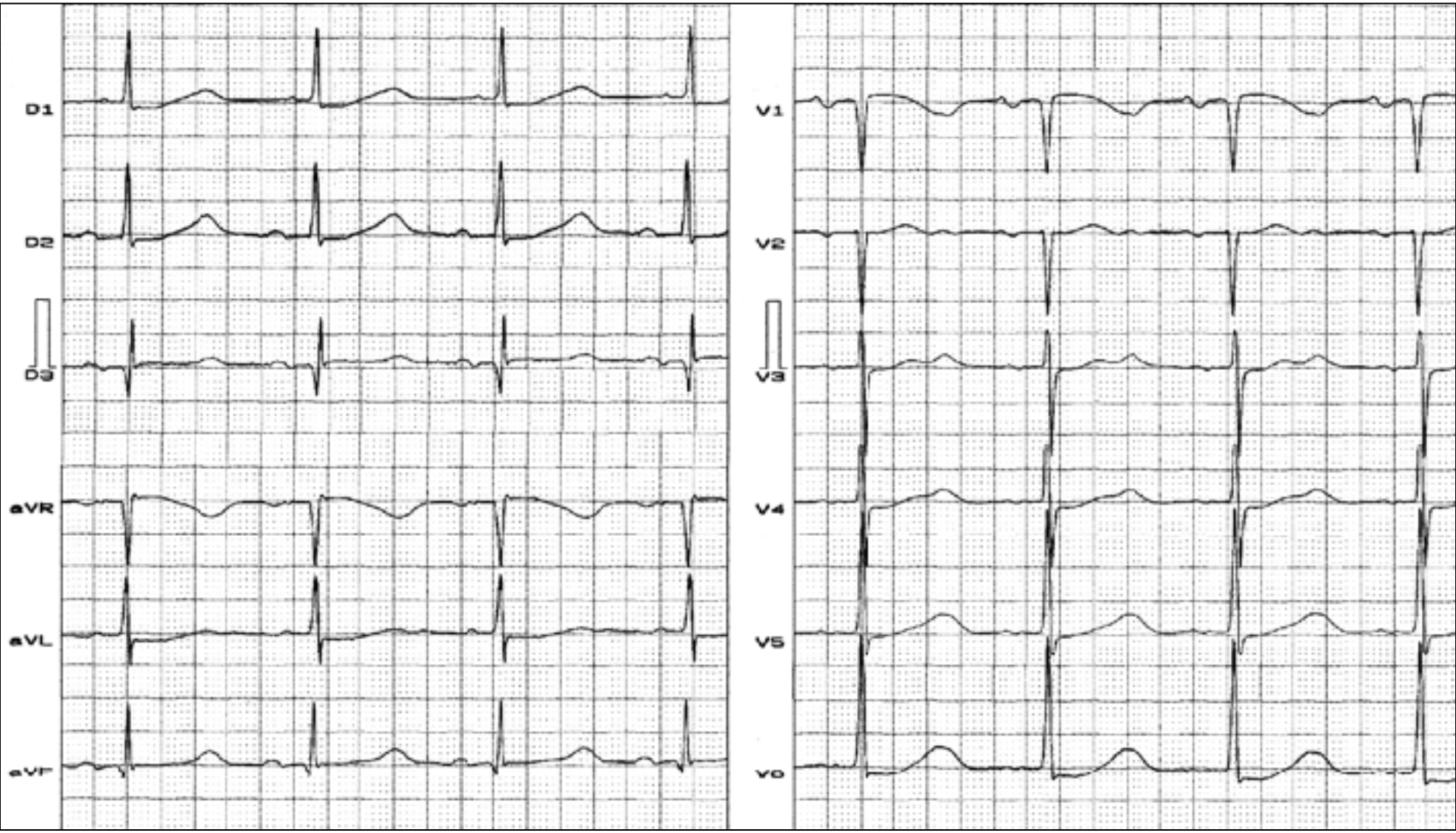

**Clinical diagnosis:** acute pancreatitis with secondary hypocalcemia. $Ca^{2+} < 8$ mg/dL.

**ECG diagnosis:** sinus rhythm, HR: 70 bpm, PR interval: 160 ms, QRS duration: 90 ms, long QT interval (480 ms) at the expense of ST segment.

**Note:** the association of long QT interval with relatively narrow and inverted T wave (I, II, aVL, and V5-V6) is very suggestive of hypocalcemia.

# 3) LQTS secondary to drugs (antiarrhythmic agent: amiodarone)

## ECG with long QT interval by chronic use of amiodarone

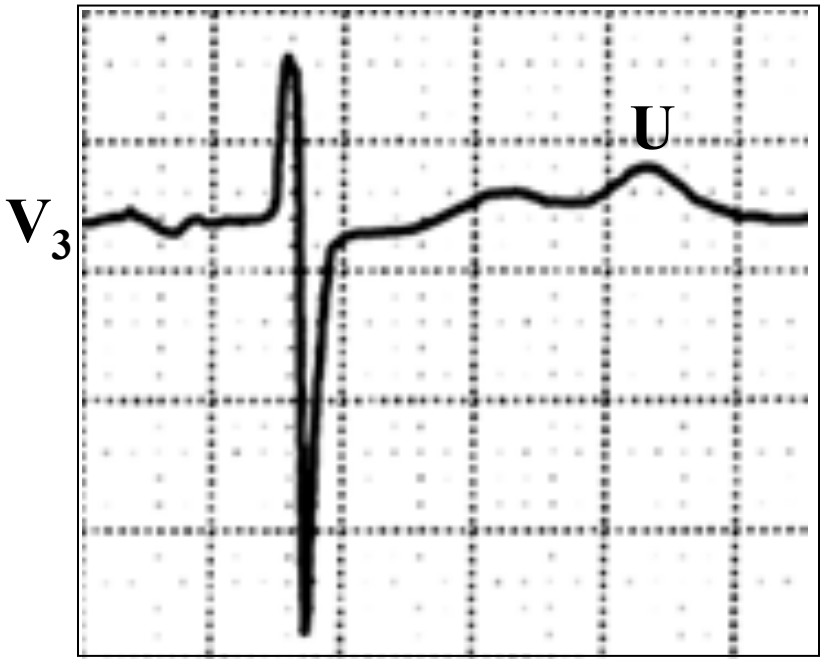



LAE; PR interval: 190 ms; QRS complex: 104 ms; long QT interval 520 ms; QT interval + U: 716 ms; T and U wave are difficult to differentiate; notch is observed between the end of T wave and the onset of the U wave.

## Secondary or iatrogenic forms

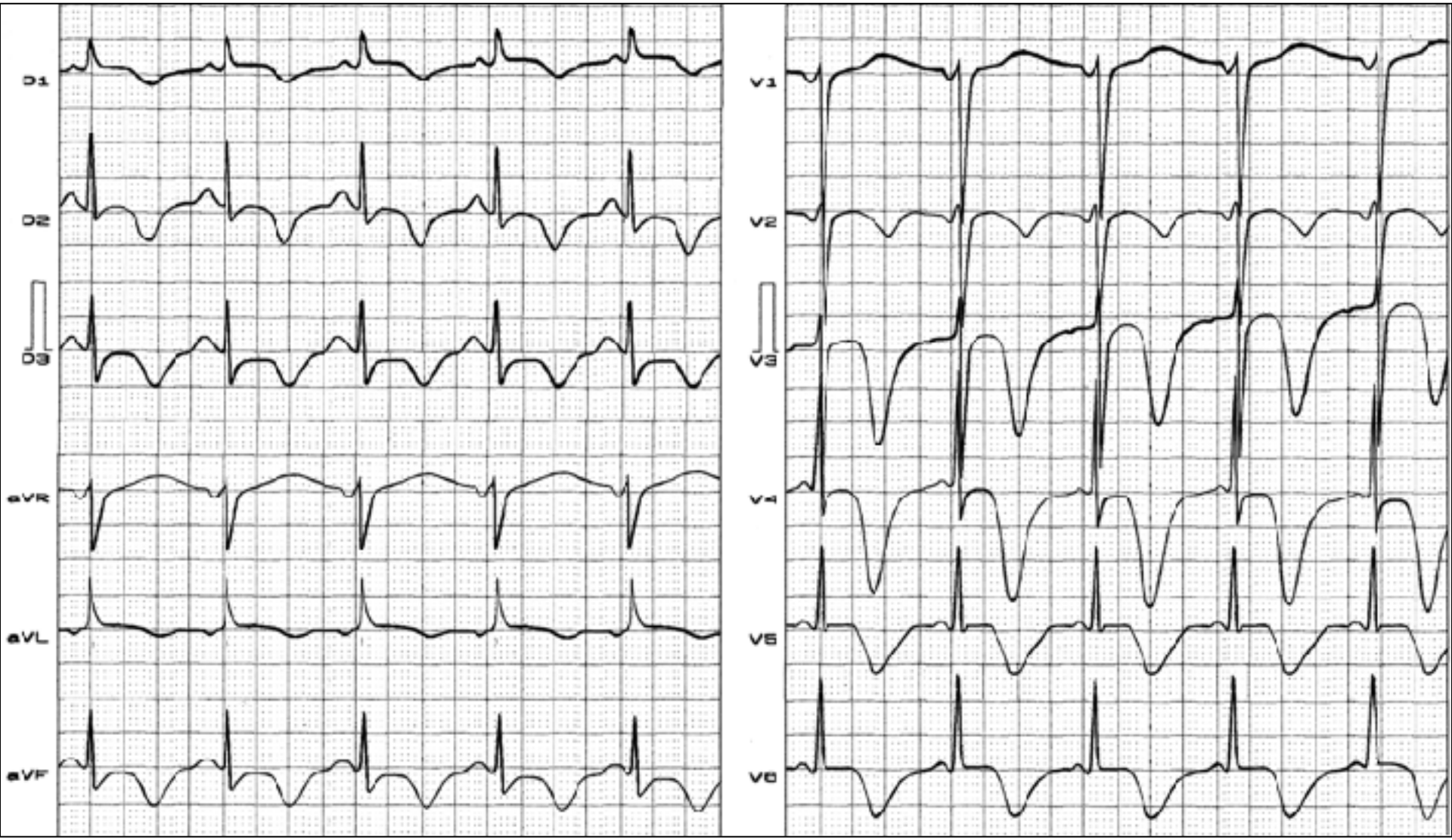
## Antiarrhythmic agents: amiodarone

**Typical ventricular repolarization with chronic use of amiodarone**



# 4) LQTS secondary to central nervous system diseases

**Name:** EAD; **Age:** 68 y/o; **Sex:** F; **Ethnic group:** Caucasian; **Date:** 01/21/1999; **Weight:** 65 Kg; **Height:** 1.65 m; **Medication in use:** Enalapril + Hydrochlorothiazide




**Clinical diagnosis:** subarachnoid hemorrhage.
**ECG diagnosis:** long QT interval, great-width and inverted T waves: giant T waves.

# Electrovectorcardiographic aspect 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 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 cut off 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 has 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. Table 1

| SQT Variant | QTc duration | Gene symbol and effect | Author |
|---|---|---|---|
| **SQT 1** | 260-280 ms | hERG (human ether-ã-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 LQT 9 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($\boldsymbol{I_{K1}}$) in contrast to the loss-of-function of the potassium channels in the long QT syndromes.

Initial outward potassium channel in phase 1

**Phase 1:** This phase presents 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 & by J point elevation in Brugada syndrome and early repolarization syndromes.

This 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 or 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, 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 (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 $I_{to2}$ 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**

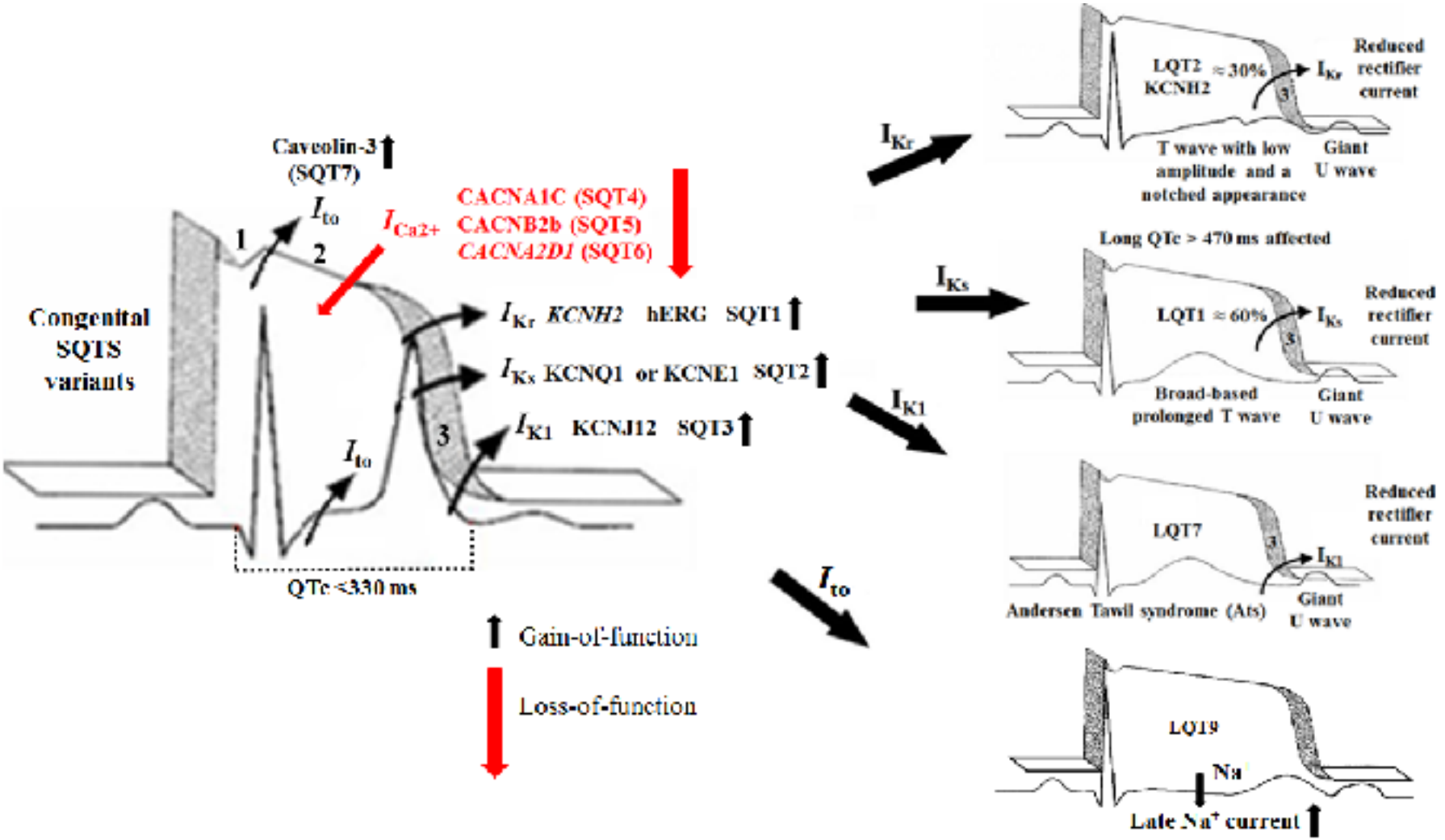
| **$I_{to1}$ channel of AP of ventricular myocardium** | | | | | | |
|---|---|---|---|---|---|---|
| Cation | | α subunit protein | Cation | | α subunit protein | Cation |
| $K^+$ | Transient rapid outflow $I_{to1}$ current | pore-forming protein isoforms Kv4.3/4.2$K_V$4.2 and Kv4.3 Probable clone. | $K^+$ | Transient rapid outflow $I_{to1}$ current | pore-forming protein isoforms Kv4.3/4.2$K_V$4.2 and Kv4.3 Probable 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. $I_{Cl\ AMPc}$ 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, blood volume 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.** $\mathbf{I_{Cl\text{-}edema}}$ 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.

V. $Na^+$ outflow through the $Na^+/Ca^{2+}$ exchanger channel operated reversely. Inward $Na^+$ through $Na^+/Ca^{2+}$ exchanger channel, operating in a reverse way.

Schimpf et al reviewed the clinical, electrophysiologic, and molecular features of 15 reported cases and 2 unpublished cases of short QT syndrome type 1, 2, and 3 (609622) (Schimpf 2005).




The figure shows the representation of monophasic action potentials and ECGs of the four congenital SQTS potassium channels variants and their respective counterparts 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).

## 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 atrial fibrillation 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 atrial and ventricular fibrillation. All three affected members of the family received implantable cardioverter defibrillators, 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. Six 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 atrial and ventricular fibrillation in 3 of 4 patients.

SQT1 is caused by a gain of function substitution in the HERG (human Ether-a-go-go Related Gene, in italic or KCNNH2 in the new nomenclature) is the gene that encodes the pore-forming alpha subunit of a voltage-gated potassium 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 IKr channel HERG (KCNH2). The mutations dramatically increase IKr, leading to heterogeneous abbreviation of action potential duration and refractoriness, and reduce the affinity of the channels to IKr blockers. The occurrence of sudden cardiac death in the first 12 months of life in two patients suggests the possibility of a link between KCNH2 gain of function mutations and sudden infant death syndrome.

## 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 physiologic 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 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 base and peaked T waves. Her 35-year-old father had a short QT interval (320 ms) and a history of nearsyncopal 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 describe a mutation (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

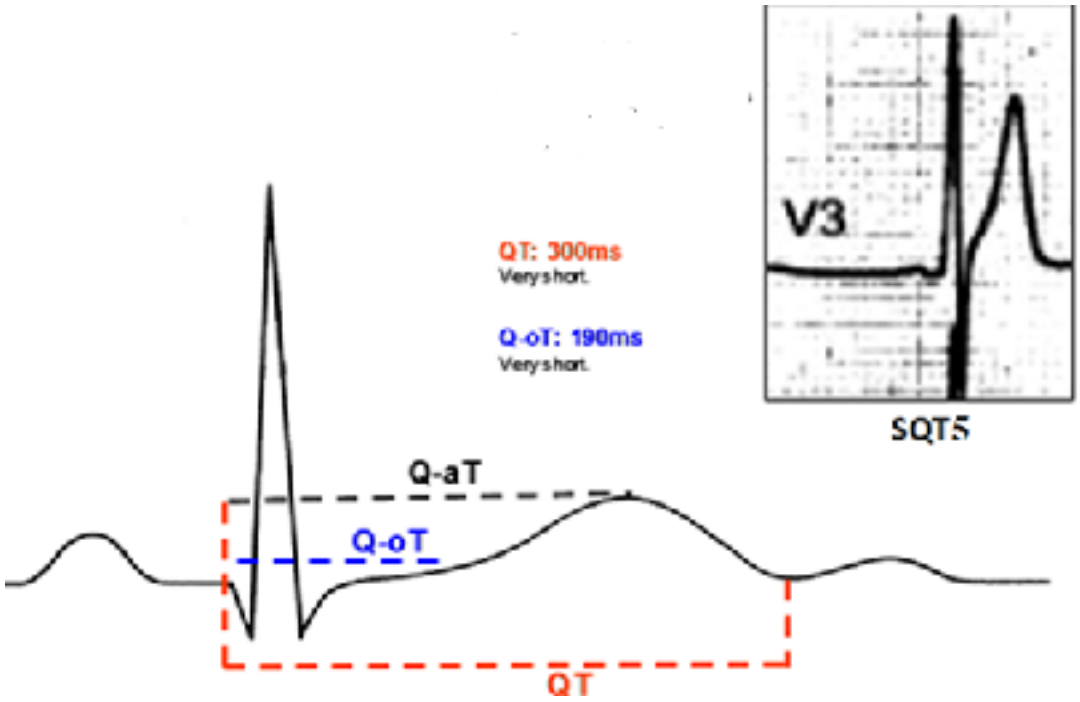
It have been associated with Brugada syndrome (BrS), short QT syndrome, and Timothy syndrome (LQT8). The mutations in the LTCCs are detected in a high percentage of probands with J-wave syndromes associated with inherited cardiac arrhythmias, suggesting that genetic screening of Ca(v) genes may be a 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 in fant 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 $\leq$ 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).

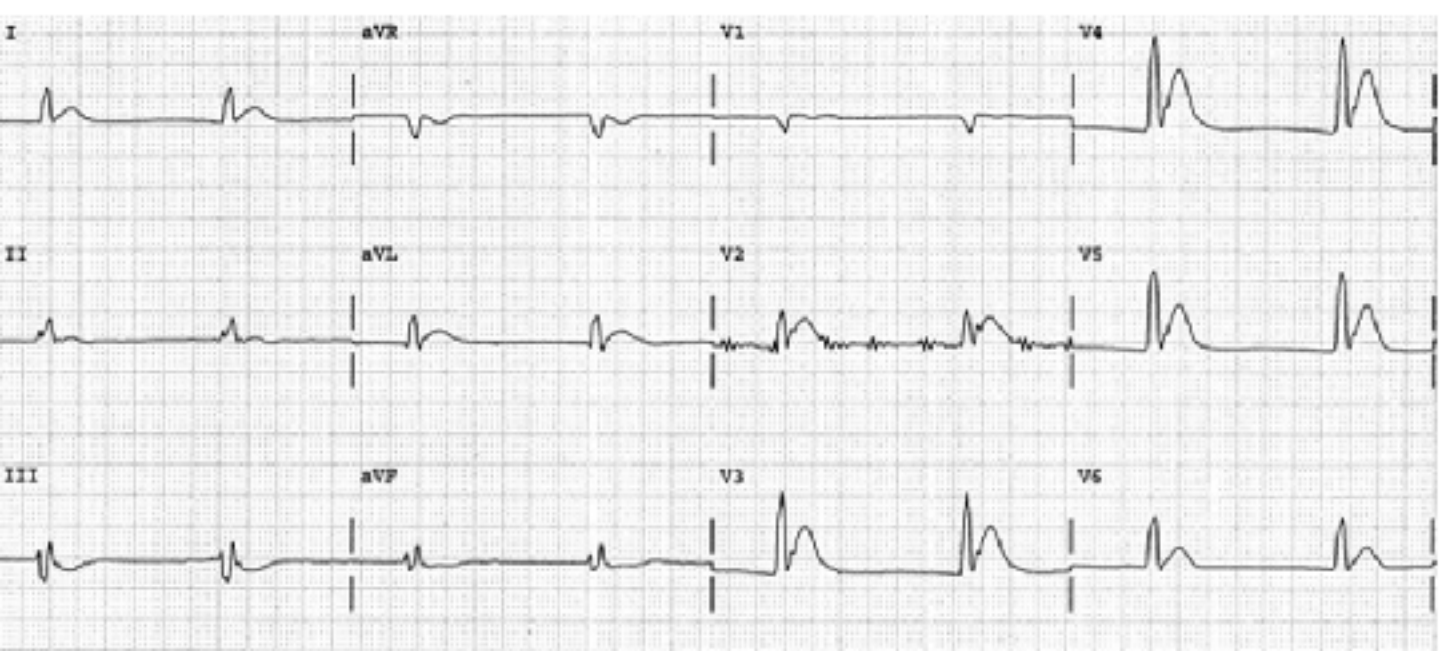
SQT4: Gene symbol: *CACNB2b* ($I_{Ca}$) Gene name: Calcium channel voltage-dependent, beta 2 subunit/ (Antzelevitch 2007).

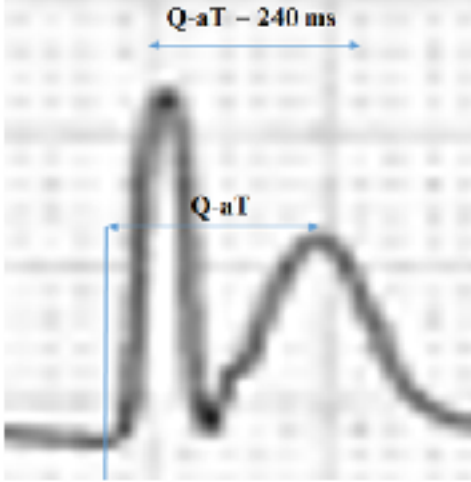
| SQT Variant | QTc duration | Gene symbol and effect | Author |
|---|---|---|---|
| **SQT 4** | 331-370ms | CACNA1C | Antzelevitch C et al. Circulation 2007;115:442 |
| **SQT 5** | 346-360 ms | CACNB2b ($I_{Ca}$) loss-of-function | Antzelevitch C et al. Circulation 2007;115:442. |

Genetic and heterologous expression studies revealed loss-of-function missense mutations in CACNA1C (A39V and G490R) and CACNB2 (S481L) encoding the alpha1- and beta2b-subunits of the L-type calcium channel. The first report of loss-of-function mutations in genes encoding the cardiac L-type calcium channel associated with a familial sudden cardiac death syndrome in which a Brugada syndrome phenotype is combined with shorter-than-normal QT intervals (331-370).




Missense mutations in CACNA1C (A39V and G490R) and CACNB2 (S481L) encoding the alpha1- and beta2b-subunits of the L-type calcium channel. We observe that these mutations have a Q-aT interval extremely short( 240ms) and ST segment absent, consequently the genotype has an hypercalcemic like" phenotype because Q-aT values < 270 ms are typical of severe hypercalcemia.




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, alpha 1C subunit Antzelevitch et al. Circulation 115: 442, 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 border- line shortened QT intervals, acquired causes of short QT interval should be excluded. Table

# Acquired and other genetic causes of short QT/QTc interval

| |
|---|
| 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, |
| Hypercalcemia |
| Hyperthermia |
| Acidosis |
| Effect of catecholamine |
| 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). |
| Autonomic tone alterations |
| in response to atropine |
| Dysautonomia of Chronic Fatigue Syndrome with QTc mean values of 371 a 384 ms (Naschitz 2006). |
| 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) Itis a sex chromosomal aneuploidy (47,XXY) affecting 1/660 males.<br>QTc was shortest among testosterone treated males with KS, while untreated and thus hypogonadal KS had QTc interval comparable to controls (Jørgensen 2015). |
| Rufinamide, a recently approved anticonvulsant, illustrates the current regulatory approach to drugs that shorten QT interval (Schimpf 2012). |

Short QT interval in other channelopaties:

- **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 (Viskin 2004) demonstrated that male patients with idiopathic ventricular fibrillation had shorter QT intervals (371± 22 ms) and suggested gender-specific cutoff values (QTc interval o 360 ms for men; QTc interval o 370 ms for women) for a short QT interval.
- **Brugada Syndrome 3:** It is caused by heterozygous mutation in the gene encoding the alpha-1C subunit of the L-type voltage-dependent calcium channel (CACNA1C; 114205) on chromosome 12p13. Antzelevitch et al (Antzelevitch 2007) reported two probands with Brugada syndrome 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 ST segment elevation in V1, saddleback ST segment elevation 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.
- **Early Repolarization Syndrome**: Classically, early repolarization (ER), defined as an elevation of the QRS-ST junction (J-point) of at least 1.0 mm (0.1 mV) from baseline in the inferior or lateral lead, manifest as QRS slurring or notching, is a common ECG finding that is generally considered to be benign but may be associated with VF in some patients. Careful attention be paid to patients with ER and J-point elevations > 2.0 mm, particularly in patients with otherwise unexplained arrhythmias or a family history of unexplained SCD. Patients with ER were more likely to be male, to have experienced symptoms during sleep, and to have a shorter QTc interval than those without ER. Nowadays it is not necessary the presence of ST segment elevation for the diagnosis of ER (Pérez 2012).

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

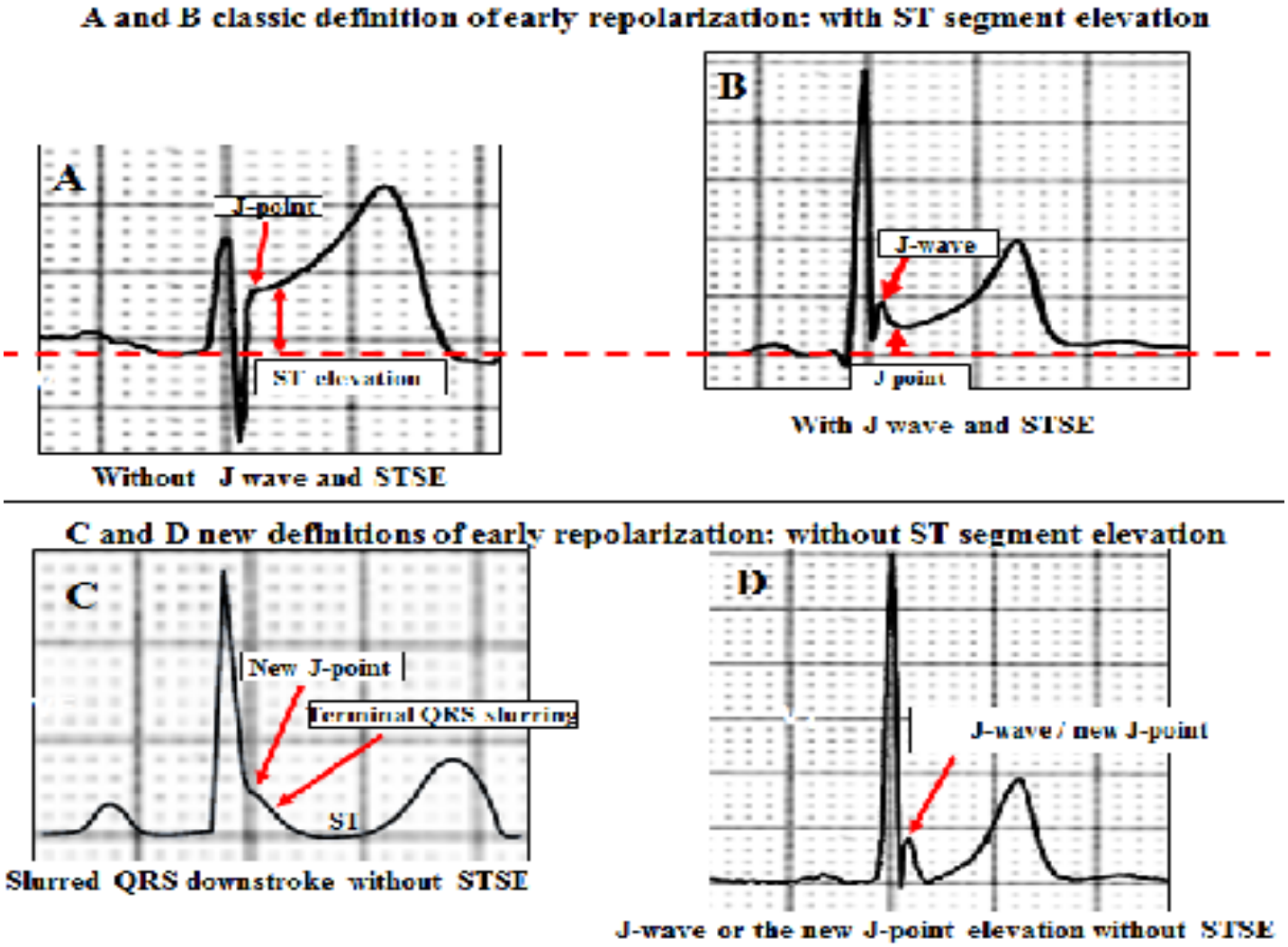
A) ER with only ST segment elevation.

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.



*Sarc$K_{ATP}$ 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 N, Gonoi T, Clement JP, Namba N, Inazawa J, Gonzalez G, Aguilar-Bryan L, Seino S, Bryan J (November 1995). "Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor". Science. 1995 Nov 17;270(5239):1166-70.

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 ≤ 330 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 electric physiological studies (EPSs).
- Autopsy did not reveal any structural heart disease

**Electrocardiographic and electrophysiological features**

The study of ECG abnormalities in channelopaties 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).

**I) 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. Figure

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 ≥ 1mm that are fused to the precedent T wave should include in the measurement. U waves < 1mm and those that are separate from the precedent T wave should be excluded.

**Case report**

Caucasian 44 asymptomatic man.

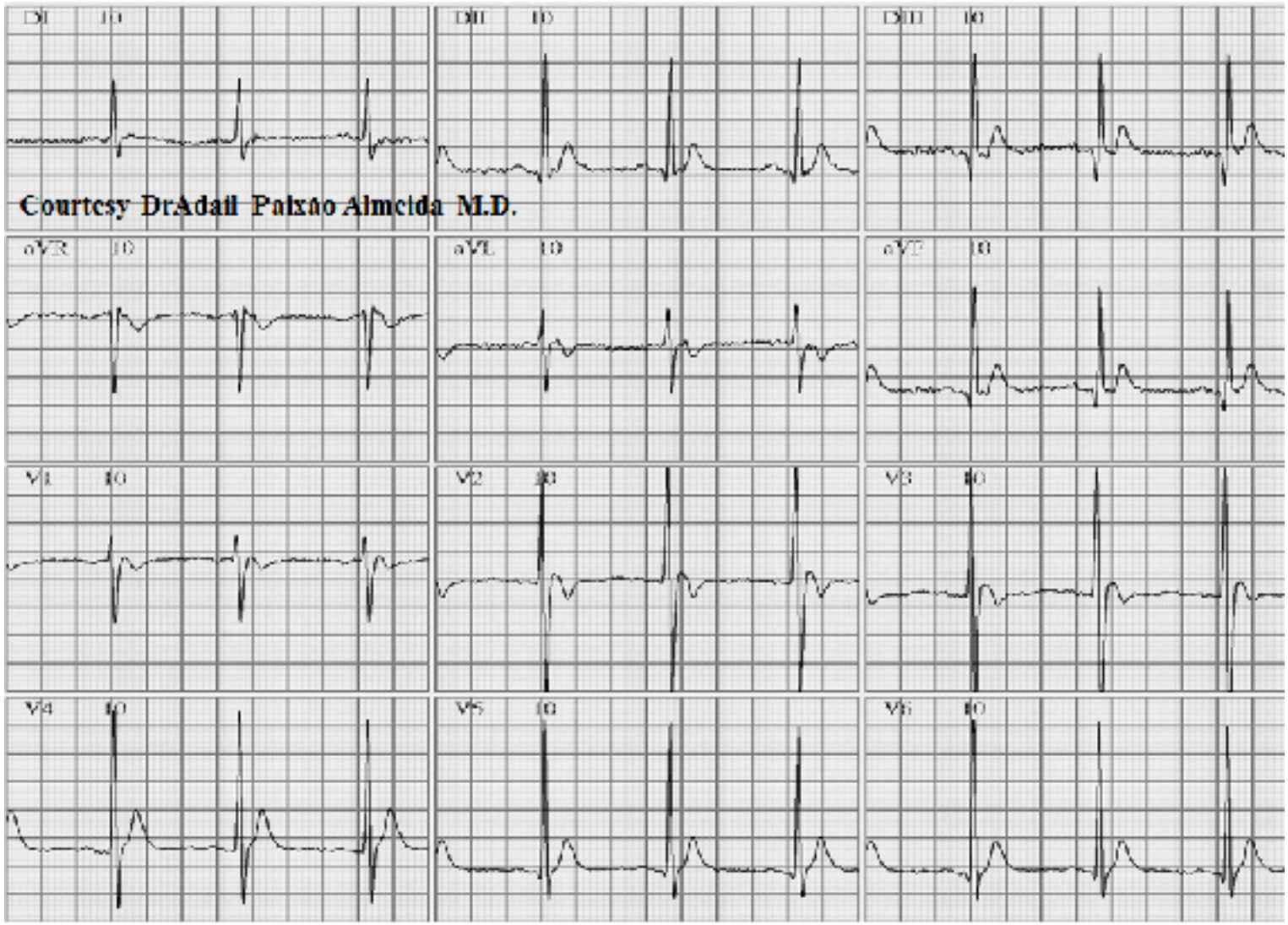
**Reason for consultation:** patient referred to a cardiologist for risk assessment of prostate biopsy under sedation. Asymptomatic.

**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.

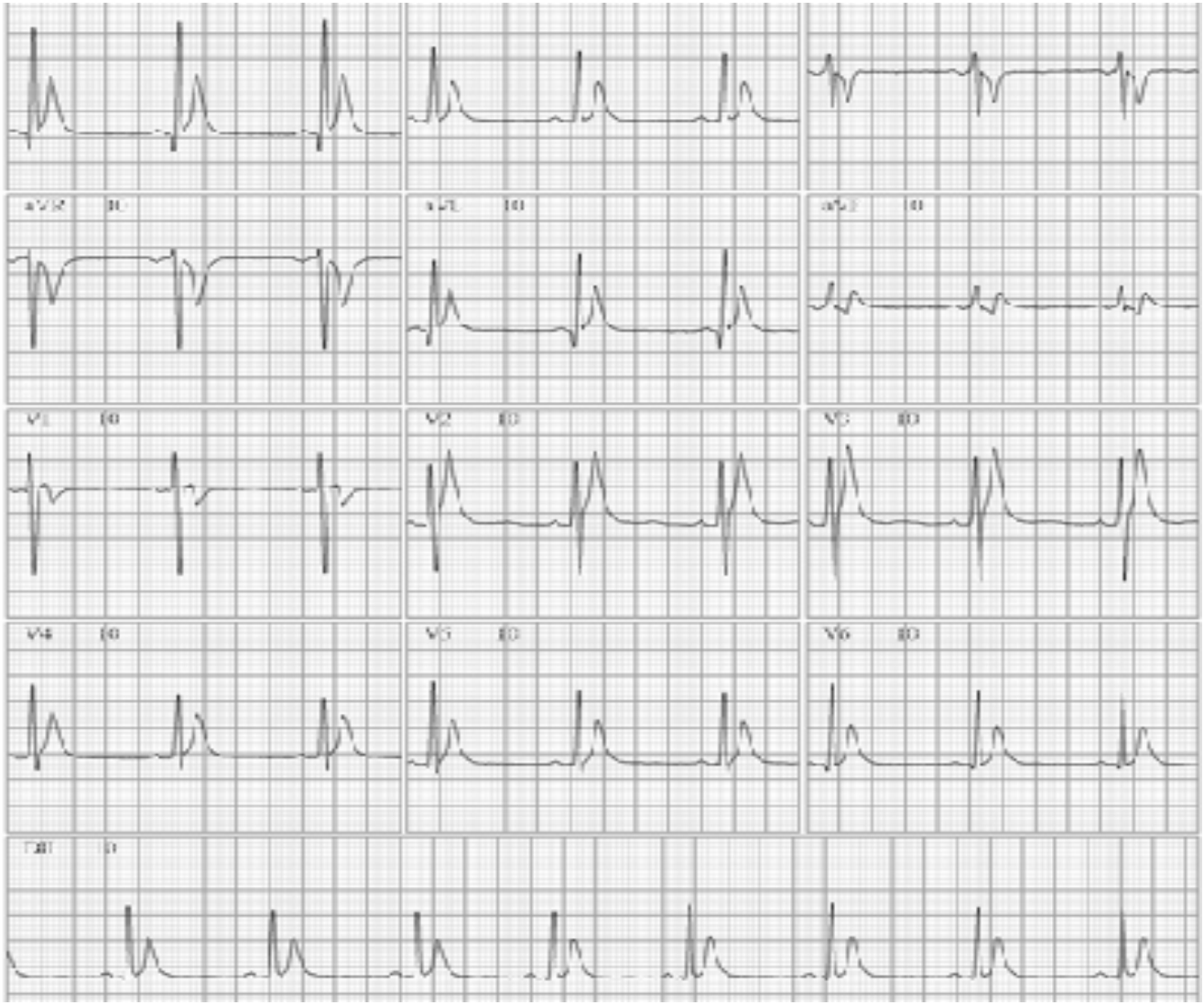
**Physical examination:** Normal. Nothing to be noted.

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

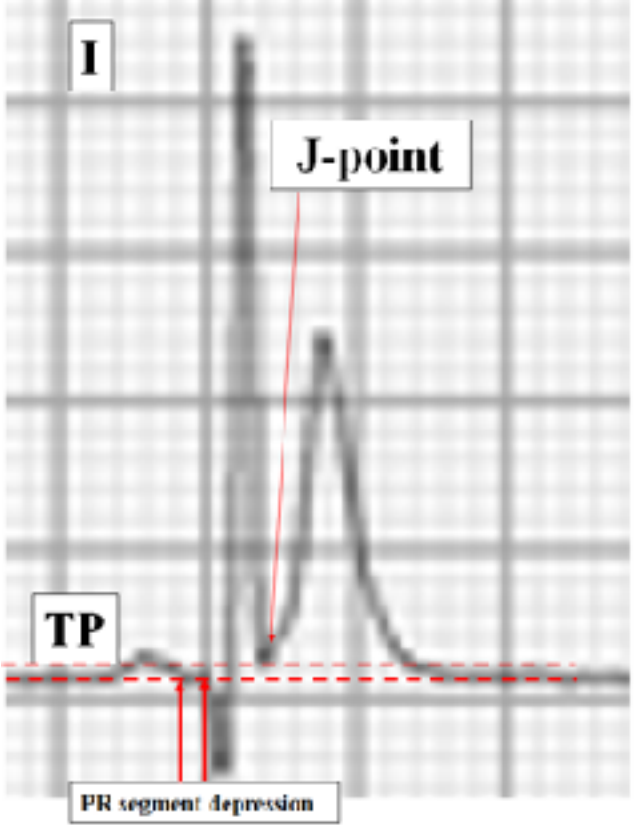


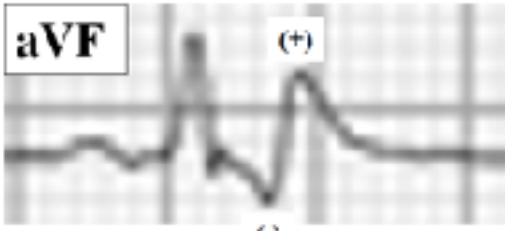

**ECG diagnosis**: sinus rhythm, heart rate (HR) = 83 bpm; SÂP + 60º, PR interval duration: 120ms, QRS duration: 60ms. SÂQRS: + 65º and to left, ST segment with minimal duration, SÂT + 63º and to back. QT = 220 ms; QTc = 353 ms (proband)

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



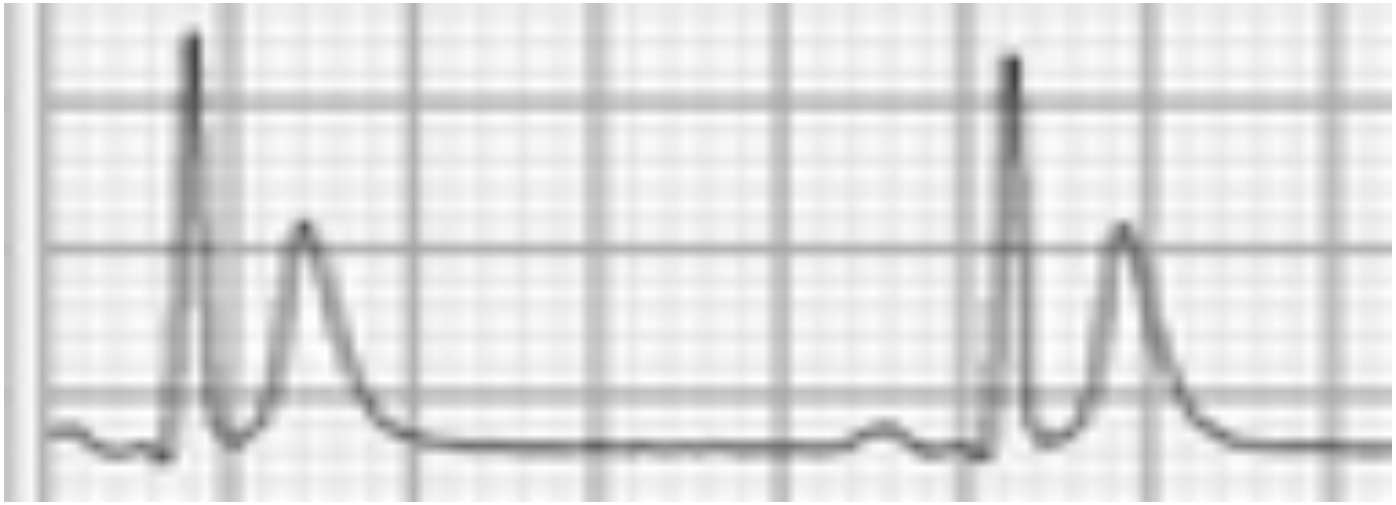
**Clinical diagnosis**: Congenital short QT syndrome with mutation in Caveolin-3 (SQT7).
**ECG diagnosis**: Sinus rhythm, HR = 68 bpm; P wave: ; SÂP + 32º, PR interval duration: 120ms, PR segment depression (> 0,5 mm) in II and V5, absence of ST segment, positive-negative T-wave or "minus-plus T wave sign" in aVF, and QT = 280 ms; QTc = 295 ms;



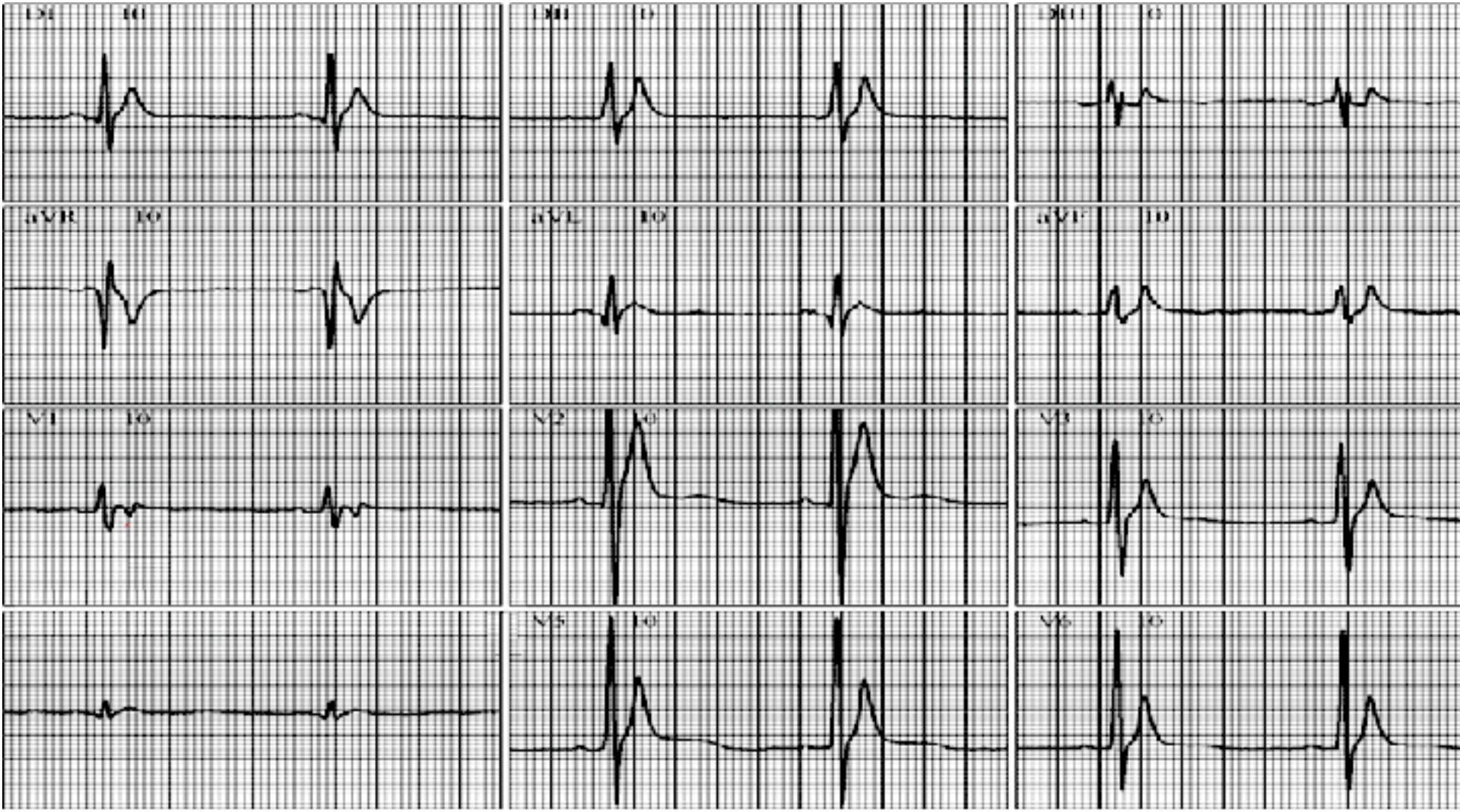




(-)

Minus-plus T wave sign



**Name**: WTC; **Gender**: Masculine.; **Ethnic group**: Caucasian.; **Age**: 23 y/o (from Bahia, Brazil in March 21, 1989); **Weight**: 68 Kg.; **Height**: 172m.; **Date**: April 24/2012; **Drugs in use**: None. It belongs to 23 yo son of the proband.



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

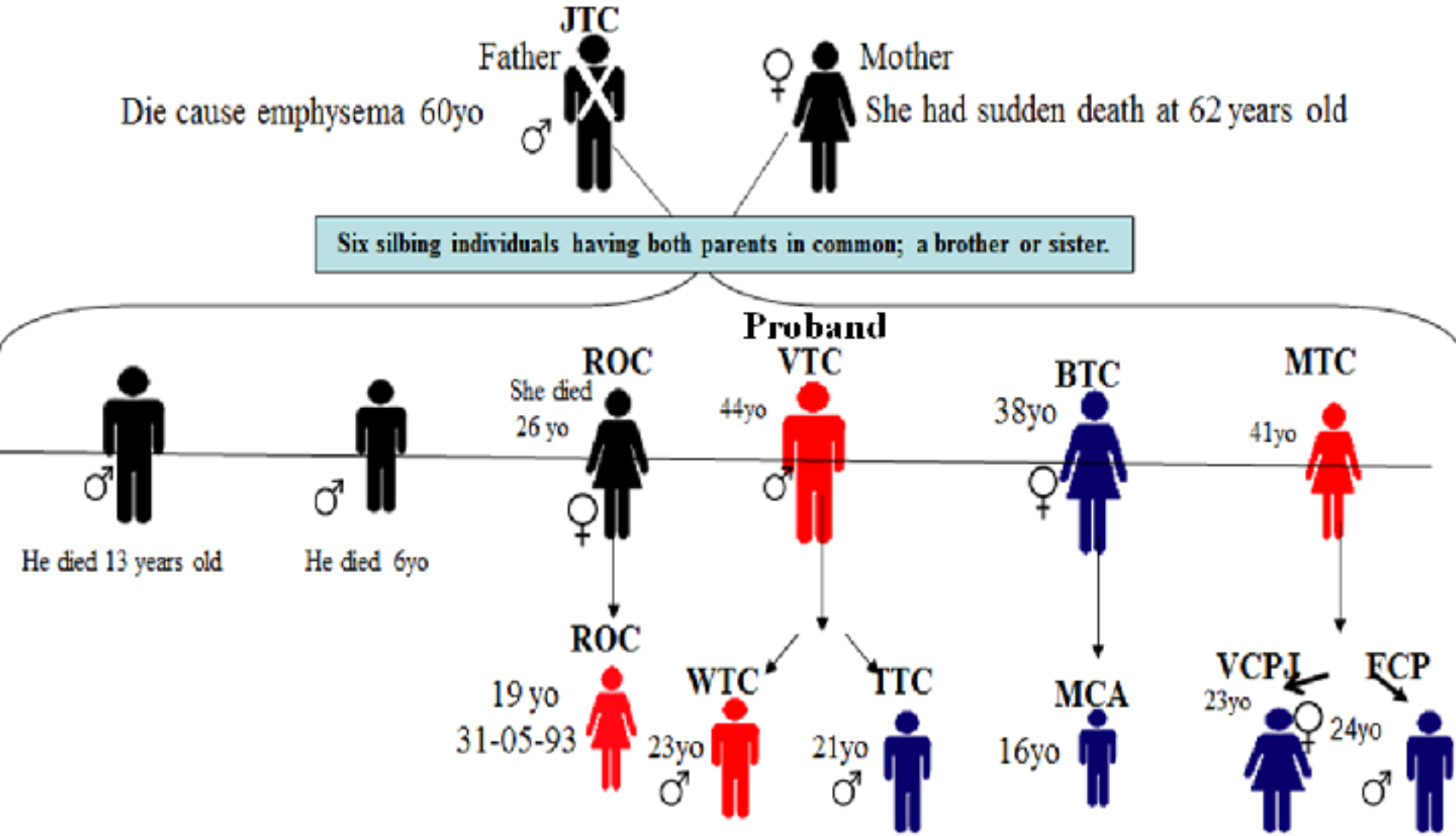
**The Latin America family tree with congenital short QT syndrome**

**Black** color human body means that he or she had suffered sudden death Black color with X mean another cause of death.

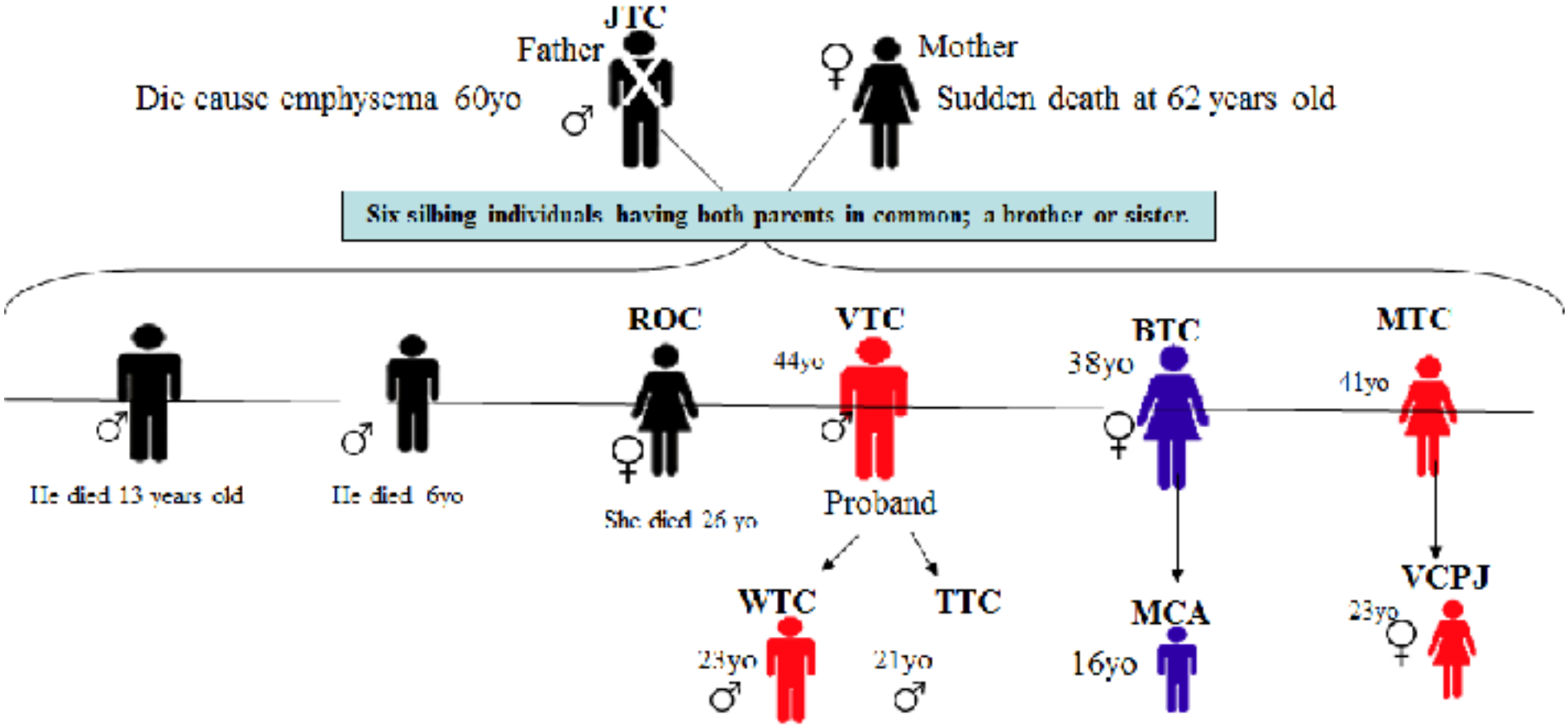
**Red** color human body means that he(or she) has the typical phenotype in his(her) electrocardiogram.

**Blue** color human body means that she or he does not have the typical phenotype in his electrocardiogram.

An individual or member of a family being studied in a genetic investigation. Also called *index case*, *propositus*.


JTC
Father
Die cause emphysema 60yo
Mother
She had sudden death at 62 years old
Six silbing individuals having both parents in common; a brother or sister.
Proband
He died 13 years old
He died 6yo
ROC
She died
26 yo
VTC
44yo
BTC
38yo
MTC
41yo
ROC
19 yo
31-05-93
WTC
23yo
TTC
21yo
MCA
16yo
VCPJ
23yo
FCP
24yo

- **VTC:** He is the proband. Masculine, Caucasian, Weight: 84Kg.; Height: 1.79 m.; 44 years of age (he was born in Vitória da Conquista - Bahia. Brazil in February 12/1968.), He is asymptomatic and has the typical ECG phenotype. He has two sons **TTC** and **WTC.**
- **BTC**: She is daughter of the proband. She live in São Paulo City. She is asymptomatic. She has a normal ECG, QTc 465 VCG and ECG-AR She has high blood pressure.
- **MTC:** feminine, Caucasian, 41 yo, She was born in December 15/1970 in Vitória da Conquista - Bahia. Brazil; Weight: 60 Kg.; Height: 1,63m; Drugs in use: oral quinidine since 03/05/2012. Asymptomatic.
- **TTC:** He does not have the ECG phenotype; however, the U waves are visible in all leads. He was born in Vitória da Conquista - Bahia.Brazil in October 29/1991(he has 21 y/o).
- **WTC:** He has a typical ECG phenotype (very short QT interval) and different from the father (proband). Additionally, tall with narrow base T waves.
- **ROC:** Father: **JTC** - brother of **MTC** and **VTC** - Sudden death with 26 years old of age.
- **VCPJ:** She is daughter of **MTC**- She has the ECG phenotype, Caucasian, height = 1,61m, weight = 55 kg, femenine, asymptomatic, without medication, she was born in Vitória da Conquista – Bahia- Brazil. In : 06/02/1989.
- **MCA** He has not ECG phenotype He is son of **BTC;** QTc = 435ms; Weight: 60 Kg.; Height: 1,69m;
- **FCP:** He Born in Vitória da Conquista - Bahia.Brazil in July 10/1987 24yo. Normal ECG.
- **VCPJ:** She Born in Vitória da Conquista - Bahia.Brazil in February 6/1989. 23 yo. Normal ECG. Normal QT.


JTC
Father
Die cause emphysema 60yo
Mother
Sudden death at 62 years old
Six silbing individuals having both parents in common; a brother or sister.
He died 13 years old
He died 6yo
ROC
She died 26 yo
VTC
44yo
Proband
BTC
38yo
MTC
11yo
WTC
23yo
TTC
21yo
MCA
16yo
VCPJ
23yo

**VTC:** He is the proband. Masculine, Caucasian, Weight: 84Kg.; Height: 1.79 m.; 44 years of age. (He born in Vitória da Conquista - Bahia. Brazil in February 12/1968.), He is assymptomatic. He has the typical ECG phenotype He has two sons **TTC** and **WTC.**

**BTC**: She is daughter of proband. She live in SP City. She is assymptomatic. She has a normal ECG, QTc 465 VCG and ECG-AR She has high blood pressure.

**MTC:** feminine, Caucasian, 41 yo, She born in December/15/12/1970 Vitória da Conquista - Bahia. Brazil; Weight: 60 Kg.; Height: 1,63m; Drugs in use: oral quinidine since 03/05/2012. Asymptomatic.

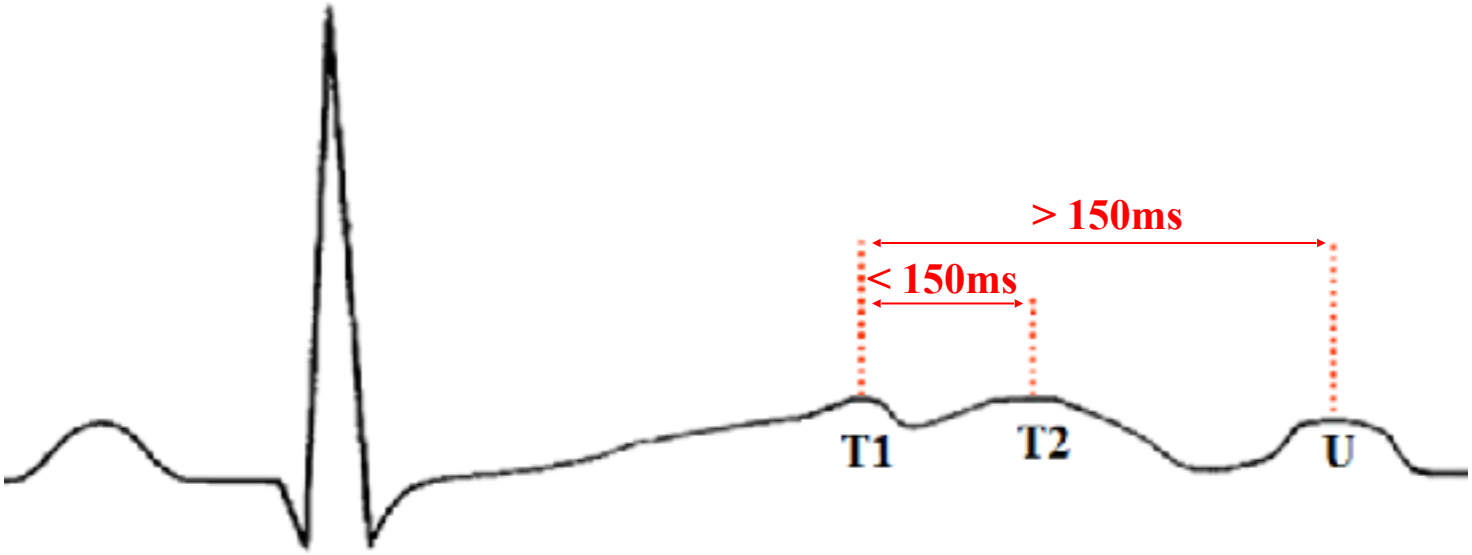
**TTC:** He has not the ECG phenotype, however the U waves are visibles in all leads. He Born in Vitória da Conquista - Bahia.Brazil in October 29/1991( He has 21 yo).

**WTC:** He has a typical ECG phenotype.(very short QT interval) and different of the father (proband) additionally tall with narrow base T waves.

**ROC:** Father: **JTC** - brother of **MTC** and **VTC** - Sudden death with 26 years old of age. **VCPJ:** She is daughter of. **MTC**- She has the ECG phenotype Caucasian Height = 1,61m - Weight = 55 - Femenine – asymptomatic Without medication – She Born in Vitória da Conquista – Bahia- Brazil. In : 06/02/1989 –

**MCA** He has not ECG phenotype He is son of **BTC QTc 435ms** Weight: 60 Kg.; Height: 1,69m;

# Differentiation between bimodal T wave from T-U interval

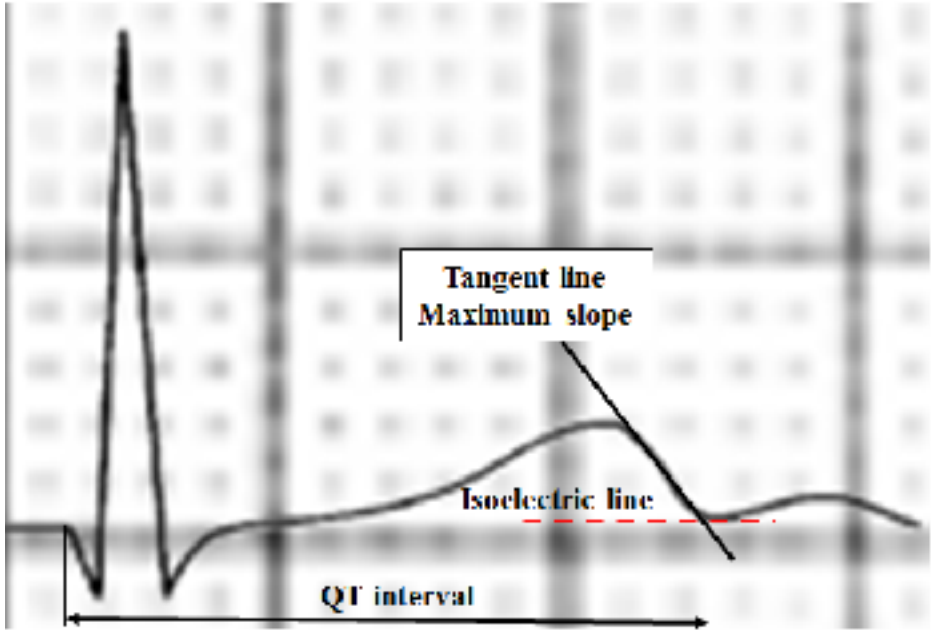


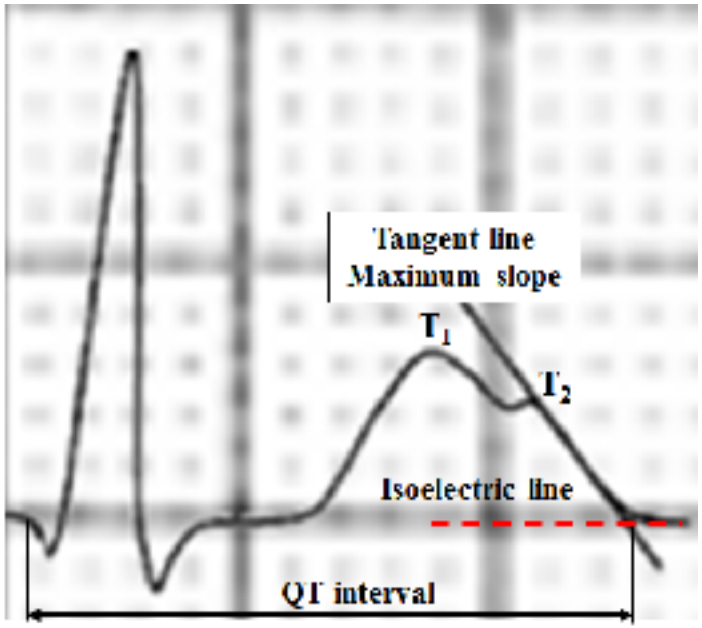

The second apex of bimodal T wave (T2) is at a distance < 150 ms of the first module (T1). The T1-U interval is always > 150 ms (Lepeschkin 1956).

## The end of T wave is determinate by maximum *slope intercept method*

The end of T is defined as the return of the T wave to the T-P baseline. The intercept between the tangent line and the isoelectric line is defined as the end of the T wave,\. The QT interval is measured from the beginning of the QRS complex to the end of the T wave on a standard ECG. There are no available data on which lead or leads to use for QT interval measurement. This method defines the final of the T waves as the intercept between the isoelectric lines with the tangent drawn through the maximum down slope of the T wave. When the T wave is notched, the QT interval is measured form the beginning of the QRS complex extending to the intersection point between the isoelectric line and the tangent drawn from the maximum down slope of the second notch, T2. The second apex of bimodal T wave (T2) is at a distance < 150 ms of the first module (T1). The T1-U interval is always > 150 ms.

The second apex of bimodal T wave (T2) is at a distance < 150 ms of the first module (T1).
The T1-U interval is always > 150 ms.



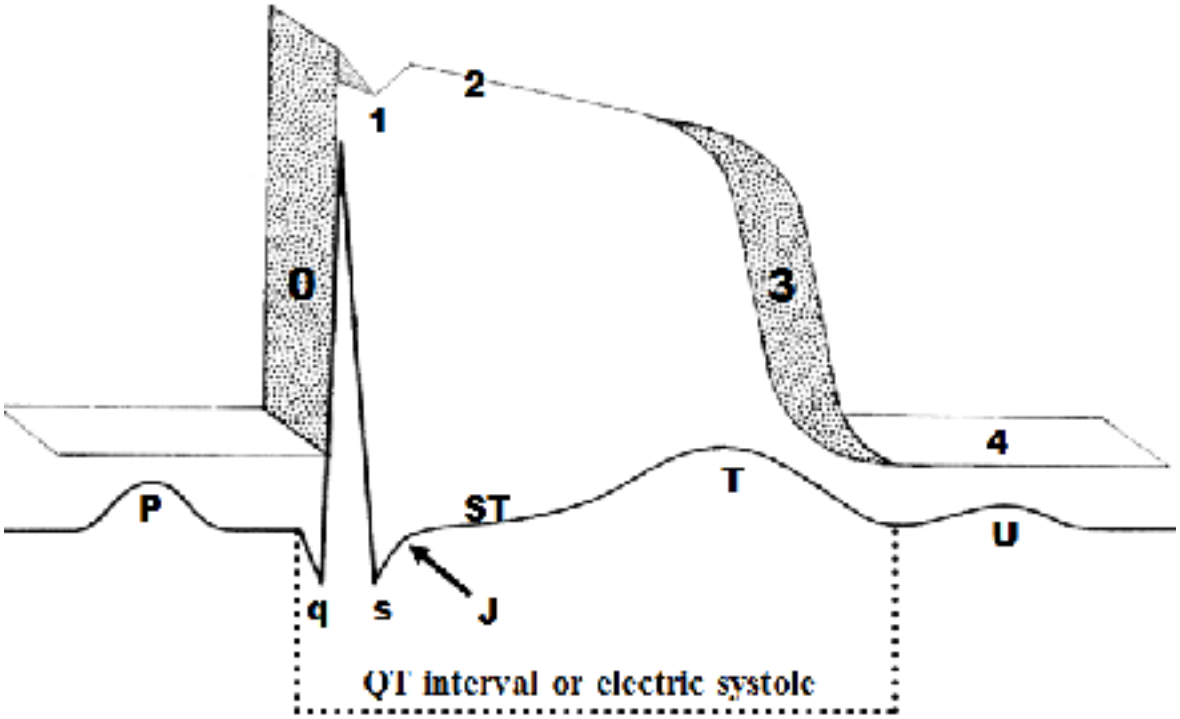

Therefore, we have to correct QT duration (QTc) according to the rate using the formula proposed by Bazett in the 1920s,(Bazett 1920) where the corrected QT is calculated using the Bazzet's formula.

$$QTc = \frac{\text{Measured QT}}{\sqrt{RR}}$$

Bazett´s formula has been criticized because it tends to provide an inappropriately short QTc at slow rates and not suitable long QTc at higher rates. Several competing methods have been developed:
Fridericia: **$QTcF = QT/3\sqrt{RR}$** published an alternative correction using the cube root of RR (Fridericia 1920)
Framingham: $QTc = QT + 0.154\ (1-RR)$
Hodges: $QTc = QT + 105(1+RR-1)$

None of the formulas has been shown to be clearly superior, so despite its obvious shortcomings.
Bazett's formula correction for the QT interval is used for automated analysis and large clinical trials. QT duration is inversely proportional to heart rate. The range of normality of QT interval in adults varies between 350 ms, 440 ms. both short, and long QT intervals can be susceptible to life-threatening ventricular arrhythmias.
It is important to remember that for every individual there is a different relation between the QT interval and the heart rate. Although the rate–correction formulae are useful clinically, they may not be accurate enough, especially when assessing the minor changes of the QT interval induced by drugs. The suggested QTc values using the Bazett's formula for diagnosis QT prolongation was determinate by Moss & Robinson (Moss 1992).
In 1993, it was first proposed that shorter than normal QT intervals (< 400 ms) are associated with a 2.4-fold increased risk for SCD. A prolonged and a shortened mean QTc interval over 24 hours is associated with a more than twofold risk of sudden death compared with intermediate mean QTc values (400-440 ms). Neither short nor long-term variability in QTc had a distinct relation with the risk of sudden death. (Algra 1993).
Recently from a database of 6.4 million ECGs obtained among 1.7 million persons was used. An internal, population-based method for heart rate correction (QTcreg) was used and all ECGs with QTcreg ≤ 300 ms were manually validated. Linked health plan databases were used for covariate and survival ascertainment. QTcreg ≤ 300 ms was extraordinarily rare and was associated with significant ECG abnormalities and reduced survival.with a 2.6-fold increased risk of death (Iribarren 2014).
The major point of difference was the short duration of the red kangaroo ventricular action potential (AP) compared to those of the placental mammals, and compared to atrial cells from the kangaroos. It is suggested that this explains the short QT interval reported by others for kangaroo ECGs, and that it may be implicated in the high frequency of sudden death previously noted in these marsupials (Campbell 1989).
Following 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 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 healthy population.

The European SQTS registry considers SQTS if patients had a QTc interval of ≤ 360 (in lead 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 o 340 ms) (even if they were asymptomatic); or if patients had a short QT interval (QTc interval r360 ms, in lead II or V5) with a family history of SQTS.
Giusstetto et al (Giustetto 2006) refer that SQTS patients exhibited a QT < 320ms and a QTc < 340ms.




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.

Long QTc intervals are considered values between 450 to 470ms for men and 460 to 480 ms for women. Long QT syndrome is possible with QTc values between 390 to 450 ms for men and 400 to 460ms for women. These case when indicated additional tests are indicated: repeated ECG, Holter, T-wave morphology, exercise, epinephrine challenge, adenosine-challenge. Normal QTc interval is considered with values between 360 to 390 ms for men and 370 to 400ms for women.

With these values, congenital SQTS is supported in the presence of syncope, atrial fibrillation, positive familial background, T wave morphology and characteristic electrophysiological study. Values of QTc < 330 ms in men and 340ms in women are considered diagnosis for congenital SQTS even if asymptomatic (Viskin 2009). The occurrence of sudden cardiac death in the first 12 months of life in 2 patients suggests the possibility of a link between KCNH2 gain of function mutations and sudden infant death syndrome. Values of the QTc in the six genetic variants of congenital SQTS are SQT1 286 2, ± 6ms, SQT2 302 ms, SQT3 315-330 ms, SQT4 331-370 ms, SQT5 346-360ms, and SQT6 329ms. Table xx

**Table xx**

| | Men | Women |
|---|---|---|
| **Very long QTc** | ≥ 470 ms | ≥ 480 ms |
| **Long QT interval** | 450 ms to 470ms | 460 to 480 ms |
| **Normal QT interval** | 360ms to 390 ms | 370ms to 400ms |
| **Congenital SQTS** | < 330 ms | < 340ms |

**Observation:** in patients with severe hypercalcemia values of QTc < 270ms. Hypercalcemia results in either shortening of phase2 of the action potential and concomitant shortens the ST segment.

In severe hypercalcemia the PR interval and the QRS complex are frequently prolonged and second degree or third degree AV block is possible. The J wave has been occasionally reported (Sridharan 1984).

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

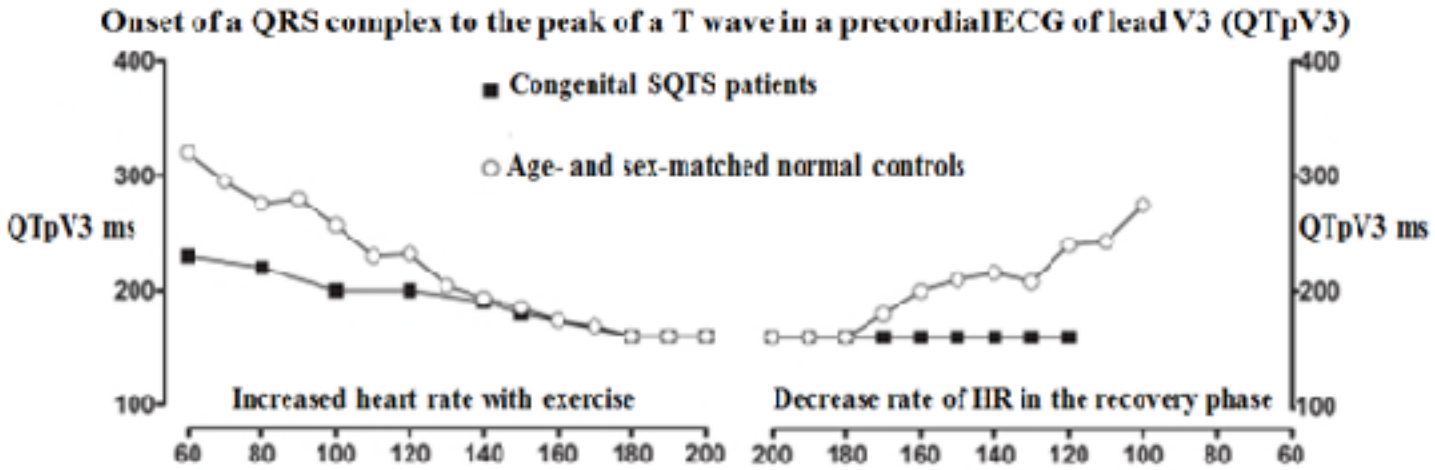
| Author | QT interval | $QT_C$ interval |
|---|---|---|
| **Lower normal limit of the QT interval** | | |
| **Moss 1993, Luo S 1994** | 330 ms (children 310 ms) | 360-380 ms |
| **Vincent 1992** | | 360 ms (M) – 370 ms (F) |
| **Definition of "short QT"** | | |
| **Gussak 2000, Gaita 2003** | < 300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

## II) 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 is 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. Figure



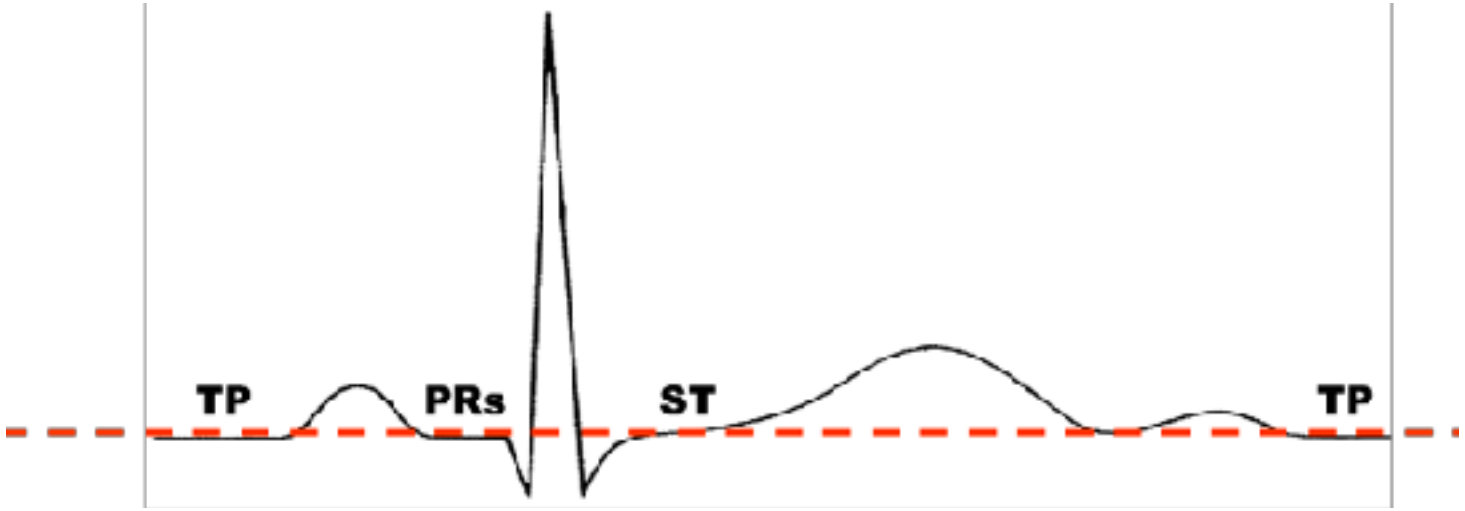
This will result in misinterpretation of the QTc interval with a faster HR and subsequently false-negative diagnosis of this possibly fatal syndrome. Holter monitoring can be helpful in this situation because it allows measurement of the QTc during a period of slower heart rate, such as sleep. Reduced rate-adaptation of QT interval. The QT-RR relationship is less linear and its slope is less steep in the SQTS patient as compared with control subjects.

Quinidine restores the relationship toward control values. QRpV3 denotes the interval form the beginning of QRS complex to the peak of T wave, measured in lead V3. The QT-RR relationship lack of rate dependence Therefore, QTc corrected by any formula will fail to reflect the true QTc. At rapid rates, QTc will falsely approximate normal values leading to a false-negative diagnosis. This is particularly important for the diagnosis of SQTS in pediatric populations, where resting HR is >100 bpm. Sometimes, Holter monitoring shows impaired adjustment of QT interval with change in HR. Long-term ECG monitoring becomes necessary in such cases to make the correct diagnosis. The range of HRs is increased at baseline by using ambulatory electrocardiogram recordings in addition to those collected under semisupine, resting conditions (Garnett 2012).

Quinidine is a Class IA antiarrhythmic drug –isomer of quinine found in the bark of the cinchona tree. The drug affects depolarization and repolarization by blocking $Na^+$ and $K^+$ channels respectively. Quinidine blocks the fast $Na^+$ current; $I_{to1}$ channel or transient outward current, inward rectifier $I_{K1}$, delayed rectifier: $I_{Ks}$, $I_{Kr}$ and $I_{Kur}$, I $K_{ATP}$ or adenosine triphosphate ATP sensitive potassium channel, $IK_{\text{-Ach}}$, alpha 1 and alpha 2 adrenergic receptors: can cause orthostatic hypotension and reflex sinus tachycardia; $M_2$ muscarinic receptor. In short QT syndrome oral quinidine is effective in suppressing the gain of function in $I_{Kr}$ responsible for SQT1 variant with a mutation in HERG and thus restoring normal HR dependence of the QT interval and rendering VT/VF noninducible. Additionally, quinidine prolongs the QT interval into the normal range, restored the HR dependence of the QT interval toward a range of adaptation reported for normal subjects (Wolpert 2005).

## III) PR or PQ segment depression (PQD)

Regarding the level of PRs, in normal conditions is at the same level as ST segment (isoelectric) and TP segment of precedent beat.




Usually, PR segment (end of P wave up to QRS complex onset), ST segment (from J point or the end of QRS up to the beginning of the T wave) and TP segment (from the end of the T wave up to the P wave of the following cycle) 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.

**PR (PRs) or PQ segment:** it stretches from the end of P wave to the onset of QRS complex. The PR segment is leveled when it is at the same level of the PR segment of the beat being studied. If the PR segment falls below the baseline (TP segment of precedent beat), then it is said to be depressed.

**ST segment:** it stretches from the from the J point (union of ST with the end of QRS complex) up to the onset of the T wave.

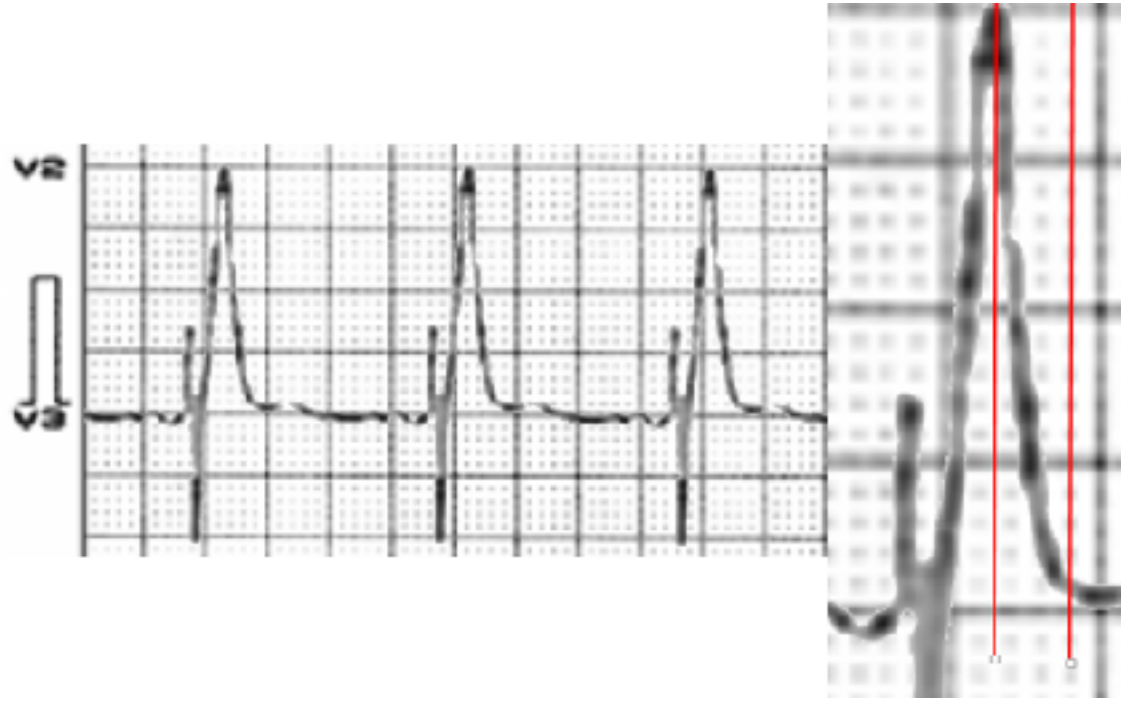
**TP segment:** it stretches from the end of T wave to the onset of the P wave of the next cycle. TP segment is between the end of the T wave and the beginning of the next P wave. It is the true isoelectric interval in the electrocardiogram. In other words the PR segment changes are relative to the baseline formed by the precedent TP segment of anterior beat.

# Clinical causes of PR segment depression

- Atrial fibrillation
- Acute inferior myocardial infarction (poor prognosis when present). PR segment depression or elevation in-patient with acute myocardial infarction scenario indicates concomitant atrial ischaemia or iinfarction. The ST segment indicates an infarct in the ventricle, the PR segment indicates an infarct in the atria. Diagnostic criteria for an atrial infarct are: PR segment elevation > 0.5mm in V5 and V6 with reciprocal depression in V1 and V2, PR segment elevation > 0.5mm in I and depression in II and III, > 1.5mm PR segment depression in precordial leads and > 1.2mm PR segment depression in I,II or III in combination with atrial arrhythmias (Liu 1961). PR-segment depression ≥ 1.2 mm in inferior leads was found in 1.9% of patients with acute inferior MI. This ECG sign represents a subgroup of patients with extensive atrial ischemia. This sign is associated with a high frequency of atrioventricular block, supraventricular arrhythmias and cardiac rupture, with high in-hospital mortality (Jim 2006).
- PR segment depression in III and concomitant PR segmente elevation in I and aVL is indicative of infarction on the posterior wall of the right atrium (Radojevic 2012).
- Acute pericarditis: In these cases, there is also some concave to the top ST segment elevation
- **Acute myopericarditis:** occurs in the presence of diffuse inflammation of the pericardial sac and superficial epicardium from a multitude of infectious and inflammatory processes. This inflammation results in a current of myocardial injury resulting from the epicardial irritation manifested by a number of ECG findings: ST segment elevation with PR segment depression, normalization of the ST segment abnormality with T wave inversion, and eventual normalization of the ECG over a period of days to several weeks. In myopericarditis, the most common location for PR depression was lead II (55.9%), while this ECG finding least likely appeared in lead aVL (2.9%). PR depression in any lead had a high sensitivity (88.2%), but low specificity (78.3%) for myopericarditis. The combination of PR depressions in both precordial and limb leads had the most favorable predictive power to differentiate myopericarditis from STEMI (positive 96.7% and negative power 90%) (Porela 2012).
- Extensive atrial damage.
- During ablation of the left upper pulmonary vein in patient with atrial tumors.

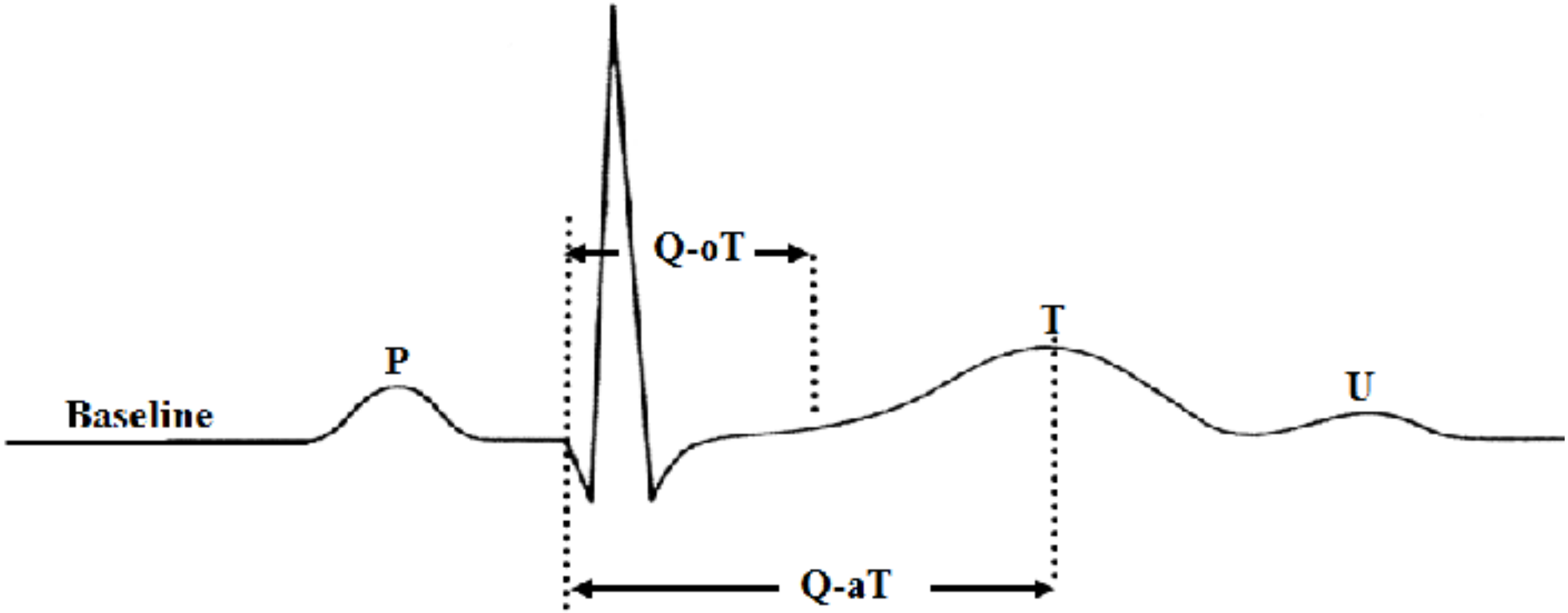
- Cardiac tamponade, fluid collects in the pericardium. Because the pericardium is stiff, the heart is compressed, resulting in filling difficulties. Tamponade can be the result of pericarditis or myocarditis. After a myocardial infarction a tamponade can also develop; this is called Dresslers' syndrome. In case of cancer, increased pericardial fluid may develop. This is usually caused by pericarditis carcinomatosis, meaning that the cancer has spread to the pericardium The ECG shows: sinus tachycardia, low QRS voltage, electrical alternans and PR segment depression.
- Congenital Short QT syndrome: Digitalized 12-lead ECGs of SQTS patients were evaluated for PR depression in all leads and for QT intervals in leads II and V5. PR depression was defined as 0.05 mV(0.5mm) depression from the isoelectric line(TP segment of precedent beat). The study shows that 81% patients with SQTS reveal PQD. As PQD is rarely observed in healthy individuals, this ECG feature may constitute a novel marker for SQTS in addition to a very short QT interval (Tülümen 2014).

**IV) Absent or minimal ST segment "hypercalcemic like phenotype"**



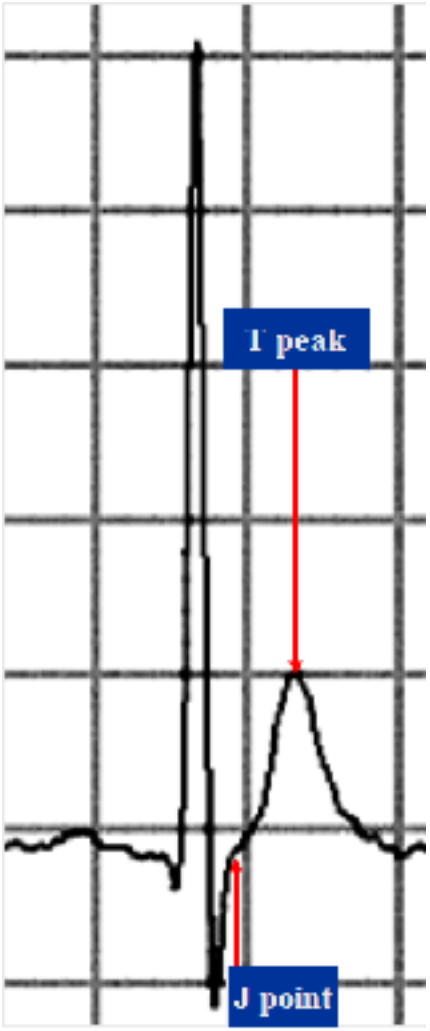
T-wave originates directly from QRS without identifiable ST segment. Additionally the distance between T-apex/T-end = 100 ms: transmural dispersion of repolarization.

- Short Q-oTc interval: interval that extends from QRS onset up to T wave onset, corrected by heart rate.
- Short Q-aTc interval: interval that extends from QRS onset up to apex T wave corrected by heart rate.



**V) Short J point-T peak interval <120 ms**

The J point-T peak interval is the distance from J point to T peak Values <120 ms have value for the diagnosis of the congenital SQTS (Gollob 2011).




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

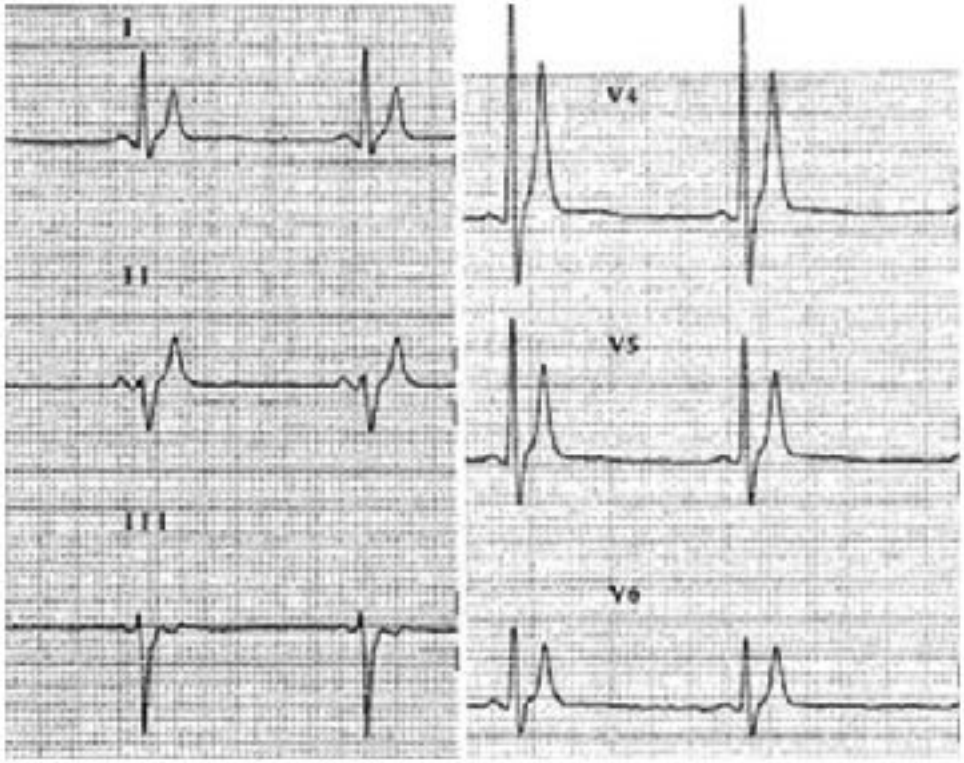
The Short QT Syndrome diagnostic criteria is based on a point score system as follows:

| QTc in miliseconds | Pontuation |
|---|---|
| < 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 |

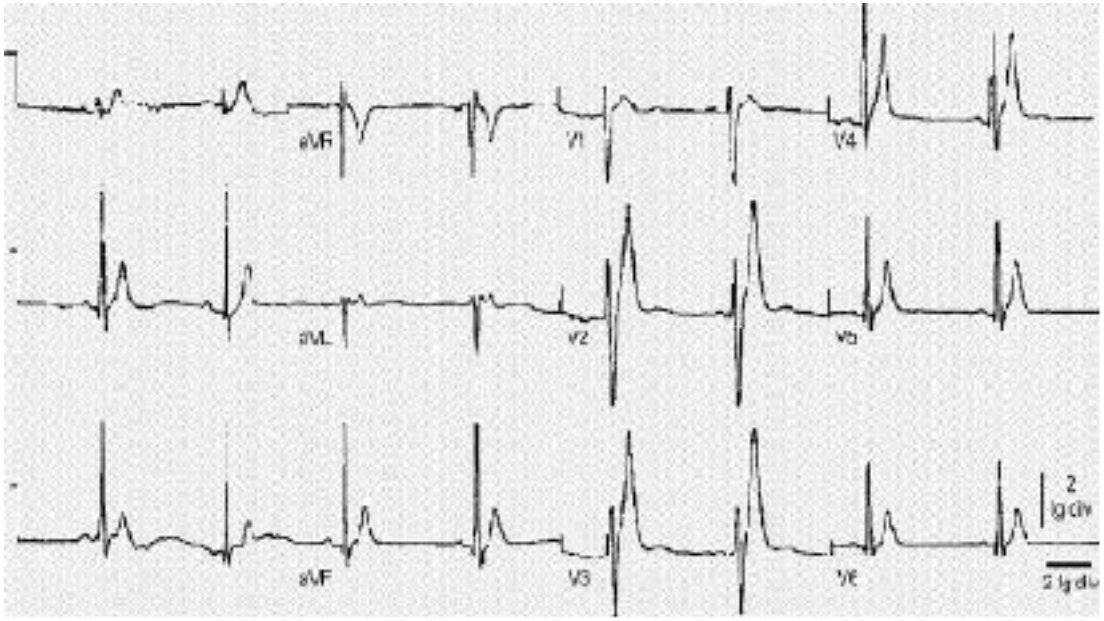
**Interpretation**: High-probability: ≥ 4 points; Intermediate probability: 3 points; Low probability: ≤ 2 points.

**VI) 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 (Gaita 2003).




Twelve lead ECG showing typical SQT1 features: tall, narrow and peaked T waves, QT 280 ms. Reproduced with permission from Gaita (Gaita 2003).



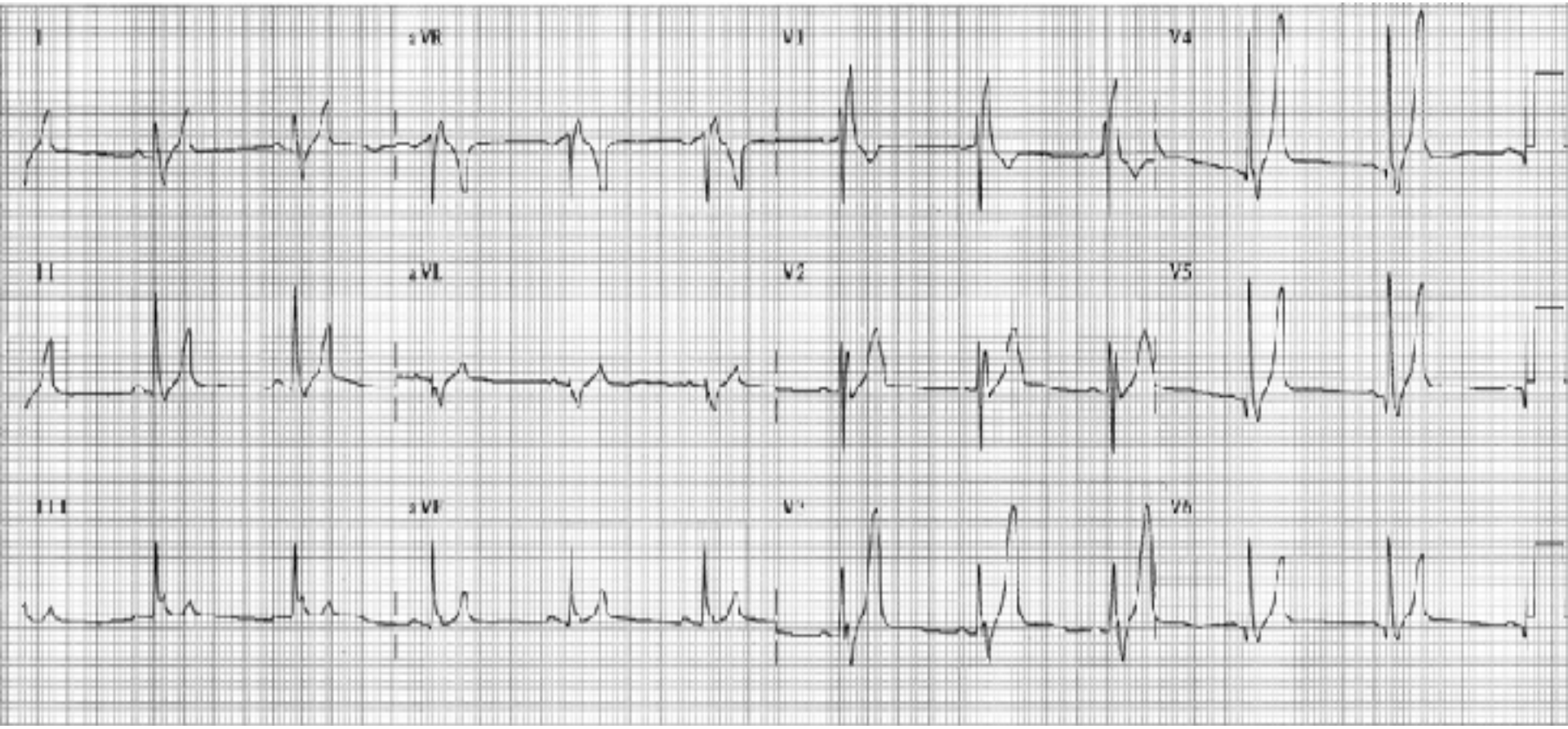

Electrocardiogram of a patient with short QT syndrome. Observe the tall peaked T waves. Reprinted, with permission, from Brugada (Brugada 2004).

**SQT2:** the T waves appear to be symmetrical, but not as tall and narrow (Bellocq 2004; Hong 2005).

**SQT3:** asymmetrical T waves with a rather normal ascending ramp and a remarkable rapid descending terminal ramp (Priori 2005).

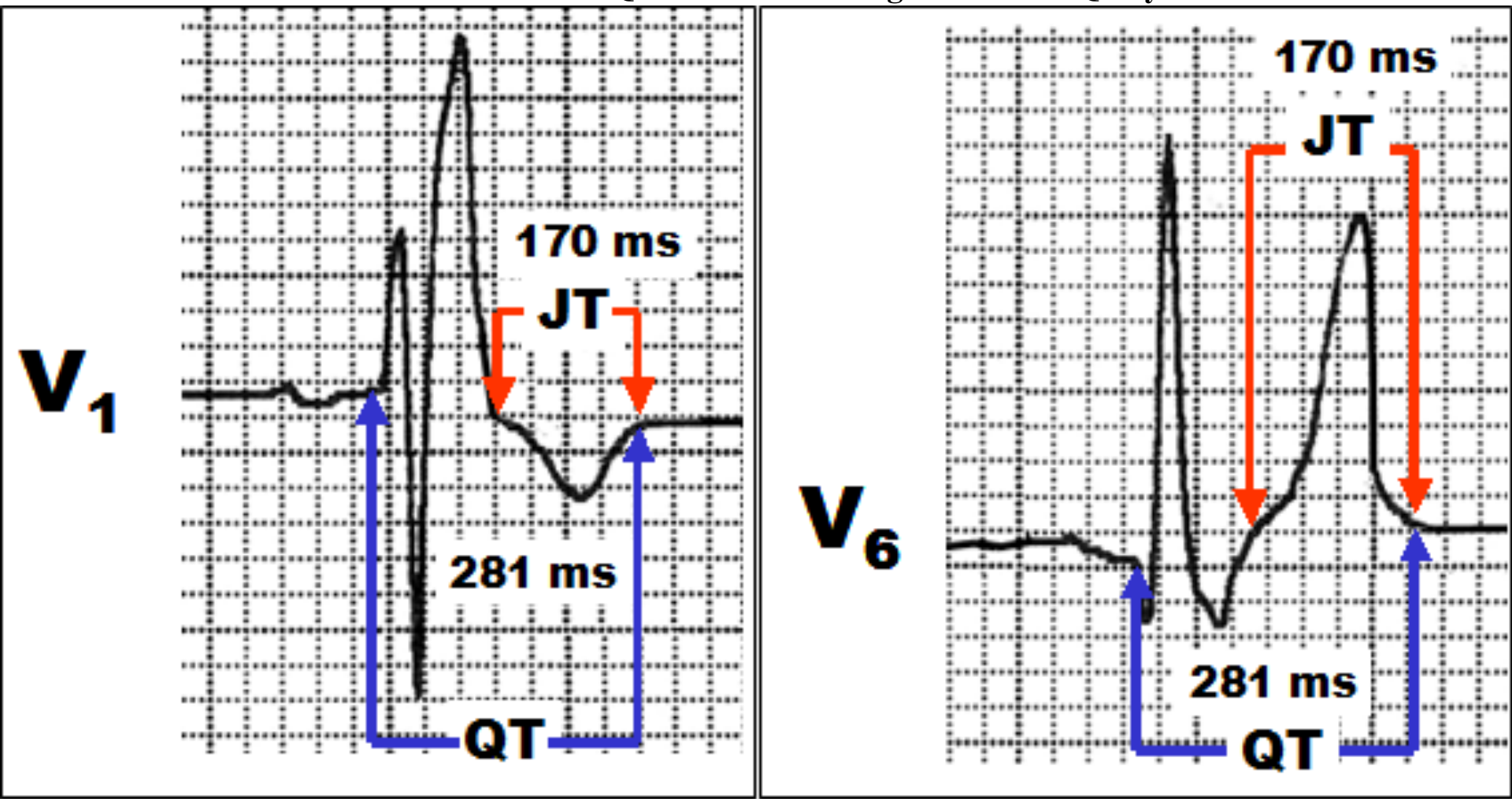
Peaked and symmetrical with a narrow base T waves ("tent-shaped") are characteristic of mild hyperpotasssemia. Usually, this is the earliest sign of hyperkalaemia. This morphological T waves are observed with slightly increased serum potassium levels (potassium level > 5.5 mEq/L and < 6.0 mEq/L). It is present only in 22% of the cases of hyperkalemia. Not too sensitive but quite specific. Similar T waves are registered eventually in congenital short QT syndrome. Additionally, peaked and symmetrical with a narrow base T waves ("tent-shaped") are observed also in metabolic acidosis and without hyperkalemia. (Dreyfuss 1989). Peaked, symmetrical T waves, with broad base is an early sign of hyperacute phase of myocardial infarction (Primeau 1969).

**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 324ms (Sagie 1992);

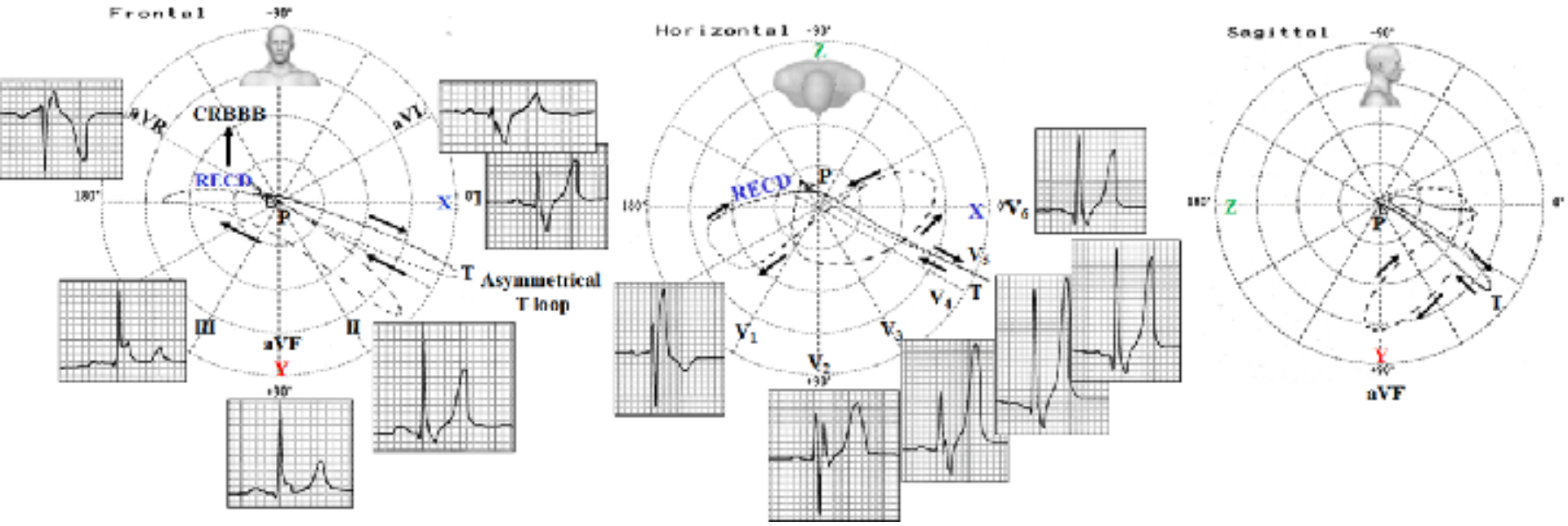
**Characteristics of JT and QT intervals in congenital short QT syndrome**




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 top right quadrant near aVR lead. Asymmetrical T-loop SÂT +20º.

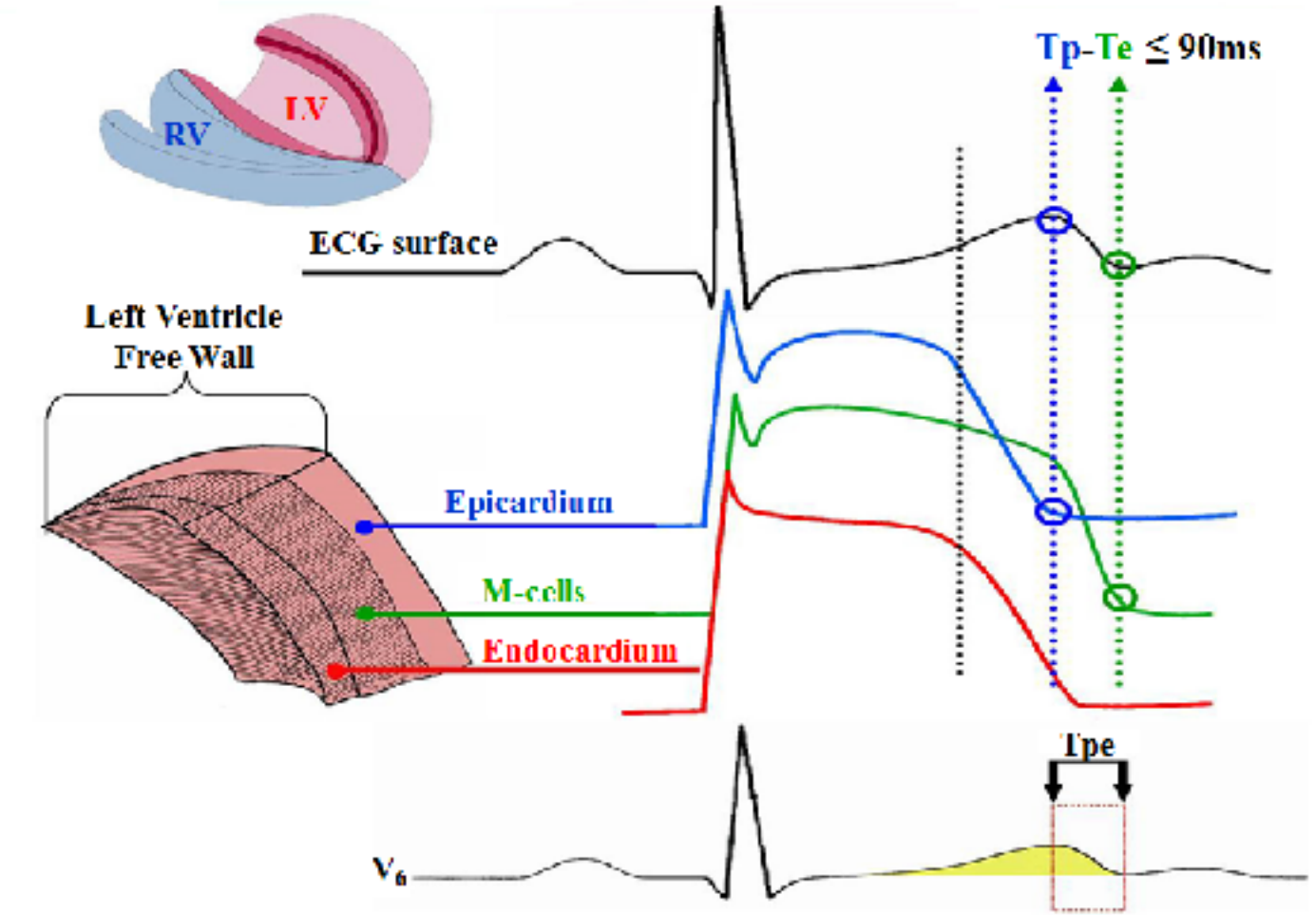
**HP** – Triphasic QRS pattern in V1-V2 and broad final S-wave in V5-V6: CRBBB. VCG Grishman-type of CRBBB: afferent loop behind the X line; triphasic rSR' pattern; short QT interval; tall T waves with narrow base from $V_3$ through $V_5$.

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

**Observation**: The VCG is conclusive that T-wave is not symmetrical because efferent limb has tears very close 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 > 92ms in women and > 94ms 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 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 > 92ms in women and > 94ms 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 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 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 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).

## VIII) 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 100bpm.

The T(p-e)/QT ratio is significantly greater in the patients at risk for arrhythmic event 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).

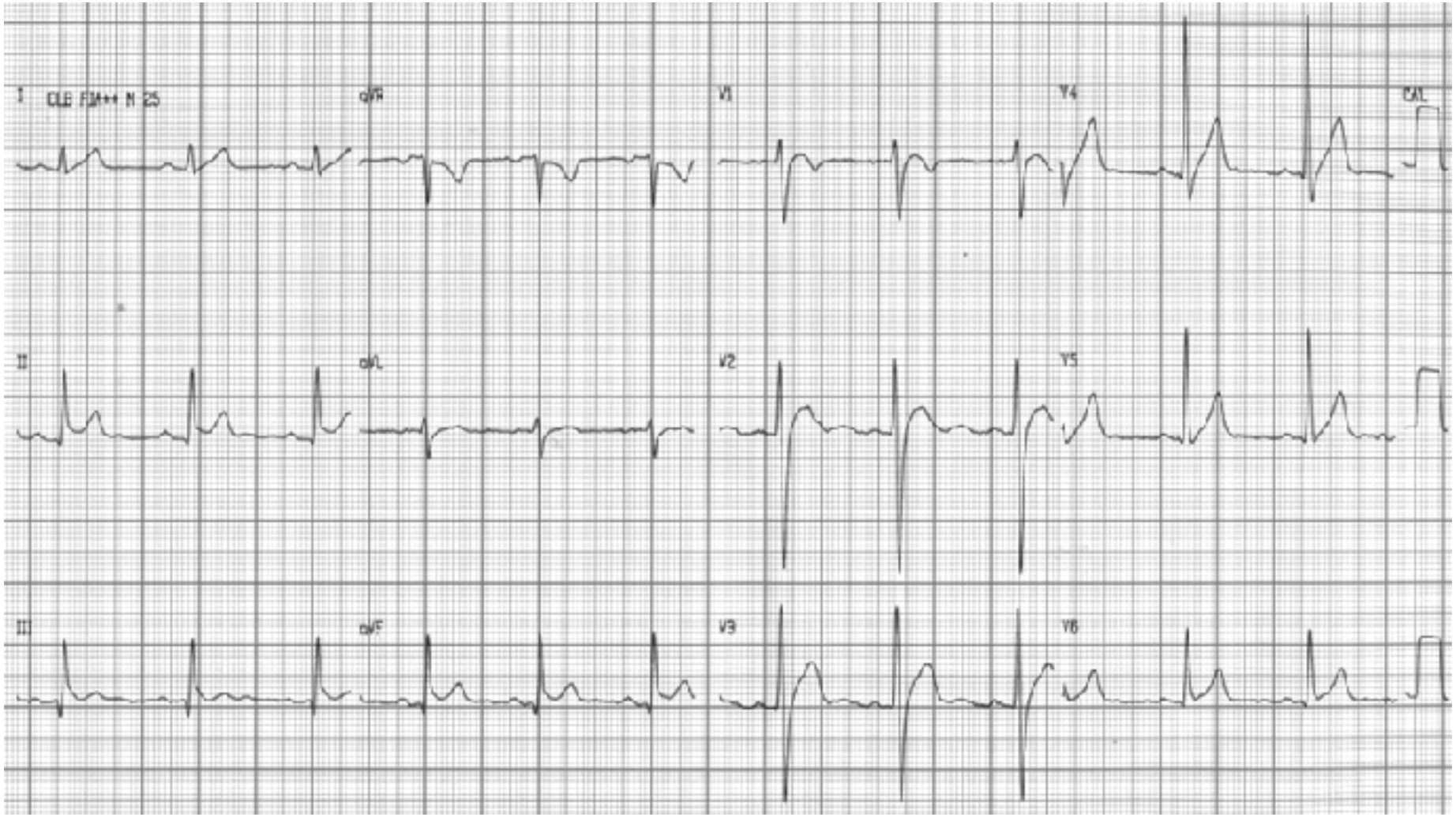
A Tp-e/QT ratio $\geq$ 0.29 in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction may serve as a prognostic predictor of adverse outcomes after successful pPCI treatment in STEMI patients (Zhao 2012).

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

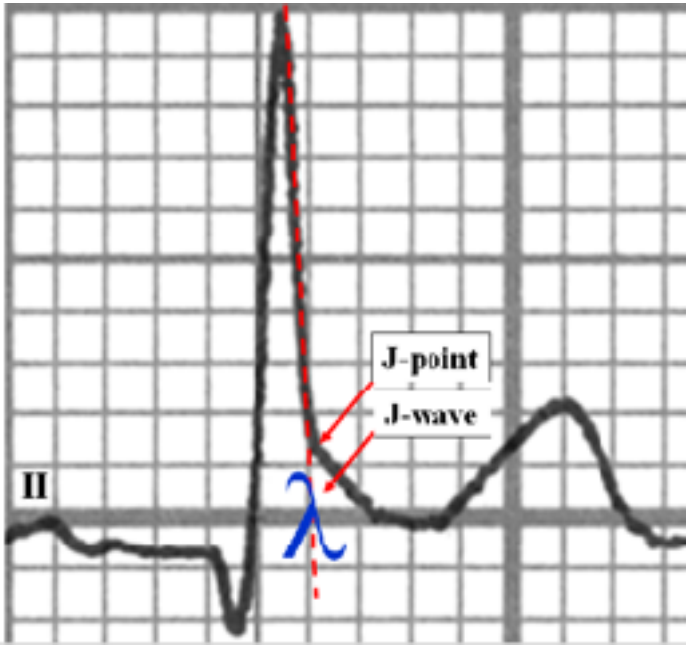
**IX) High prevalence of early repolarization. It associated with arrhythmic events**

There is a high prevalence of early repolarization in patients with SQTS. Additionally, early repolarization may be useful in identifying risk of cardiac events in SQTS (Watanabe 2010).

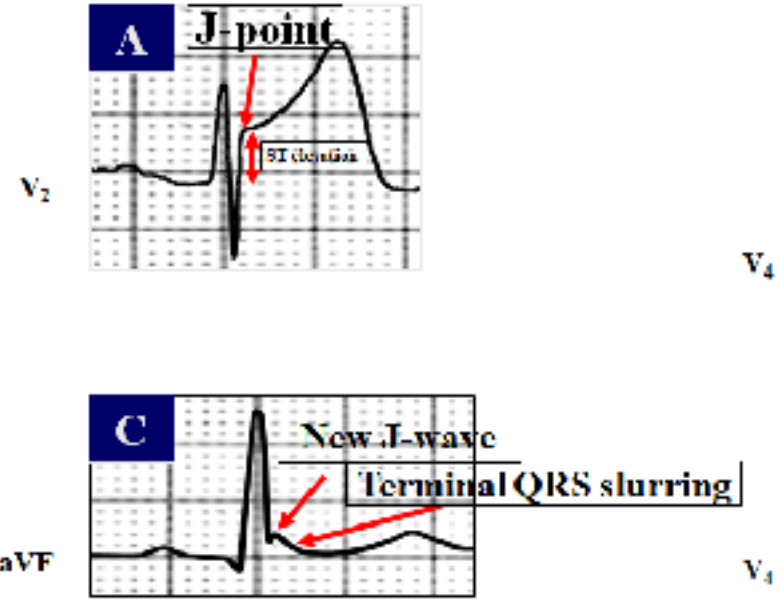
**Example of SQTS associated with early repolarization**



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




The first point of inflection of R wave descendent ramp is considered the real J-point. In these cases "The tangent line" method is ideal. ST-segment elevation = 0.8mm. We considered 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

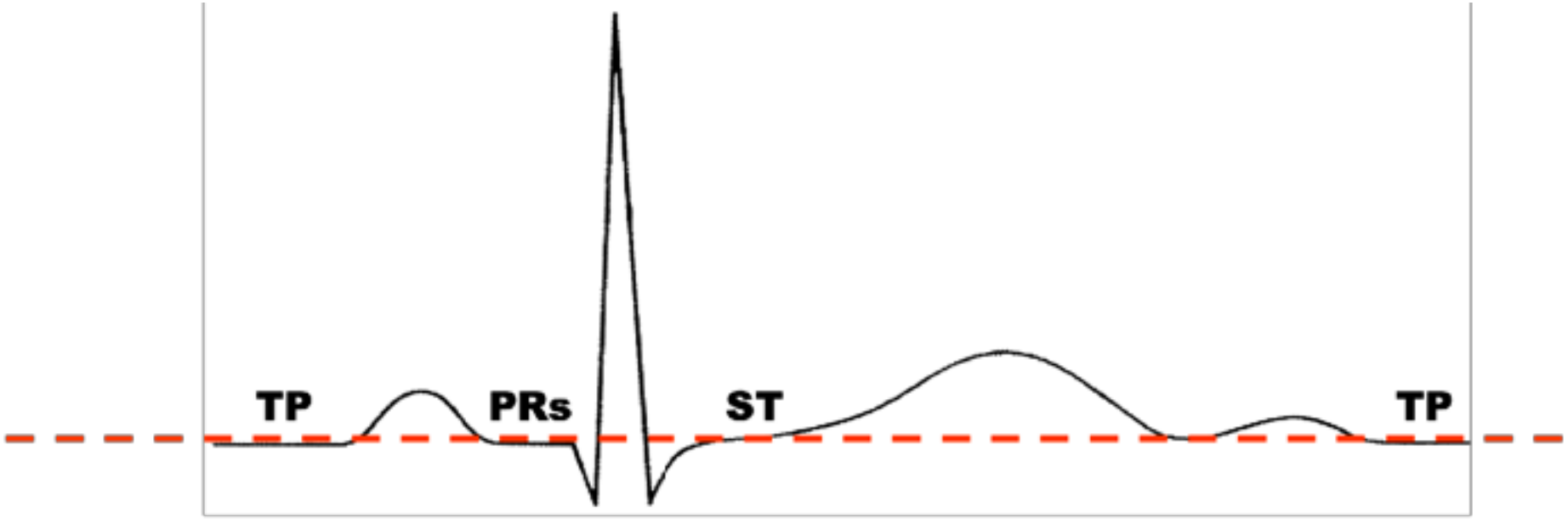
B)ERP with ST segment elevation and J-point at the end of J wave.

**New definition of ERP without ST segment elevation**

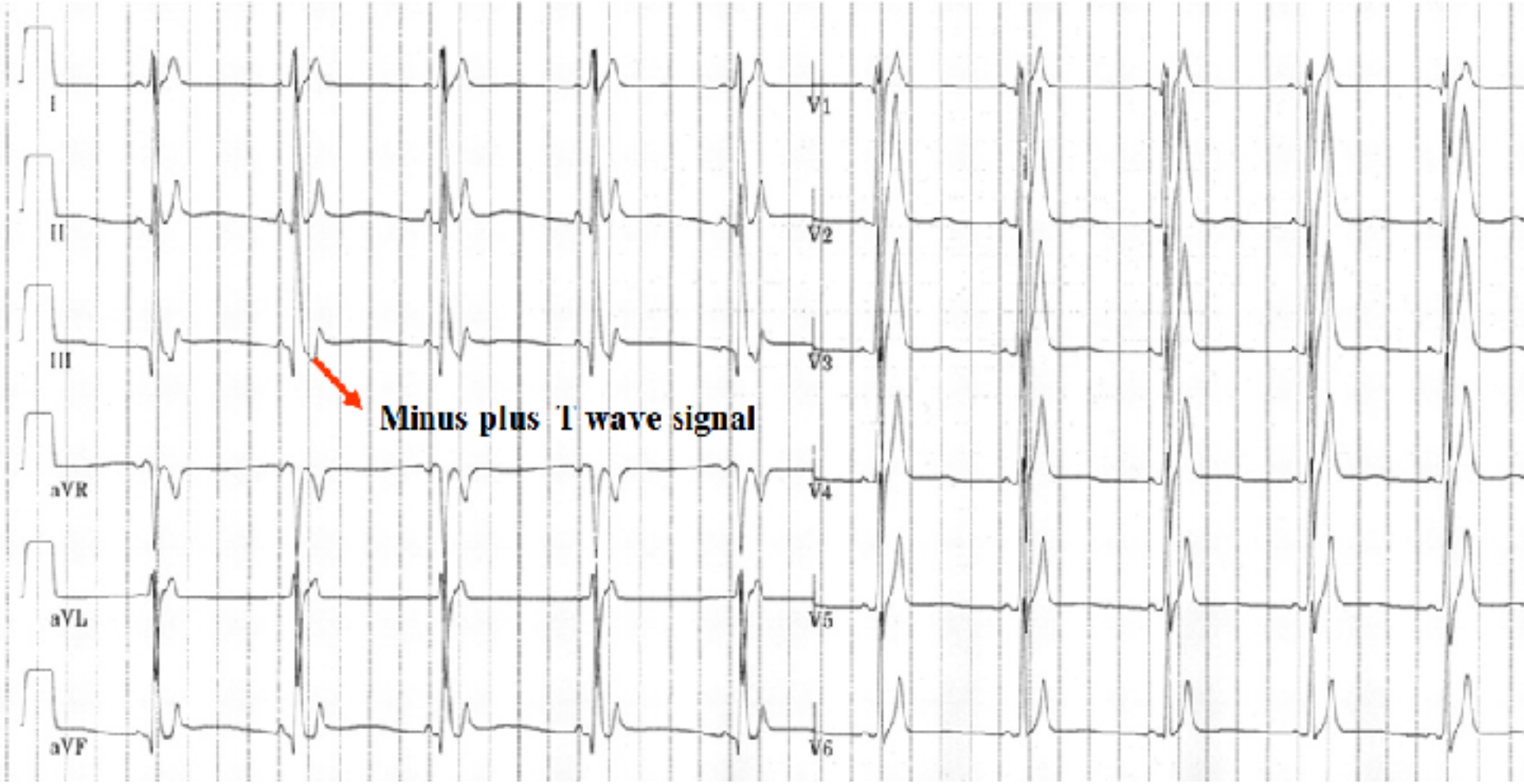
○J-point elevation and terminal QRS slurring without ST segment elevation. The first point of inflection of R wave descendent ramp is considered the real J-point. In these cases "The tangent line" method is ideal.

○J-wave without ST segment elevation (Pérez 2012).

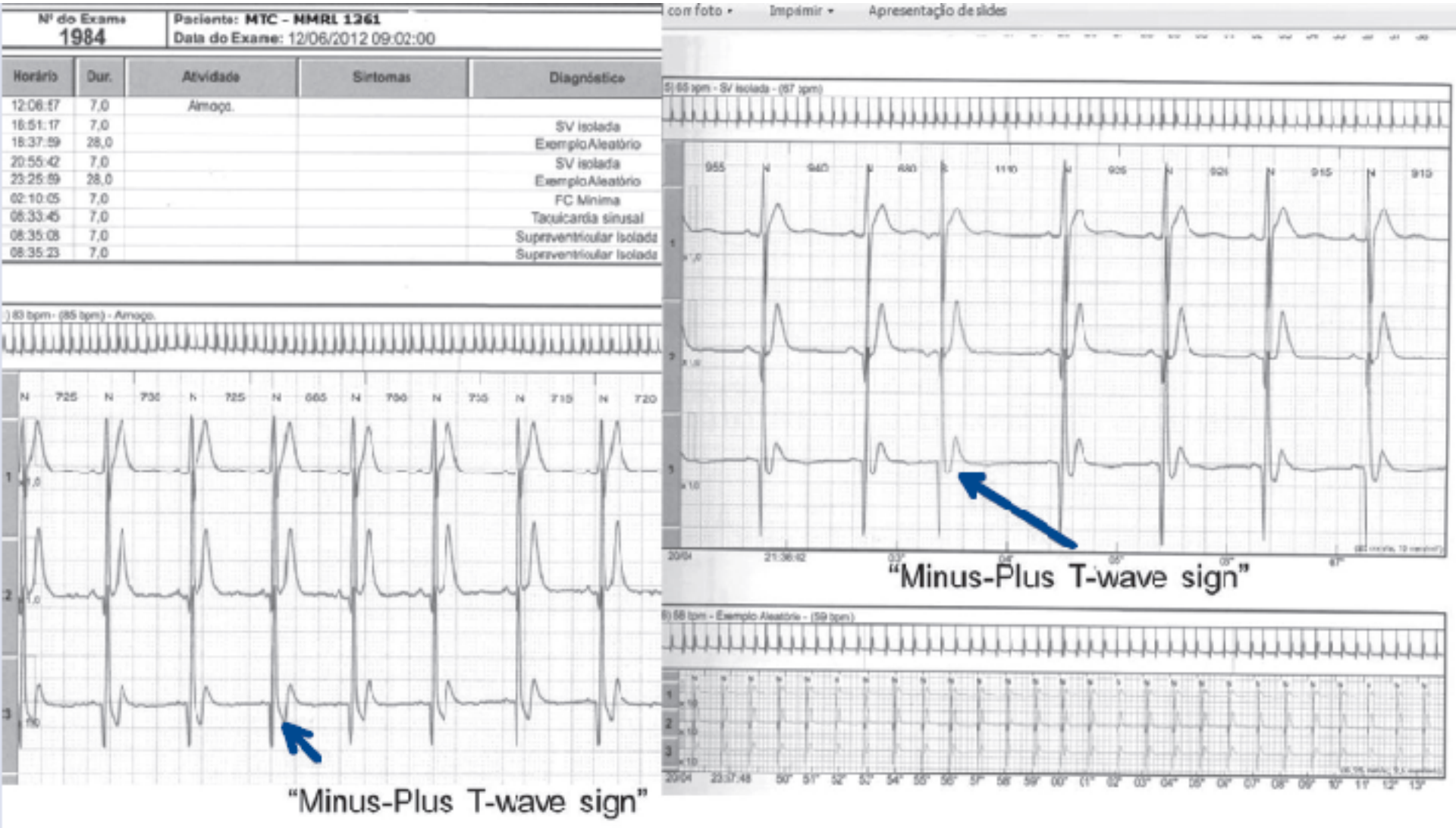
Usually, PRs (end of P wave up to QRS complex onset), STs (from J point or the end of QRS up to the beginning of the T wave) and TP (from the end of the T wave up to the P wave of the following cycle) segments are at the same level. The figure shows a normal ECG and a line of dots pointing out the level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



**X)** **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 (Schimpf 2005).




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 genetypic/phenotypic relationship?

## XI) Eventual prominent U wave

The U wave is the last, inconstant and smallest deflection of ECG that is recorded immediately after T wave and before the P of the following cycle, of equal polarity to the preceding T, i.e. positive where T also is. Voltage of U is always lower than 50% of the width of the preceding T and generally between 5% and 25% of it. Usually it does not exceed 1 mm, being in average of 0.33 mm. If it reaches 1.5 mm or more, it is considered high, however, there may be normal U waves of up to 2 mm (0.2 mV) in II and from $V_2$ to $V_4$. The U wave is Located immediately after the T wave during the protodiastolic phase of the cardiac cycle (diastolic isovolumetric phase and of fast filling) concomitant to the second noise and with phase 4 of action potential (AP); frequently absent; occasionally hard to distinguish from the preceding T wave; better observed during bradycardia and sometimes related to torsades de pointes (TdP). Additionally, the inscription of the U wave in SQTS patients coincided with aortic valve closure and isovolumetric relaxation, supporting the hypothesis that the U wave is related to mechanical stretch. The interval from aortic valve closure to the beginning of the U wave was 8 +/- 4 ms in patients with SQTS and 15 +/- 11 ms in control subjects.

- When HR is = or < 65bpm the U wave is visible in 90% of cases;
- When HR is between 80 bpm and 95 bpm the U wave is visible in 65% of cases;
- When HR is > 96bpm the U wave is visible in 25 % of cases;
- SAU points towards the left. Thus, U wave is better observed in V3 (between V2 and V4);
- The U wave is better observed in precordial leads when compared to FP leads.

### Causes of prominent U waves

- Hypokalemia (remember the triad of ST segment depression, low amplitude T waves, and prominent U waves) Abnormally prominent U waves are characteristically seen in severe hypokalaemia.
- Hypercalcemia
- Hypomagnesaemia
- Hypothermia
- Sinus bradycardia accentuates the U wave The most common cause of prominent U waves is bradycardia
- Forced inspiration

- Post-exercise
- Class 1A(quinidine, procainamide) and Class 3 antiarrhythmics(sotalol amiodarone)
- Phenothiazines (thioridazine)
- Raised intracraial pressure: In the setting of intracranial hemorrhage.CNS disease with long QT intervals (often the T and U fuse to form a giant "T-U fusion wave")
- LVH (right precordial leads with deep S waves)
- Mitral valve prolapse (some cases)
- Hyperthyroidism thyrotoxicosis
- Exposure to digitalis
- Epinephrine
- Congenital long QT syndrome
- Acquired long QT syndrome (Antzelevitch 1995)
- Congenital Short QT syndrome (Schimpf 2008)
- Complete AV block
- Left ventricular hypetrophy
- Hypertrophic cardiomyopathy and others cardimyopathies

**Brazilian family with congenital short QT syndrome**

XII) The response to exercise testing is a slight reduction of the QT interval during the increase in heart rate.

XIII)Frequent R-on-T premature ventricular contractions triggering sustained polymorphic VT (Portugal 2014).

XIV)Short refractory periods and tendency for inducible AF and VF were seen in EPSs. Diseases that abbreviate the cardiac action potential (AP) by increasing the strength of repolarizing transmembrane currents are highly arrhythmogenic. It has been proposed that optogenetic tools could be used to restore normal AP duration (APD) in the heart under such disease conditions.

**Presence of arrhythmias**

I) Supraventricular arrhtyhmias

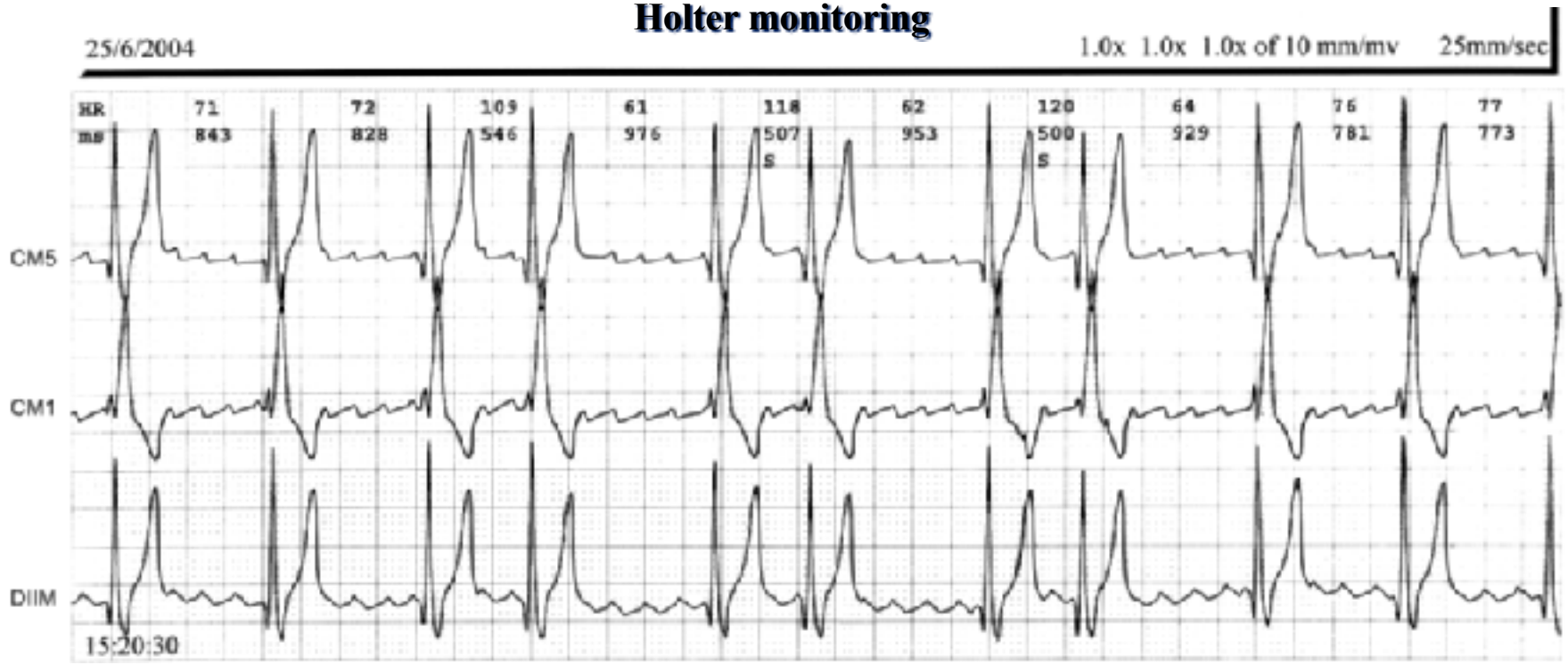
- Paroxysmal atrial fibrillation episodes
- Supraventricular arrhythmias

High tendency to Paroxysmal Atrial fibrillation episodes

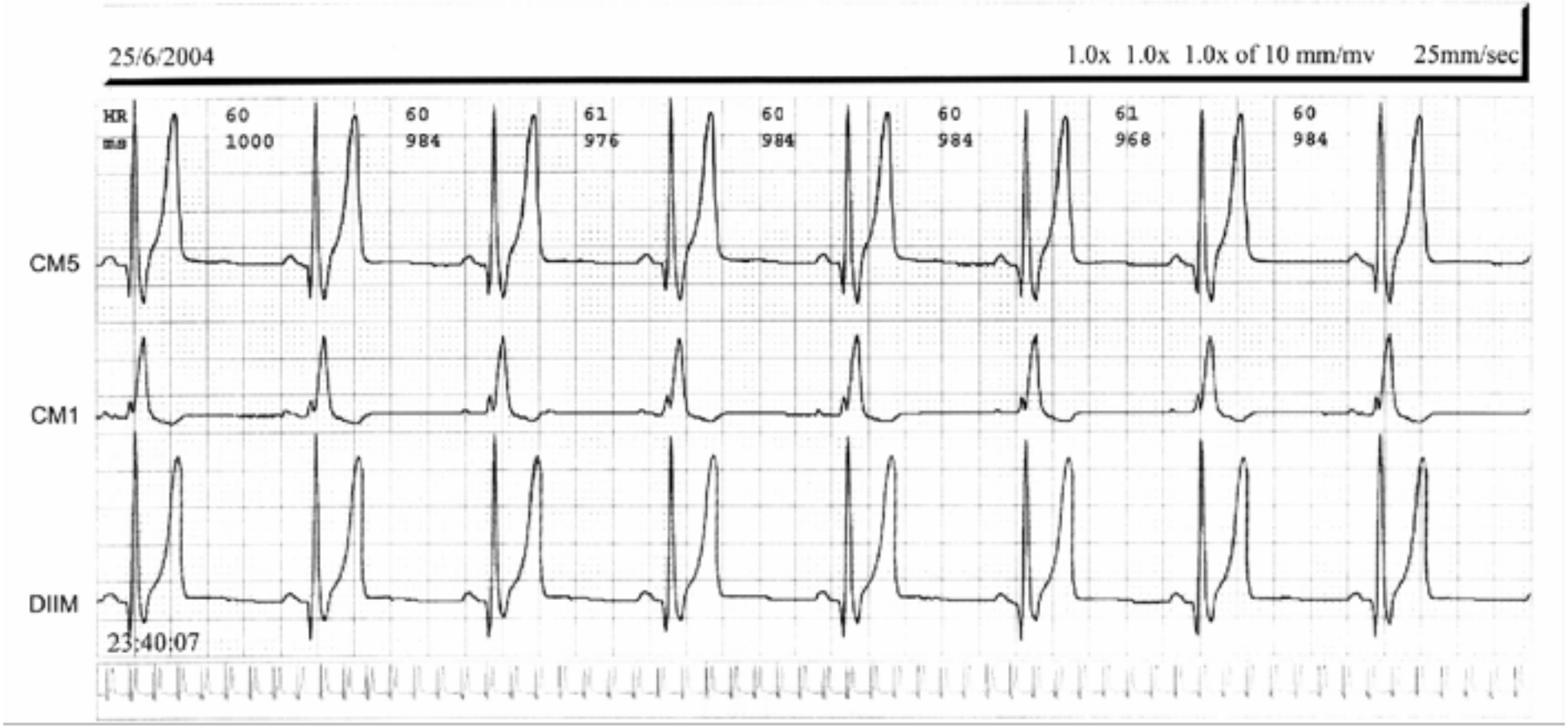
Atrial fibrillation and slow ventricular response

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.

**Holter monitoring**



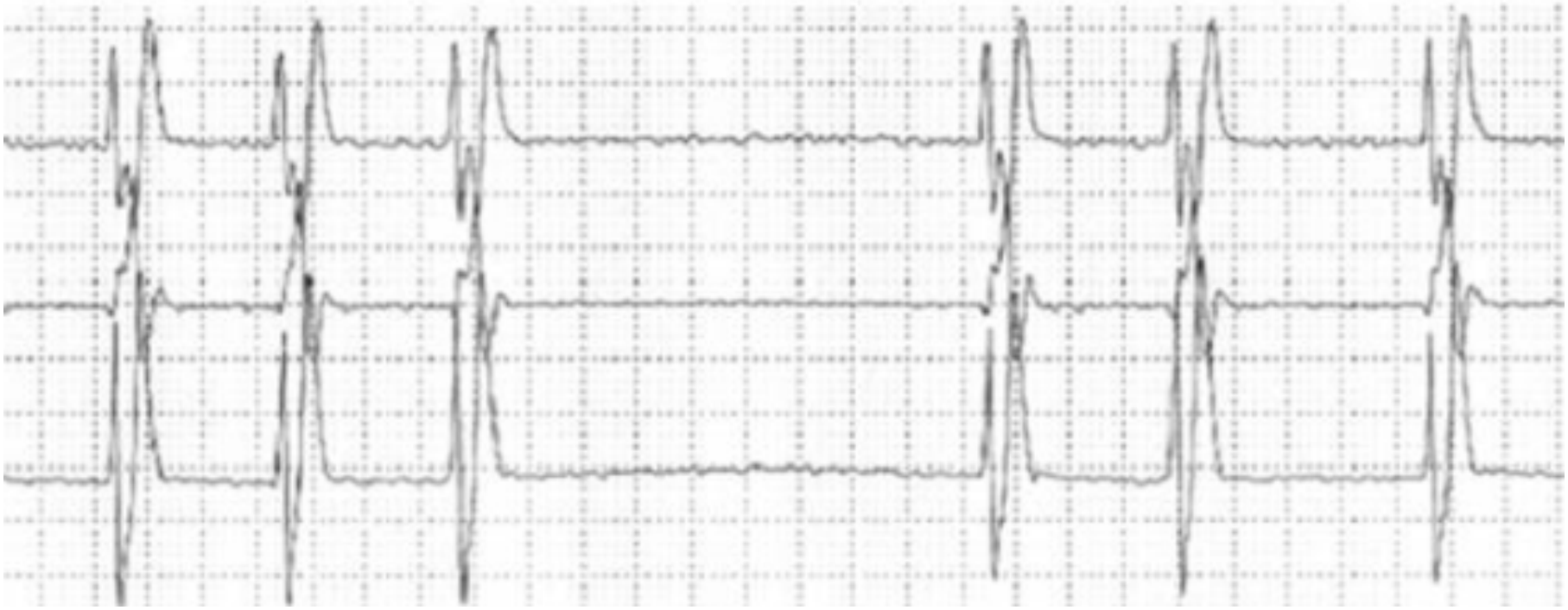

In this tracing we can see a short period of gross atrial fibrillation. The patient described palpitations. Congenital short QT syndrome is associated to high incidence of paroxysmal atrial fibrillation, the electrophysiological mechanism of which would be caused by very short action potential with heterogeneous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



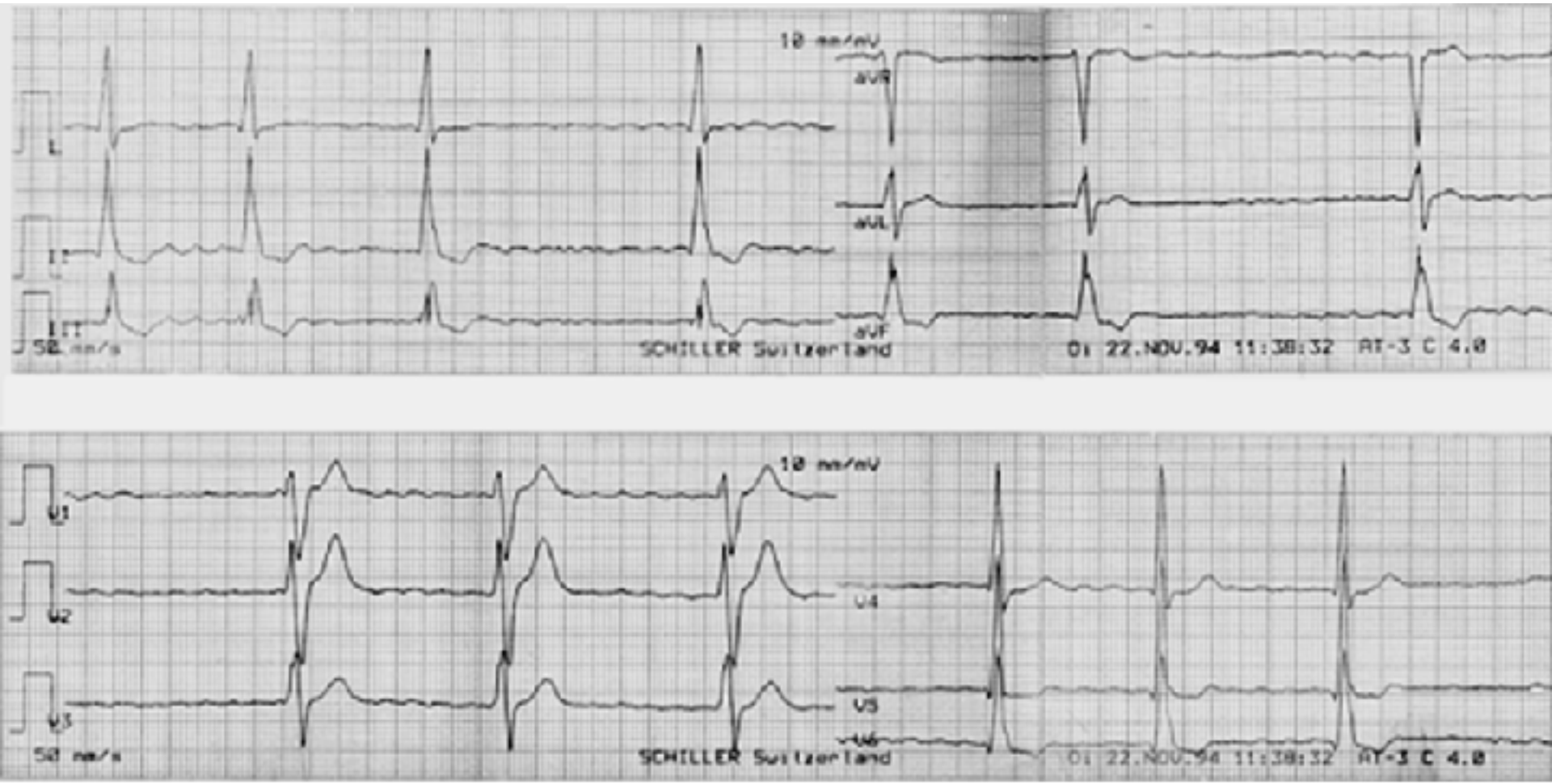

Sinus rhythm, tall/ peaked, narrow-based T waves or pseudo symmetrical T-wave in a patient with SQTS. Approximately 8 hours later during the same test, the patient spontaneously reversed into sinus rhythm.

Vlillafañe 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 (Villafañe 2014).

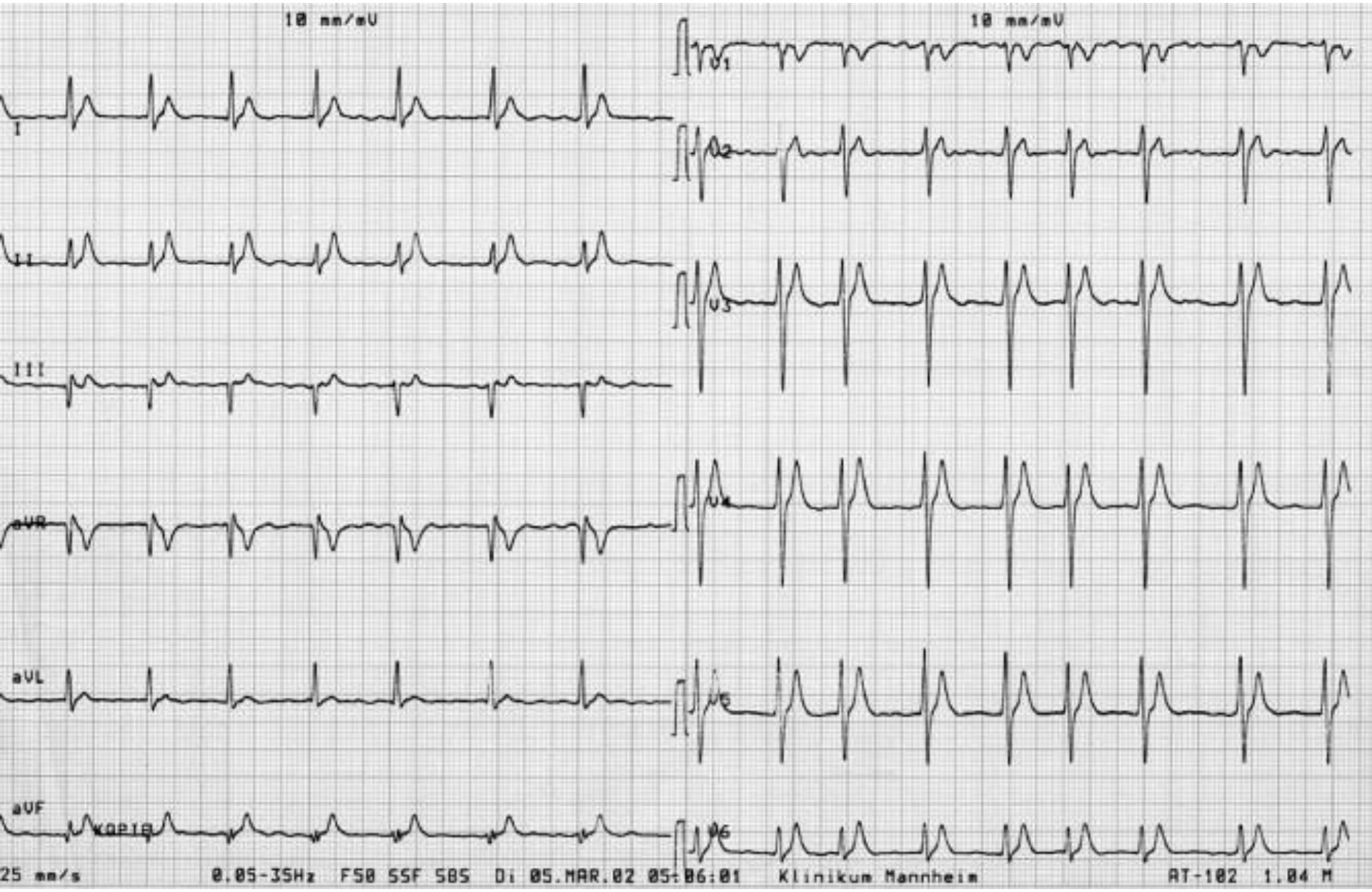
A KCNQ1 mutation (SQT2) causes age-dependant bradycardia and persistent atrial fibrillation.(Ki 2014). The description of a novel, de novo gain of function mutation in KCNQ1, responsible for atrial fibrillation and SQTS in utero indicates that some of these cases may have a genetic basis and confirms 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.

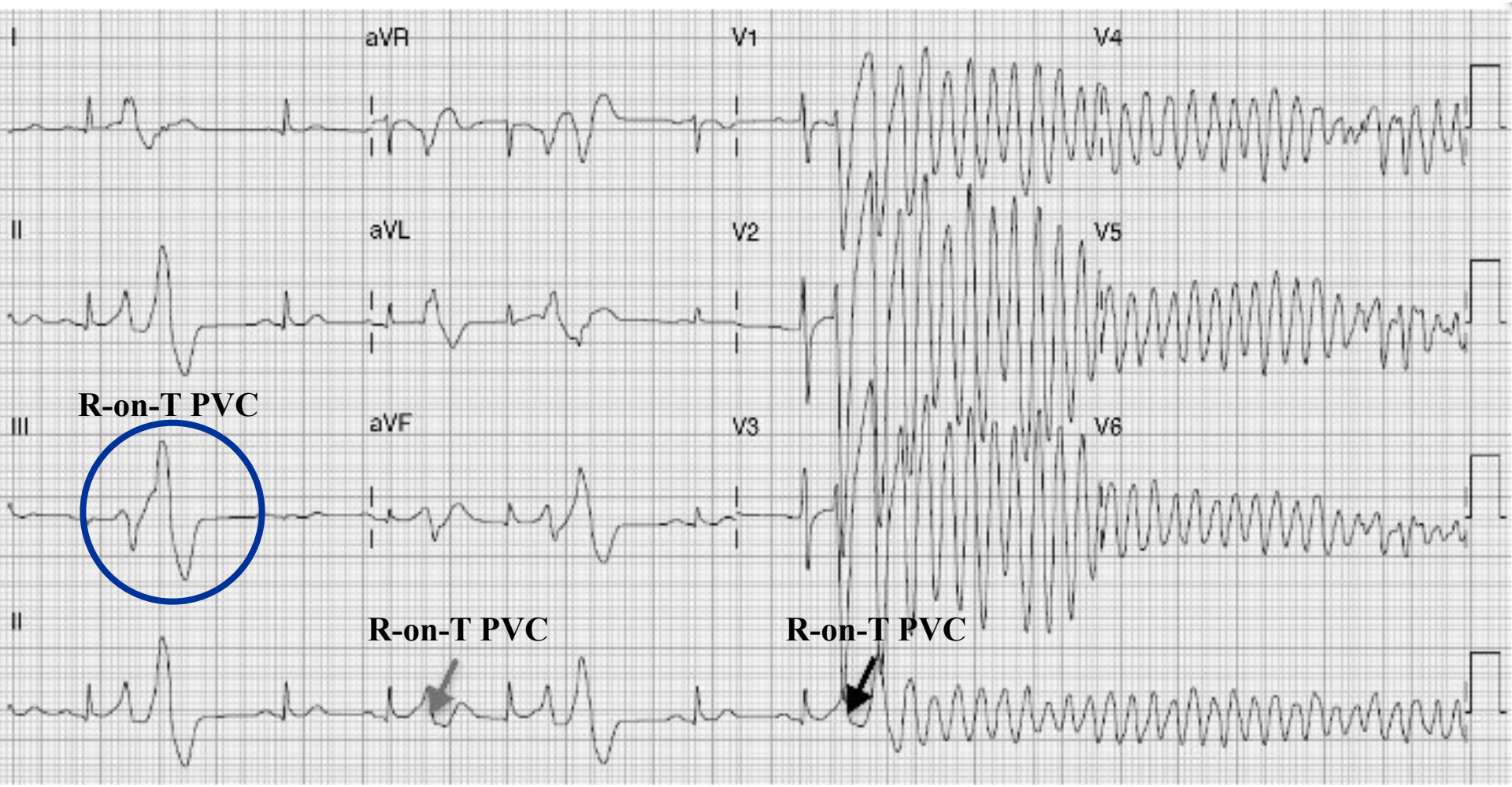



* Presentation named Supraventricular tachycardias and Brugada Syndrome from Brugada Syndrome Consensus Conference held in Lake Placid – NY – September 11-14 2003 by Prof. Martin Borggrefe MD, Ph.D.


10 mm/mV
10 mm/mV
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
25 mm/s
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 (Portugal 2014).

# Genetic cardiac diseases easily detectable by ECG

| Main cardiac channelopathy phenotypes and genetic cardiomyopathies |
|---|
| **A) Without apparent structural heart disease** |
| • Brugada syndrome (BrS) |
| • Congenital long QT syndrome (LQTS) |
| • Short QT syndrome (SQTS) |
| • Idiopathic Ventricular Fibrillation (IVF) |
| • Early Repolarization Syndrome (ERS) |
| • Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) |
| • Familial Progressive Cardiac Conduction Defect (PCCD): Lenegre disease |
| • Familial atrial fibrillation: polymorphisms on KCNE1, KCNQ1, and KCNH2 |
| • Sudden Infant Death Syndrome (SIDS) |
| • Overlapping clinical phenotypes or mixed forms: Brugada syndrome associated with LQT3, Brugada syndrome associated with Progressive Cardiac Conduction Defect, Brugada syndrome associated with sinus node dysfunction Brugada and sick sinus syndrome, Brugada syndrome associated with atrial standstill, SQTS with concomitant Brugada-like ECG pattern |
| **B) With structural heart disease** |
| • Hypertrophic Cardiomyopathy (HCM) |
| • Arrythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) |
| • Familial Dilated Cardiomyopathy (FDCM) |
| • Conduction disease with abnormal heart: NKX2-5 mutations (transcription factors), PRKAG2 mutations (pretein kinase subunit), LMNA gene mutations (Lamin A/C), some muscular dystrophies (SCN5A sodium channel mutations). |

# J wave syndromes

J wave syndromes are a spectrum of variable phenotypes characterized by the appearance of prominent electrocardiographic J waves (or Osborn waves) with a risk of ventricular fibrillation (VF), including the inherited Brugada syndrome (BrS), traditional early repolarization syndrome (ERS), idiopathic ventricular fibrillation (IVF) with J wave in inferior leads as well as acquired arrhythmias linked to the acute ST−segment elevation myocardial infarction (MI) and hypothermia. Although they may bear differences with regard to the ECG lead location, amplitude, and underlying causes of J wave, these disease entities share a similar ionic and cellular basis, risk factors, and similar clinical outcomes.

J wave syndromes were first defined by Yan et al. in a Chinese journal in 2004 (Yan 2004) and has gained worldwide recognition in the past decade.[2−4] J wave syndromes.

J wave is a positive deflection immediately following the QRS complex of the surface ECG or be in part buried inside of the QRS as notching or slurring.[3,5] J wave may be accompanied by an ST segment elevation, traditionally referred to as an early repolarization (ER) pattern (Antzelevitch 2011).

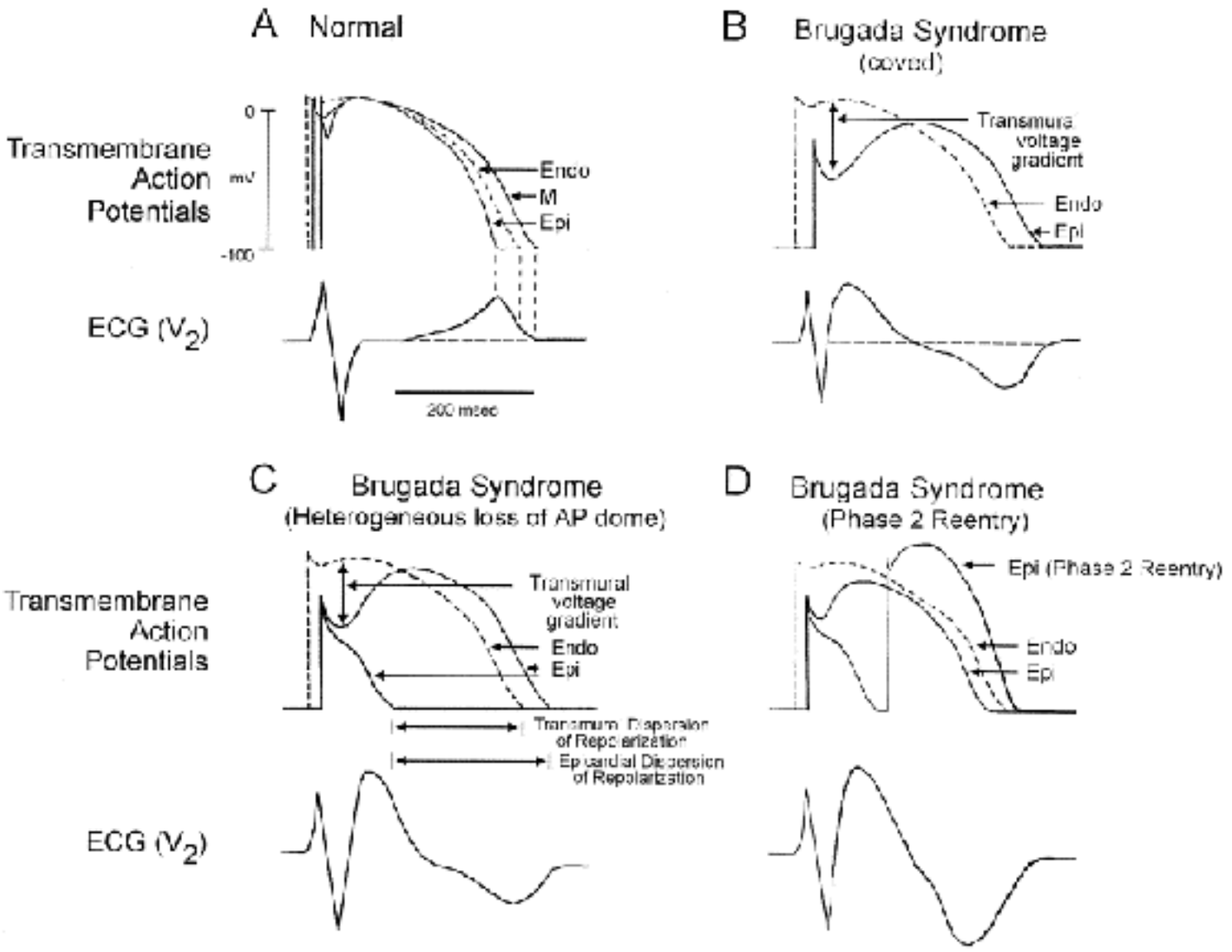
J wave was demonstrated as early as in the last century. J wave (QRS slurring or notching) was first reported in an experimental model of hypercalcemia (Kraus 1920), followed by hypothermia−induced J waves in an accidentally frozen man by Tomaszewski, who described the wave as a very slowly inscribed deflection between the QRS complex and the ST segment of the ECG (Tomaszewski 1938). Shipley and Hallaran described J wave in healthy young individuals shortly afterward (Shipley 1936). J wave was later named as Osborn wave after being highlighted by a landmark study in which Osborn described hypothermia−induced J wave in hypothermic dogs and its accentuation prior to VF (Osborn 1953). Over the past decades, J waves have been increasingly recognized in subjects with central nervous system disorders (Hersch 1961), clinical hypercalcemia (Sridharan 1984), BrS (Brugada 1992; Yan 1996), IVF (Kalla 2000; Haïssaguerre 2008), and myocardial ischemia (Yan 2004; Jastrzebski 2009). Especially, J wave has gained a great deal of attention after determining it as a sign of a substrate capable of generating fatal VT/VF. Underlying ionic and cellular basis of Ito−mediated J wave was elucidated in the days when the arterially perfused ventricular wedge preparation was first developed in 1996 (Yan 1996) Ito is the main current contributing to the repolarizing phase 1 of the AP.

It is a result of the movement of K+ from the intracellular to the extracellular (Niwa 2010). $I_{to}$ is rapidly activated and deactivated (Wettwer 1993). It is activated after the fast increase of the membrane potential following the phase 0 of the AP (Niwa 2010). Once activated, the outward flow of ($K^+$ ) ions from inside the cells constitutes Ito and causes the transmembrane potential to decrease. This decrease of the transmembrane potential is known as repolarization. Ito is then quickly deactivated, stopping the repolarization and ending the phase 1 of the AP (Niwa 2010; Wettwer 1993). A distinct AP notch mediated by Ito in epicardium, rather than endocardium, produces a transmural voltage gradient during early ventricular repolarization that is, contributory to registration of J waves on the ECG. Several lines of evidence determined the higher density of Ito in the epicardium compared to the midmyocardial (M) region and significantly greater than the endocardial region of canine ventricle. Similar results were obtained in subepicardial and subendocardial myocytes from human ventricles (Wettwer 1994; Näbauer 1996). Factors that affect the gating properties of Ito or ventricular activation sequence can modify the appearance of the J wave. For example, because of its slow recovery from inactivation, $I_{to}$ is reduced following faster heart rate, resulting in a decrease in the amplitude of the J waves.

## Phase 2 Reentry, An Initiator for Ventricular Fibrillation

If the Ito−mediated epicardial AP notch is deep enough, complete loss of epicardial AP dome may occur. During transition to complete loss of epicardial AP dome, a few electrical alterations occur (Yan 2004): The dome is markedly delayed immediately prior to its complete loss, resulting in paradoxical AP prolongation "downslope ST segment elevation," which in fact is a giant J wave, followed by a negative T wave (Shu 2005); once the epicardial AP dome is completely lost, AP duration shortens ≈ 40%,(**Yan GX 1999**) causing a marked increase in TDR (Antzelevitch 2010); complete loss of the dome is often heterogeneous across the epicardium: That is, complete loss of the dome with significantly AP shortening occurs in some areas, but the delayed AP dome remains in others (Yan 1999; Yan 2003). Due to a marked difference in AP duration and the property of the delayed dome similar to ER (Guo 2007), the dome may produce a new AP in the areas where complete loss of epicardial AP is present, leading to formation of short−coupled PVCs, which can be capable of originating PVT/VF.

Because it is the propagation of the dome at AP phase 2, it is termed as phase 2 reentry, also demonstrated in humans.[62] Phase 2 reentry is the initiator for VF in all of the J wave syndromes regardless of the locations of J wave on the ECG (D) (Antzelevitch 2001).




Schematic representation of RV epicardial action potential (AP) changes thought to underlie the ECG manifestation of Brugada syndrome.

# Acquired J Wave Syndromes

J wave syndromes can be acquired, which share the similar properties with those of inherited J wave syndromes, including ECG features and the underlying mechanism for VF (Antzelevitch 2010; Cui 2010). Hypothermia−induce J wave is well−known, and the study that showed J wave accentuation prior to VF can be dated back to 1953 (Osborn 1953). Hypothermia can produce distinct J waves, resulting in phase 2 reentry and VF (Gurabi 2014). Note, hypothermia−induced J waves can be confined to some selected leads or manifest globally in all leads. Under normal conditions, much of the J wave is buried inside the QRS complex. With hypothermia, the epicardial AP notch is evidently accentuated, and transmural conduction is slowed bringing about to a prominent J wave (Antzelevitch 2011). It seems that there is no prominent gender−related discrepancy in manifestation of hypothermia−induced VF. This may be due to the powerful potential of hypothermia to significantly amplify the magnitude of J waves, which can then abate the basically gender−related diversity of J wave. Another more common type of acquired J wave syndromes is ischemia−induced J wave syndrome (Yan 2004; Cui 2010; Wang 2008; Li 2009). During early phase of acute MI in canine experiments, phase 2 reentry causes R−on−T ectopic beats capable of initiating VF (Yan 2004). Intrinsically, much higher density of Ito in right compared to left ventricular epicardium may be responsible for an increased incidence of ischemia−induced VF. This is further supported by clinical observation of higher incidence of primary VF in individuals with acute inferior MI who have right ventricular involvement (8.4%) than those without (2.7%), or with an anterior MI (5.0%) (Mehta 2001).

# J wave syndromes

| | Inherited | | | | Acquired | |
|---|---|---|---|---|---|---|
| **Characteristics** | **ERS type 1** | **ERS type 2** | **ERS type 3** | **BrS** | **Ischemia mediated VT/VF** | **Hypothermia mediated VT/ VF** |
| Average age of first event | 35 years | | | | 30-40 years | |
| Anatomic location | Anterolateral left ventricle | Inferior left ventricle | Left and right ventricles | RVOT | Left and right ventricles | Left and right ventricles |
| Leads displaying J point/ J wave | I, V4-V6 | II, III, aVF | Global | V1-V3 | Any of 12 leads | Any of 12 leads |
| Response of J wave/ST elevation to Bradycardia or pause | ↑ | ↑ | ↑ | ↑ | NA | NA |
| Response of J wave/ST elevation to Na−channel blockers | ↓→ | ↓→ | ↓→ | ↑ | NA | NA |
| Male predominance | 75% | | | 80% | | |
| VT/VF | Rare common in healthy athletes | Yes | Yes, electrical storm | Yes | Yes | Yes |
| Sex dominance | Male | Male | Male | Male | Male | Male |
| Response to quinidine | | | | | Limited data | |
| J wave/ST elevation | ↓ | ↓ | ↓ | ↓ | | |

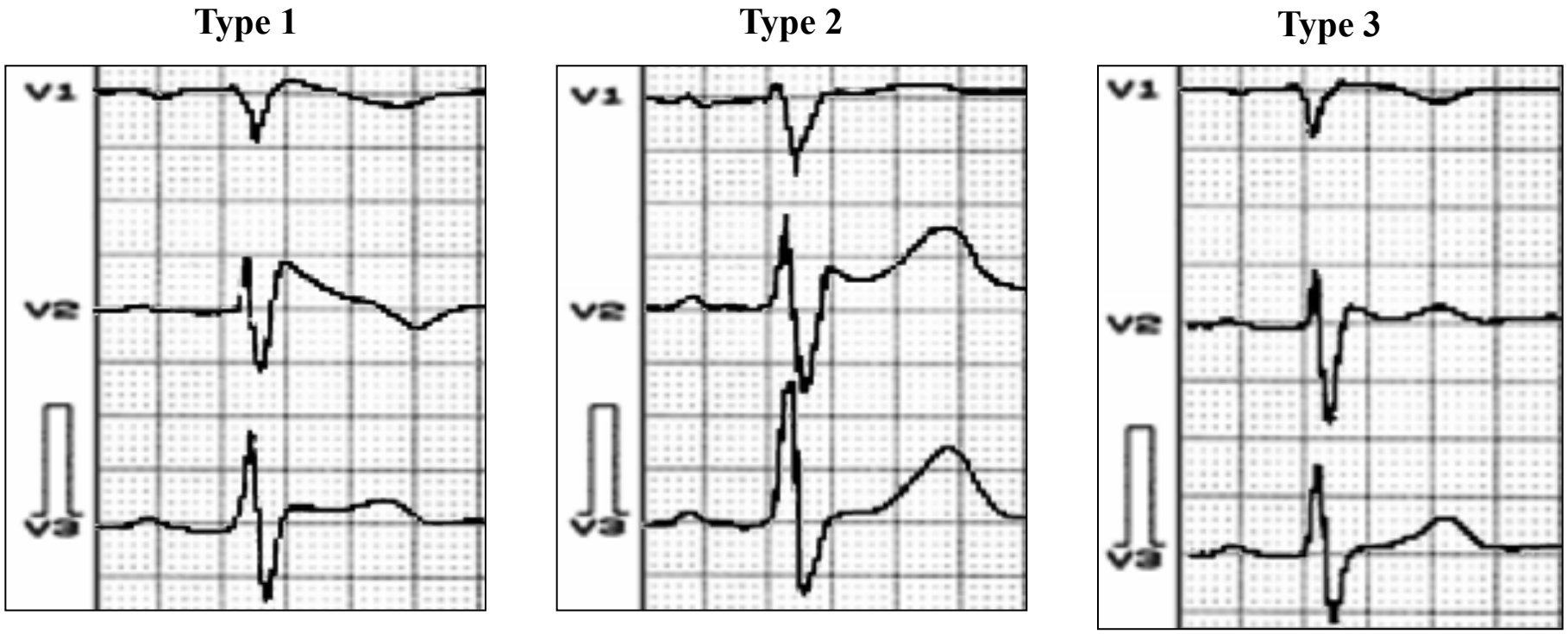
| | Inherited | | | | Acquired | |
|---|---|---|---|---|---|---|
| **Characteristics** | **ERS type 1** | **ERS type 2** | **ERS type 3** | **BrS** | **Ischemia mediated VT/VF** | **Hypothermia mediated VT/ VF** |
| VT/VF | ↓ | ↓ | ↓ | ↓ | | ↓ |
| Response to isoproterenol | | | Limited data | | NA | NA |
| J wave/ST elevation | ↓ | ↓ | | ↓ | | |
| VT/VF | ↓ | ↓ | | ↓ | | |
| Gene mutations | CACNA1C, CACNB2B | KCNJ8, CACNA1,CAC NB2B KCNJ8, CACNA1, CACNB2B | CACNA1C | SCN5A, CACNA1C, CACNB2B, GPD1L, SCN1B, KCNE3, SCN3B, KCNJ8, CACNA2D1, KCND3, MOG1, ABCC9, HCN4, KCNH2, KCNE5 | SCN5A | Not available. |

ERS: Early repolarization syndrome; BrS: Brugada syndrome; VT: Ventricular tachycardia; VF: Ventricular fibrillation; NA: Not available

# Brugada syndrome: Brugada syndrome diagnosis criteria (Antzelevitch 2005)

1. Absence of apparent structural heart disease
2. Absence of drugs effects, electrolyte disturbance and CHD
3. Documented PVT/VF
4. Family history of SCD at <45 years old in first-degree relatives
5. Type 1 ECG Brugada pattern (Coved-type) in proband and family members
6. Induction of VT/VF with Programmed Electrical Stimulation
7. Syncope, cardiac arrest or nocturnal agonal respiration.

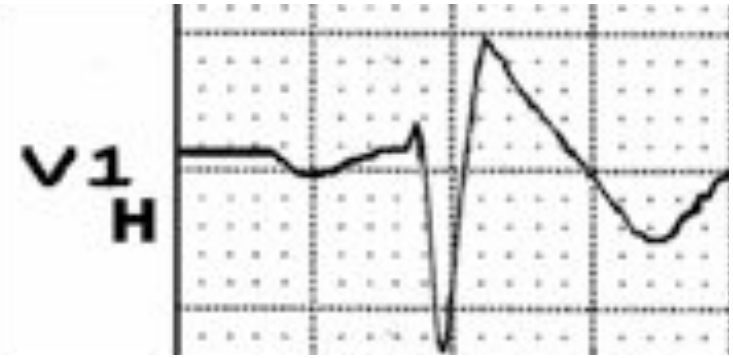
# ECG types from first consensus report (Wilde 2002)

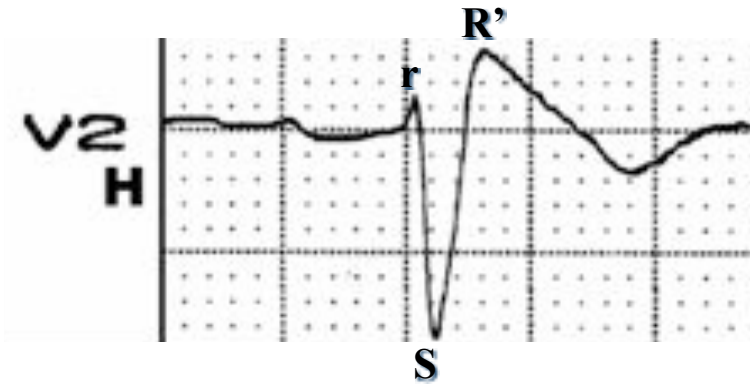



**Type 1:** ST-segment elevation is triangular or coved to the top ("coved type") ≥ 2mm (0.2mV) elevation in >1 right precordial lead $V_1$-$V_3$ in the presence or absence of a sodium-channel blocker and followed by negative symmetrical T wave. Type 0 as coved-type ST elevation without a negative T wave (Take 2011).
**Type 2**: J point and ST segment elevation ≥ 2mm (0.2mV) with saddleback appearance, and remains at least 1 mm above the isoelectric line, followed by positive or biphasic T wave.
**Type 3:** J point and ST segment elevation < 1mm and with variable shape: whether coved type or saddleback appearance. In Type 3, the terminal section of the ST segment never exceeds 1 mm above the isoelectric line.
Note that Type 2 and 3 patterns are characterized by the same general shape of the J-ST-T wave, but the ST segment elevation in type 3 pattern is slightly less than 0.1 mV.

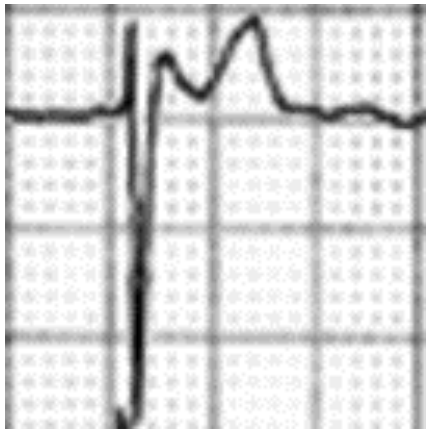
# New ECG classification

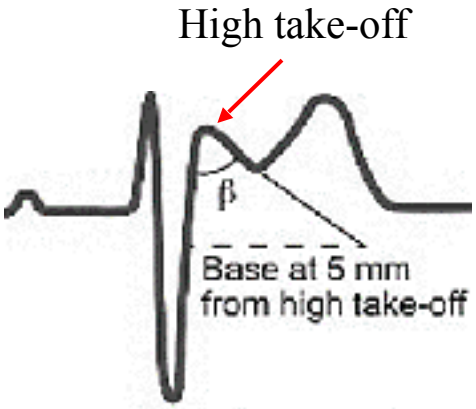
**Type 1 Brugada pattern**: J point and ST segment elevation ≥2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on right precordial leads ($V_1$-$V_2$ or from $V_1$ through $V_3$) and/or high right precordial leads $V_{1H}$, $V_{2H}$ and $V_{3H}$.




**Type 2 Brugada pattern**: it has ST segment elevation with saddleback shaped, high take-off angle broad, β angle always > 36° and base of the triangle from high take-off of 5 mm.

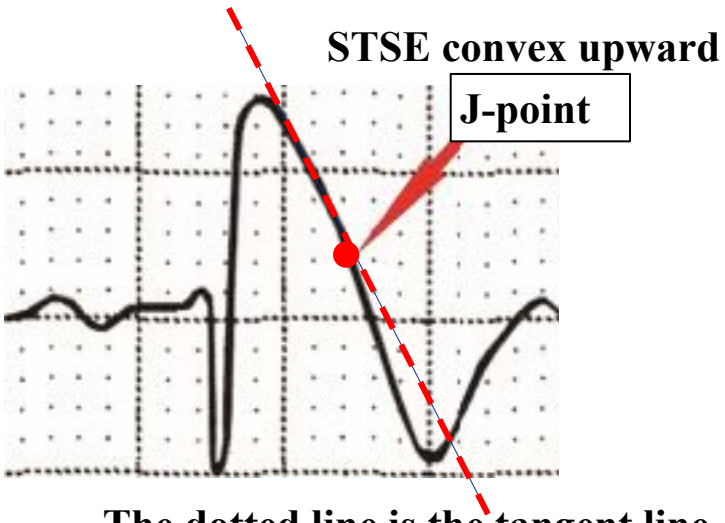




# Proposal of classification of type 1 Brugada pattern

## Right precordial leads

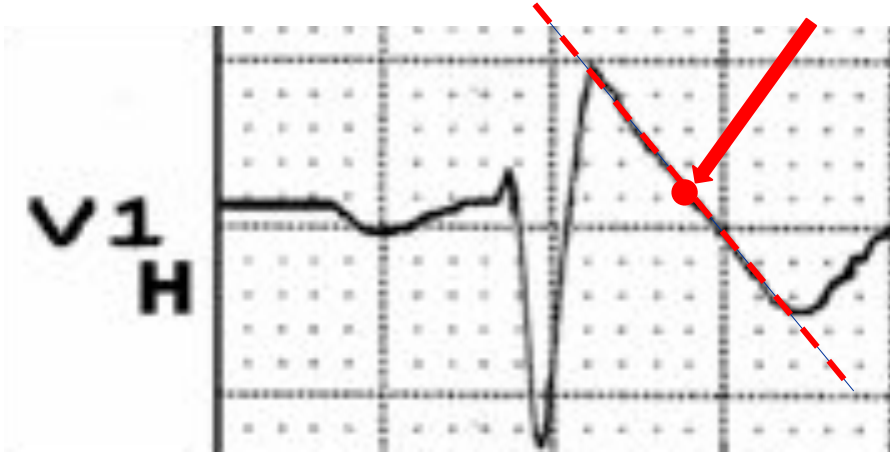
### Subtype 1A




The dotted line is the tangent line

### Subtype 1B

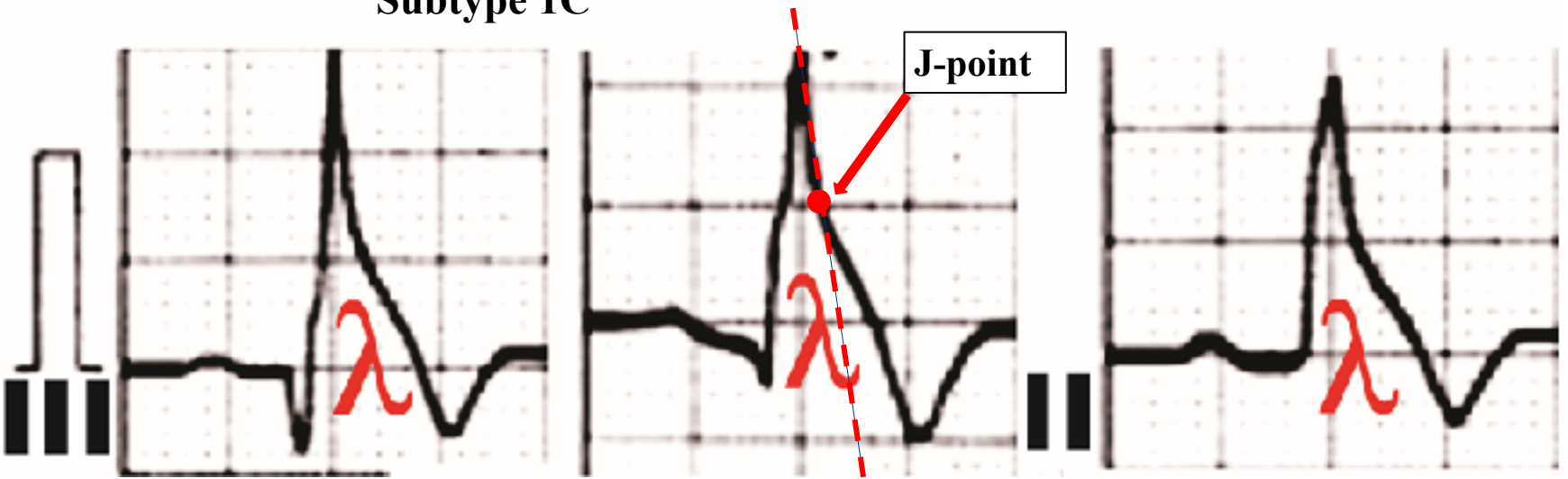
STSE rectilinear oblique descendent



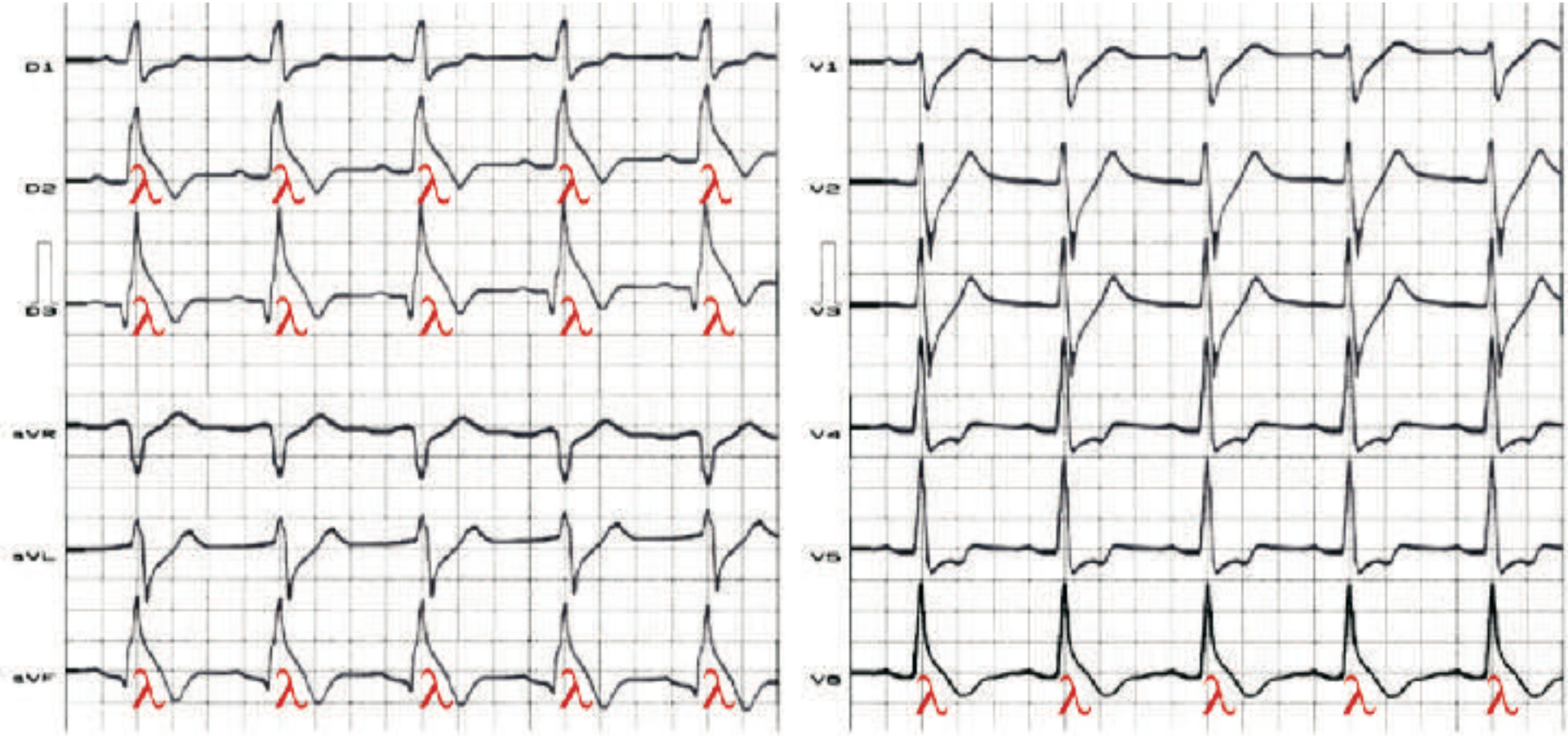

The dotted line is the tangent line

## Inferior leads

### Subtype 1C

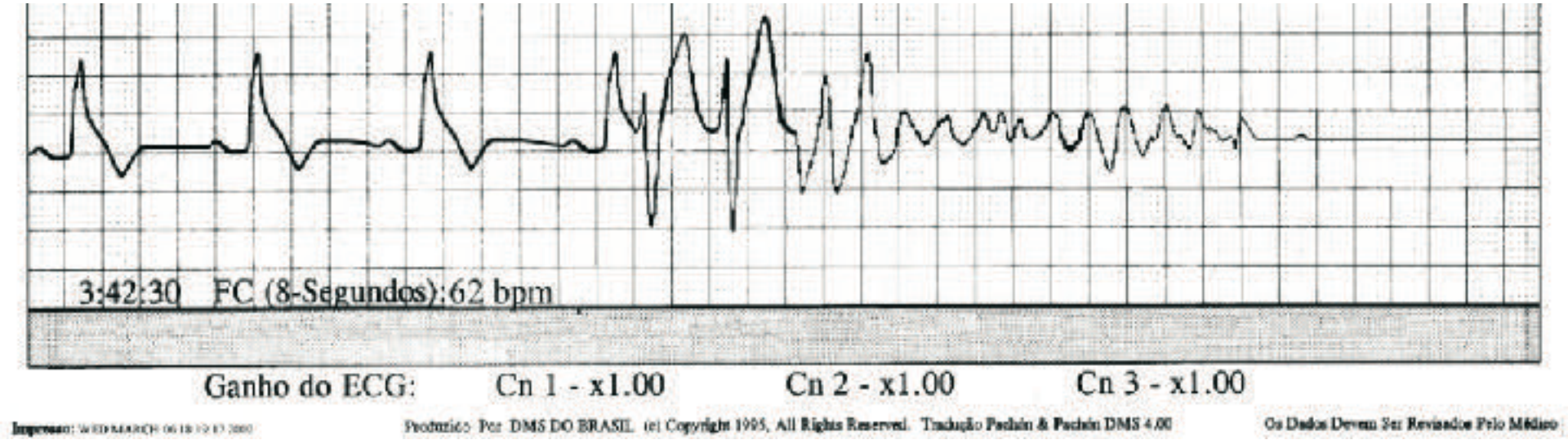


# Example of subtype 1C ECG Brugada pattern




**The ECG shows persistent ST segment elevation in the inferior and apical leads, associated to concomitant reciprocal or mirror image in the anterior wall that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia.**

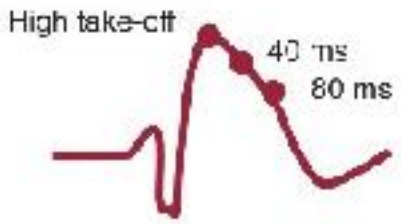
***Riera AR, Ferreira C, Schapachnik E, et al. Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. J Electrocardiol. 2004 Apr; 37: 101-104***




Holter monitoring recorded the final event by Holter, manifested by PVT episode with initial short-coupling ventricular premature contractions (R on T) that ended quickly in VF and asystole.

Pattern 1C of repolarization has been observed in acute myocardial infarction by Kukla et al (Kukla 2007). These authors raised the hypothesis that the "Lambda-like ST" could be a new marker of risk of acute infarction with ST segment elevation.

In the new ECG criteria, only 2 ECG patterns are considered: pattern 1 identical to classic type 1 of other consensus (coved pattern) and pattern 2 that joins patterns 2 and 3 of first consensus (saddle-back pattern) (Bayés de Luna 2012).





**Type 1 Brugada pattern in V1-V2:**

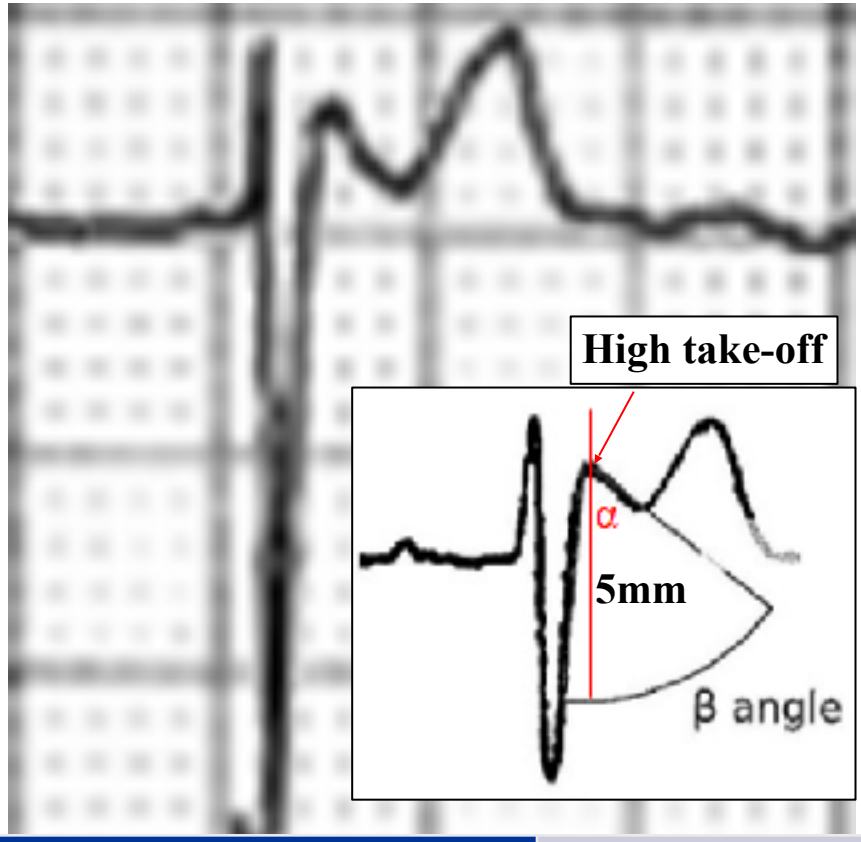
- At the end of the QRS, na ascending ST segment with a high take-off of at least 2 mm followed by a convex to the top or rectilinear downsloping ST segment. There are a few cases where high take-off is between 1 and 2 mm.
- There is no clear r' wave.
- The high take-off does not correspond to the J-point.
- At 40 ms of take-off, the decrease in amplitude of ST segment is 4 mm (it is much higher in RBBB and athletes).
- ST segment at high take-off > St segment at 40 ms > ST segment at 80 ms
- ST segment is followed by negative and symmetric T-wave.
- The duration of QRS in V1 is longer than in RBBB and longer than in V6 (mismatch).

**Type 2 Brugada pattern in V1-V2:**

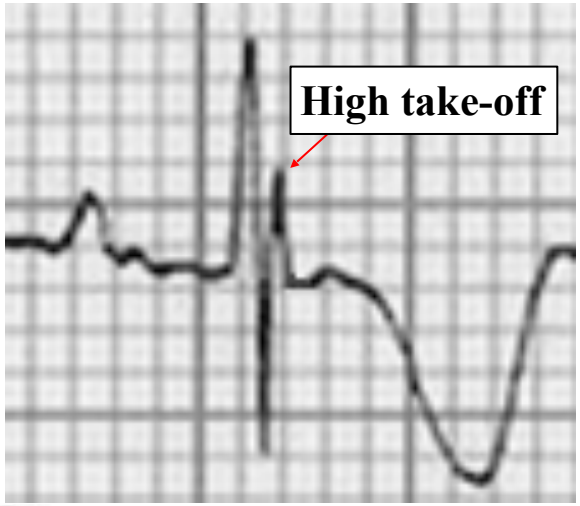
- High take-off that does not coincide with the J-point ≥ 2 mm.
- The descending arm of r' coincides with the beginning of ST segment.
- ST segment upslope is at least 0.5 mm.
- ST segment is followed by positive T wave in V2.
- The characteristics of the triangle formed by r' enables the diferente criteria to be defined that are useful for diagnosis: a) the duration of the base of the triangle formed by r'at 5 mm from the high take-off is greater than 3.5 mm, and b) the duration of the QRS in Brugada type 2 syndrome is longer than in other cases with r' in V1, and there is a mismatch between V1 and V6.

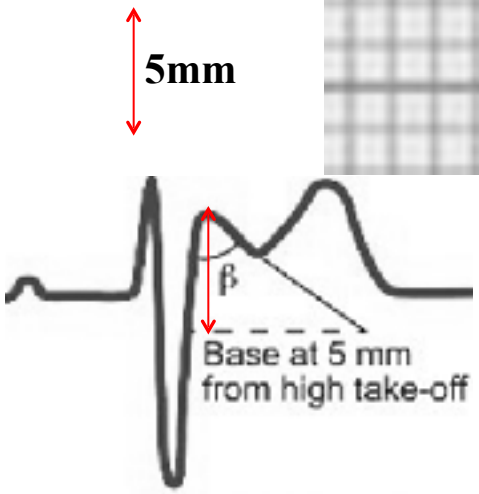
# Type 2 Brugada pattern versus ordinary “innocent” incomplete RBBB

## Type 2 Brugada pattern




## Ordinary “innocent” incomplete RBBB




*Chevallier at al. J Am Coll Cardiol. 2011 Nov 22;58(22): 2290-8.*

*Ohkubo et al. Int Heart J. 2011;52(3):159-63.*

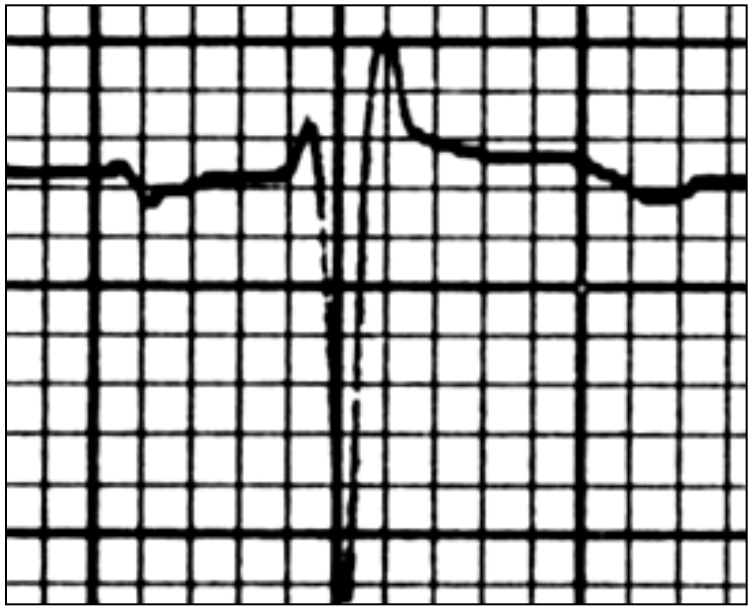
| | | |
|---|---|---|
| **β angle** | > 36° | Acute |
| **α angle** | Mayor | Minor |
| **T-wave** | Positive or plane | Negative |
| **Duration of triagle base from the high take-off at 5mm** | Greater than 3.5 mm | Minimal |
| **High take-off** | Wide | Acute |

# Typical Brugada type 1 pattern after ajmaline injection (80 mg)

**Name:** BAAS; **Age:** 53 years old **Race:** Caucasian; **Weight:** 95 Kg **Height:**1,85m;
**Sex:** Male; **Date:** 06/17/2005.

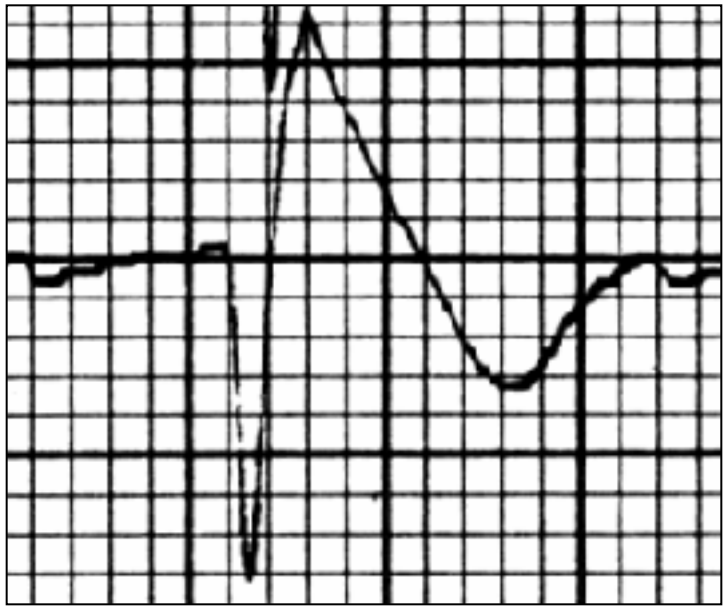
**ECG <u>before</u> ajmaline injection**

$V_1$



**ECG <u>after</u> ajmaline injection 80 mg**

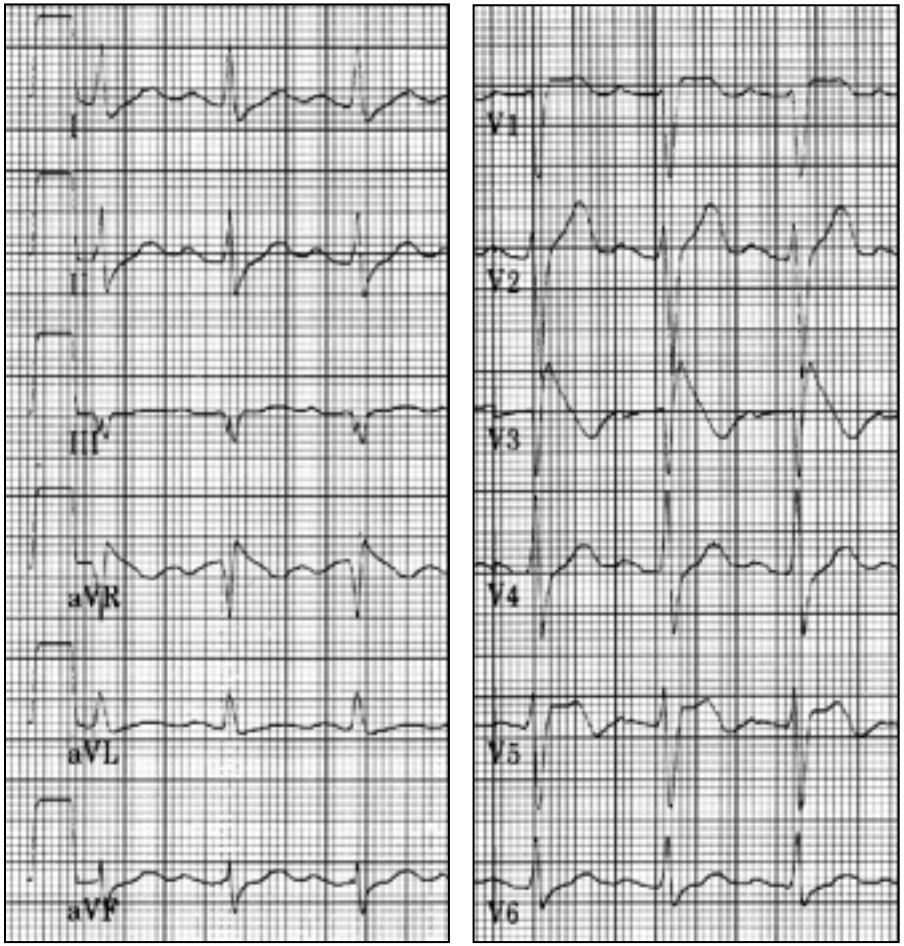
$V_1$



**Type 1**

# Typical Brugada type 1 pattern after ajmaline injection (80 mg)

**Name:** BAAS; **Age:** 53 years old; **Race:** Caucasian; **Weight:** 95 Kg; **Weight:**1.85m;
**Sex:** Male; **Date:** 06/17/2005.

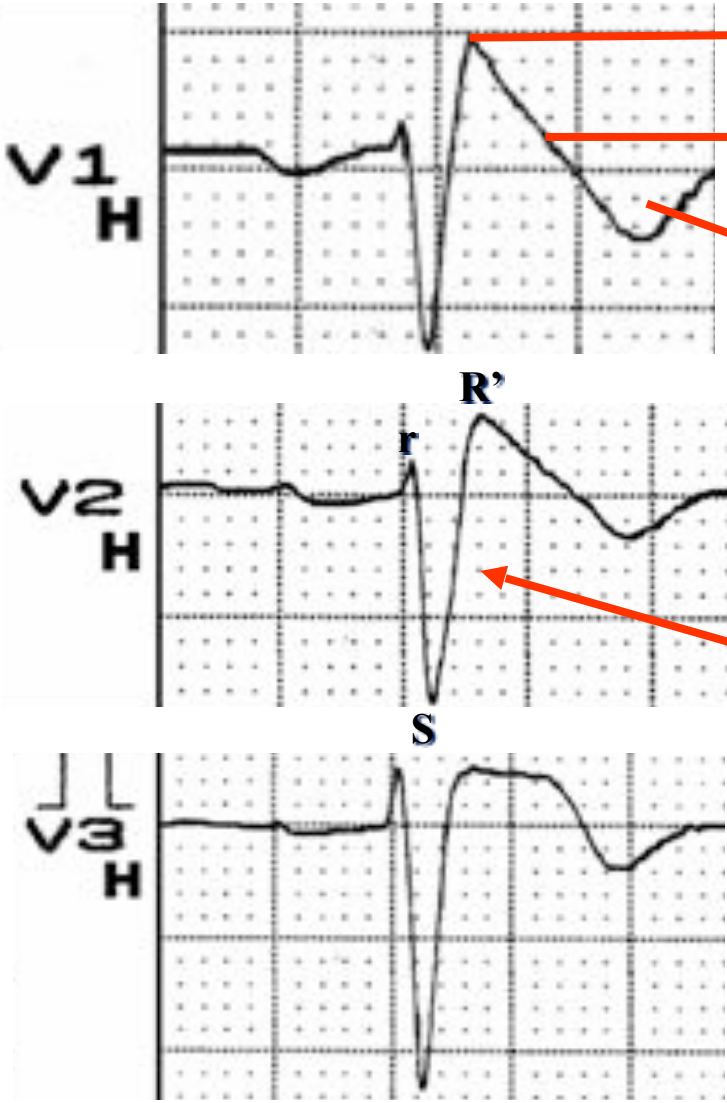



**V3=V1**

**V5=V2**

# Value of ECG and VCG in the diagnosis and prognosis of the Brugada syndrome

## Signature ECG-change




**High take-off: it is not the end of QRS complex**

**STSE rectilinear oblique descendent. Impossible to determinate J-point location**

**Negative symmetrical T-wave**

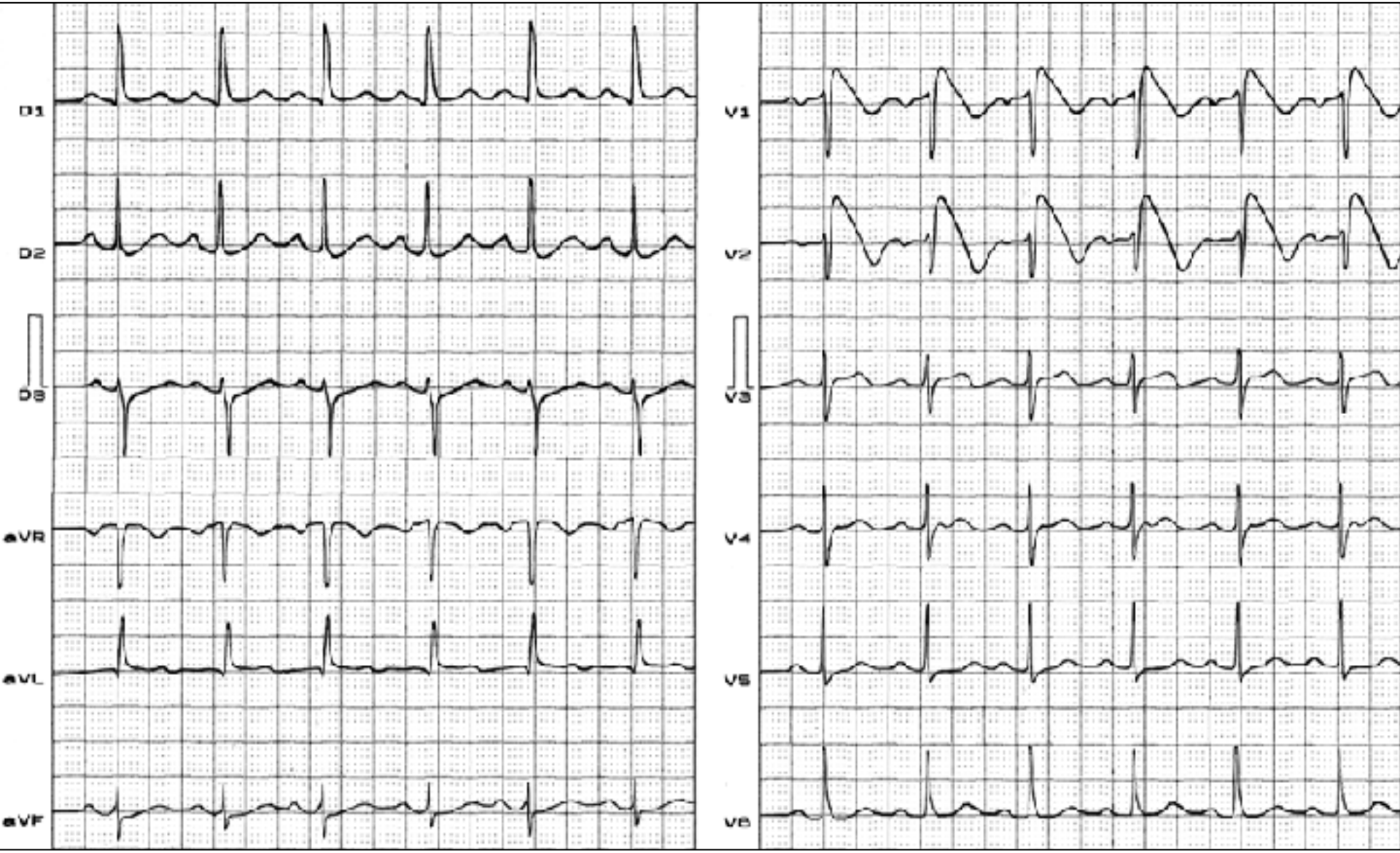
**Type 1 ECG Brugada patten**

**Triphasic QRS complex with broad final R' wave rSR'**

**Truly Right Bundle Branch Block?**

Type 1 Brugada pattern: J point and ST segment elevation ≥2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on right precordial leads ($V_1$-$V_2$ or from $V_1$ through $V_3$) and/or high right precordial leads $V_{1H}$, $V_{2H}$ and $V_{3H}$.

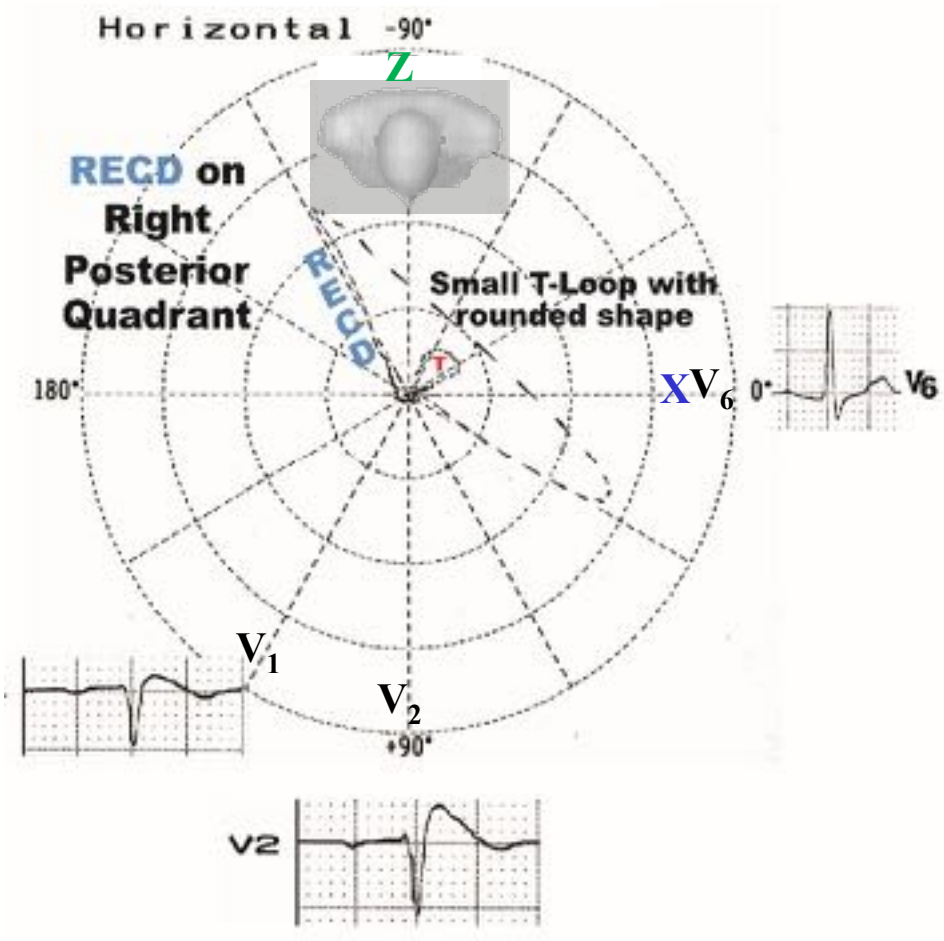
**Name**: SJC; **Sex**: M; **Age**: 32 y/o; **Ethnic group**: Caucasian; **Weight**: 82 Kg; **Height**: 1,76 m;
**Date**: 09/01/2001



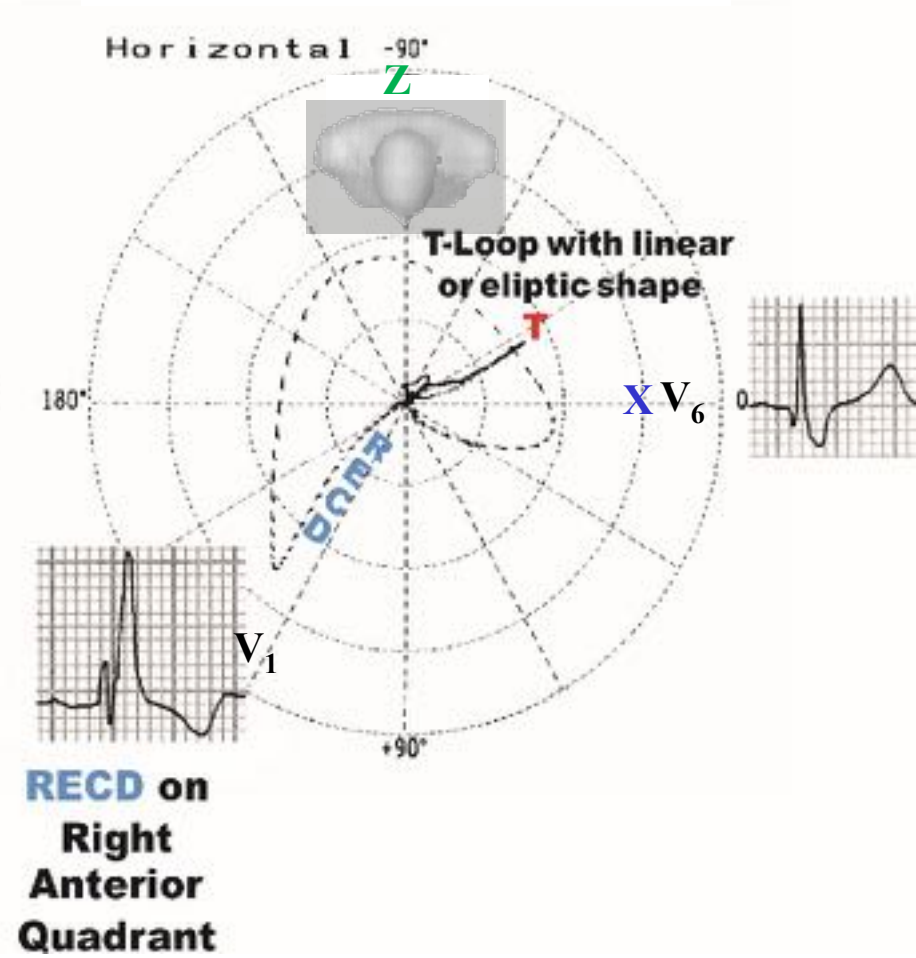

**Clinical diagnosis**: Symptomatic Young man with Brugada syndrome.
**ECG diagnosis**: Type 1 Brugada pattern without RBBB.

# ECG/VCG correlation in the horizontal plane

## Type 1 Brugada pattern

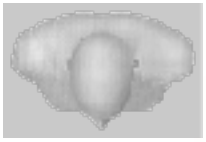



## Truly RBBB pattern

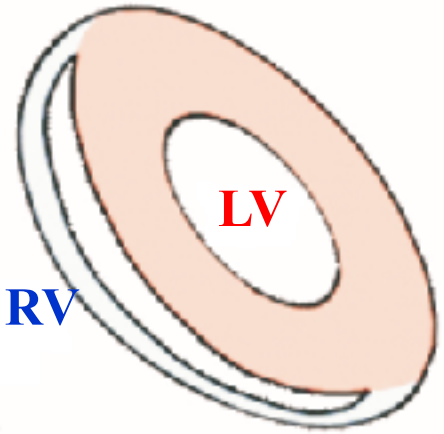



RECD on right posterior quadrant

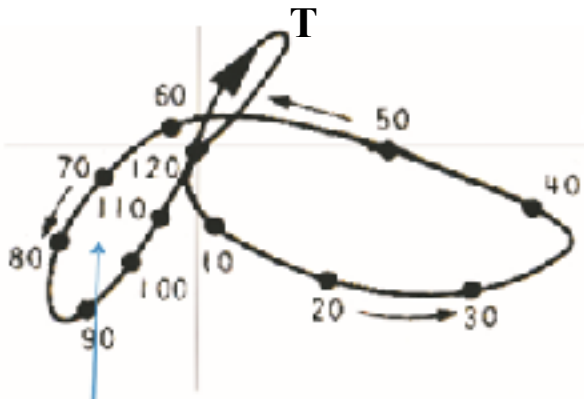
(Pérez-Riera 2012)



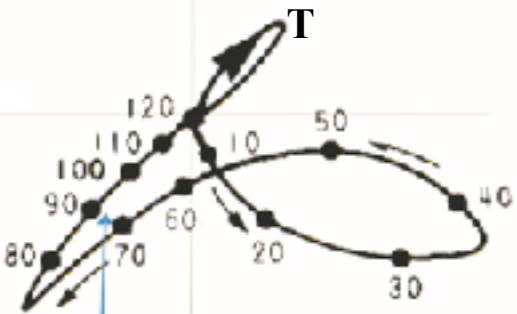


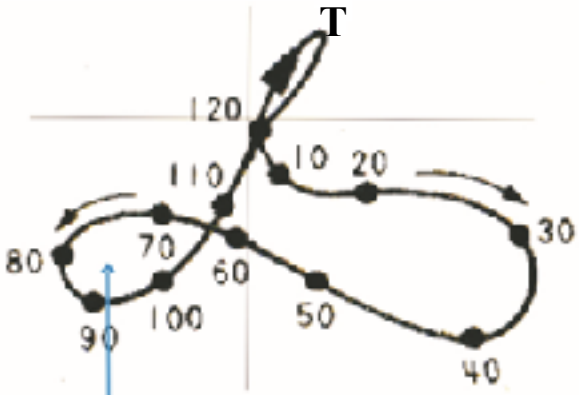

**Grishman type or type I**




**Cabrera type or type II**




**Type III or C**

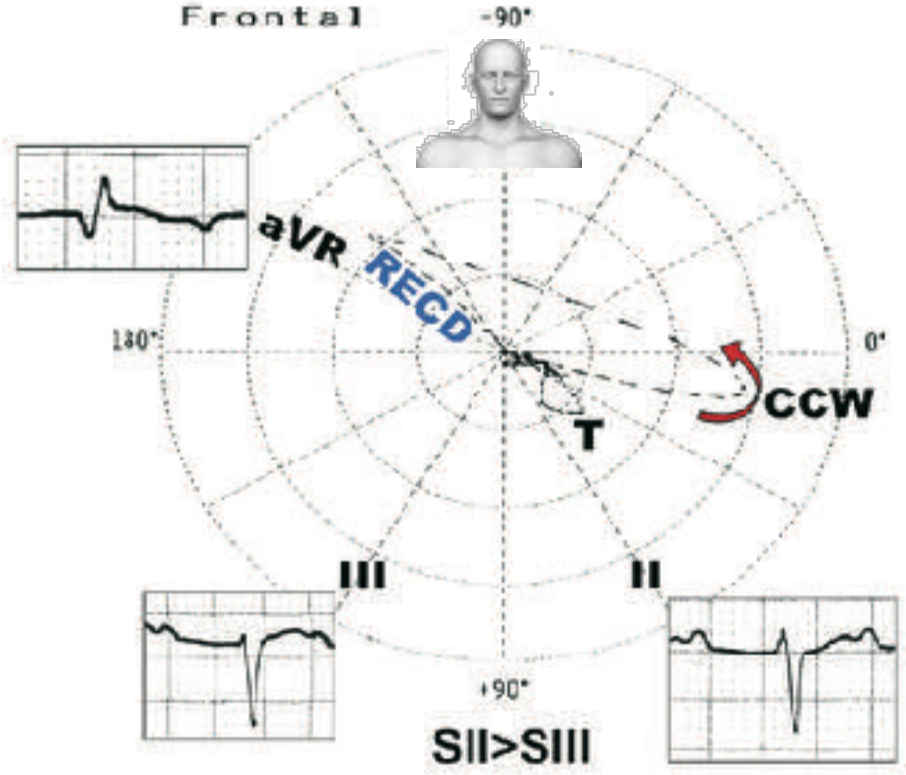



**"Finger-like" terminal appendix**

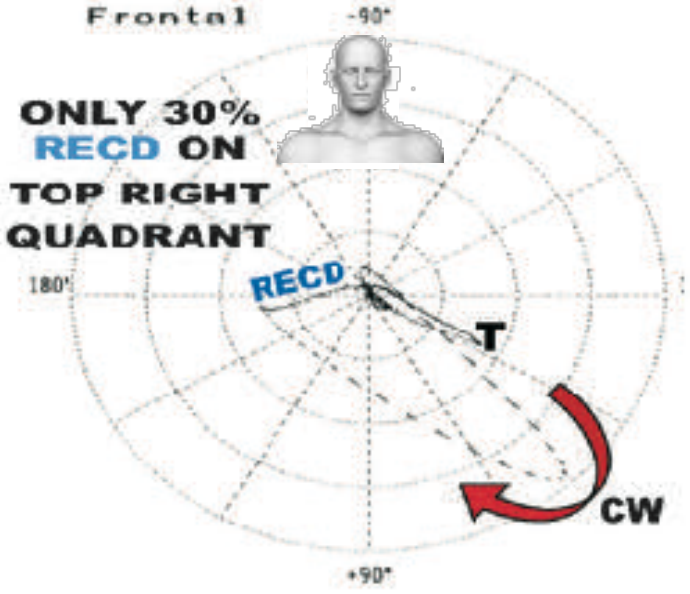
# FRONTAL PLANE

## ECG/VCG Group I

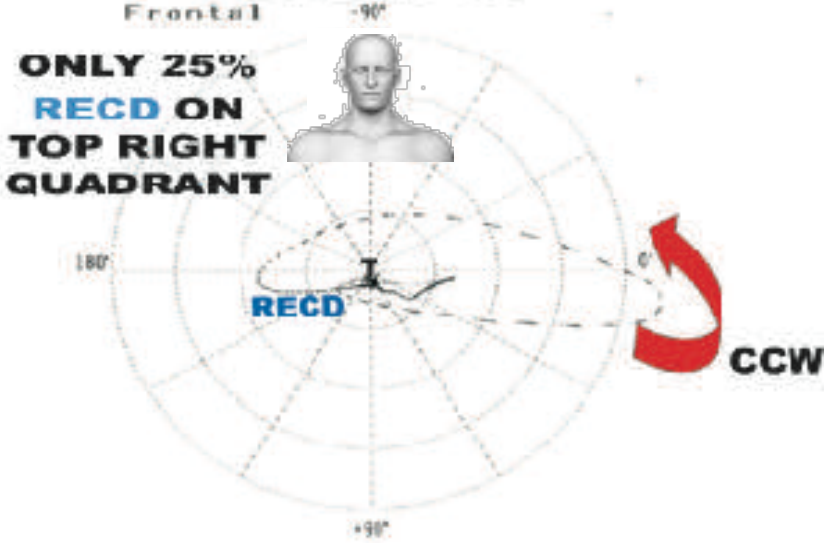
**RECD ON TOP RIGHT QUADRANT 10 (90.9%)**




## VCG Group II

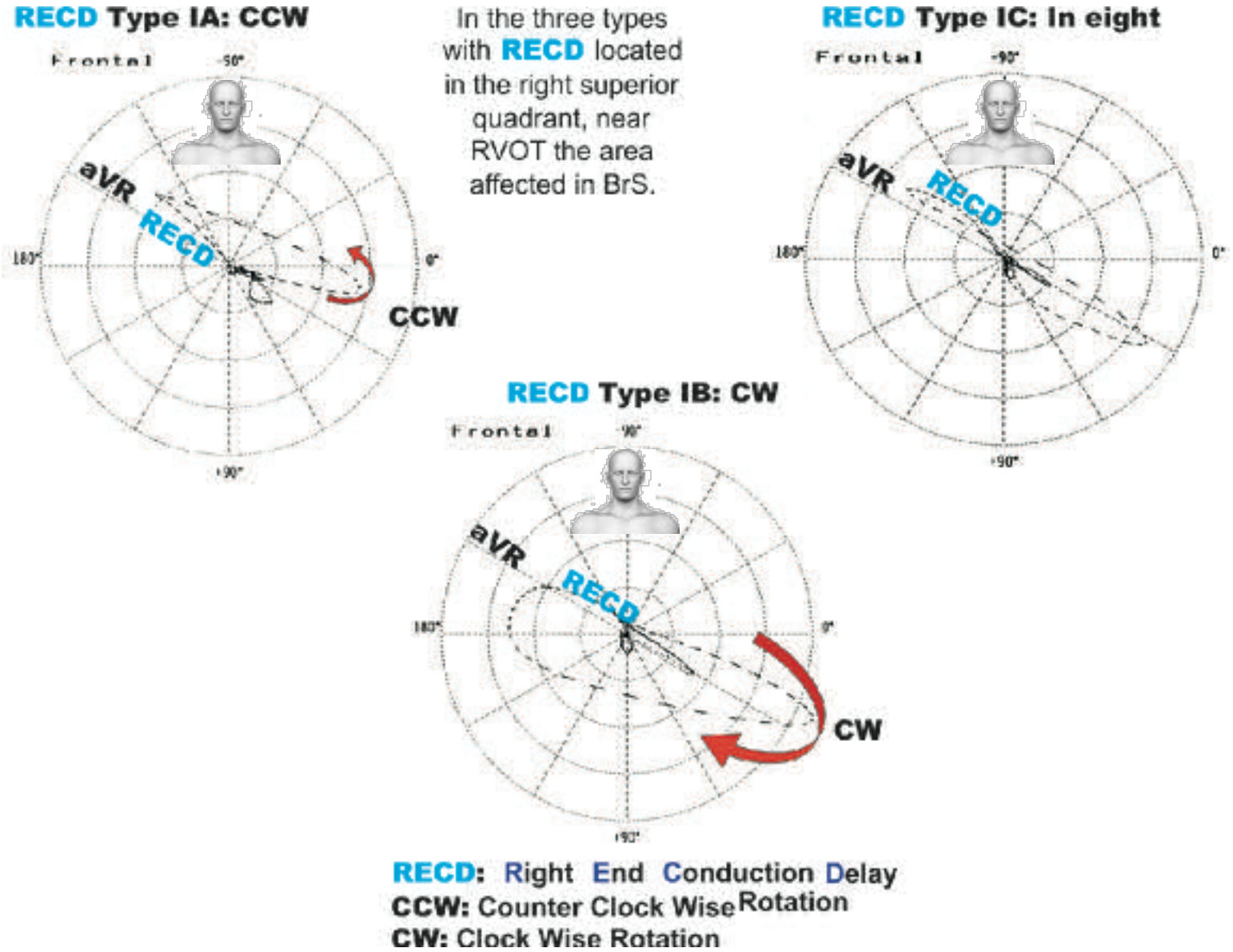



## VCG Group III

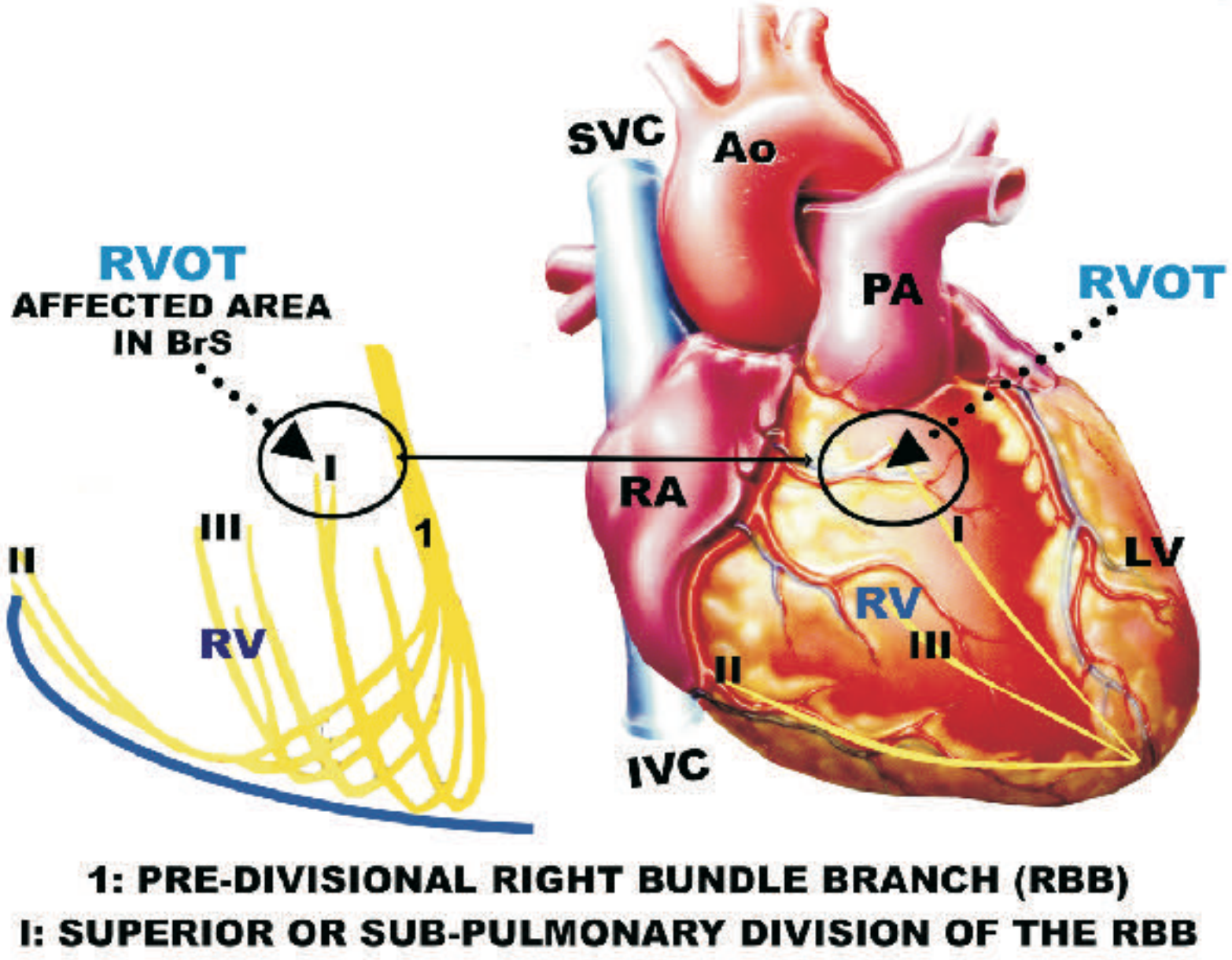



**RECD= Right End Conduction Delay**
**CW= Clock Wise Rotation**
**CCW= Counter Clock Wise Rotation**

# QRS loop types in the frontal plane

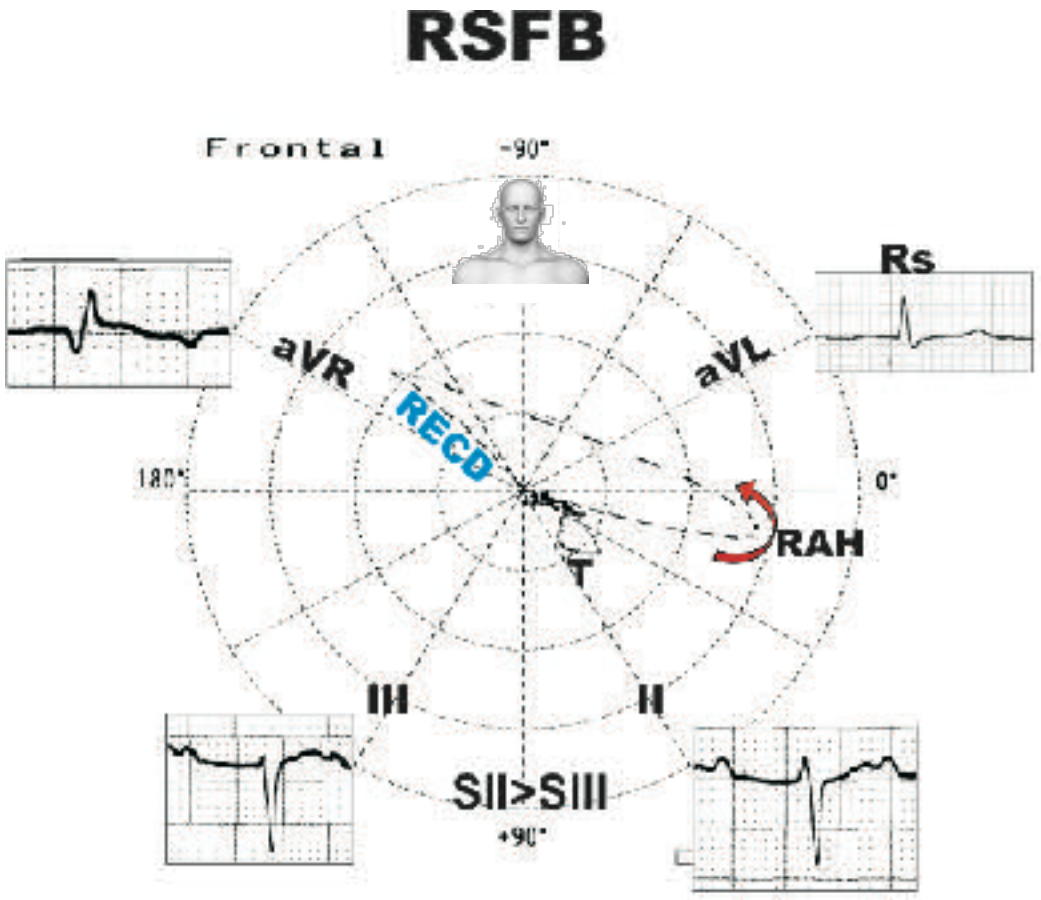


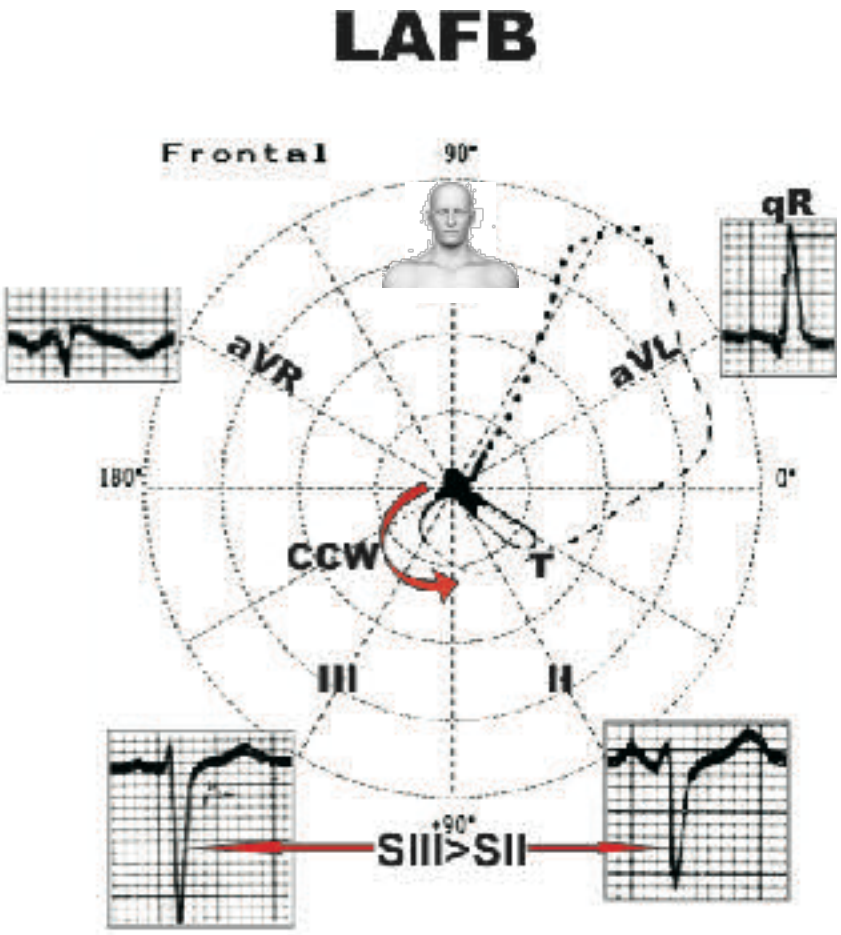

The figure shows the three possible types of QRS loop rotations in BrS in the frontal plane. The type IA with counter clock wise rotation (CCW) of QRS loop and extreme superior QRS axis deviation: Right Superior Fascicular Block.




The figure shows the three hypothetical contingents of fibers (I, II and II) on free wall of right ventricle, and the partial superior right Hissian system affected in BrS: "Right Superior Fascicular Block" (depolarization mechanism.)

# ECG/VCG differential diagnosis between left anterior fascicular block and right superior fascicular block (Pérez Riera 2005)



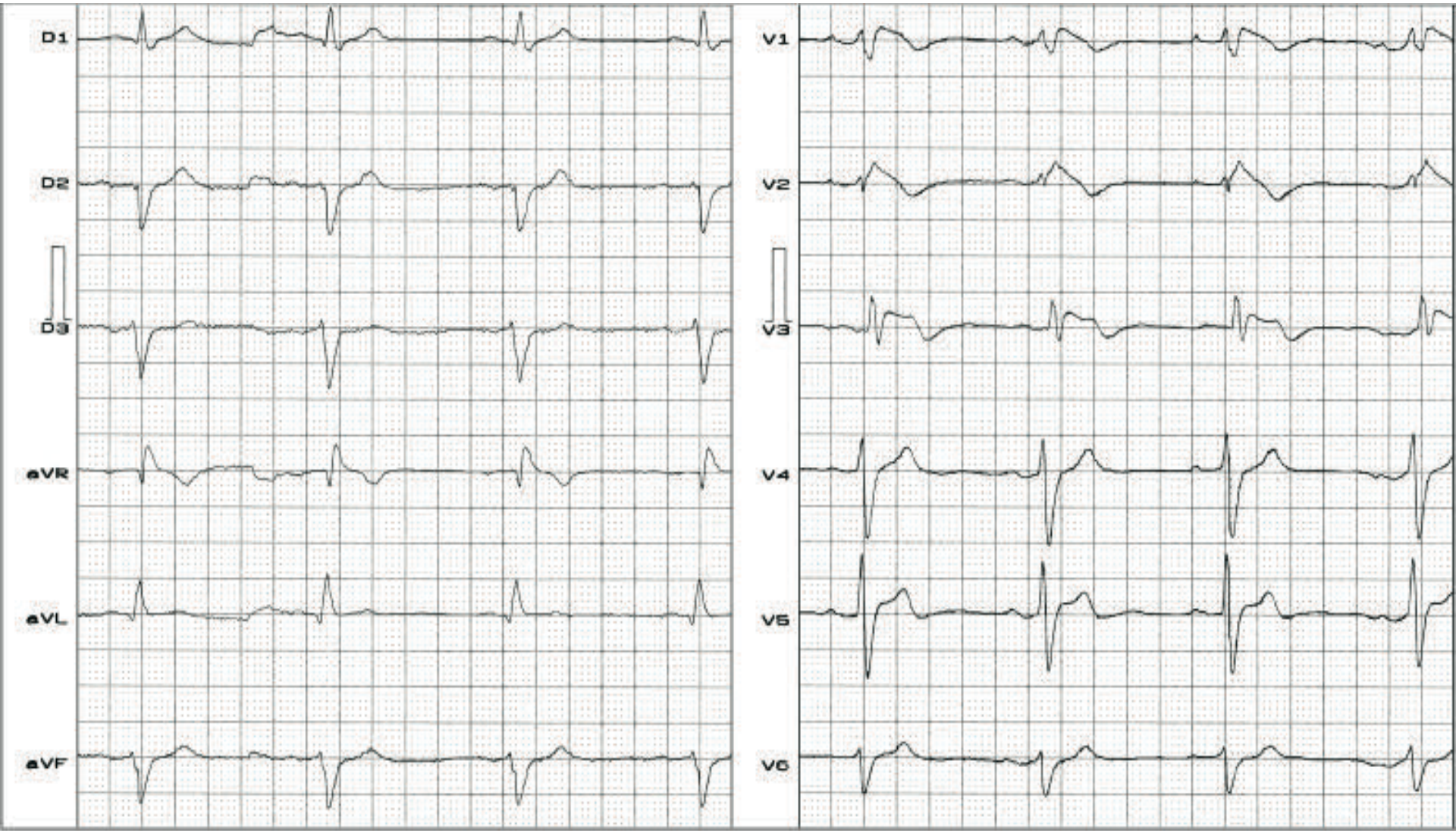




**CCW:** Conter Clock Wise Rotation

- Right Superior Fascicular Block **(RSFB)**
- Left Anterior Fascicular Block **(LAFB)**.

| | LAFB | RSFB |
|---|---|---|
| **Initial 10 ms vector of QRS loop** | Heading downward and to the right | Heading downward and to the left |
| **QRS morphology in I & aVL** | qR pattern | Rs |
| **SII/SIII ratio** | SIII>SII | SII>SIII |
| **Location of end conduction delay (ECD)** | In the left superior quadrant when present | In the right superior quadrant (Pastore 1983) |
| **Prominent R wave in aVR (R-wave ≥ 0.3 mV)** | Absent | It could be present and it is called aVR sign (Babai Bigi 2007). |
| **Morphology of QRS loop of vectorcardiogram in the horizontal plane** | Similar to normal | Similar to type-C right enlargement pattern: initial vector to the front and leftward, counter clockwise rotation and 20% or more of the area of the loop located in the right posterior quadrant in the horizontal plane (Luna Filho 1989) |

**Name:** MK **Age:** 38 y.o; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 68kg; **Height:** 1,70m



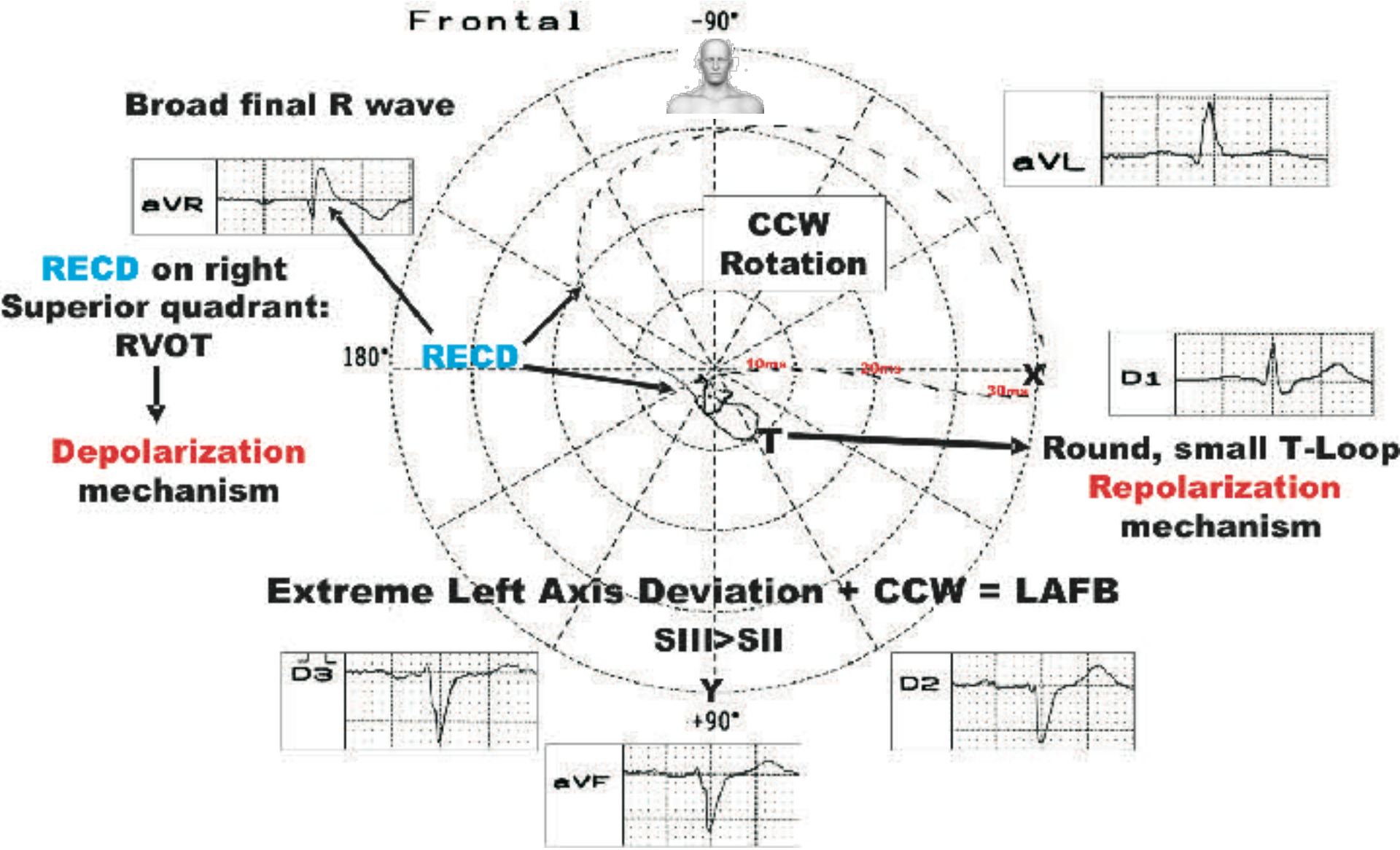

**Clinical diagnosis:** Syncope. Positive familiar background of sudden death in young (≤35yo) first-degree relative. Genetic research performed: negative.

**ECG disgnosis:** Sinus bradychardia (HR < 60 bpm), Brugada type 1 ECG pattern, prolonged QRS duration, aVR signal : final R wave of aVR lead >3mm, fQRS in V1-V2.

Extreme left axis deviation: Left anterior fascicular block? or Right superior fascicular block?

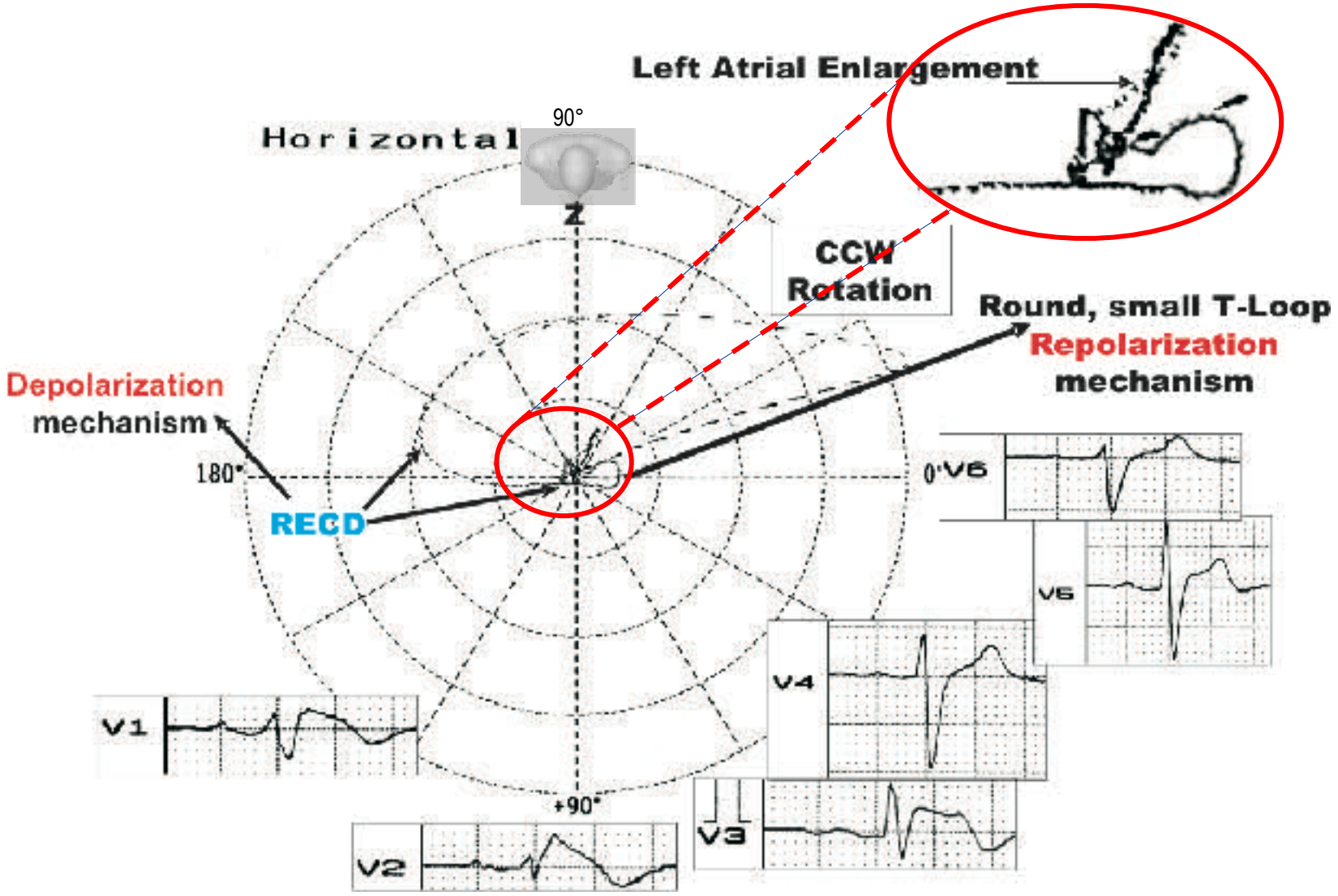
# ECG/VCG correlation in the frontal plane

**Name:** MK; **Age:** 38yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 68kg; **Height:** 1,70m



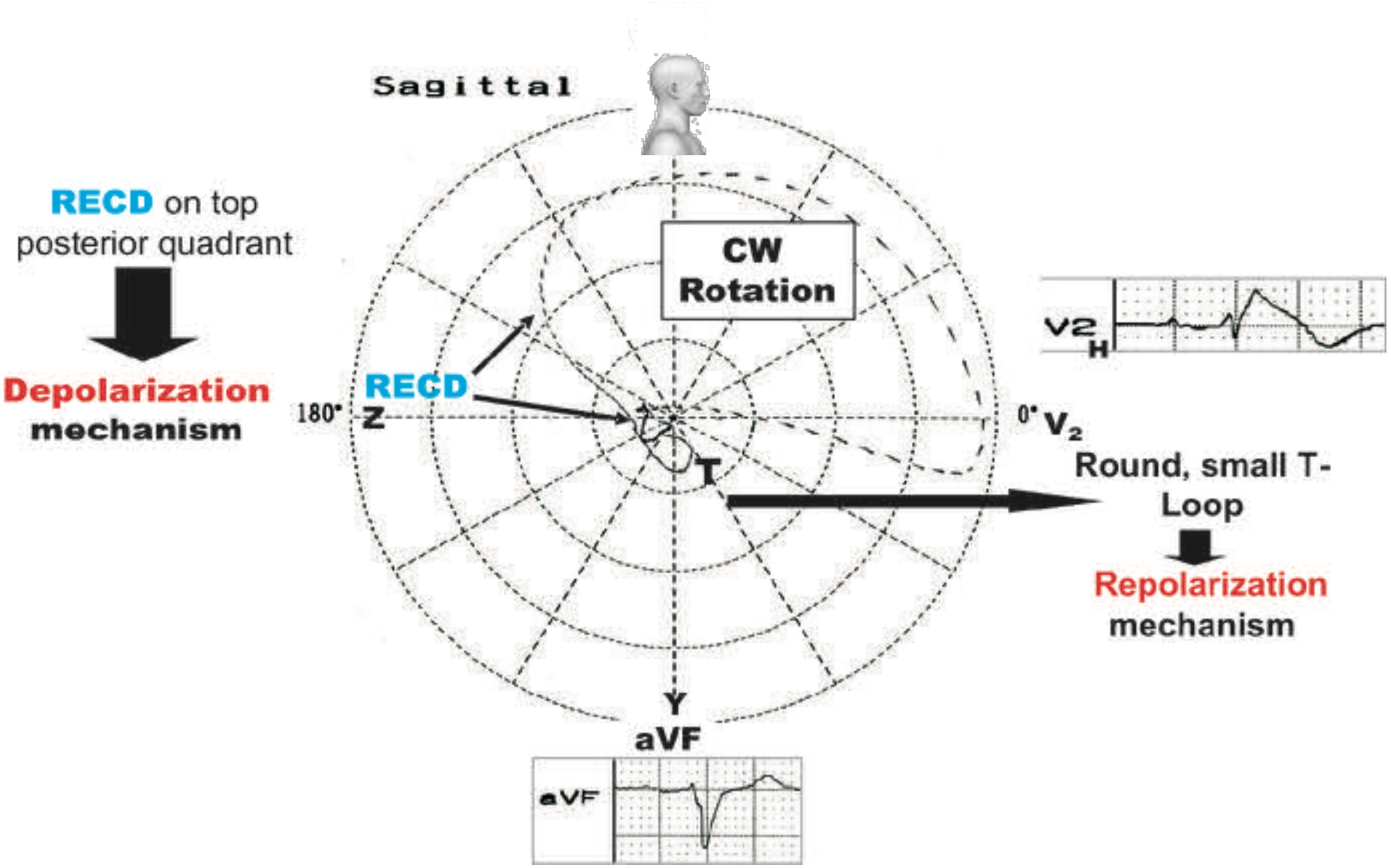
# ECG/VCG correlation horizontal plane

**Name:** MK; **Age:** 38yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 68kg; **Height:** 1,70m.



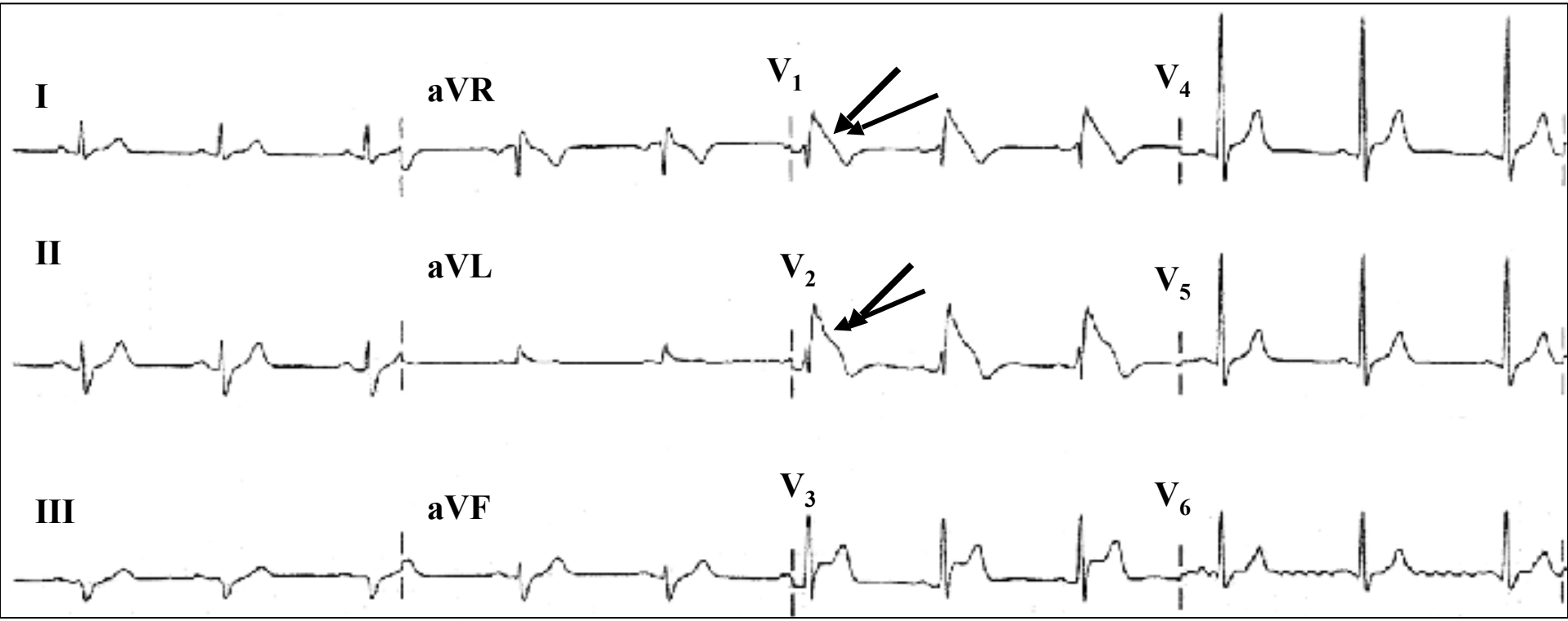
# ECG/VCG correlation in the right sagittal plane

**Name:** MK; **Age:** 38yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 68kg; **Height:** 1,70m



# ECG with typical type 1 Brugada pattern and final part broadening by superior fascicle block of RBBB

Male, 56-year-old patient (03/16/2002). He complained of atypical precordial pain.

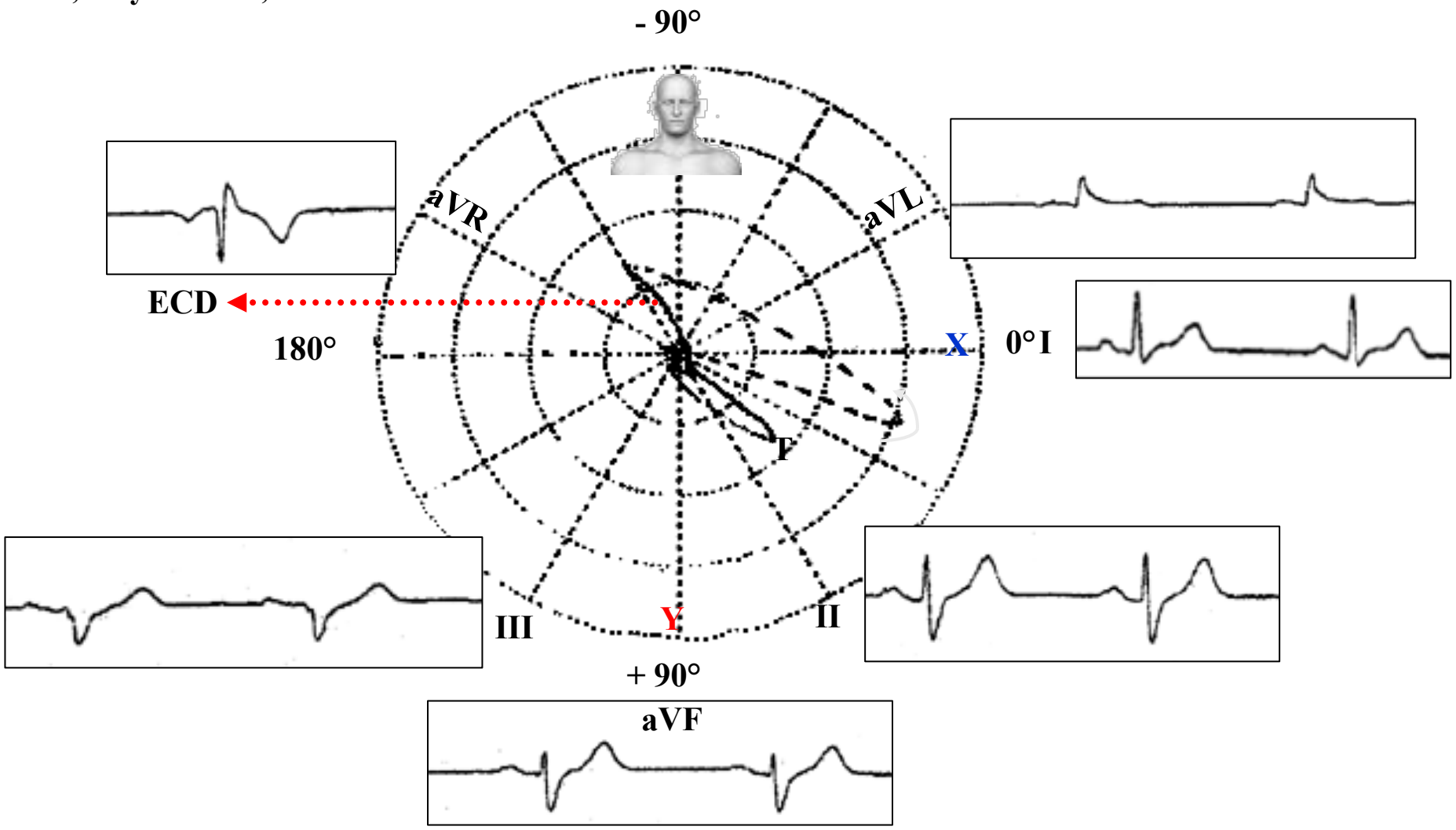



Final part widening by the superior, anterosuperior or subpulmonary fascicle of the RBBB, type I according to our classification. Extreme shift of SAQRS to the left in the left superior quadrant –45°. ST segment and J point elevation with convex to the top morphology in $V_1$ and $V_2$ and saddle type in $V_3$. aVR with D wave broadening: "crista delay" or RV outflow tract widening. S waves in left precordial leads $V_5$-$V_6$. SII >SIII. This information is very important for a differential diagnosis with left anterior fascicular block. Structural heart disease was not detected with noninvasive and invasive methods.

**Conclusion:** ECG with typical Brugada type 1 pattern, and final part widening by superior fascicle block of RBBB.

# ECG/VCG correlation of Brugada syndrome in the frontal plane

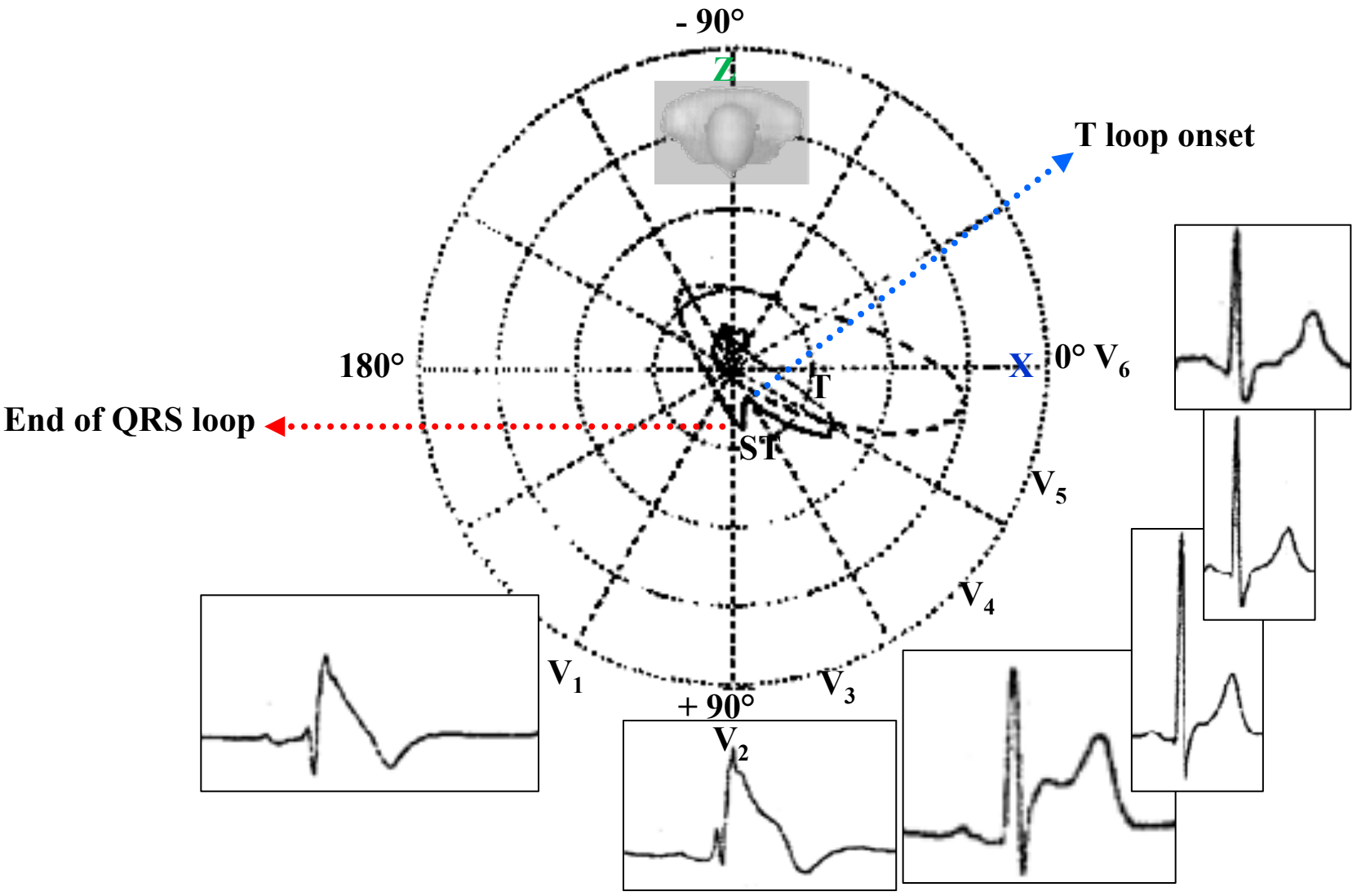
**Male, 56 years old; Date: 03/16/2002.**




**Conclusion**: it is the first VCG of Brugada syndrome shown in world literature. End conduction delay (ECD) by superior fascicle of RBBB. Type IA of our classification.

# ECG/VCG correlation of Brugada syndrome in the horizontal plane

**Male, 56 years old; Date: 03/16/2002.**

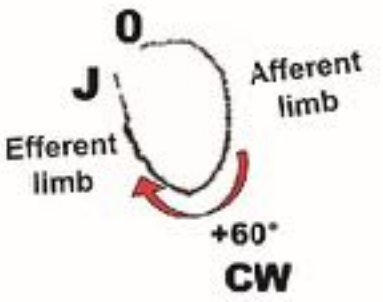



The end of QRS loop does not coincide with T loop onset (as it occurs in normal conditions) since there is elevation both in the J point and the ST segment.

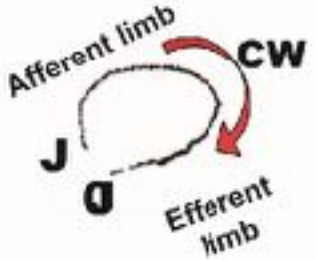
# T LOOPS CHARACTERISTICS IN ALL THREE GROUPS

## GROUP I
**Type-1 Brugada ECG Pattern**

**Frontal Plane**

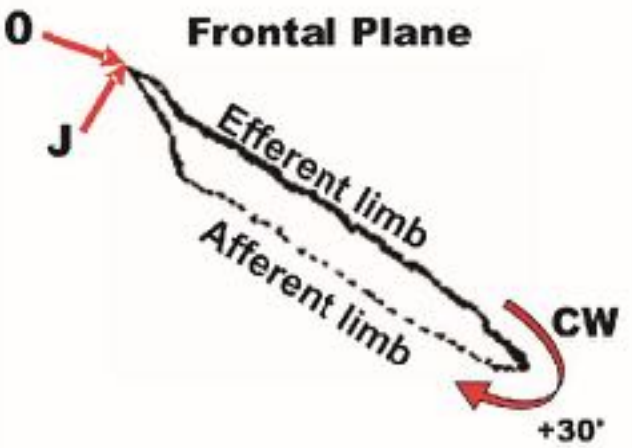



**Horizontal Plane**




## GROUP II
**IRBBB**

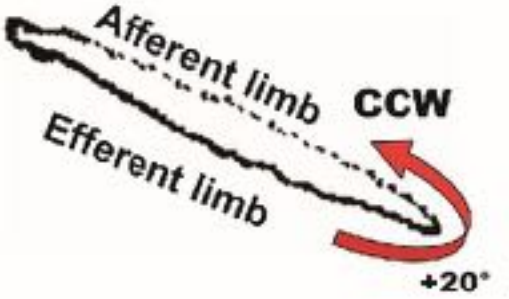
**Frontal Plane**



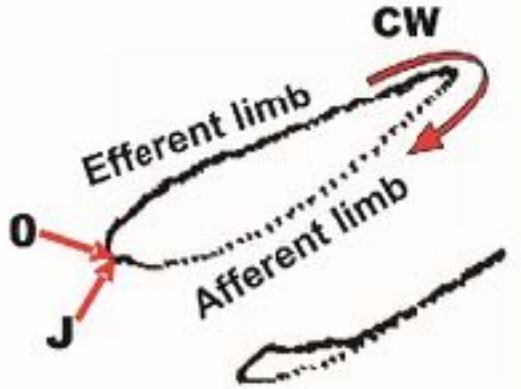

**Horizontal Plane**


## GROUP III
**CRBBB**

**Frontal Plane**

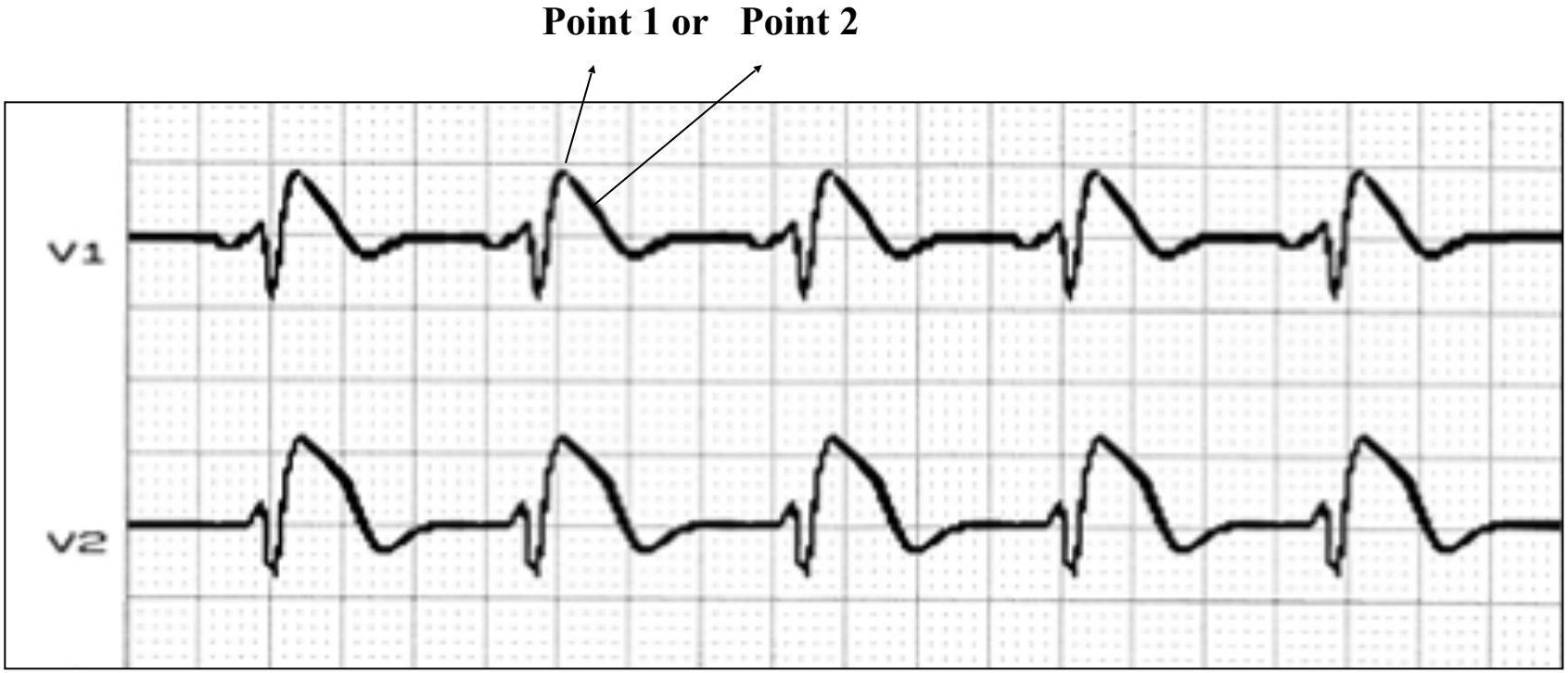



**Horizontal Plane**



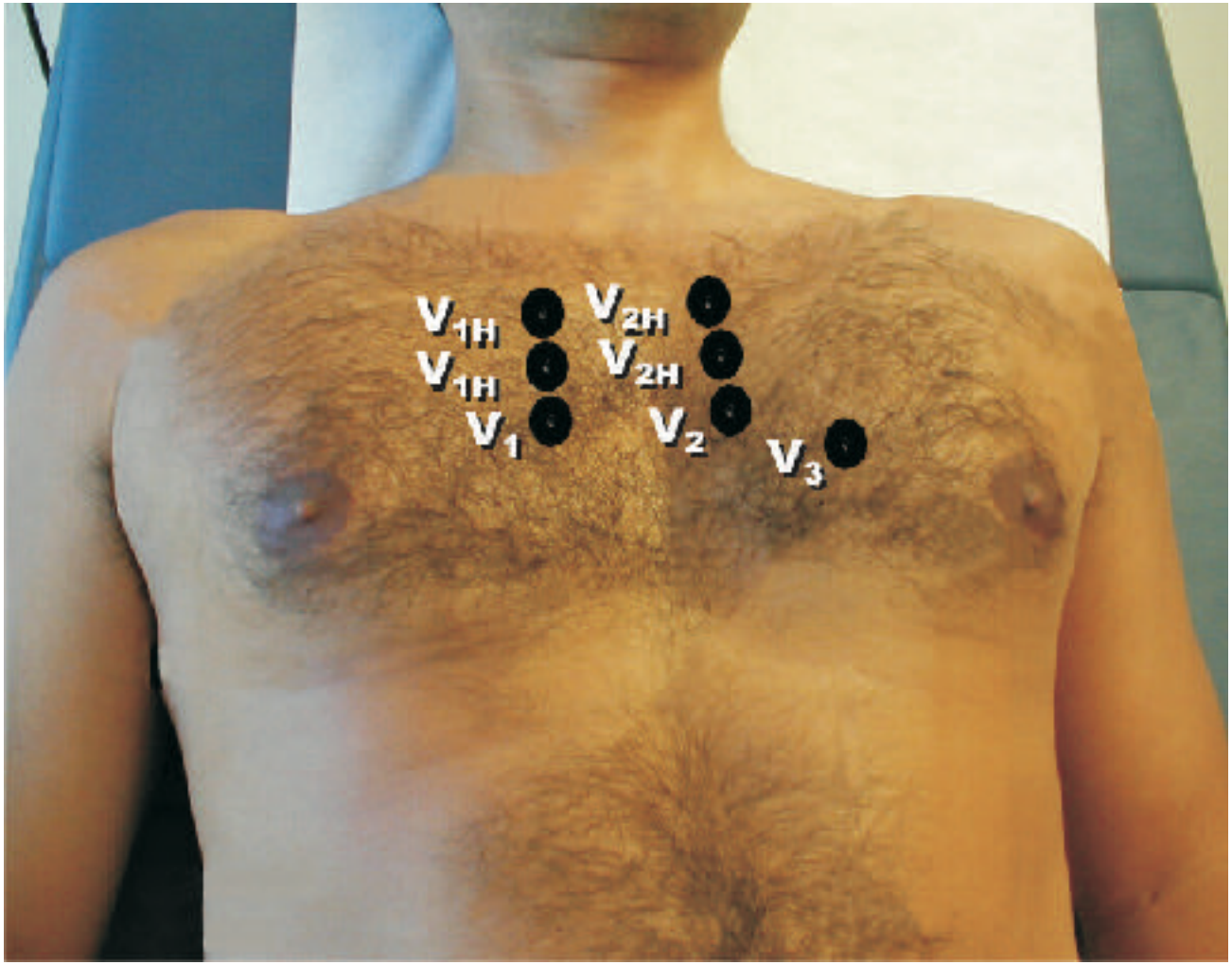

**CW:** Clockwise Rotation, **CCW** Conterclockwise Rotation

# Where is the end of QRS complex?




**Answer: point 2**

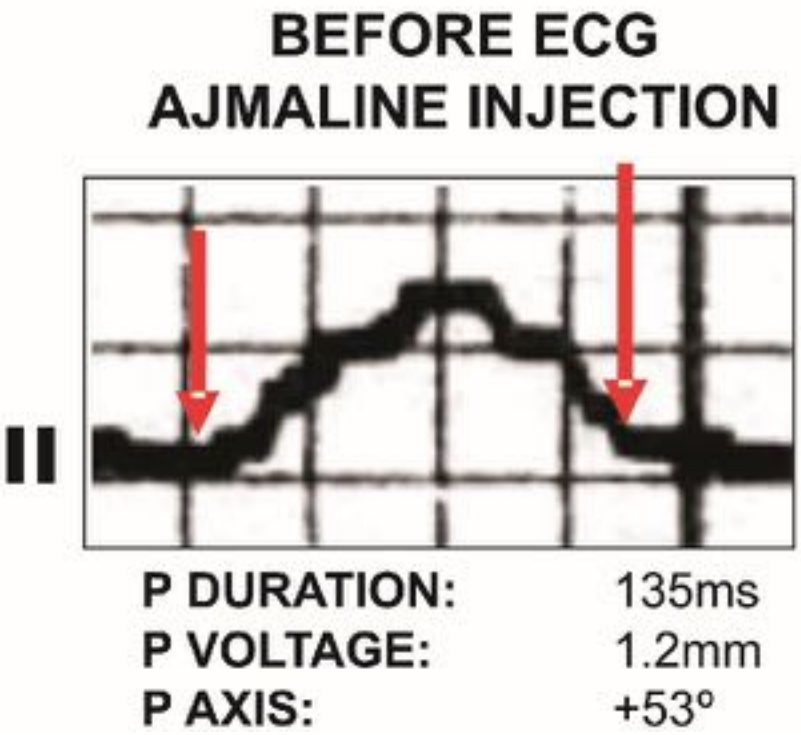
# Localization of right precordial leads and accessory high parasternal leads (Butz 2010)

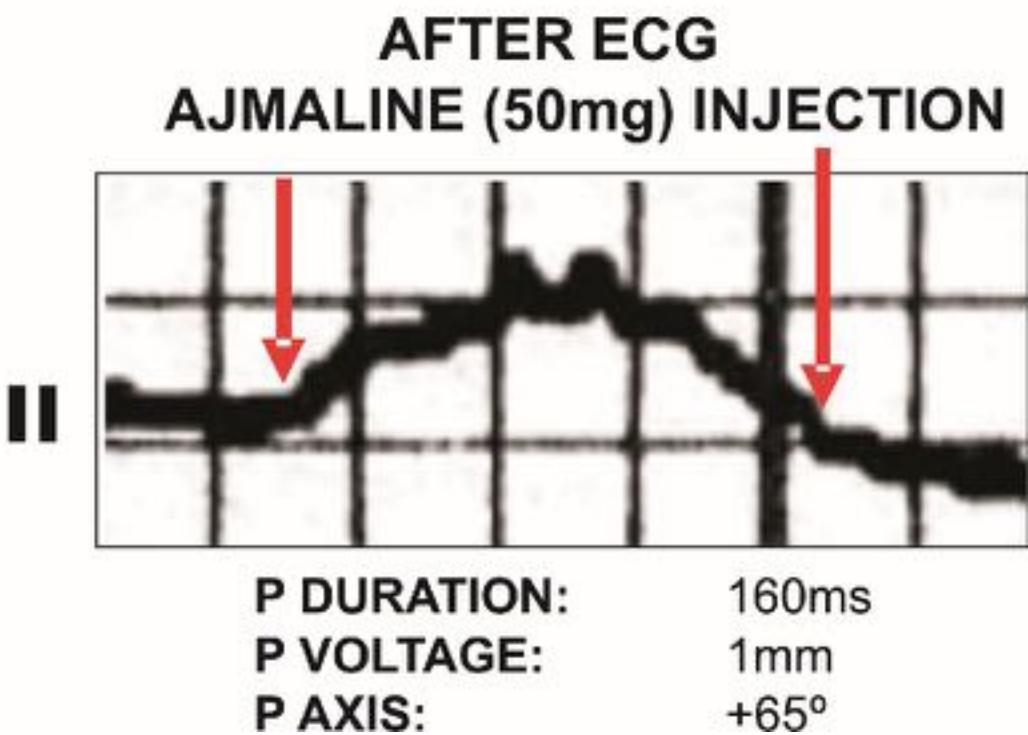



$V_1$ – over the 4th intercostal space, just to the right of the sternum.
$V_2$ – over the 4th intercostal space, just to the left of the sternum
$V_3$ – midway between V2 and V4.
$V_{1H}$ – over the 3rd or 2nd intercostal space, just to the right of the sternum.
$V_{2H}$ – over the 3rd or 2nd intercostal space, just to the left of the sternum.

# ECG markers in identifying patients at risk in the Brugada syndrome

1. Augmented P-wave duration in lead II, P-wave dispersion (Letsas 2009).
2. PR prolongation consequence of HV split or HV prolongation (Miyamoto 2011).
3. Presence of prominent final R wave on aVR lead R wave ≥ 3 mm or R/q ≥ 0.75 in lead aVR (aVR sign). Slow conduction at the RVOT may contribute to the induction of VF by PVS (Babai Bigi 2007).
4. The presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period < 200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic ICD (Priori 2012).
5. Inferolateral early repolarization (Kamakura 2009).
6. Prolonged QRS duration measured from lead II or lead V2 ≥ 120ms (Junttila 2008).
7. QTc interval more than 460 ms in lead V2 (Take 2011) and QT-interval prolongation in right precordial leads (Pitzalis 2003). Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block.
8. $T_{peak} - T_{end}$ prolongation and $T_{peak} - T_{end}$ dispersion (Castro Hevia 2006).
9. Dynamic alterations in the amplitude of the ST elevation (Take 2011).
10. Loss of rate-dependent QT dynamics (Sangawa 2009).
11. The presence of horizontal (as opposed to rapidly ascending) ST segment after the J point (Takagi 2013).
12. Augmentation of the ST segment elevation during the early recovery phase of exercise test (Makimoto 2010).
13. Deep negative T wave in lead V1 (Miyamoto 2011).
14. The presence of atrial fibrillation (Kusano 2008).
15. The presence of Late potentials (LPs) (Ikeda 2001).

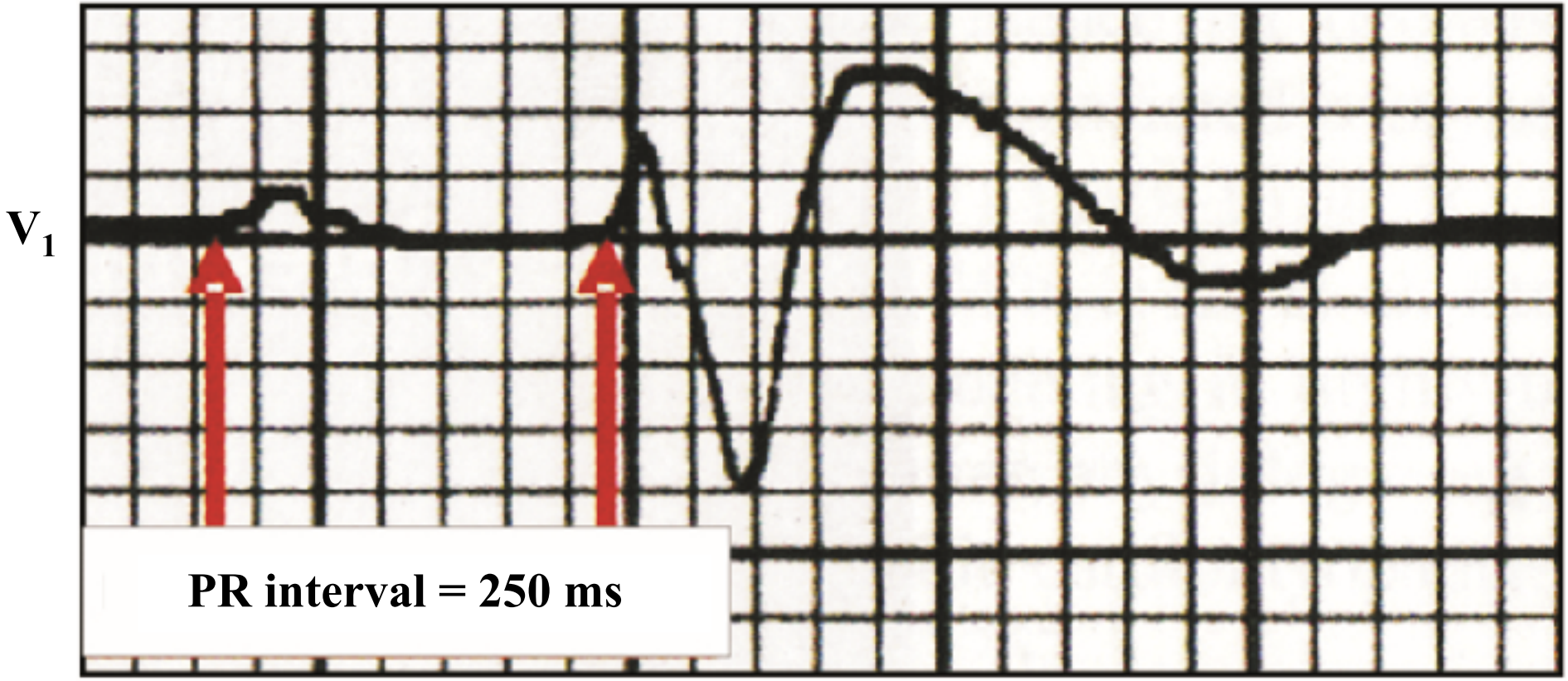



The tracing shows the P wave in a patient with BrS and positive SNC5A mutation preformed before and immediately after ajmaline test (1mg/kg).

P wave duration (Pd) before the injection is prolonged (Pd=135ms). After drug administration Pd wave increase more (Pd=162ms).

These atrial dromotropic disorders could be the substrate for reentrant atrial tachycardias such as AF.

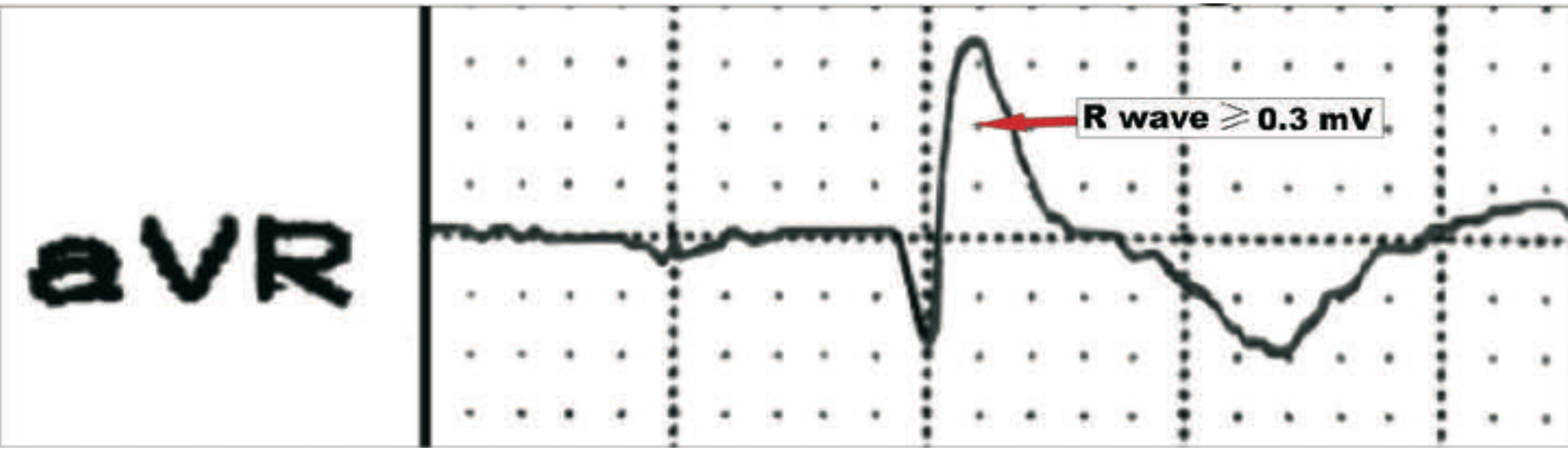



The figure shows a tracing of a symptomatic patient with Brugada syndrome after intravenous ajmaline injection. First-degree atrioventricular block (PR interval = 216 ms) and Brugada type-1 ECG pattern in $V_1$ lead (positive test).

In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes figures of 100msec (**Yokokawa 2007**). This prolongation of the PR interval is observed predominantly in cases where the SCN5A gene mutation can be proven (carriers). The presence of a prolongued HV interval is possible in HBE by the existence of intra-His or infra-His block.

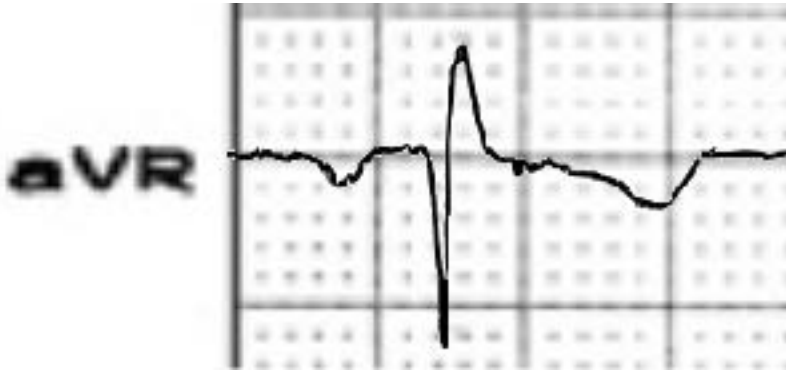
PR prolongation consequence of HV split or HV prolongation is considered another ECG risk marker (**Miyamoto 2011**).

# The aVR sign

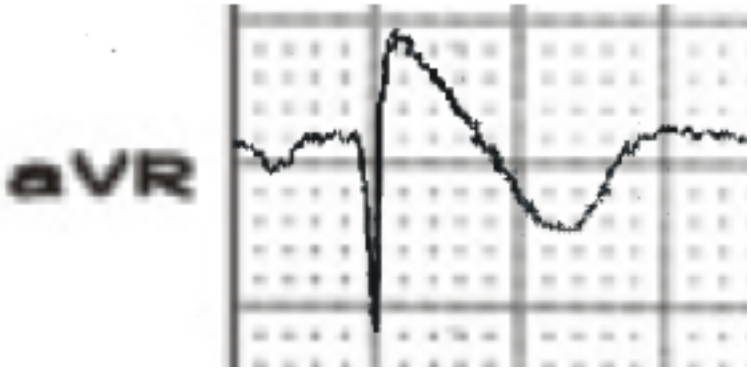



**aVR sign: final R wave of aVR lead >3mm**

**A** **Date:** Friday September 30, 2011.

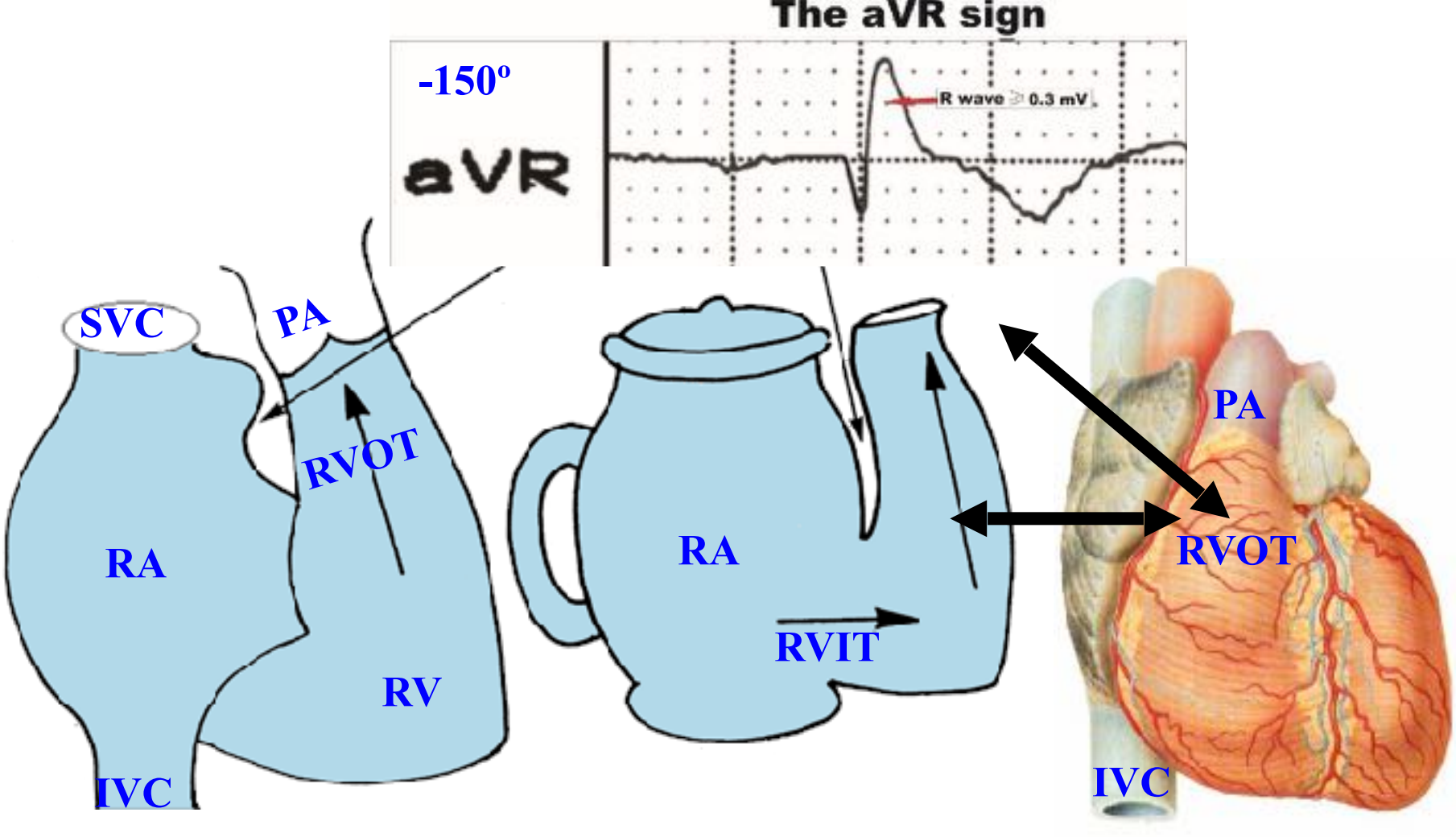



**B** **Date:** Tuesday October 4, 2011.



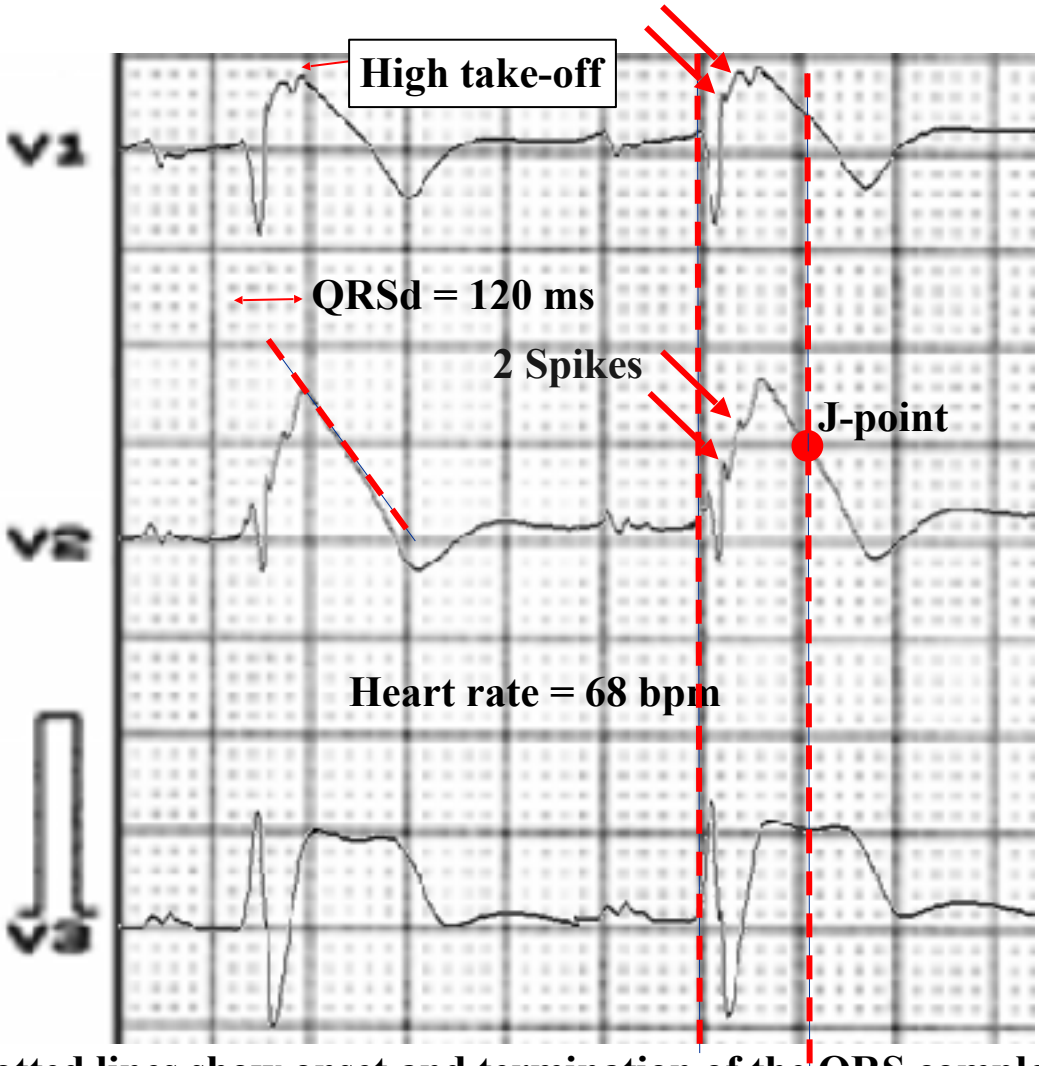

**Terminal broad R-wave of the QRS complex in lead aVR (Babai Bigi 2007)**

The aVR sign: Presence of prominent final R wave on aVR lead R wave ≥ 3 mm or R/q ≥ 0.75 in lead aVR (aVR sign). Slow conduction at the RVOT may contribute to the induction of VF by PVS.




The BrS affects predominantly the right ventricle in the right ventricle outflow tract (RVOT) epicardium (Doi 2010). The larger part of clinical evidence supports the presence of right end conduction delay (RECD) as part of the process of BrS pathophysiology in the RVOT, as a consequence of structural abnormalities in the heart as part of BrS (Coronel 2005). On the other hand, in the concealed forms of arrhythmogenic right ventricular cardiomypathy/ dysplasia (ARVC/D), the RECD pattern can also be observed showing type-1 ECG pattern. This pattern was shown many years ago by Guy Fontaine et al (Hayashi 2010).

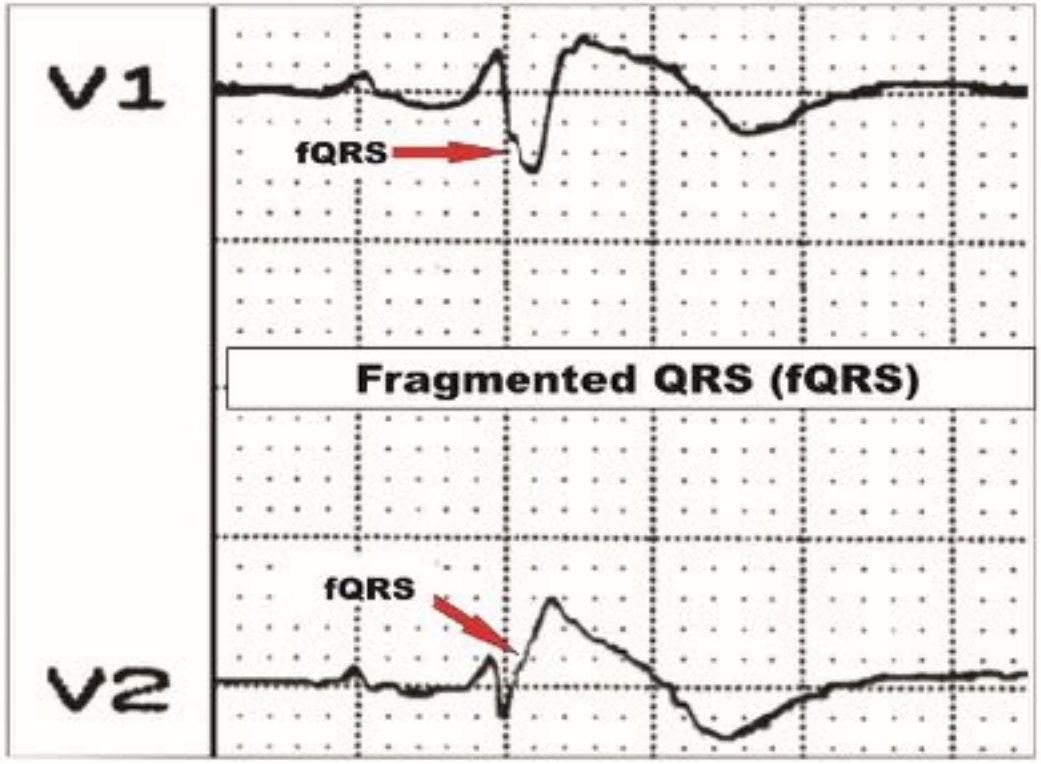
# Fragmented QRS in Brugada Syndrome




Two spikes are observed at the upstroke of the S wave in leads $V_1$ and $V_2$.

**Dotted lines show onset and termination of the QRS complex**

Fragmented wide QRS complex in a 35-year-old Asian male patient with BrS. f-QRS appears to be a marker for the substrate for spontaneous VF in BrS and predicts patients at high risk of syncope. It is a conduction abnormality within the QRS complex (**Morita 2008**).



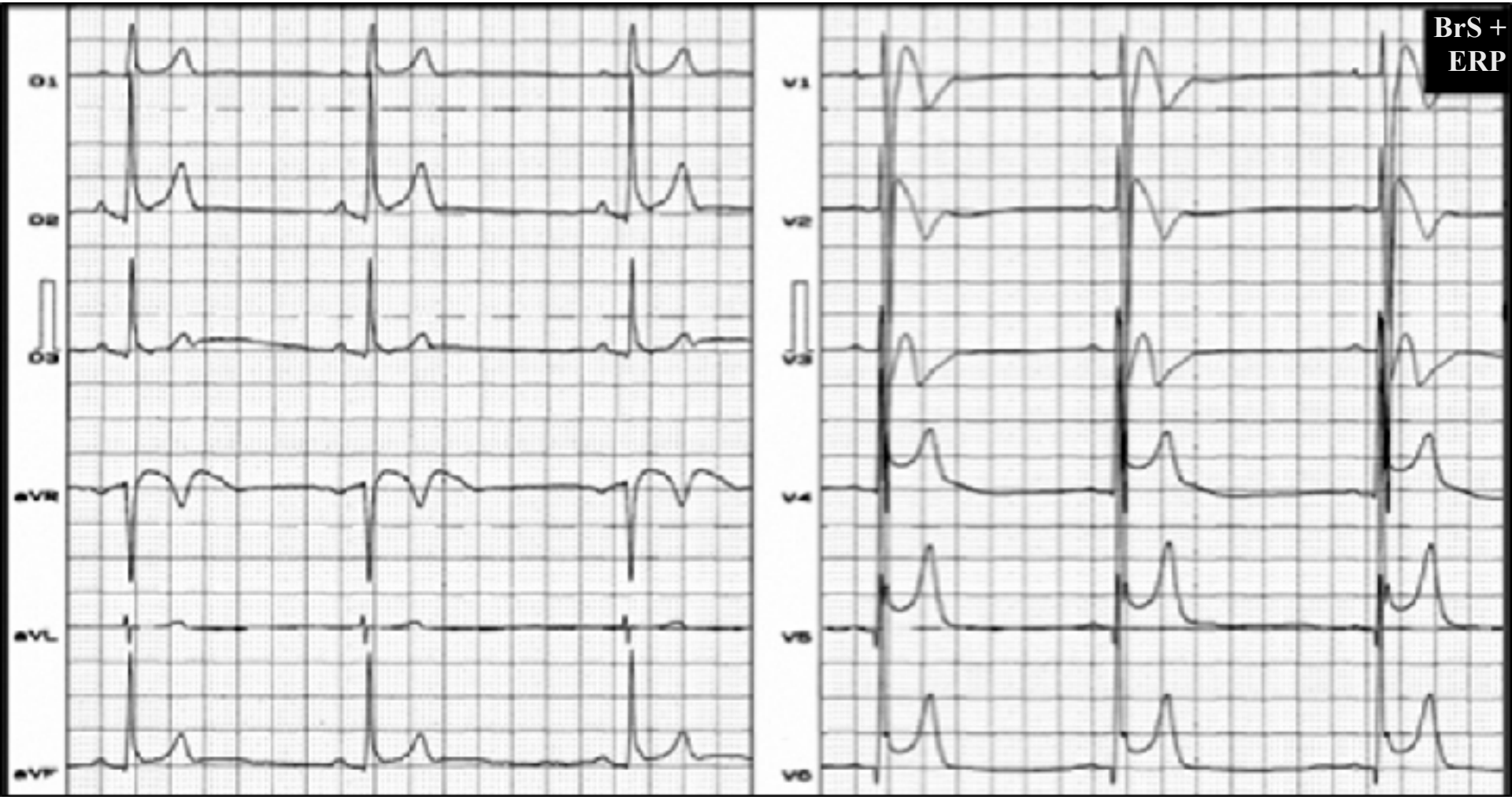

Presence of a "notch" within a non-wide QRS complex in two adjacent leads ($V_1$-$V_2$.): f-QRS. It is a non-invasive marker of events (Das 2009).

## Entities where fQRS is used as non-invasive marker of events (Das 2009)

- **Coronary artery disease (Das 2010)** where it represents a conduction delay of the stimulus and is associated to an increase in mortality and arrhythmic events in these patients.
- **Non-ischemic cardiomyopathies (Das 2010). In non-ischemic dilated cardiomyopathy with narrow QRS to predict dyssynchrony (Tigen 2009)**
- **Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (Peters 2008)**
- **Cardiac sarcoidosis (Homsi 2009)**
- **Congenital heart diseases (Moss 2010)**
- **Brugada syndrome (Haraoka 2010)**
- **Acquired long QT syndrome (Yuce 2010)**

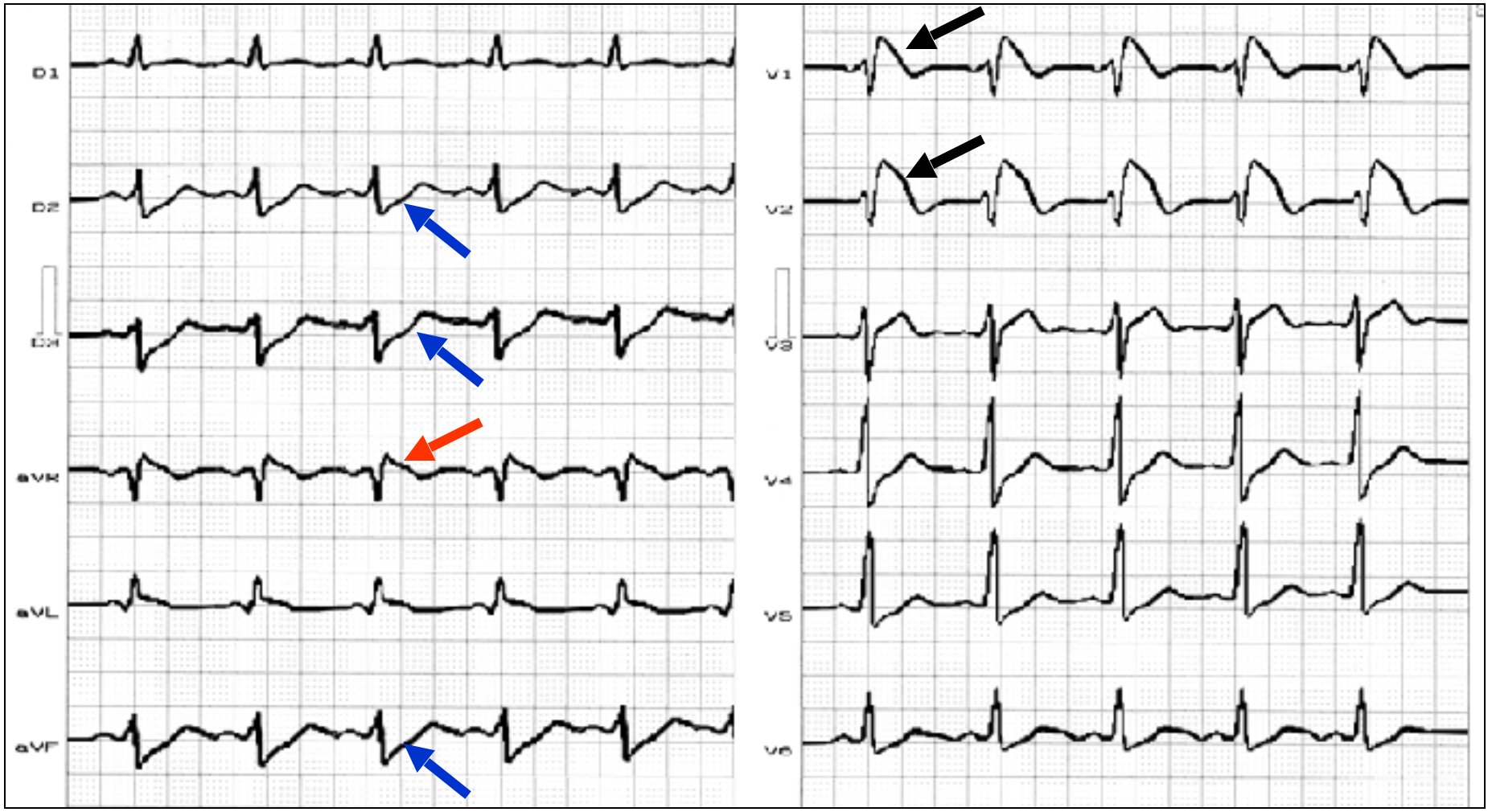
The existence of fQRS plays an important role in the appearance of Torsades de Pointes (TdP) in patients with acquired long QT interval.

# Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities



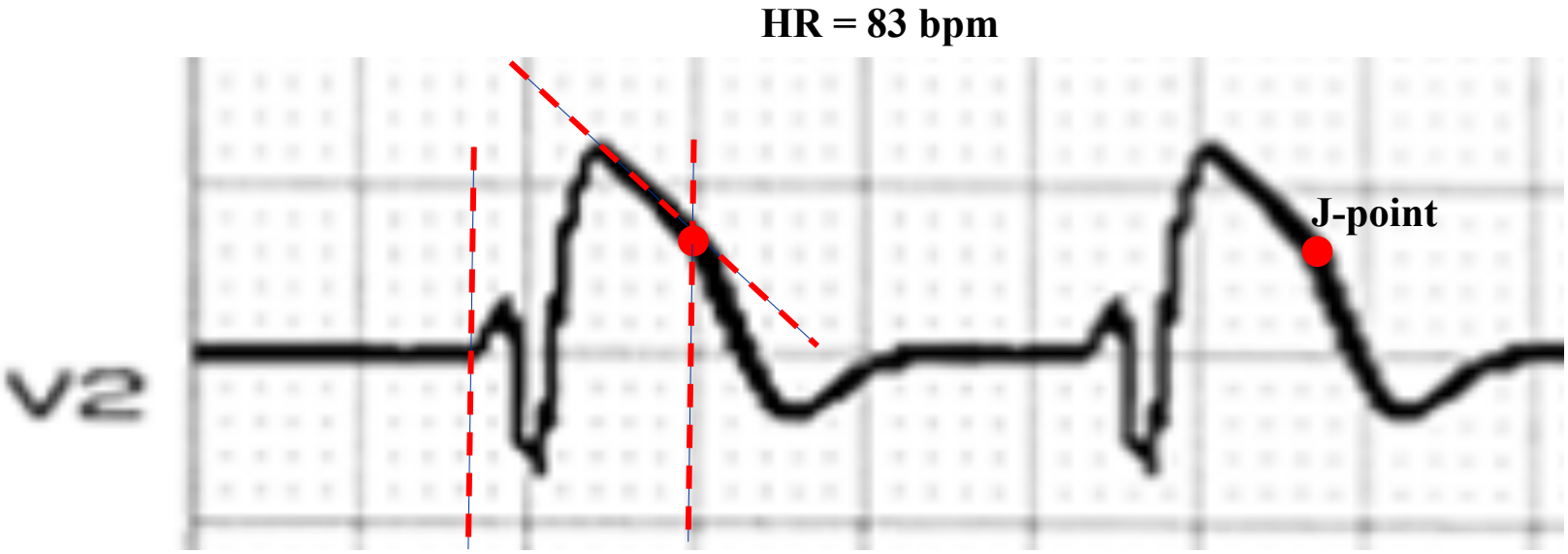

Coexistence ECG that shows concomittant early repolarization pattern in inferior lateral leads associated with type 1 Brugada pattern in Young soccer player Caucasian man (**McIntyre 2012**).

# Typical ECG of Brugada Syndrome

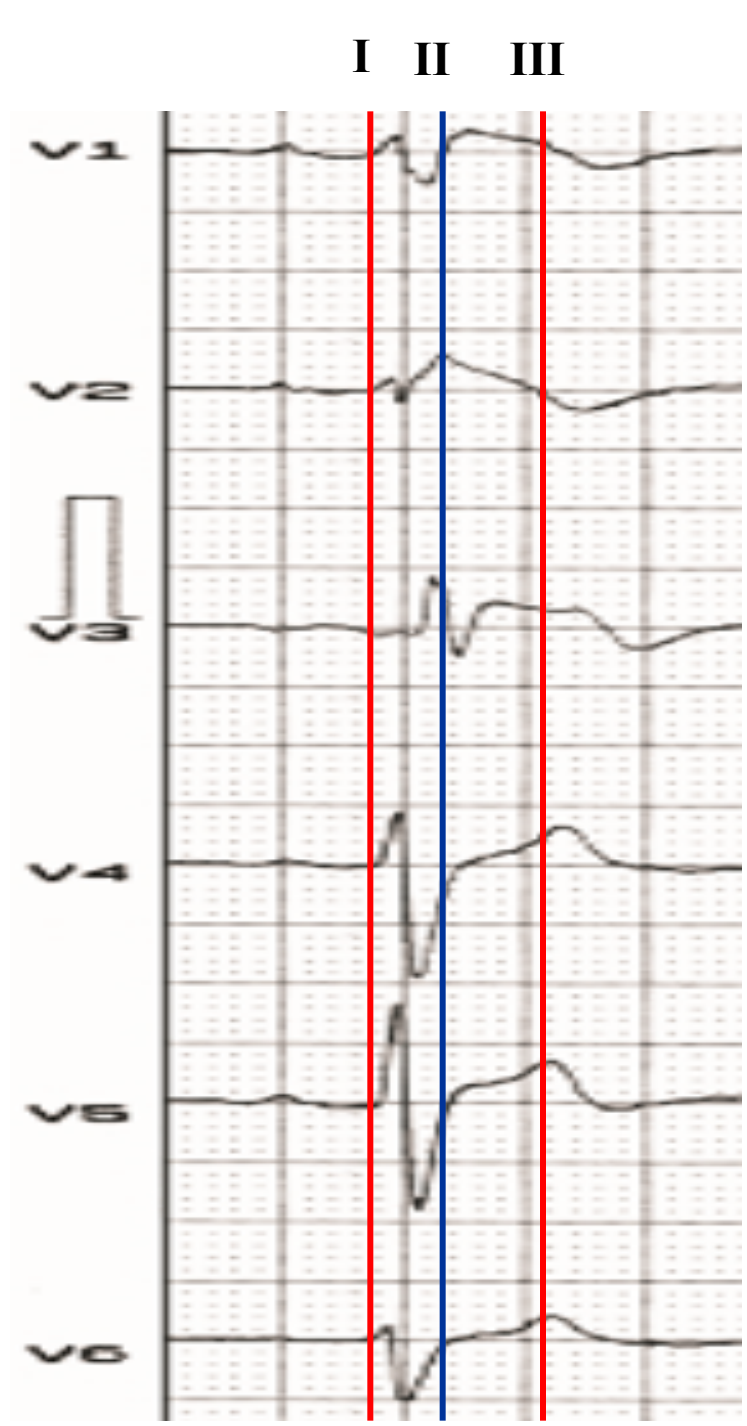



J point and ST segment elevation, convex to the top, ST segment in right precordial leads from $V_1$ through $V_2$ (black arrows): Brugada sign or idiopathic J wave. Unipolar aVR lead that heads toward the RV epicardium above the outflow tract, which shows subtle ST segment and J point elevation (red arrows). Inferior leads show reciprocal or mirror images (blue arrows).

# Prolonged QRS duration measured from lead II or lead V2 ≥ 120ms (Junttila 2008)



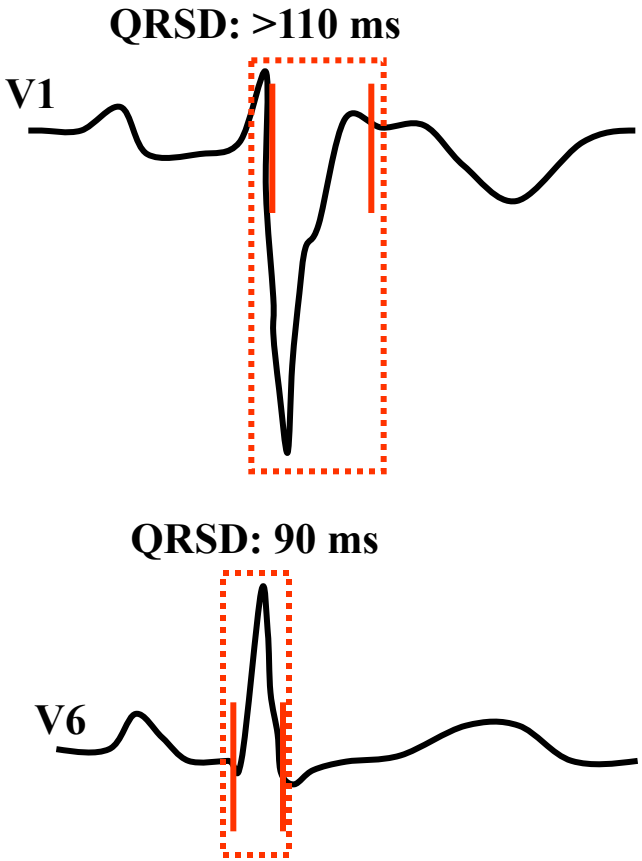

**Vertical dotted lines show onset and termination of the QRS complex in V2.**
**In this case QRSd = 165 ms. It is an ECG marker of events.**



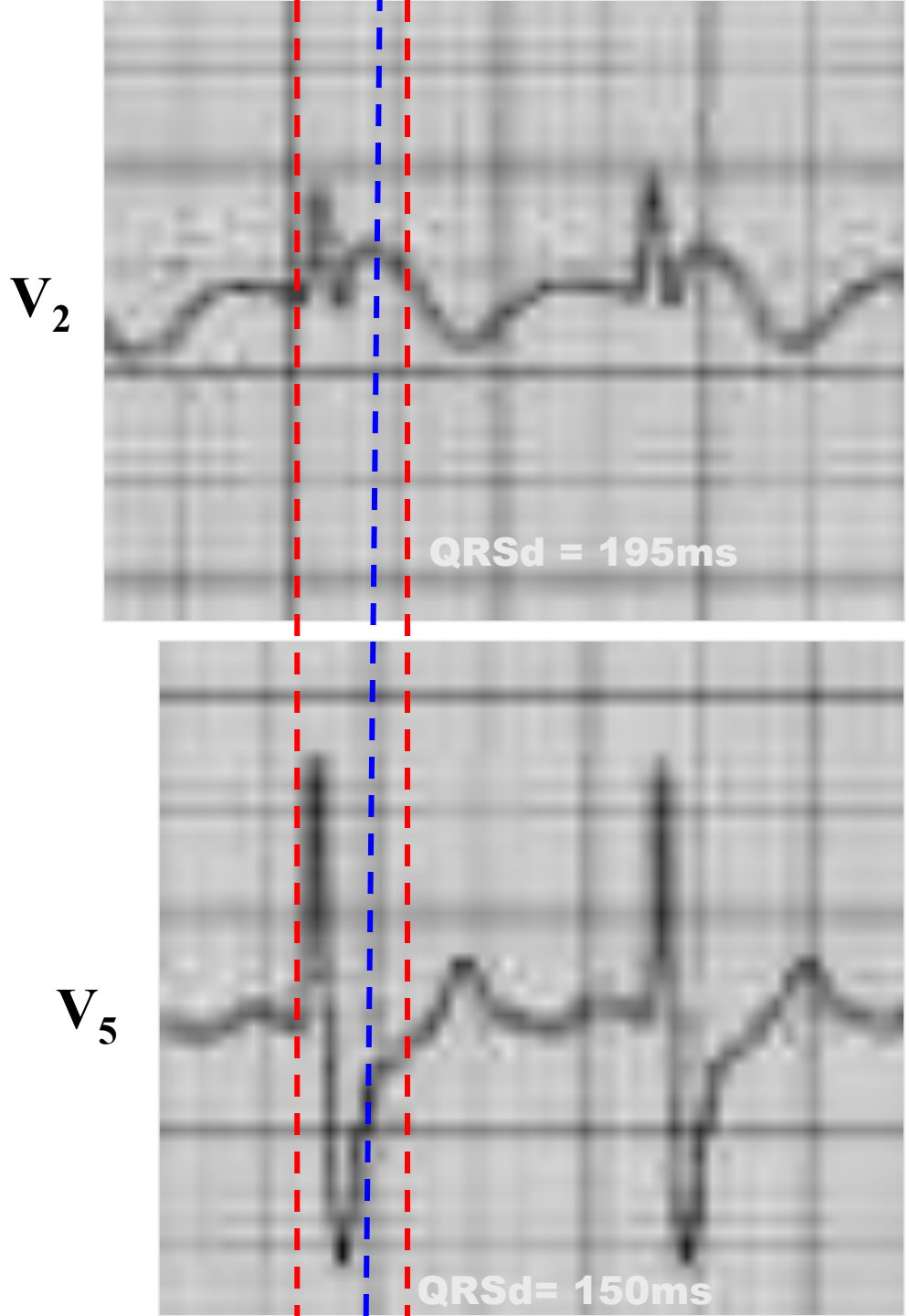

**Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block**

I: Onset of the QRS complex
II: Termination of the QRS complex from V4-V6
III: Termination of the QRS complex from V1-V3

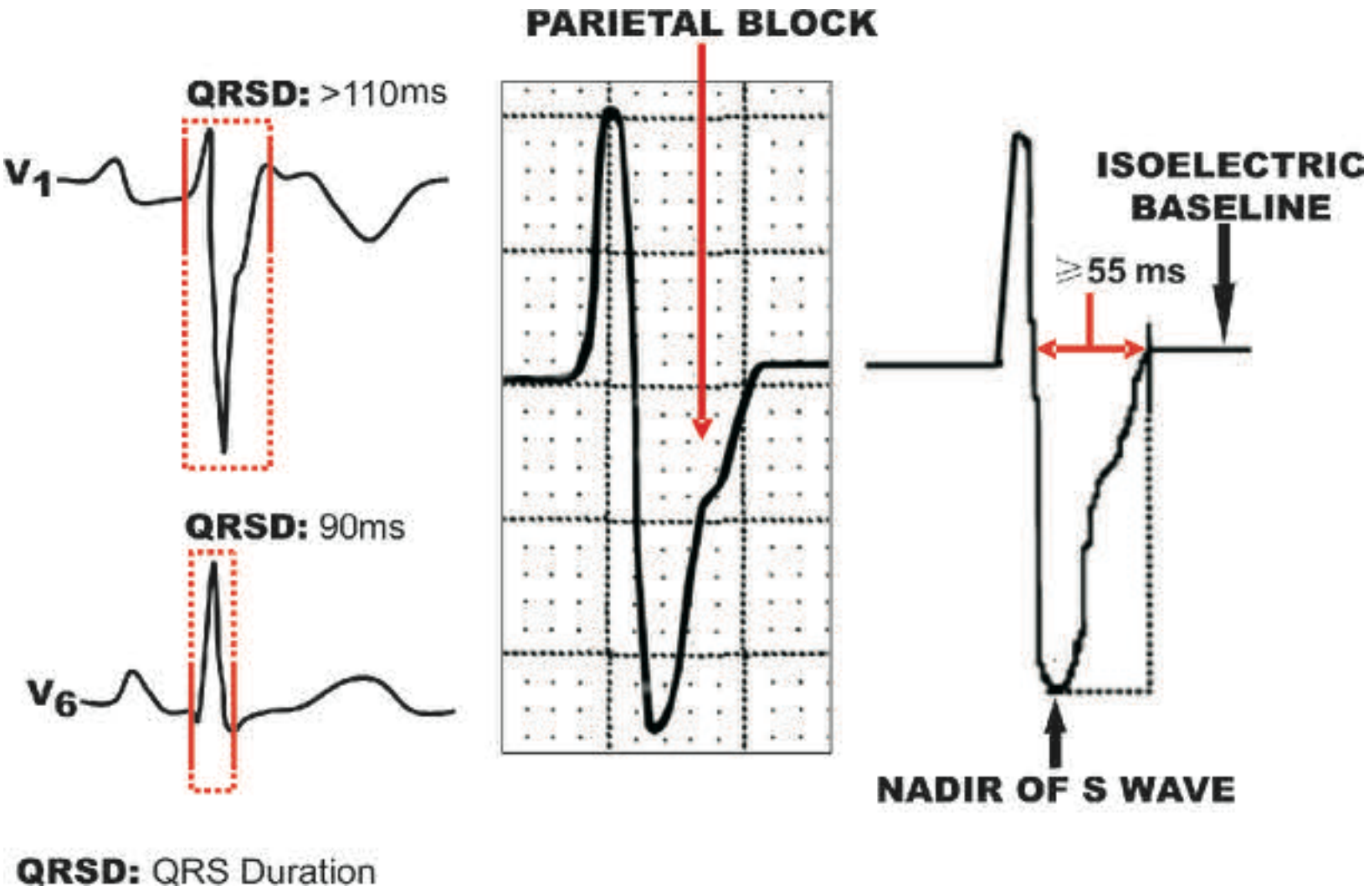
QRSD of $^{V1+V2+V3}/_{V4,V5,\ V6} \geq 1.2$. This feature is considered typical of ARVC/D, but it is also observed in BrS (Pitzalis 2003).




50 mm/s 20 mm/mV



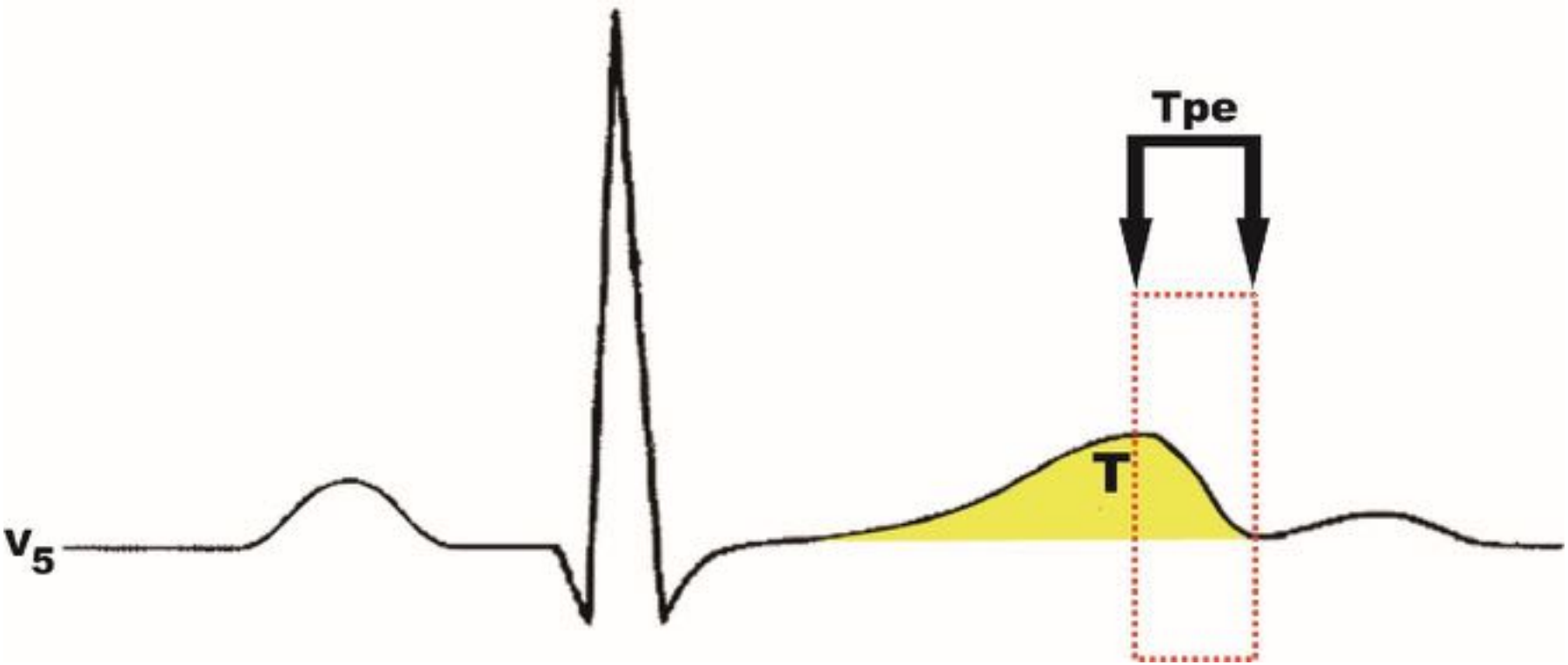

Pitzalis et al (Pitzalis 2003) identified selective prolongation of QT interval duration in the right precordial leads ($V_1$ to $V_3$) in comparison to the left ones (V4 to V6). As the QT interval is made up by ventricular depolarization (QRS) plus ventricular repolarization (ST/T) we think that this selective prolongation represents a certain degree of parietal block in the RVOT, as the one observed in ARVC/D. If the QT interval is prolonged only from V1 to V3, being normal or lesser from V4 to V6, it is clear that this increase may be due to prolongation of ventricular depolarization (QRS complex) and/or by ST/T prolongation (repolarization). If we admit that in BrS there is some degree of branch block, clearly the QT interval prolongation is due partly to this. The QTc interval constitutes the classical measurement for ventricular repolarization; however, this parameter includes ventricular depolarization (QRS), and therefore represents the so-called electric systole, which includes depolarization (QRS) and ventricular repolarization (ST/T = JT interval).




Pitzalis et al (Pitzalis 2003) identified selective prolongation of QT interval duration in the right precordial leads ($V_1$ to $V_3$) in comparison to the left ones (V4 to V6). As the QT interval is made up by ventricular depolarization (QRS) plus ventricular repolarization (ST/T) we think that this selective prolongation represents a certain degree of parietal block in the RVOT, as the one observed in ARVC/D.

# $T_{peak} - T_{end}$ prolongation and $T_{peak} - T_{end}$ dispersion

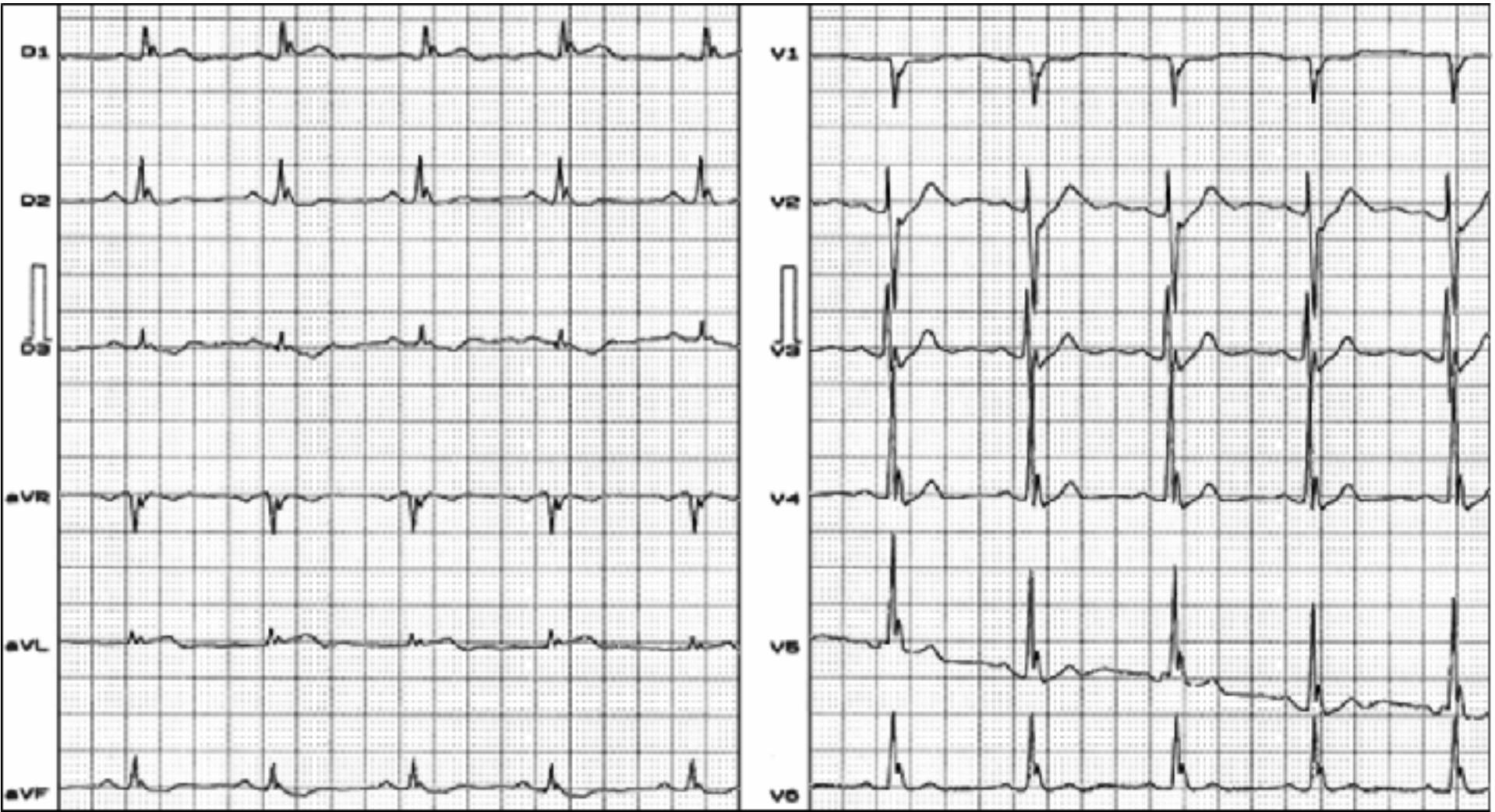
The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the $V_5$ lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patients carriers of BrS



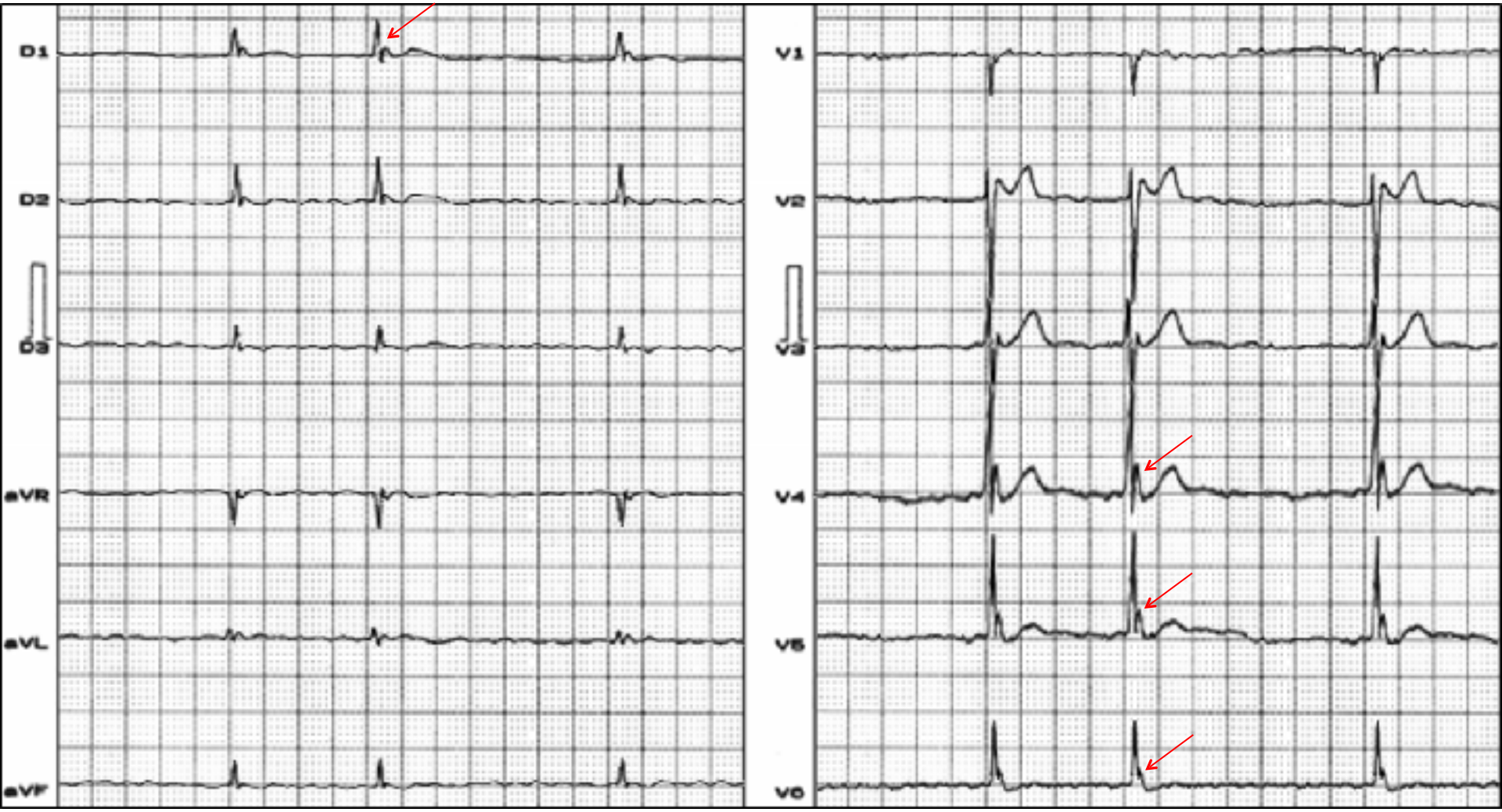

Interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias.

Bigi et al. (Bigi 2007) studied the clinical predictors of AF in BrS. Of the 28 patients with Type 1 ST-segment elevation ECG pattern, 15 had paroxysmal AF. All of them had previous life-threatening cardiac events (8 had syncope, 2 had VF, 4 had polymorphic VT, and 1 had aborted SCD). Multiple regression analysis did not show any correlation between various parameters such as left atrial size, age, and P-wave dispersion. The authors concluded that the history of previous life threatening cardiac events is the strongest predictor of AF in Brugada syndrome.

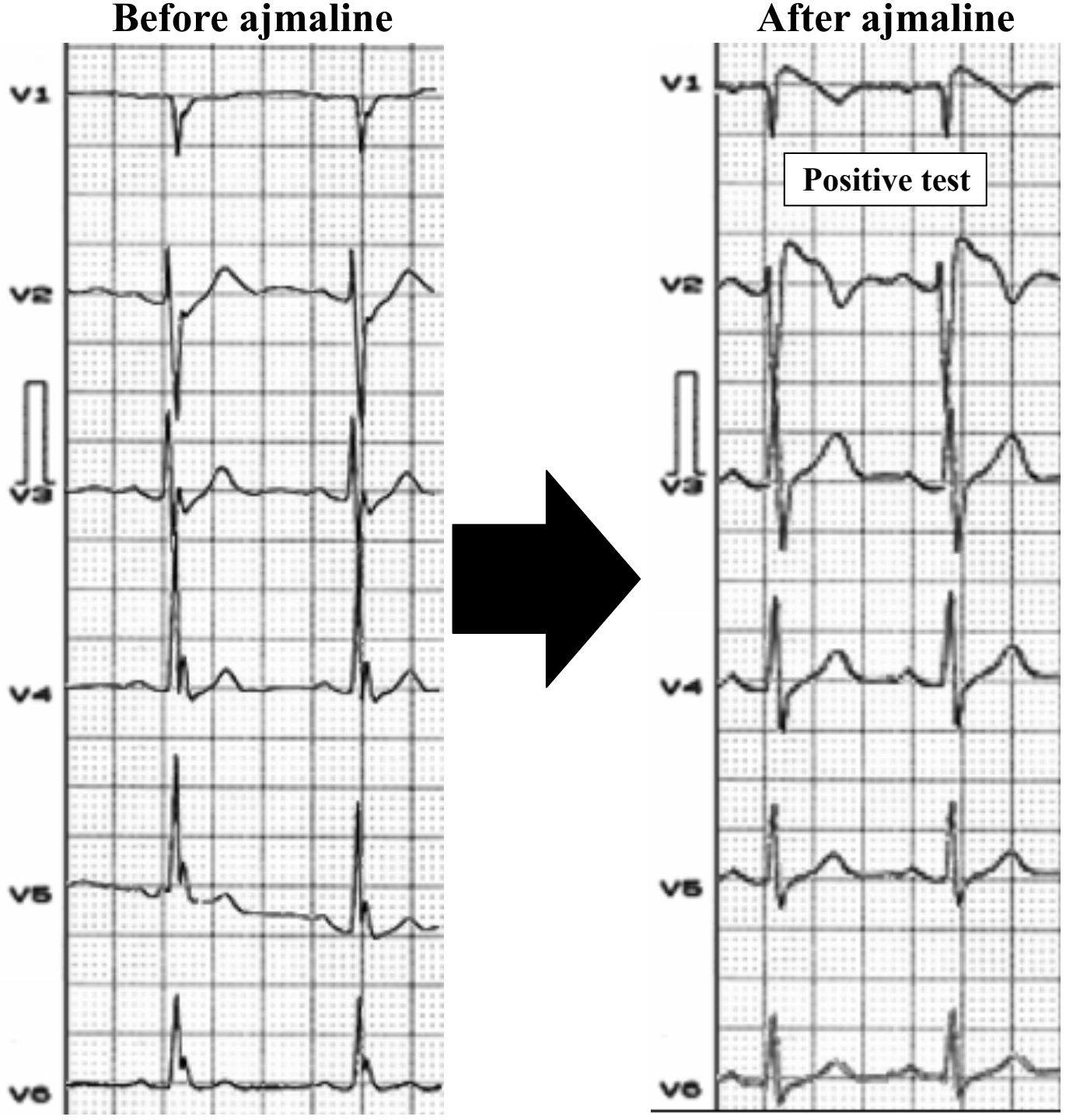
**Sinus rhythm J-wave in anterolateral and inferior leads without ST segment elevation**

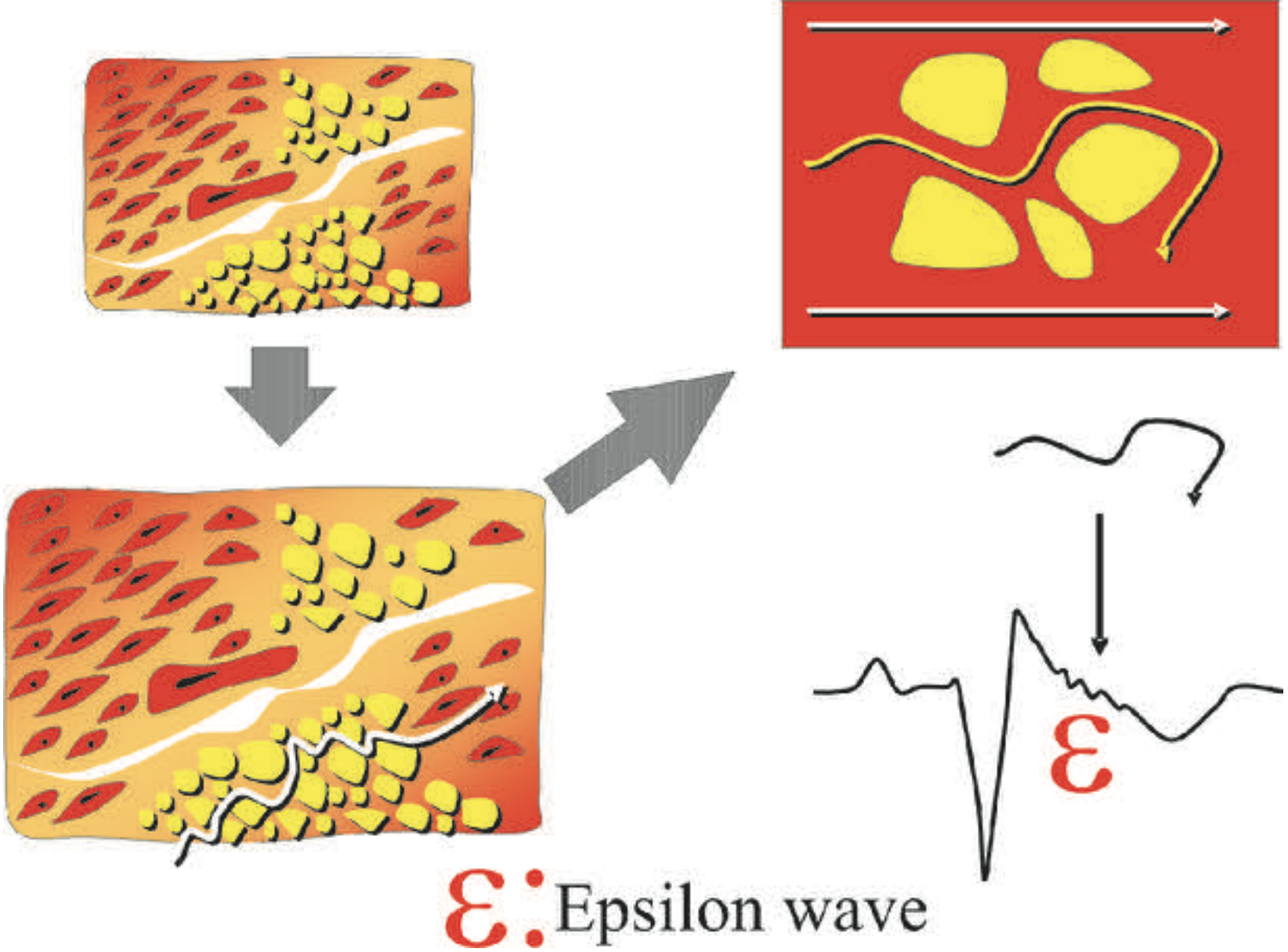


**The patient during atrial fibrillation J-wave in anterolateral leads without ST segment elevation and type 2 Brugada pattern in V2**

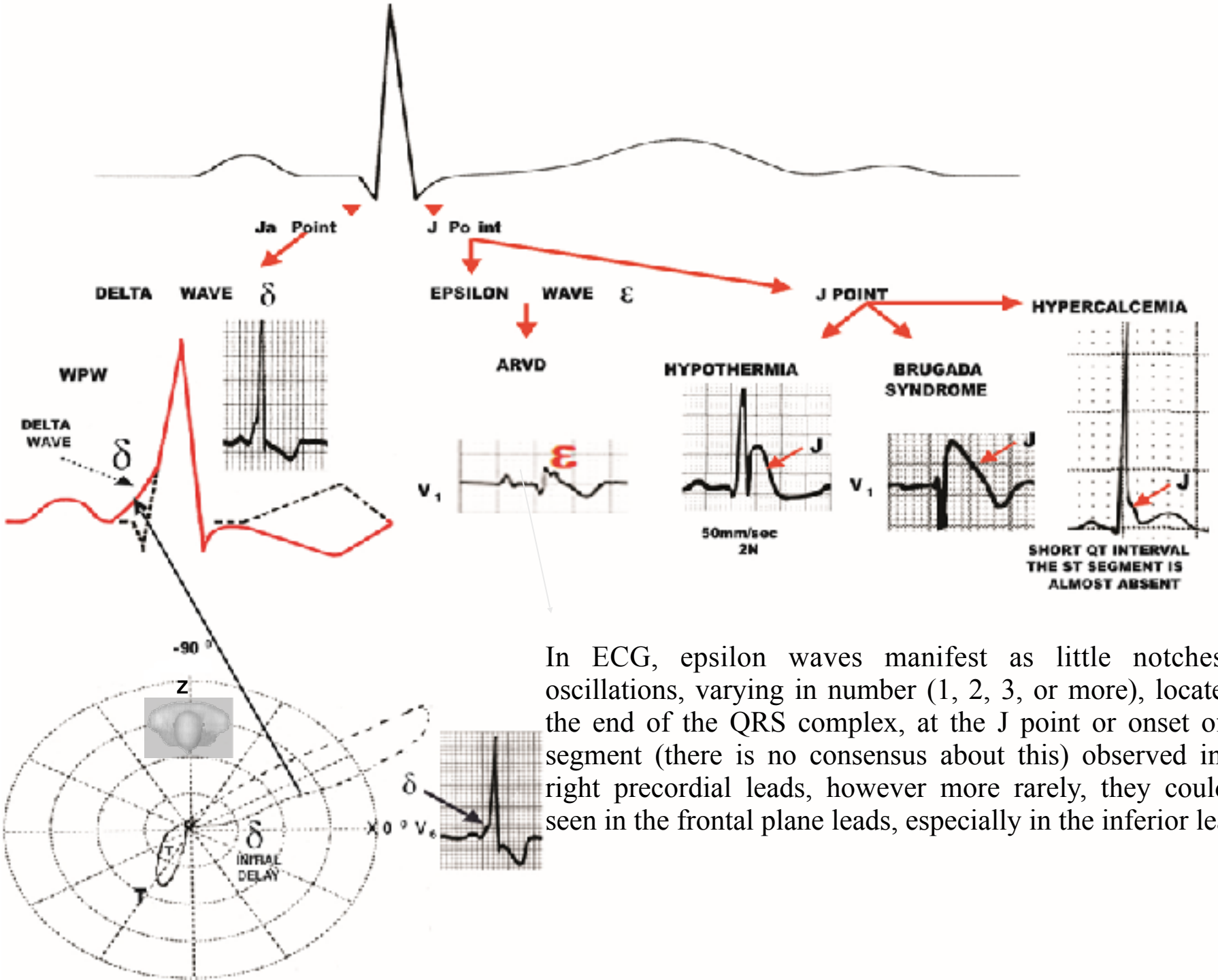



We performed intravenous ajmaline test. See next slide.

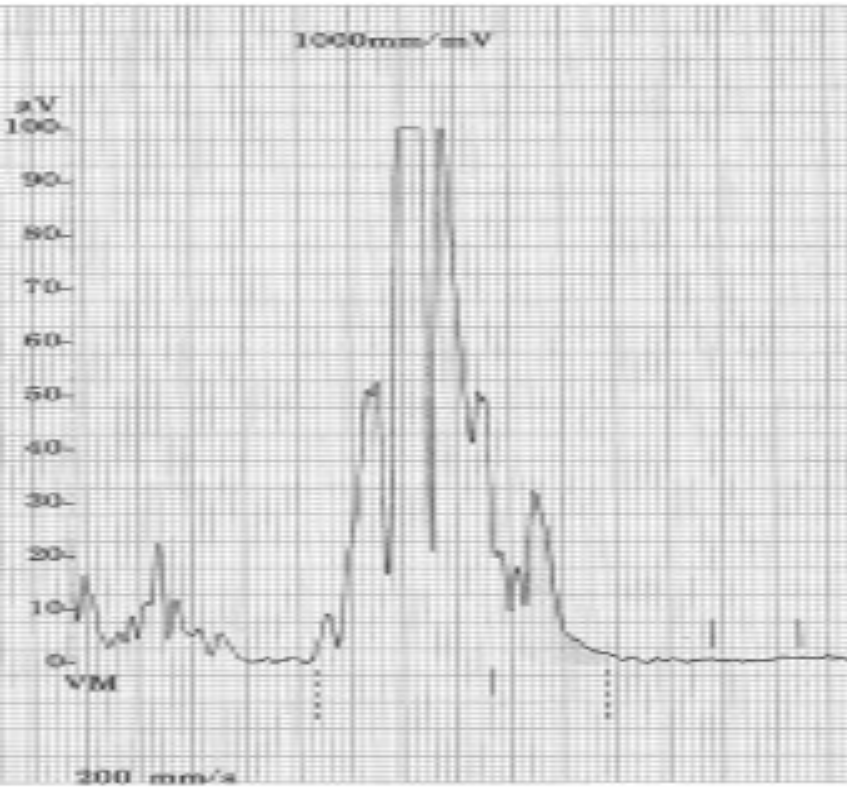

Before ajmaline
After ajmaline
V1
V2
V3
V4
V5
V6
V1
Positive test
V2
V3
V4
V5
V6

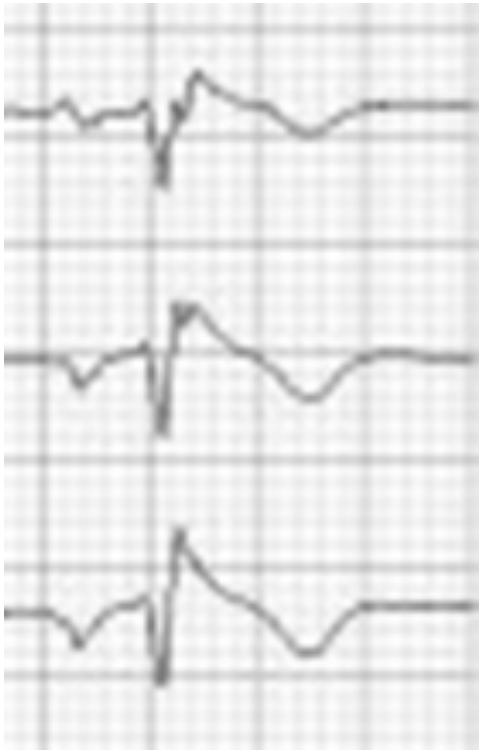



Epsilon waves (ε) correspond to late potentials or low amplitude and short duration oscillations at the right ventricle free wall (dysplasic triangle) in patients with ARVC/D, and rarely in other entities, such as Brugada syndrome.




In ECG, epsilon waves manifest as little notches or oscillations, varying in number (1, 2, 3, or more), located at the end of the QRS complex, at the J point or onset of ST segment (there is no consensus about this) observed in the right precordial leads, however more rarely, they could be seen in the frontal plane leads, especially in the inferior leads.

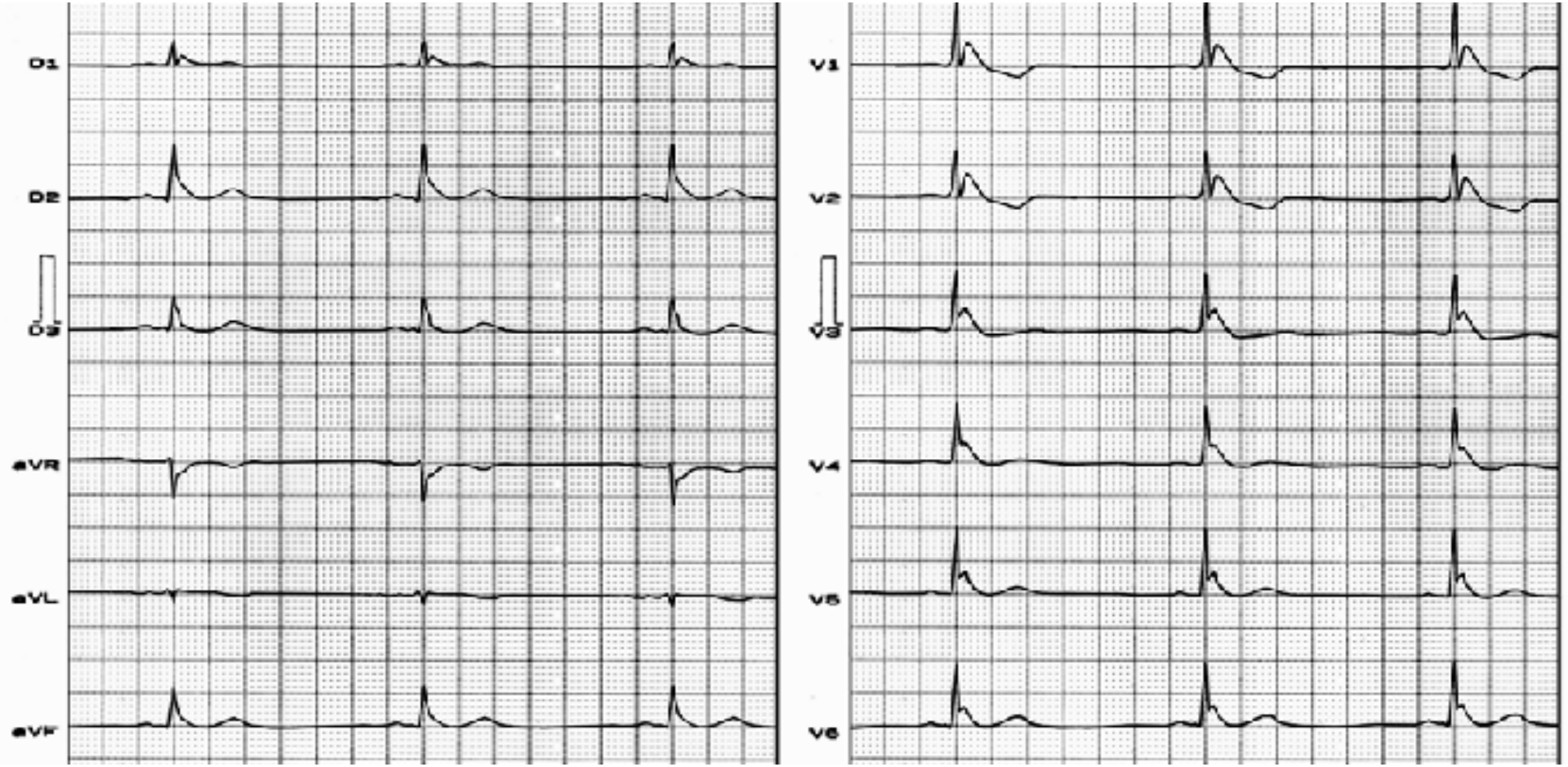


A signal-averaged ECG (SAECG) with abnormal LPs in a 60-year-old asymptomatic man and spontaneous type 1 Brugada ECG pattern. The total filtered QRSd = 137 ms
The duration of the high frequency low amplitude (HFLA) < 40 μV
The root-mean-square voltage (RMS) in the terminal 40 ms of the QRS are 137 ms, 55 ms and 15 μV, respectively (all three parameters are abnormal).
The role of the standard time-domain SAECG in BrS is limited by

a) Inability to detect conduction abnormalities *within* the QRS complex
b) Uncertain value in patients with BBB, and \
c) The use of a single-lead ECG complex, which is derived from the XYZ orthogonal leads and does not contain any regional information.

# Malignant Early Repolarization Pathological J or malignant waves Idiopathic ventricular fibrillation associated with early repolarization pattern (*ERP): the "Haïssaguerre pattern"*



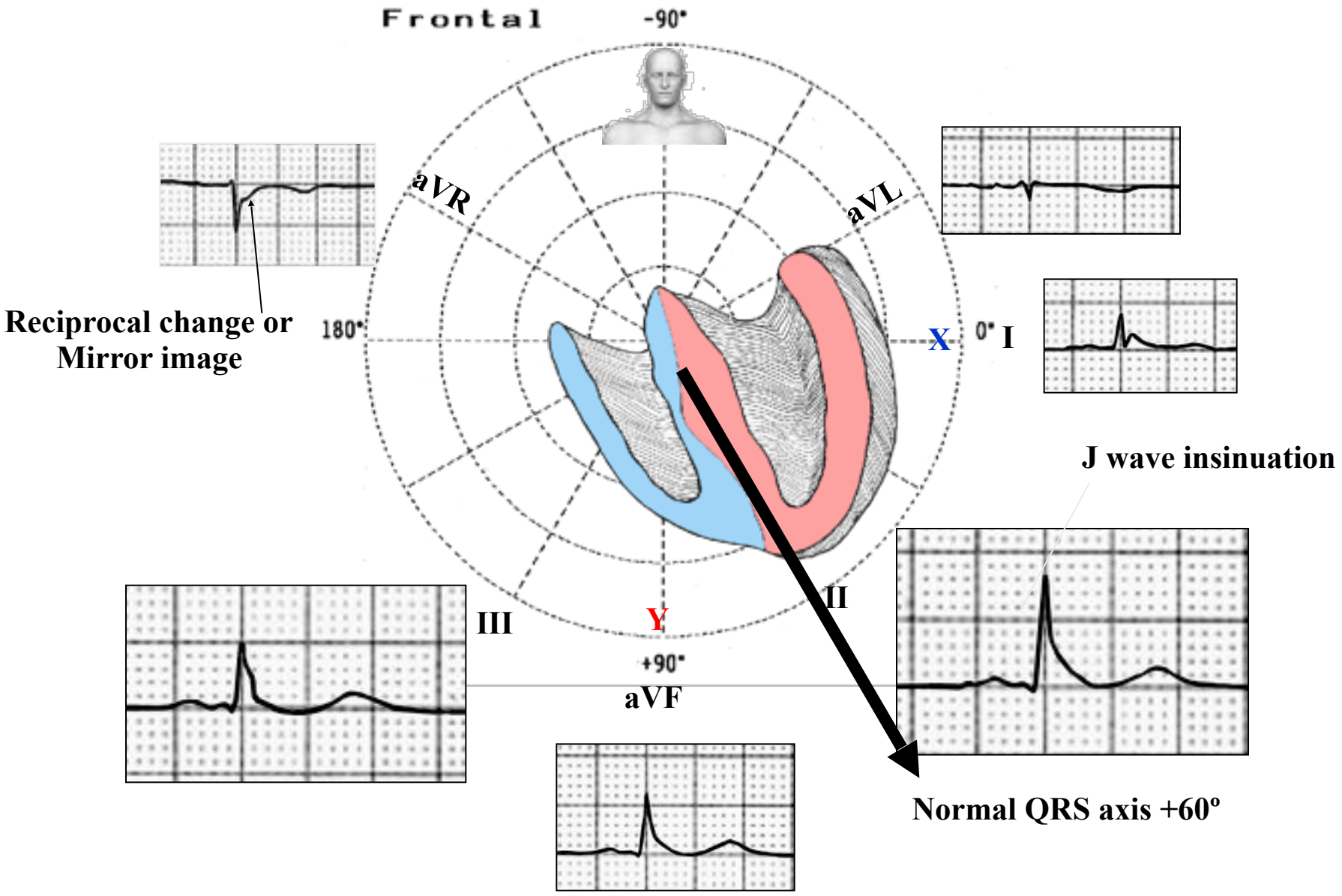

Subtype 3 shows an ER pattern registered globally in the inferior, lateral and right precordial leads> This variant is associated with the highest level of risk for the development of VF storms. ( **Nam 2008**). In subtype 3, the Brugada waves may be seen together with giant J waves in other ECG leads. Although the Brugada waves are not called ER, their underlying mechanism is identical to that of the ER patterns

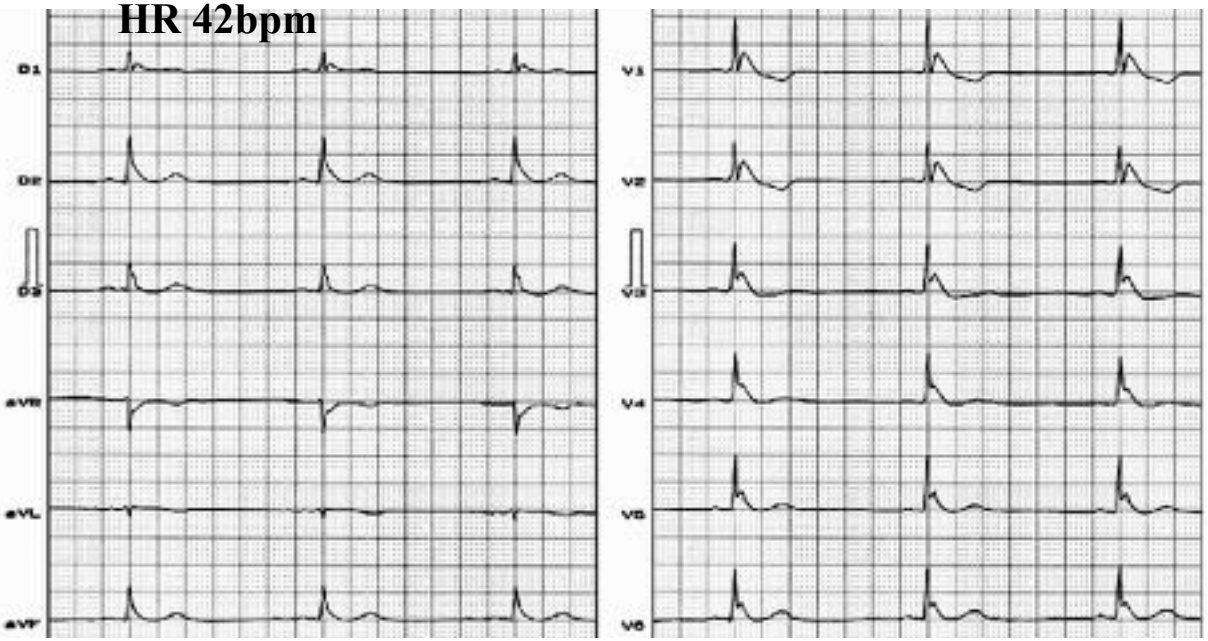
**MER** "Monstrous Early Repolarization," or

"Sami Viskin pattern"
Deserved eponym
Dear Sami!!!
Andrés




Classical case of Type 3 Early Repolarization Syndrome (ERS) (Yan 1996; Antzelevitch 2005)

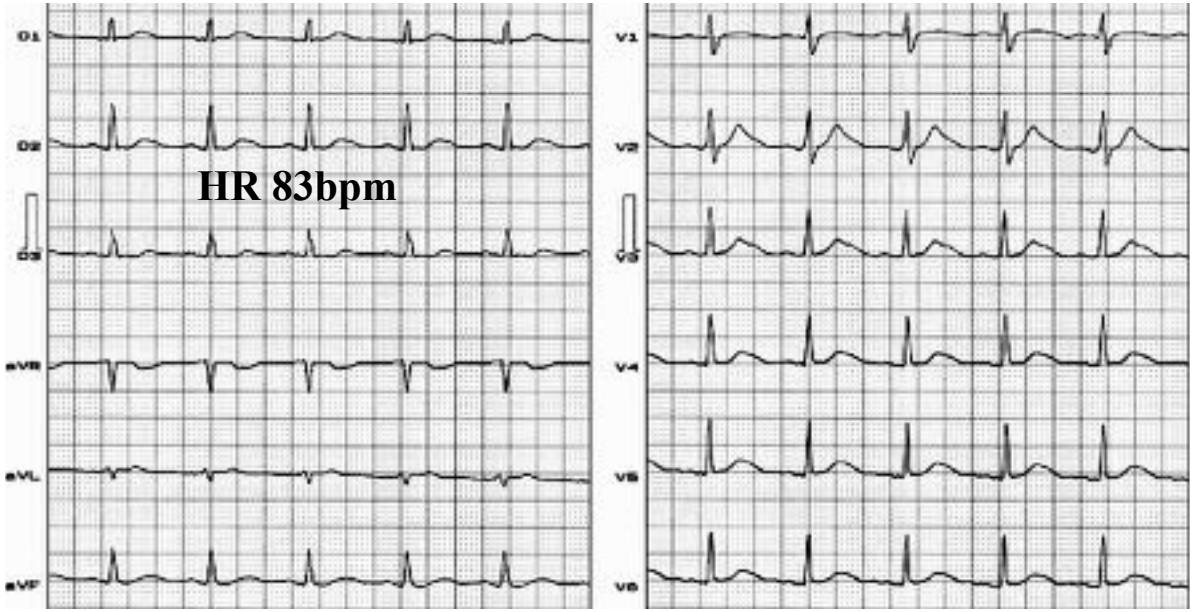

Frontal
-90°
aVR
aVL
180°
0° I
X
Y
+90°
aVF
III
II
Reciprocal change or
Mirror image
J wave insinuation
Normal QRS axis +60°




**A**: Basal tracing. We observe J-wave across all precordial and inferior leads.

**B:** ECG after two days after oral quinidine 1500 mg/day

Comments: The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalize the elevation of the ST segment. Additionally, it could improve repolarization due to its vagolytic effect (M2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone.



# Early repolarization pattern

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

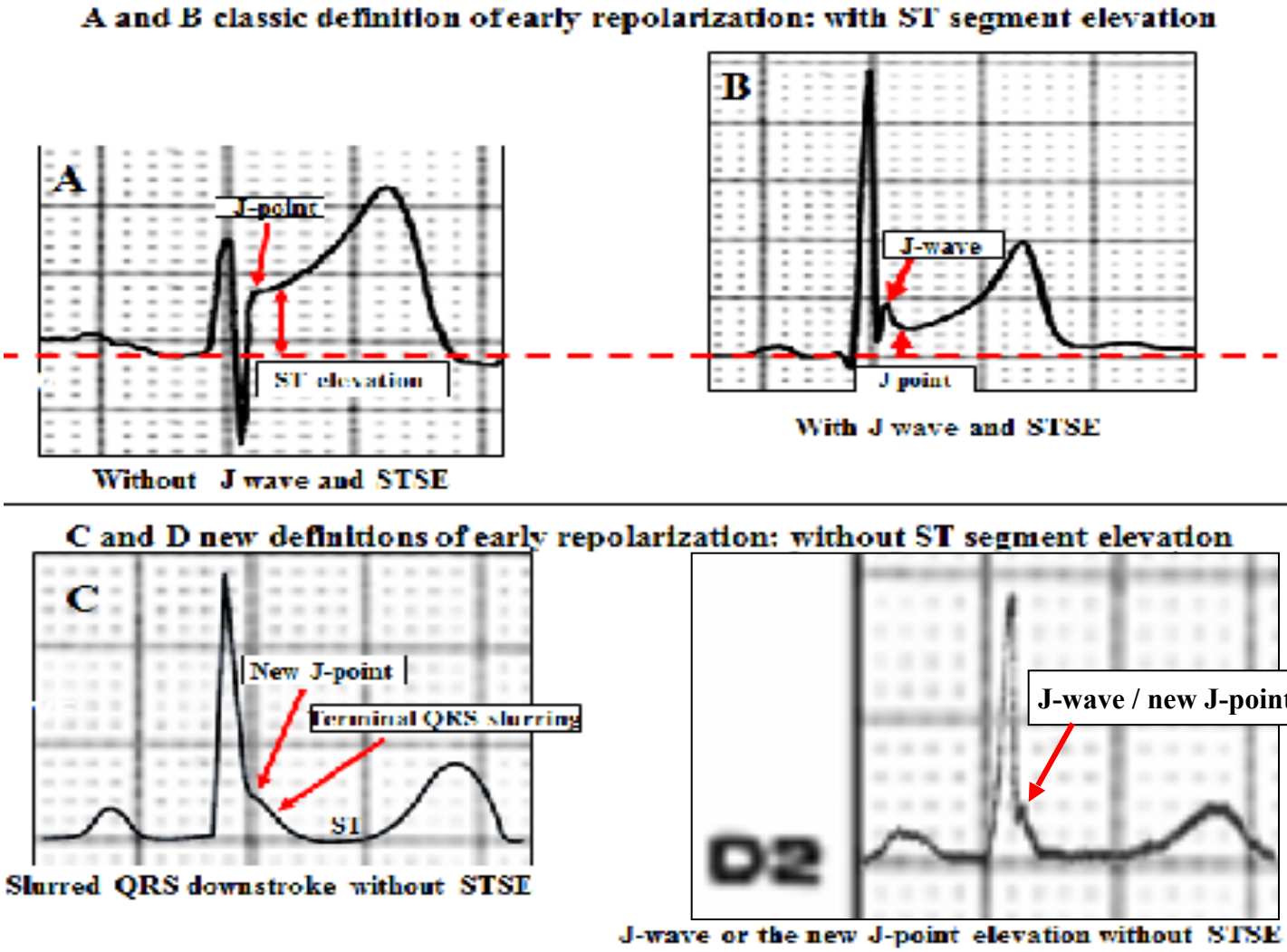
A) ER with only ST segment elevation.

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

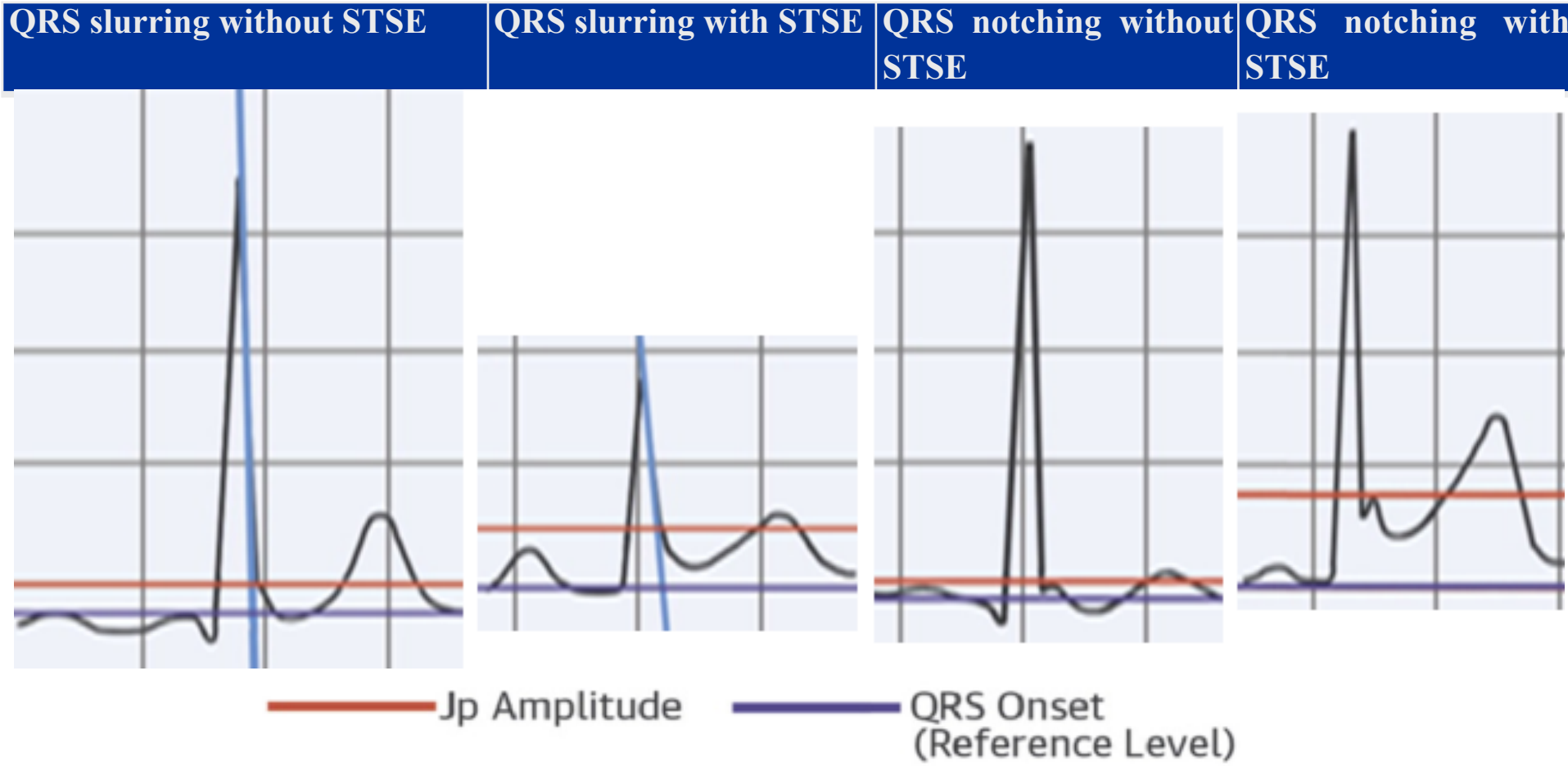
**C and D New concept of ER without ST segment elevation**

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

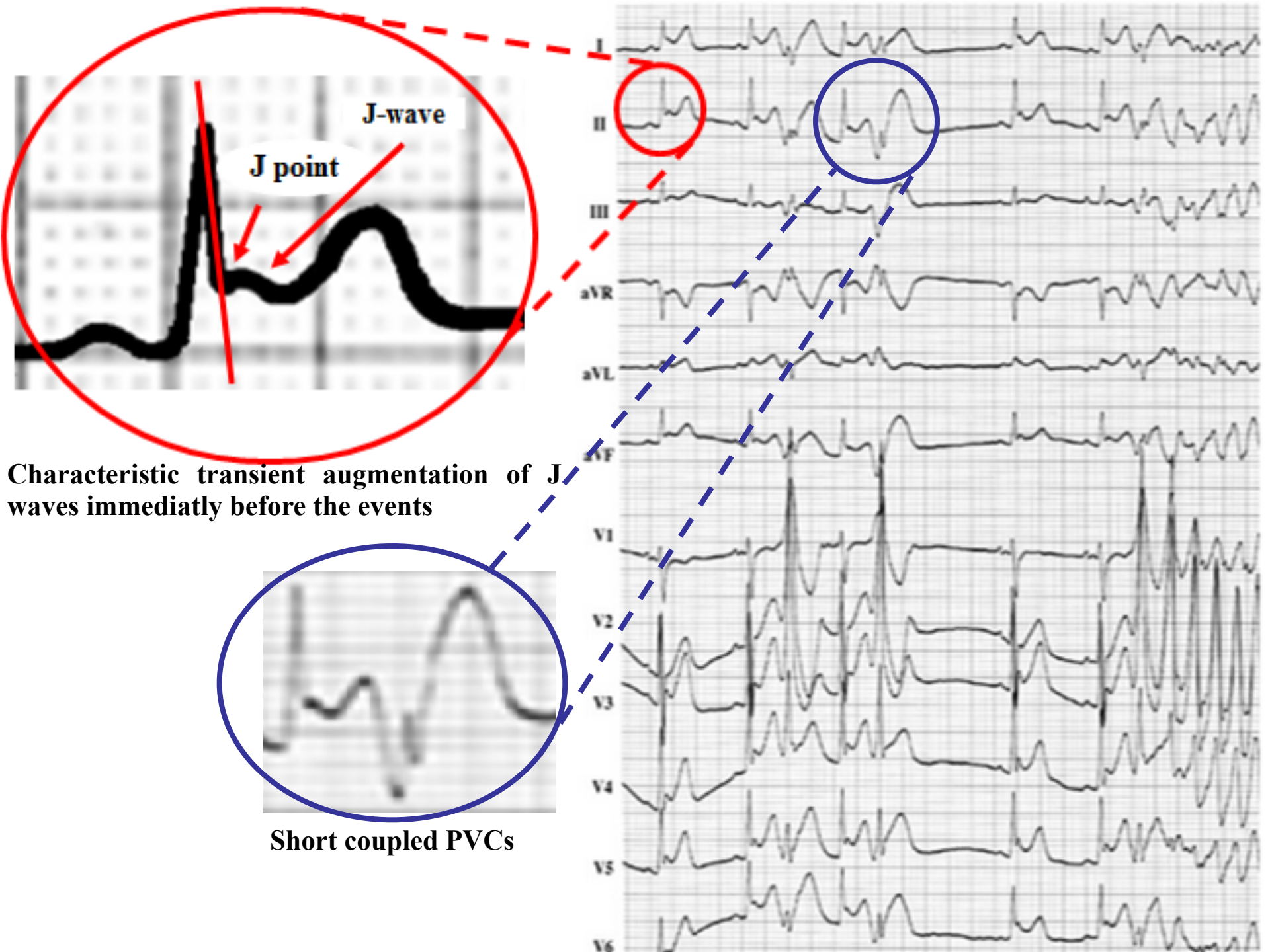
D) J-wave without ST segment elevation.



The new definition of ERP requires the peak of an end-QRS notch and/or the onset of an end-QRS slur as a measure, denoted Jp, to be determined when an interpretation of early repolarization is being considered. One condition for early repolarization to be present is Jp ≥ 0.1 mV, while ST-segment elevation is not a required criterion.




The upper salmon line indicates the notch or slur amplitude, J peak (Jp), while the lower purple line indicates the baseline used as a reference with respect to which amplitudes should be measured. The blue lines indicate tangents to the initial component of the R-wave downslope. All of these waveforms are illustrations of the early repolarization pattern. (**Macfarlane 2015**)



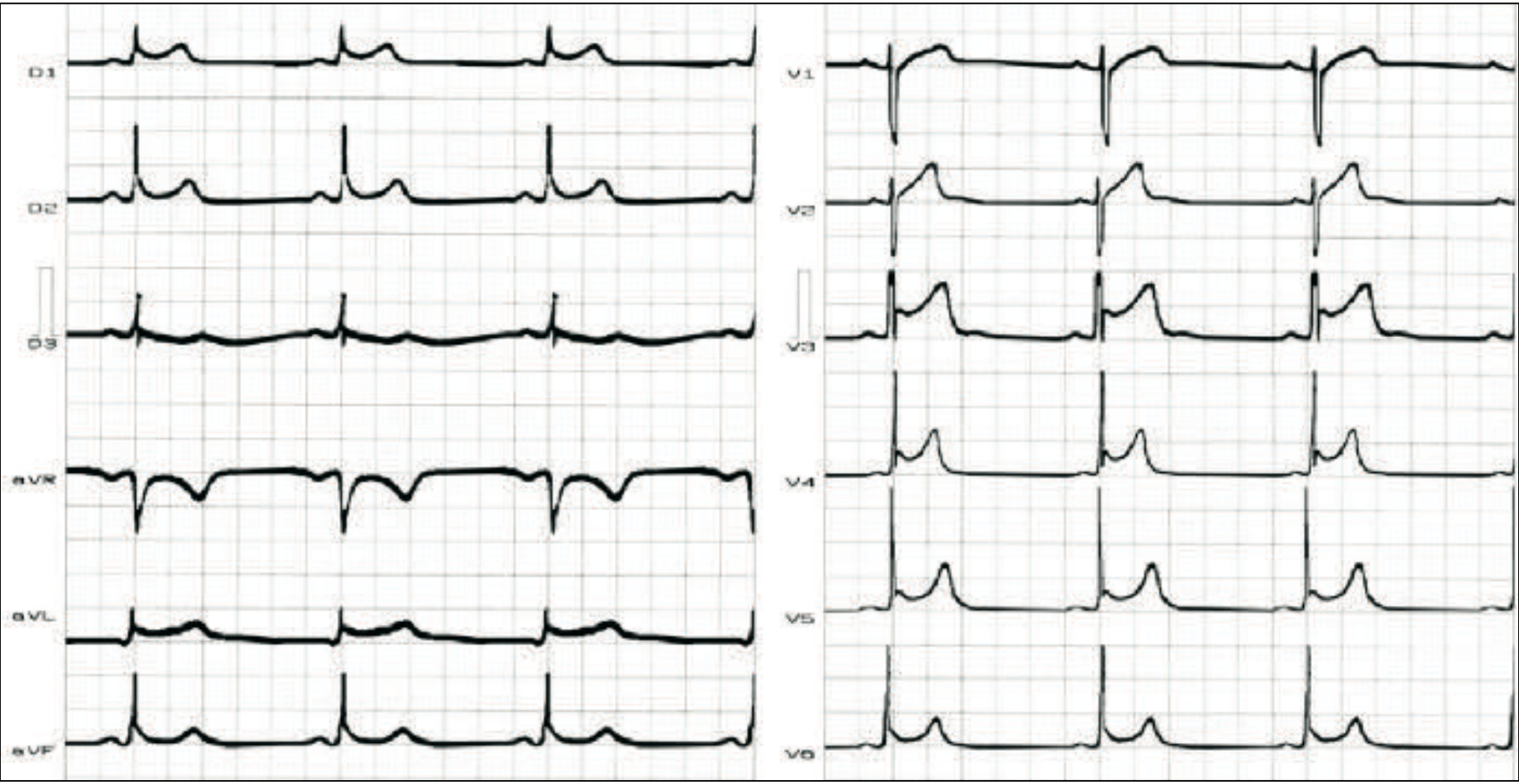

**Characteristic transient augmentation of J waves immediatly before the events**

**Short coupled PVCs**

# Malignant versus benign early repolarization pattern

| | Malignant ERP | Benign ERP |
|---|---|---|
| Resuscitation from cardiac arrest or documented VF | Yes, very suggestive | Assymptomatic |
| Positive Family history for SCD in Young relative | Possible | Absent |
| Sinus bradycardia | No | It is the rule |
| Axes of QRS, ST segment and T wave | Frequently discordant | Oriented to the same direction |
| Mirror or reciprocal image | Frequently in several leads | Only aVR |
| Transient augmentation of J waves | Characteristic | Absent |
| Short coupled PVCs | Frequently | Absent |
| Co-existing channelopaties such as BsS, SQTS, idiopathic VF | Frequently | No |
| ST segment elevation | Frequently > 2 mm | Usually < 2 mm |
| Widespread J waves in inferior and lateral leads and/or globally across leads | Strong signal | No |
| J waves convex upward or lambda wave pattern | It is the rule | ST concave upward followed by T waves of great voltage and polarity matching QRS |
| J waves in the inferior leads | Also present | Possible |
| J waves in lateral leads, tal R waves, rapidly ascending ST segments | No | Characteristic |

**Name:** DAS;**Age:** 24yo; **Gender:** Male; **Ethnic Group:** Afro-descendent; **Weight:** 82 kg; **Height:** 1.91 m**;** **Biotype:** Mesomorphic; **Profession:** professional basketball player.




**ECG diagnosis:** sinus bradycardia, (HR 50 bpm). Notch or slurring of terminal portion of the QRS complex (J point). J point and ST segment elevation concave upward > 4 mm from V3 to V5. **Observation:** Unfortunately, concave ST morphology cannot be used to rule out ST elevation from AMI with left anterior descending coronary artery occlusion because it is common in these circumstances. The ST elevation is most frequently evident in lead $V_4$. Reciprocal ST segment depression only in aVR.

**Conclusion:** sinus bradycardia, ERP.

# Similarities between early repolarization pattern and Brugada syndrome

- Both are much more frequent in the male gender.
- Both are predominantly observed in young adults.
- Both do not present apparent structural heart disease.
- Both frequently present conduction disorder patterns in the right His system.
- Both may present discrete QRS interval widening. In the ERP of athletes' hearts, a mild increase in QRS duration is observed (100 ms to 110 ms) in 15% of the cases caused by physiologic hypertrophy of the RVOT, which is translated in the ECG into the appearance of final r' wave that does not exceed 5 mm and that is lower than the preceding S in the same lead: rSr'(196). In BrS, as we have already mentioned, there may be a selective increase of QRS duration in the right precordial leads (Pitzalis 2003).
- Both may display saddleback pattern quite frequently.
- Both may reverse ventricular repolarization pattern during stress test.
- Both improve ventricular repolarization with endovenous isoproterenol, probably because the drug reduces repolarization dispersion which triggers VF events (Hiss 1962).
- Both have a shortening of phase 2 action potential due to electrophysiologic substrate, in the ventricular epicardium thickness by intensification of the notch in phase 1, mediated by the *I*to channel (Yan 1996).
- Both may have modification in the *I*to and $I_{Ca}{}^{++}{}_{-L}$ channels by electrophysiologic substrate, which explains the J point and ST segment elevation causing intensification of the notch in phase 1 and decrease in phase 2 duration in the ventricular epicardium thickness (Antzelevitch 2000).
- Both may affect in different degrees, ventricular repolarization in the right precordial leads (Bianco 2001) as well as in the lateral wall (V4-V6) and inferior leads I, II, and III (atypical forms of BrS).

# Brugada Phenocopies

**“ An environmental condition that imitates or copies one produced by a gene”**

In order to learn about the morphological classification of Brugada Phenocopies, please visit the website

www.brugadaphenocopy.com.

Brugada phenocopies are clinical entities that present with an ECG pattern identical to either the type 1 or type 2 Brugada patterns yet differ etiologically from true Brugada syndrome. The pattern presents in association with an identifiable condition and, upon resolution of that condition, the ECG pattern normalizes.

Brugada phenocopy is not due to a congenital sodium channel abnormality. Indeed, the defining feature of Brugada phenocopy is the absence of true congenital Brugada syndrome. Therefore a provocative test with a sodium channel blocking agent such as ajmaline, flecainide, or procainamide will not reproduce the ECG pattern (Baranchuk 2012).

## The Brugada ECG Pattern

True congenital Brugada syndrome is characterized by two ECG patterns in the right precordial leads (V1-V3). These patterns involve ST elevations that produce either the type 1 "*coved*" or type 2 "*saddleback*" patterns (Bayés de Luna 2012).

The typical type 1 pattern has a high take-off ST-segment elevation that is ≥ 2 mm followed by a downsloping concave or rectilinear ST-segment. The ST-segment in type 1 patterns is followed by a negative and symmetric T wave.

## Causes of Brugada Phenocopy

Brugada phenocopies may be induced by a multitude of clinical circumstances that have been characterized into six distinct etiological categories (Baranchuk 2012; Anselm 2014): metabolic conditions, mechanical compression, ischemia, myocardial and pericardial disease, ECG modulation, miscellaneous.

The number of reported cases of Brugada Phenocopy has steadily increased since proposal of the term and concordantly, the number of conditions known to cause Brugada Phenocopy has also increased. To date, there have been 66 reported cases of Brugada phenocopy,[4-62] 16 of which are confirmed, meeting all of the mandatory criteria for diagnosis.

Confirmed Type 1 Brugada phenocopies have been reported in the context of an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement (Anselm 2013); hyperkalemia (Recasens 2013); adrenal crisis (Dogan 2013); concurrent hypokalemia and hyponatremia (Mok 2008); acute myocarditis due to hyperesinophillic syndrome (Nayyar 2009); concurrent hypernatremia, hypokalemia, and acidosis (Kovacic 2004); hypokalemia in the context of congenital hypokalemic periodic paralysis (Gazzoni 2013); writhing of a reconstructed esophagus resulting in mechanical compression on the heart (Kaneko 2013); ketamine intoxication with concurrent acidosis (Rollin 2011); and acute cannabis intoxication (Daccarett 2007). The remaining five confirmed Brugada Phenocopies were type 2 and reported in the context of pectus excavatum resulting in mechanical mediastinal compression (Awad 2013); hyperkalemia (Ortega-Carnicer 2002); acute pericarditis (Ozeke 2006); and electrocution (Wang 2012).

## Recurrent Brugada Phenocopy

In each of the previous 13 cases, Brugada phenocopy was observed in a single clinical event. However, there are currently two known cases of confirmed recurrent Brugada phenocopy, both in the context of hypokalemia. In 2010, Tsai et al (Tsai 2010) reported a case of Brugada phenocopy in the context of hypokalemia due to thyrotoxicosis. In a brief summary, the patient presented in 2005 with sudden onset bilateral leg weakness following a large meal. The ECG demonstrated a type 2 Brugada ECG pattern and laboratory tests were significant for hypokalemia, hyperglycemia, low TRH and high free thyroxine.

With treatment and normalization of the potassium and glucose levels, the ECG resolved to a normal pattern. In 2008, this patient experienced a recurrent episode of flaccid paralysis following a heavy meal. The ECG demonstrated a type 1 Brugada ECG pattern and laboratory tests revealed hypokalemia, hyperglycemia, low TSH and normal thyroxine. Correction of the hyperglycemia and hypokalemia yet again resulted in resolution of the Brugada ECG pattern.

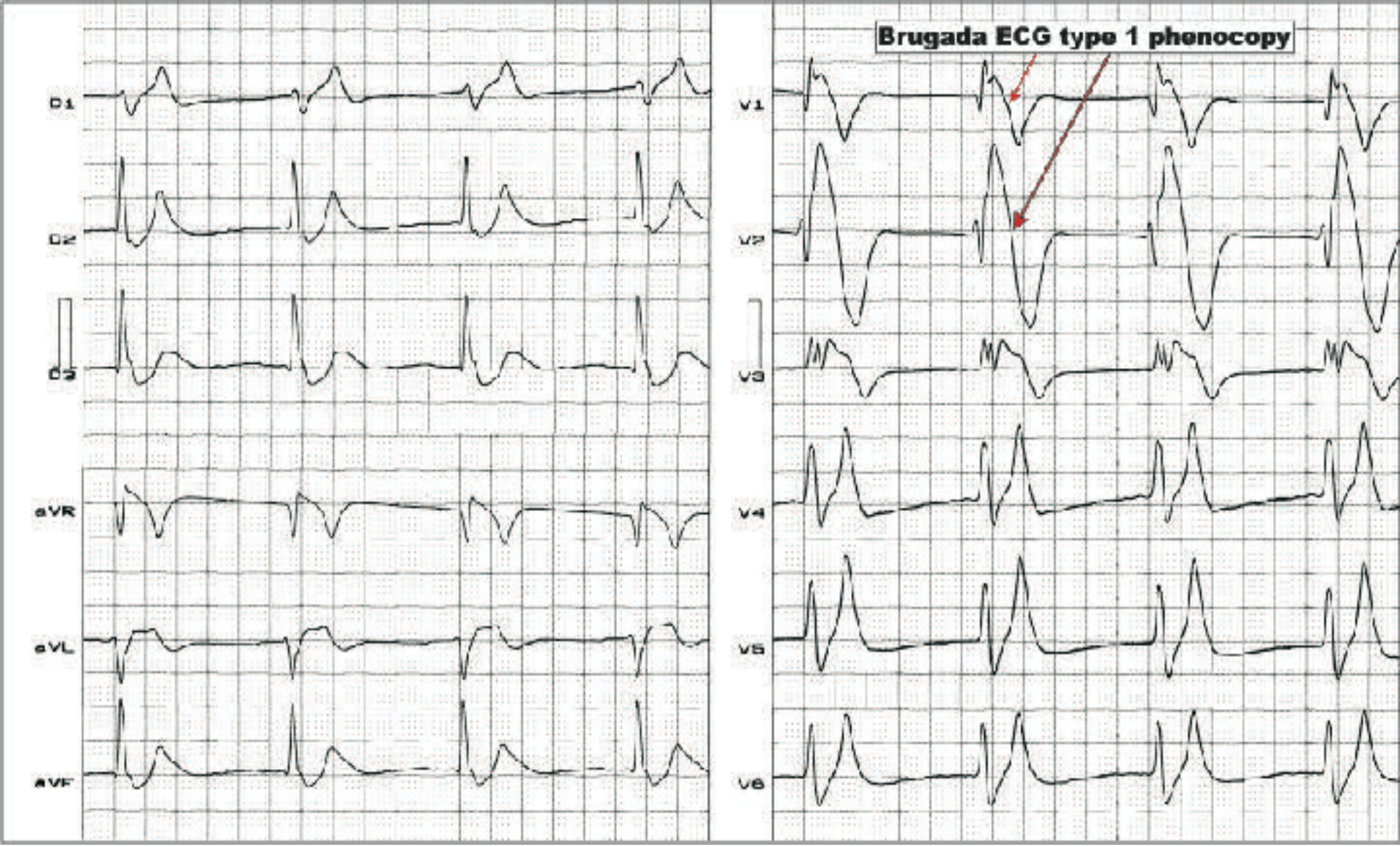
In 2013, a second case report demonstrated the clinical reproducibility of Brugada phenocopy. Genaro et al (Genaro 2013) reported the case of a man who presented to the Emergency Department with a 15-day history of diarrhea. An ECG demonstrated a type 1 Brugada ECG pattern in the setting of severe hypokalemia and acidosis. Upon correction of the metabolic abnormalities, the ECG pattern resolved. While in hospital, recurrent episodes of diarrhea resulted in hypokalemia without acidosis and an ECG demonstrated the return of the Type 1 Brugada ECG pattern. The ECG pattern resolved once again after IV.

## Diagnosis of Brugada Phenocopy

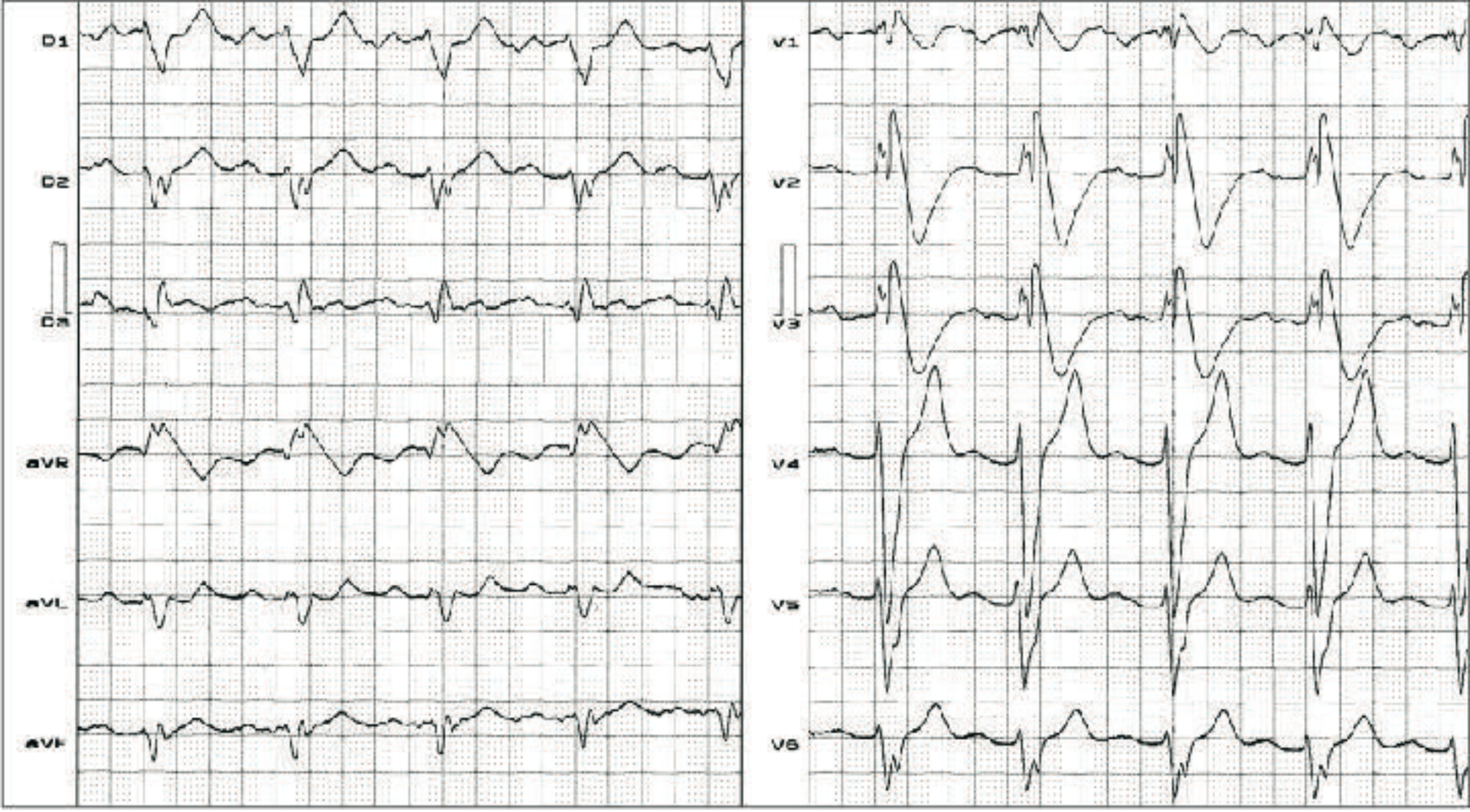
The diagnostic criteria for Brugada Phenocopy are (I-V are mandatory) (Baranchuk 2012; Anselm 2013-2014):

An ECG pattern that has a type-1 or type-2 Brugada morphology

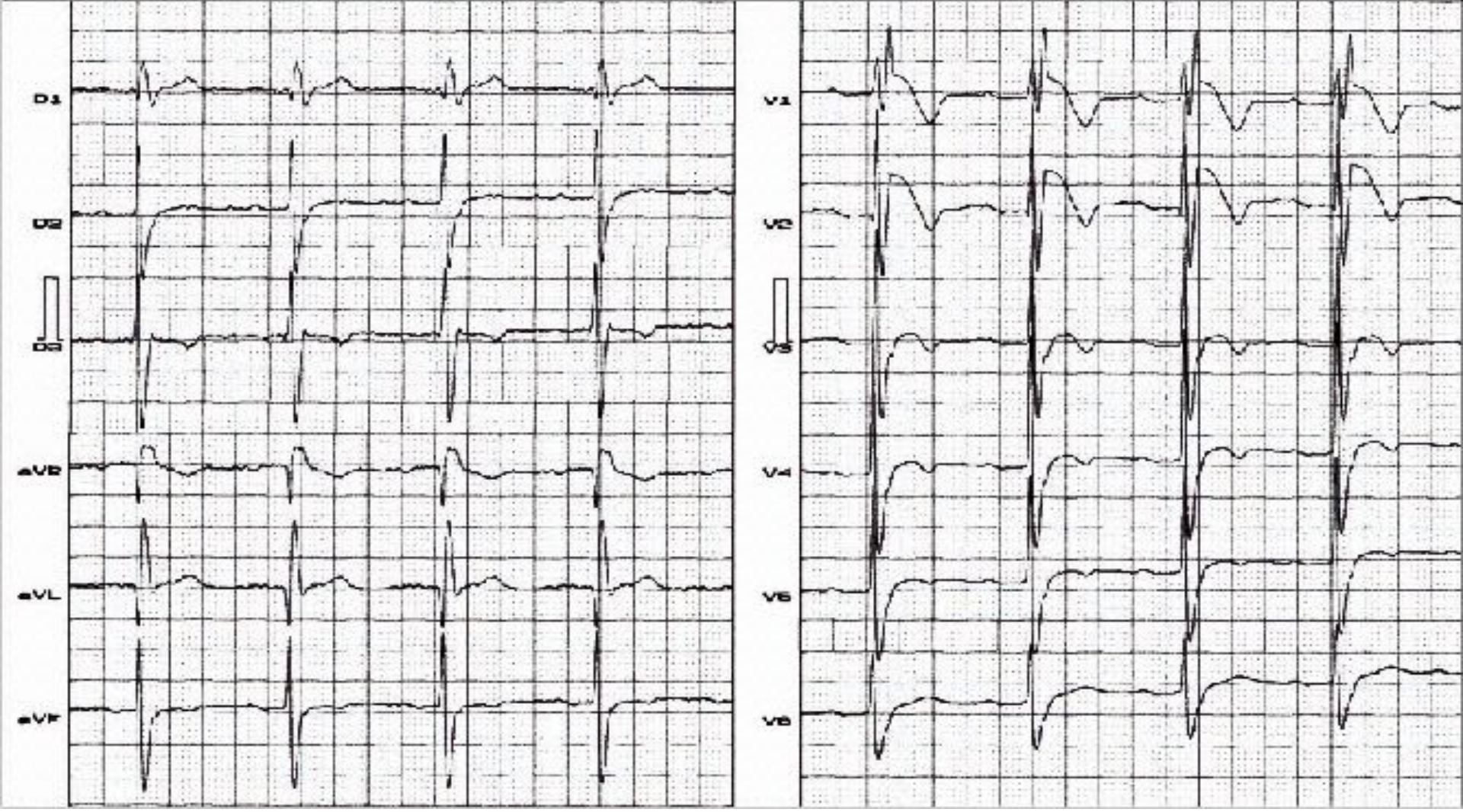
I. The patient has an underlying condition that is identifiable
II. The ECG pattern resolves upon resolution of the underlying condition
III. There is a low clinical pretest probability of true Brugada syndrome determined by a lack of symptoms, medical history, and family history
IV. The results of provocative testing with a sodium channel blocker such as ajmaline, flecainide, or procainamide are negative
V. Provocative testing is not mandatory if surgical RVOT manipulation has occurred within the last 96 hours).
VI. The results of genetic testing are negative (desirable but not mandatory because the SCN5A mutation is identifiable in only 20% to 30% of probands affected by true BrS63).
VII. Correction of the hypokalemia.




**Clinical diagnosis:** terminal renal insufficiency. Severe hyperkalemia: $K^+$ 8.7 mEq/L. This sign is known as dialyzable injury current. ECG diagnosis: very likely, junctional with P waves near J point, HR: 54 bpm, QRSd: 160 ms, ST segment elevation from $V_1$ to $V_3$ and I, aVL and aVR. $V_1$ to $V_3$ display ST segment upwardly convex pattern, similar to Brugada syndrome or Brugada phenocopy (Riera 2010), typical T waves in "tent", pointed, and with a narrow base.




**ECG diagnosis:** Left atrial enlargement, PR interval prolongation or first-degree AV block secondary to augmentation of effective refractory periods of atrioventricular node (> AH interval), His-Purkinje system (> HV interval), nonspecific intraventricular conduction disturbance, (marked abnormal ventricular activation pattern (bizarre): does not satisfy the criteria of either LBBB or RBBB), long QT interval with normal JT interval and Brugada type 1 ECG phenocopy: ST segment elevation convex to the top followed by negative T waves from $V_1$ to $V_3$ Induced Brugada-type 1 ECG pattern, is a sign for imminent malignant arrhythmias. Brugada phenocopy secondary to accidental plasma concentrations of propafenone in the toxic range.

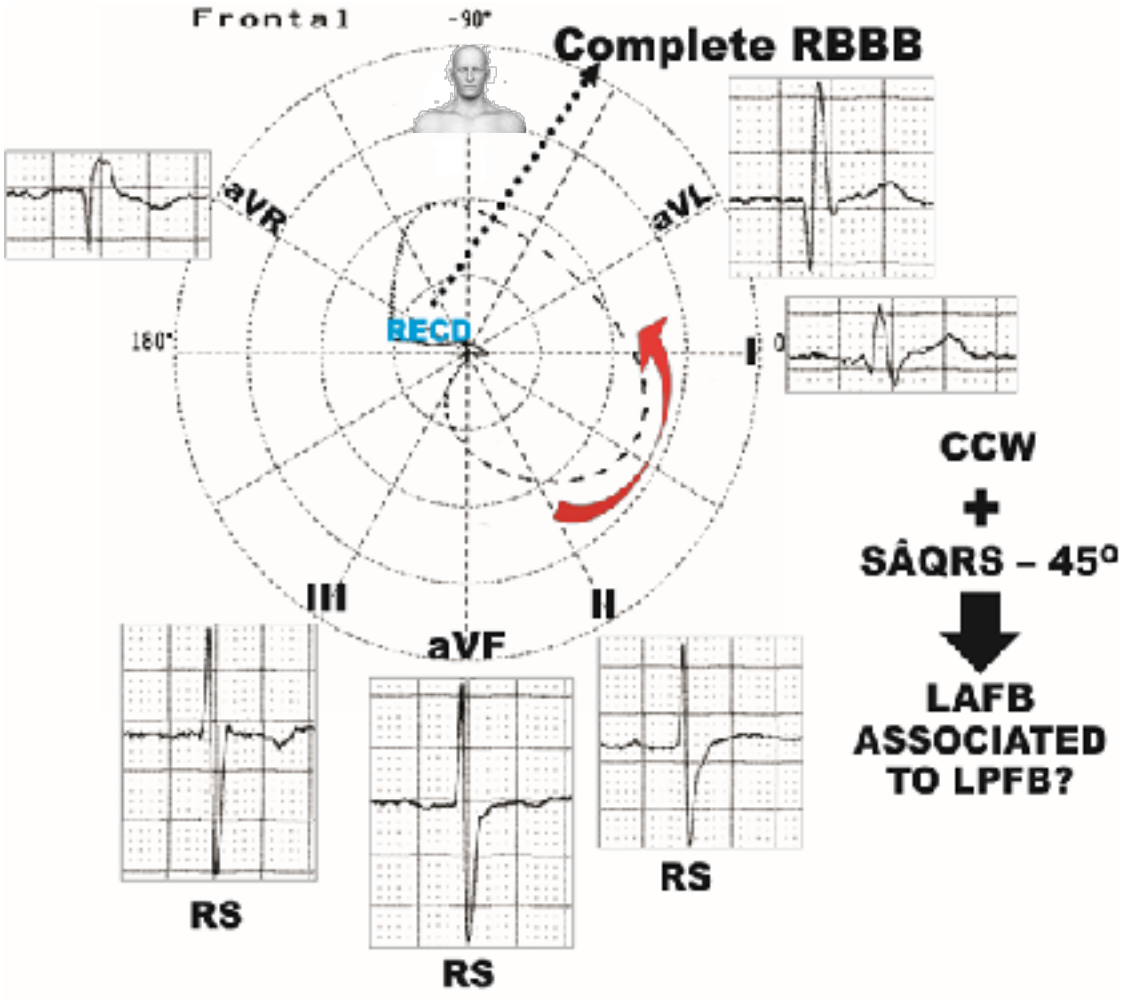



**Clinical diagnosis:** myotonic muscular dystrophy (Steinert's disease) / type 2 diabetes mellitus / high blood pressure. Brugada syndrome? Brugada phenocopy?

**ECG diagnosis:** sinus rhythm, HR: 55 bpm, PR interval: 250 ms (first-degree AV block), QRS duration: 165 ms, SÂQRS: near – 40º : Complete RBBB + left anterior fascicular block (LAFB), probable trifascicular block.

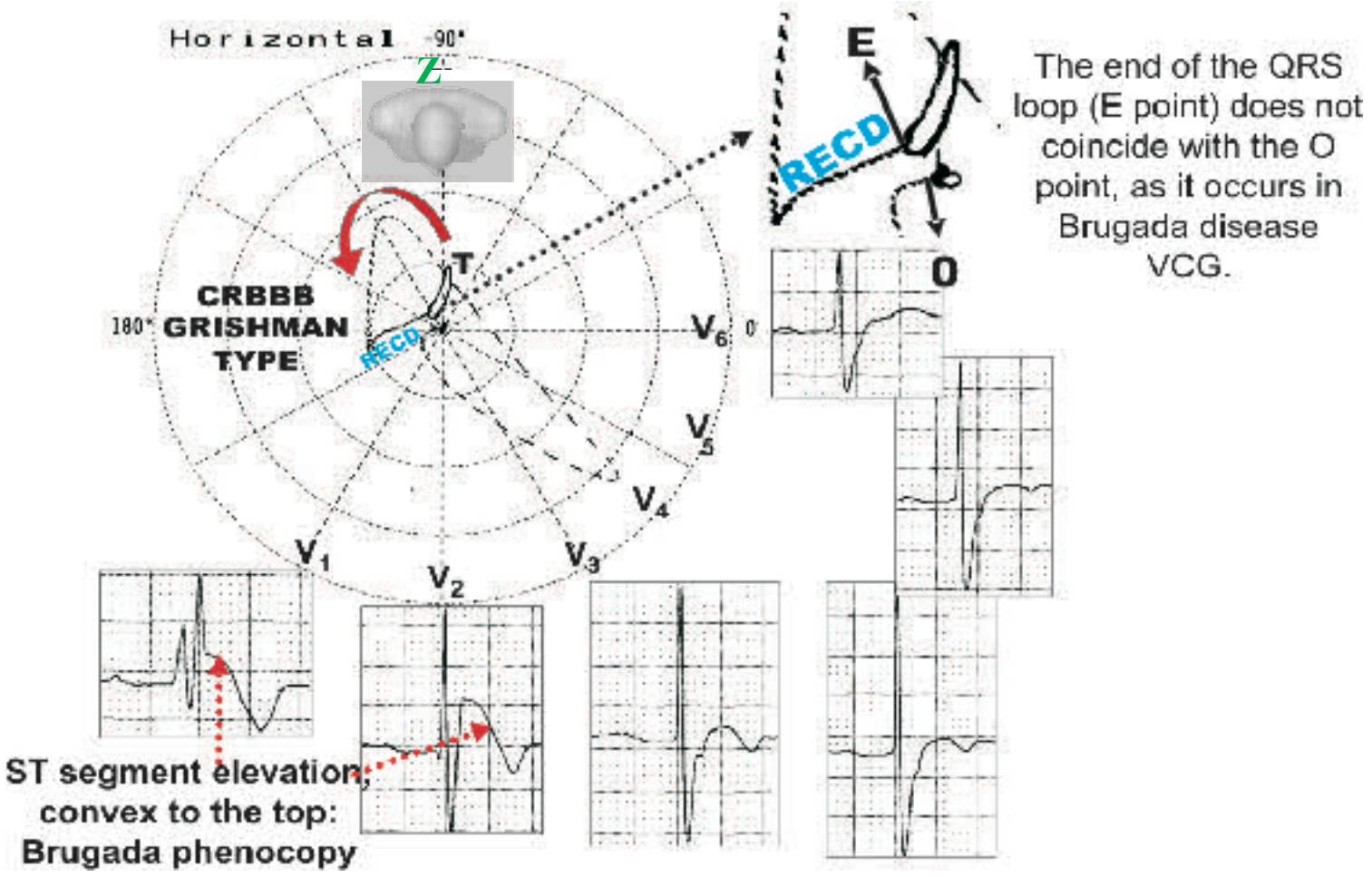
J point and ST segment elevation≥ 2mm in $V_1$ and $V_2$ followed by a negative T wave: Brugada ECG type 1 phenocopy.

# ECG/VCG correlation in the frontal plane

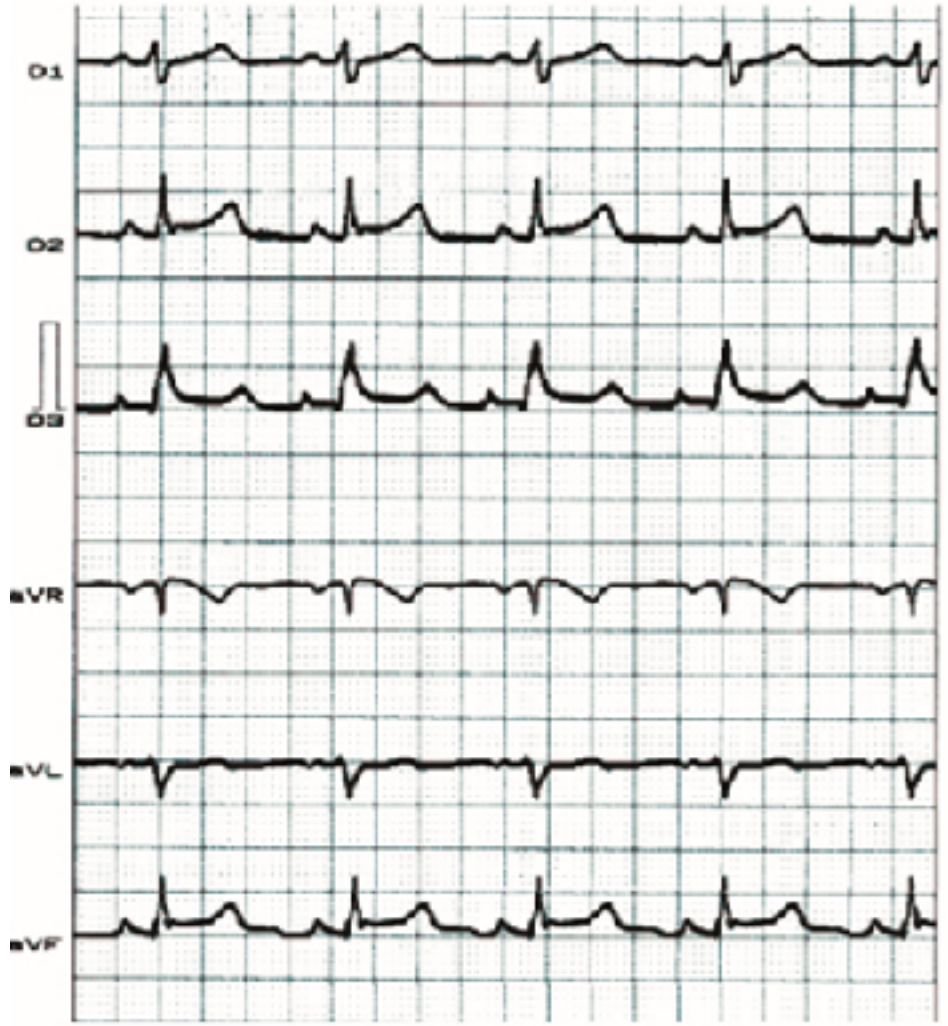



In classical LAFB, the inferior leads II, III and aVF, show rS pattern. In this case, the voltage of R waves in inferior leads are greater, originating RS pattern in these leads. Additionally, QRS loop morphology is rounded and not elliptical as in typical LPFB. Both facts (RS pattern and rounded shape) suggest some degree of associated LPFB. This suspicion is reinforced by the presence of first degree AV block, which may be pointing dromotropic difficulty in the left posterior fascicle.

# ECG/VCG correlation in the horizontal plane

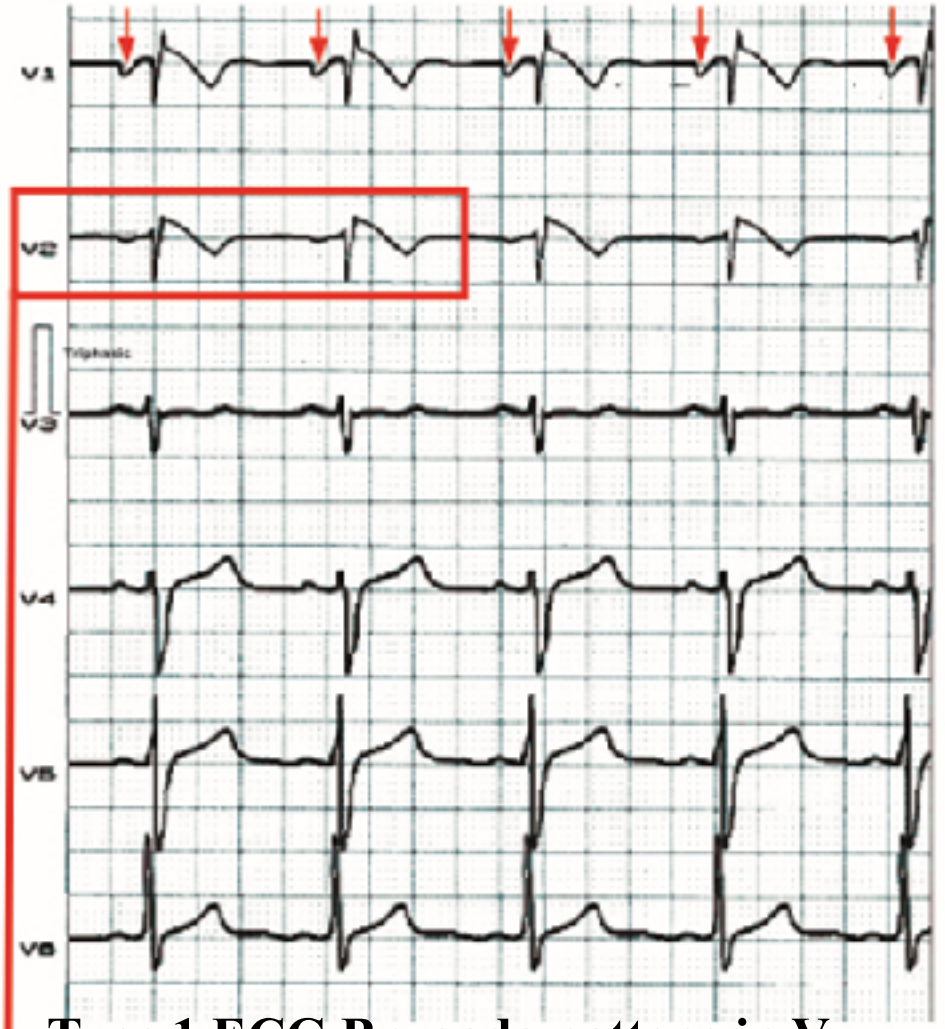



**Clinical diagnosis:** Myotonic Muscular Dystrophy (Steinert's Disease).
**ECG/VCG diagnosis:** Complete RBBB Grishman type or Kennedy type I (afferent limb of QRS loop behind X orthogonal line).
J point and ST segment elevation ≥ 2mm convex to the top followed by a negative T wave on right precordial leads: Brugada phenocopy (Nguyen 2011; Arce 2010).

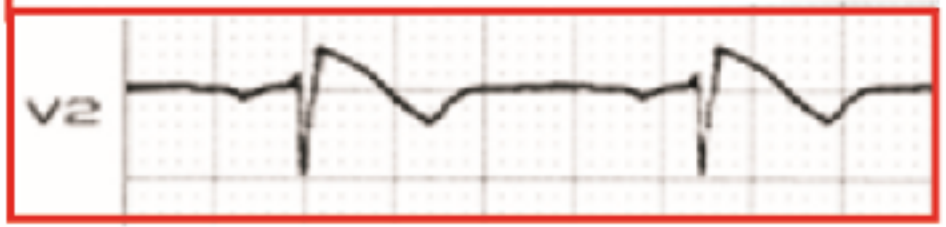



ECG of a 18yo male patient with pectus excavatum (Kataoka 2002) and Brugada type 1 ECG pattern: Brugada phenocopy.

**Negative P wave in $V_1$**




**Type 1 ECG Brugada pattern in $V_2$**



# Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare clinically and genetically heterogeneous disease characterized by exercise, adrenergic stress induced or adrenergically mediated ventricular tachyarryhtmia, with recurrent syncope of uncertain etiology after physical and emotional stress or sudden cardiac death (SCD), usually in the pediatric or juvenile age group. Sudden infant death syndrome and juvenile sudden death exert a deep social impact, due to the young age of the victims and the unexpected occurrence of death (Carturan 2007). Despite its rare occurrence, CPVT is an important cause of stress and emotion induced syncope and SCD in children (Massin 2003).

Familial occurrence has been noted in about 30% of cases.

Inheritance may be autosomal dominant (Mutations of the cardiac Ryanodine receptor gene (RyR2) or recessive associated with homozygous mutations in the gene encoding the cardiac isoform of calsequestrin (CASQ2). (calsequestrin gene CASQ2 mutations) usually with high penetrance (Laitinen 2004).

The causative genes have been mapped on chromosome 1.

Due to its potential lethal outcome, exclusion or confirmation of CPVT in children with physical and emotional syncope is mandatory.

•The entity, together with Brugada syndrome (BrS), congenital long QT syndrome (LQTS), congenital short QT syndrome (SQTS) and familial atrial fibrillation (Roberts 2003) are integrants of a group entlitled electrical heart disease, purely electrical heart diseases (Farwell 2007), primary electrical heart diseases (Makita 2007), primary electrical disorders (Schulze-Bahr 2000) ion channel diseases, channelopathies or sine material sudden death disease, because apparent structurally intact or normal hearts is observed.

➢ Genetic analysis identifies two groups of patients:

1. Sporadic or nongenotyped: Patients with nongenotyped CPVT are predominantly women and become symptomatic later in life;
2. With mutation:

- (2-A) Cardiac RyR: Autonomic Dominant (AD)
- (2-B) Calsequestrin CASQ2 Autonomic Recessive (AR) (Eldar 2003). CASQ2 mutations are more common than previously thought and produce a severe form of CPVT (Postma 2002).

# Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Mutation in four genes – RYR2, CASQ2, TRDN, and CALM1 – is known to cause CPVT or related phenotypes of adrenergically induced life-threatening arrhythmias. The presence of other as-yet unidentified loci is postulated.

| Cathecolamine- Dependent Polymorphic VT (CPVT)<br>Catecholaminergic Polymorphic Ventricular Tachycardia | | | | |
|---|---|---|---|---|
| Arrhythmia | Chromosome | Gene | Protein | Inheritance pattern |
| CPVT1 | 1q42-43 | RYR21 | Cardiac RyR | AD |
| CPVT2 | 1p11.13.3 | CASQ2 | Calsequestrin | AR |
| CPVT3 | 7p22-p14 (Bhuiyan 2007) | TRDN | ? | AD |
| CPVT4 | 14q32.11 (Nyegaard 2012) | CALM1 | | AD |

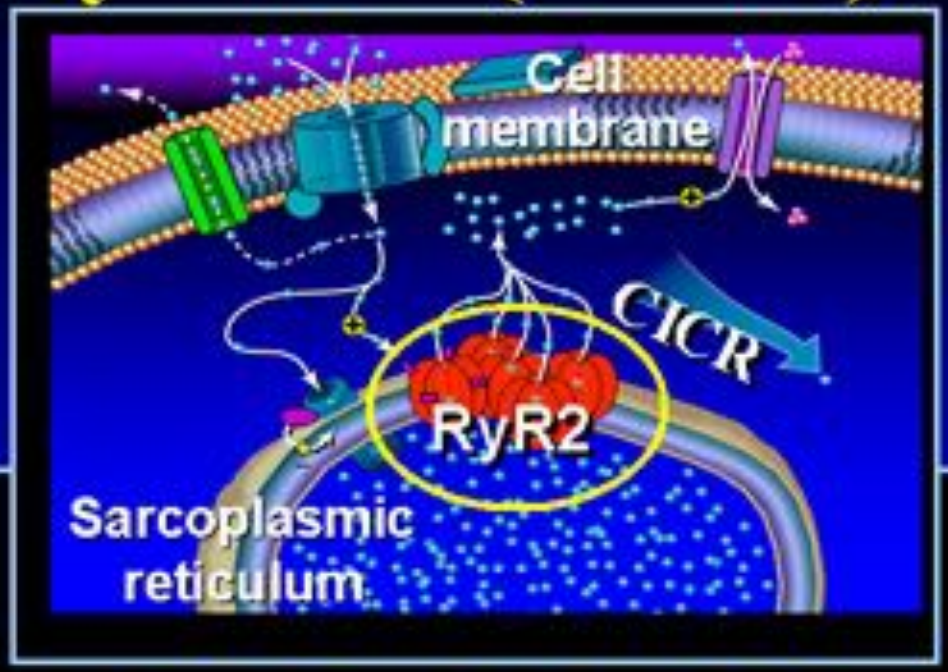
Ryanodine receptor (RyR) is the $Ca^{2+}$ -induced $Ca^{2+}$ release channel in cells. RyR1 and RyR2 are its isoforms expressed in the skeletal and cardiac muscles, respectively. Their missense mutations, which are clustered in three regions that correspond to each other, cause hereditary disorders such as malignant hyperthermia and central core disease in skeletal muscle and CPVT, a form of arrhythmogenic right ventricular dysplasia (ARVD2), dilated cardiomyopathy, sinoatrial node and atrioventricular node dysfunction, atrial fibrillation, and atrial standstill in cardiac muscle (Bhuiyan 2007; Ogawa 2007). Usually with high penetrance.

The R176Q mutation in RyR2 predisposes the heart to catecholamine-induced oscillatory calcium-release events that trigger a calcium-dependent VT (Kannankeril 2006). Research points out that patients carriers of familial CPVT with dominant inheritance pattern present a missense mutation of the SR in the CRC channel in type 2 ryanodine receptor (RyR2) where three mutations were verified: (P2328S, Q4201R, V4653F). This entity of early clinical onset and mean mortality rate of 30% up to 30 years old, is characterized by bursts of bidirectional VT and/or PVT related to exercise, (catecholamine-dependent) with no evidence of structural heart disease.

Catecholaminergic idiopathic ventricular fibrillation (IVF) is eventually observed.

# Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Cellular

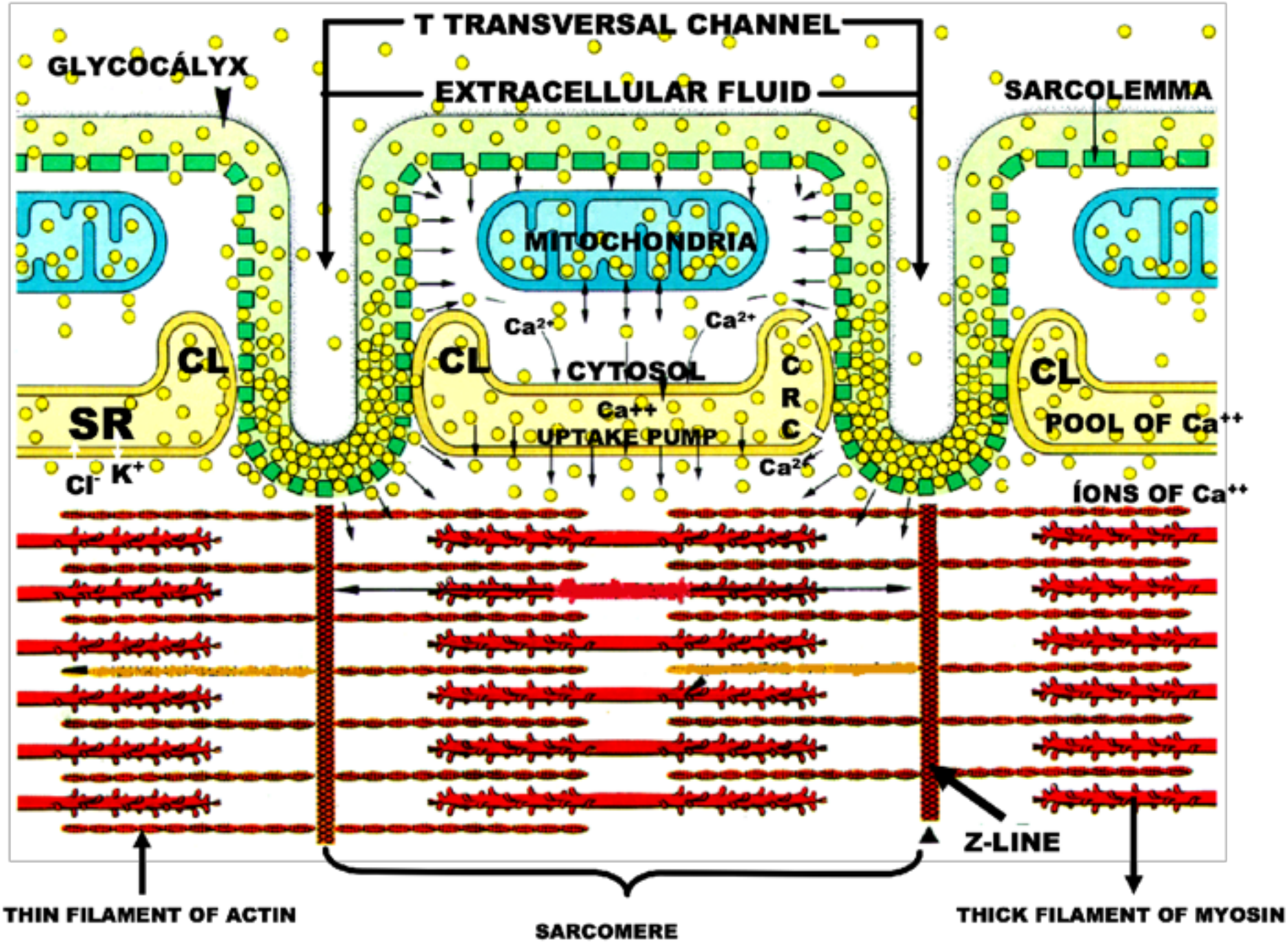



Molecular


*RyR2* (CPVT1, Ch 1q42.1-q43)

**Mutations in *RyR2* cause 2/3 of CPVT**

Priori et al. *Circulation* 2002;106(1):1479-1487


T TRANSVERSAL CHANNEL
GLYCOCÁLYX
EXTRACELLULAR FLUID
SARCOLEMMA
MITOCHONDRIA
Ca2+
Ca2+
CL
CL
CL
CYTOSOL
C
R
C
SR
Ca++
UPTAKE PUMP
POOL OF Ca++
Cl- K+
Ca2+
ÍONS OF Ca++
Z-LINE
THIN FILAMENT OF ACTIN
SARCOMERE
THICK FILAMENT OF MYOSIN

# Intracellular calcium channels of the Sarcoplasmic Reticulum (SR)

I)$Ca^{2+}$ release channel, Ryanodine receptor, hyperphosphorilated by protein kinase A (PKA) from the intracellular sarcoplasmic reticulum or CRC "Calcium Release Channel".

II)$Ca^{2+}$-ATPase uptake pump or $Ca^{2+}$ $Mg^{2+}$ ATPase (Sarcoplasmic $Ca^{2+}$ (ATPase reticulum SERCA).

III)IP3 receptor, Inositol triphosphate or IP3: inositol 1,4,5-trisphosphate (IP3) receptor channel.

The SR is an intracellular structure that holds a key role in muscular contraction and relaxation by its capacity of fast release and uptake of myoplasm from the $Ca^{2+}$ ion, by having only in the junctions with the T system of the plasmatic membrane, the so-called $Ca^{2+}$ release channel, CRC (Calcium Release Channel) or Ryanodine receptor. This channel, intracytoplasmatically located in the SR membrane, is very close to the sarcolemmal channels $I_{Ca\text{-}L}$ type and like this is voltage and time-dependent. Each $I_{Ca\text{-}L}$ type channel controls a group between 4 and 10 ryanodine receptor channels.

Each channel is a large and complex protein of 30 S, formed by four polypeptidic subunits in firm association of Mr ~560.000 with quatrefoil or tetrameric morphology that contours a single hydrophilic, cation-selective pore, with conductance for divalent cations from 100 to 150 pS with 50 mM $Ca^{2+}$ and for monovalent cations of ~750 pS with 250 mM K+ that is found in the SR membrane and plays its role by releasing the cation of the SR lumen into the cytosol (efflux). It may be blocked by Ryanodine, a toxin derived from an alkaloid plant with nanomolar affinity, and for this reason it is known as ryanodine receptor.

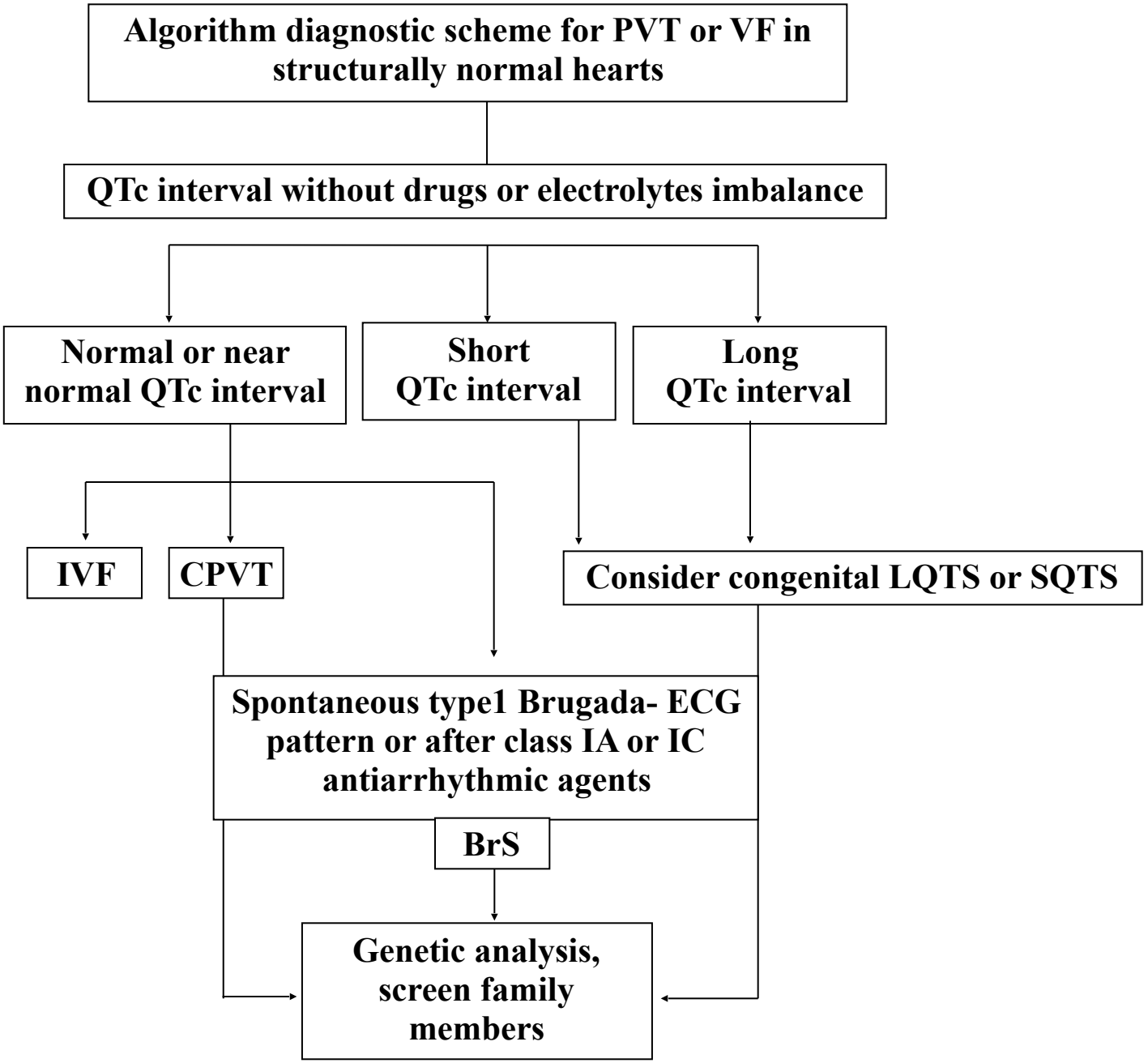
The substances that stimulate this channel improve contractility, and those that block, worsen it. It seems to be the most important channel in heart failure, since a dramatic increase has been observed in its phosphorylation (hyperphosphorylation) in patients with terminal heart failure, what would provide another basis for using β-blockers in this condition.

# Electrocardiographic features

I. **Heart Rate (HR):** baseline bradycardia tendency off drugs is observed in all carriers. (slow HR);
II. **Rhtyhm:** Sinus rhythm is the rule. Abnormalities in sinoatrial node function, as well as atrioventricular nodal function, could produce atrial fibrillation, atrial flutter and atrial standstill (sick sinus syndrome).
III. **QTc interval:** normal at resting ECG (Postma 2005).

See proposed algorithm diagnostic scheme for PVT or VF in structurally normal hearts based initially in QT interval duration.

Algorithm diagnostic scheme for PVT or VF in structurally normal hearts. Modify from Srivathsan (Srivathsan 2005).



**I. U-wave alternans:** U-wave alternans was observed in following clinical circumstances:

- After ventricular pacing at 160 bpm
- During the recovery phase after the exercise stress test
- Following a pause from sinus arrest and a change in T-wave was also noted.

Precordial $V_3$-$V_5$ are the leads showing alternans more clearly (Aizawa 2006).

**II. Arrhthmias**

A. Supraventricular arrhthmias

The atrium could be affected by the channelopaties and arrhythmia in these chambers may cause syncope. Atrial fibrillation, atrial flutter, atrial standstill, and sick sinus syndrome are eventually presen (Fazelifar 2007).

## Ventricular arrhthmias

- ➢ Ventricular arrhythmias elicited exclusively under by exercise or adrenergic stress. Typically are induced by isoproterenol infusion.
- ➢ Premature Ventricular Complex (PVCs) Calcium channel antagonist, verapamil, can suppress PVCs and nonsustained VT salvoes in CPVT caused by RyR2 mutations. Modifying the abnormal calcium handling by calcium antagonists might have therapeutic value (Swan 2005). Calcium antagonists partially suppressed CPVT in autosomal dominant cases.
- ➢ Polymorphic ventricular tachycardia (PVT) occurs during physical exercise or emotional stress. Mean heart rate during CPVT was 192 (30) beats/min. Most cases are non-sustained (72%), but 21% are sustained and 7% are associated with ventricular fibrillation.
- ➢ PVT and bidirectional in association is observed in 21% of cases in pediatric group.
- ➢ There are 100% inducement of CPVT by exercise, 75% by catecholamine infusion, and none by programmed stimulation. No late potential is recorded. Onset is in the right ventricular outflow tract in more than 50% the cases (Sumitomo 2003). His-Purkinje system is an important source of focal arrhythmias in CPVT (Cerrone 2007).
- ➢ Bidirectional ventricular tachycardia is a more typical feature.

**Concept:** Bidirectional ventricular tachycardia is regular VT with pattern of CRBBB, alternating QRS axis, determining the presence of two morphologies of QRS, secondary to change in axis (SÂQRS) in the frontal plane, from beat to beat, with differences of approximately 180º. One beat presents SÂQRS between –60º and –90º and the following, approximately +120º to +130º. The event may be both ventricular and supraventricular. The help of the His bundle electrogram is necessary to determine this.

**Possible Etiologies:** low prevalence (rare). Acquired forms are mainly observed in elderly patients. The clinical setting may be:

- Digitalis toxicity or digitalis poisoning: it is the main clinical cause (Kummer 2006);
- Digoxin and amiodarone treatment for rapid atrial fibrillation (Lien 2004);
- Herbal aconite poisoning (Smith 2005). Aconitine and its related alkaloids are known cardiotoxins with no therapeutic role in modern western medicine. The rootstocks of Aconitum plants, which contain aconite alkaloids, have been common components of Chinese herbal recipes. All patients developed symptoms of aconite toxicity within 2 h of herb ingestion. Most developed tachyarrhythmias, including VT and VF. It is necessary strict surveillance of herbal substances with low safety margins.
- Severe myocardial disease (advanced cardiomyopathy)
- Cardiac metastasis (Dorfman 2006).
- Without structural heart diseases:
  - ✓ CPVT
  - ✓ Andersen-Tawil Syndrome (ATS) mutations in KCNJ2, which encodes the apha subunit of the potassium channel Kir2.1. The mutation is present in≈ 60% of cases.

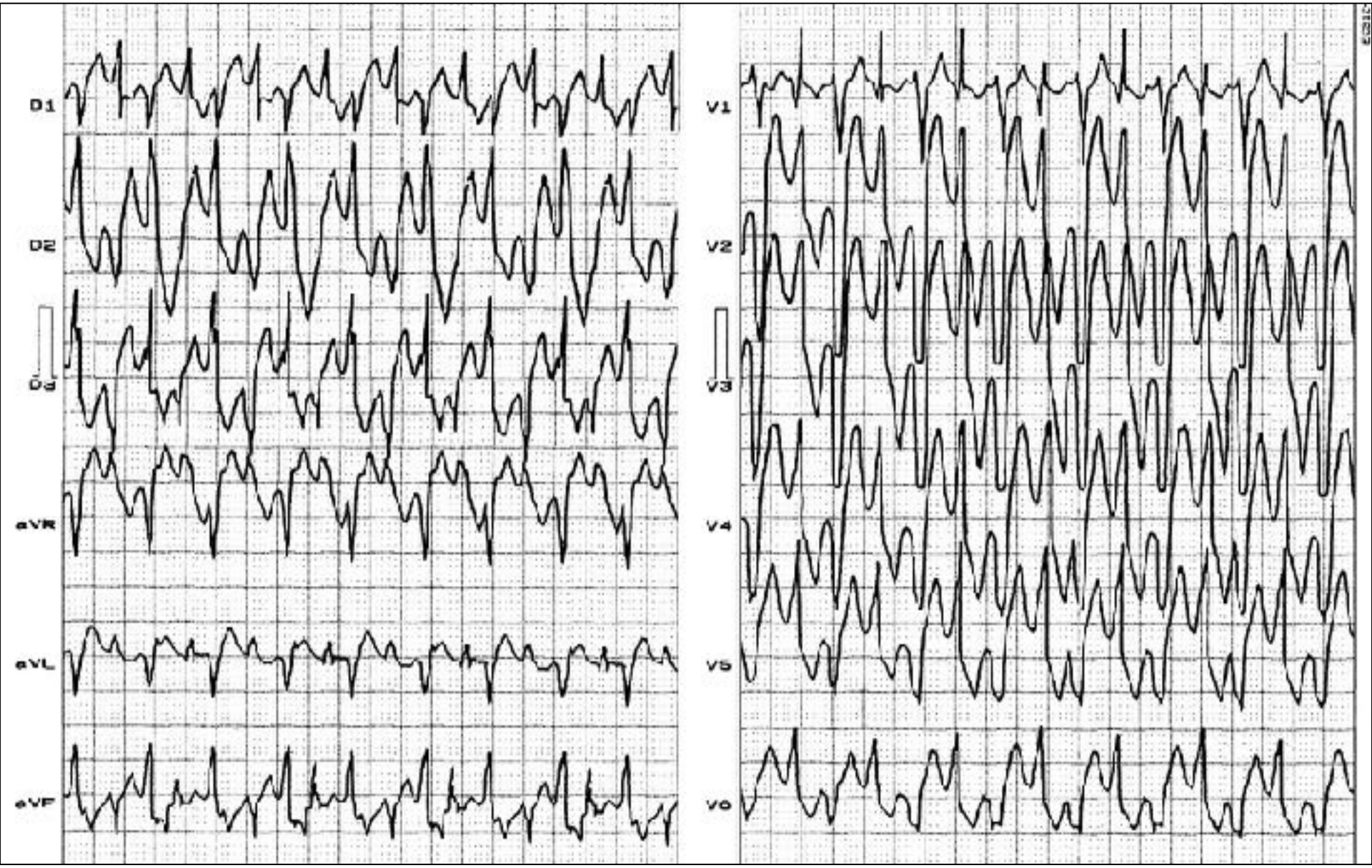
**Electrophysiological mechanism in cases of CPVT:** they are initiated by delayed afterdepolarizations and triggered activity (Mohamed 2007), with focus the origin of which is in the proximal region of the right bundle, triggering activity and alternating activation of the LV by the left anterior fascicle and posteroinferior left fascicle of the left branch. The events are caused by derangements of the control of intracellular calcium. A gain-of-function mutations of cardiac ryanodine receptor RyR2 gene is the cause of familial or CPVT. In a animal model of mutant RyR2 that is characterized by reduced FKBP12.6 binding to the RyR2 on beta stimulation, the impaired coupled gating characteristic of these mutations was modeled by reducing cooperativity of RyR2 activation. In current-clamp mode, the mutant RyR2 model exhibited increased diastolic RyR2 open probability that resulted in formation of delayed afterdepolarizations (Iyer 2007). Calsequestrin is a high-capacity $Ca^{2+}$-binding protein expressed inside the SR, an intracellular $Ca^{++}$release and storage organelle in muscle. Patients with a missense mutation of the calsequestrin 2 gene (CASQ2) are at risk for CPVT. This mutation (CASQ2(D307H)) results in decreased ability of CASQ2 to bind $Ca^{2+}$ in the sarcoplasmic reticulum (SR). The CASQ2(D307H) mutation manifests its pro-arrhythmic consequences due to store-overload-induced $Ca^{2+}$ release and delayed afterdepolarization formation due to excess free SR $Ca^{2+}$ following rapid pacing and beta-adrenergic stimulation (Faber 2007).

The arrhythmogenic CASQ2 (D307H) mutation impairs SR Ca++ storing and release functions and destabilizes the Ca++ -induced Ca2+ release mechanism by reducing the effective Ca++ buffering inside the SR and/or by altering the responsiveness of the Ca++ release channel complex to luminal C Ca2+. These results establish at the cellular level the pathological link between CASQ2 mutations and the predisposition to adrenergically mediated arrhythmias observed in patients carrying CASQ2 mutation (Viatchenko-Karpinski 2004).

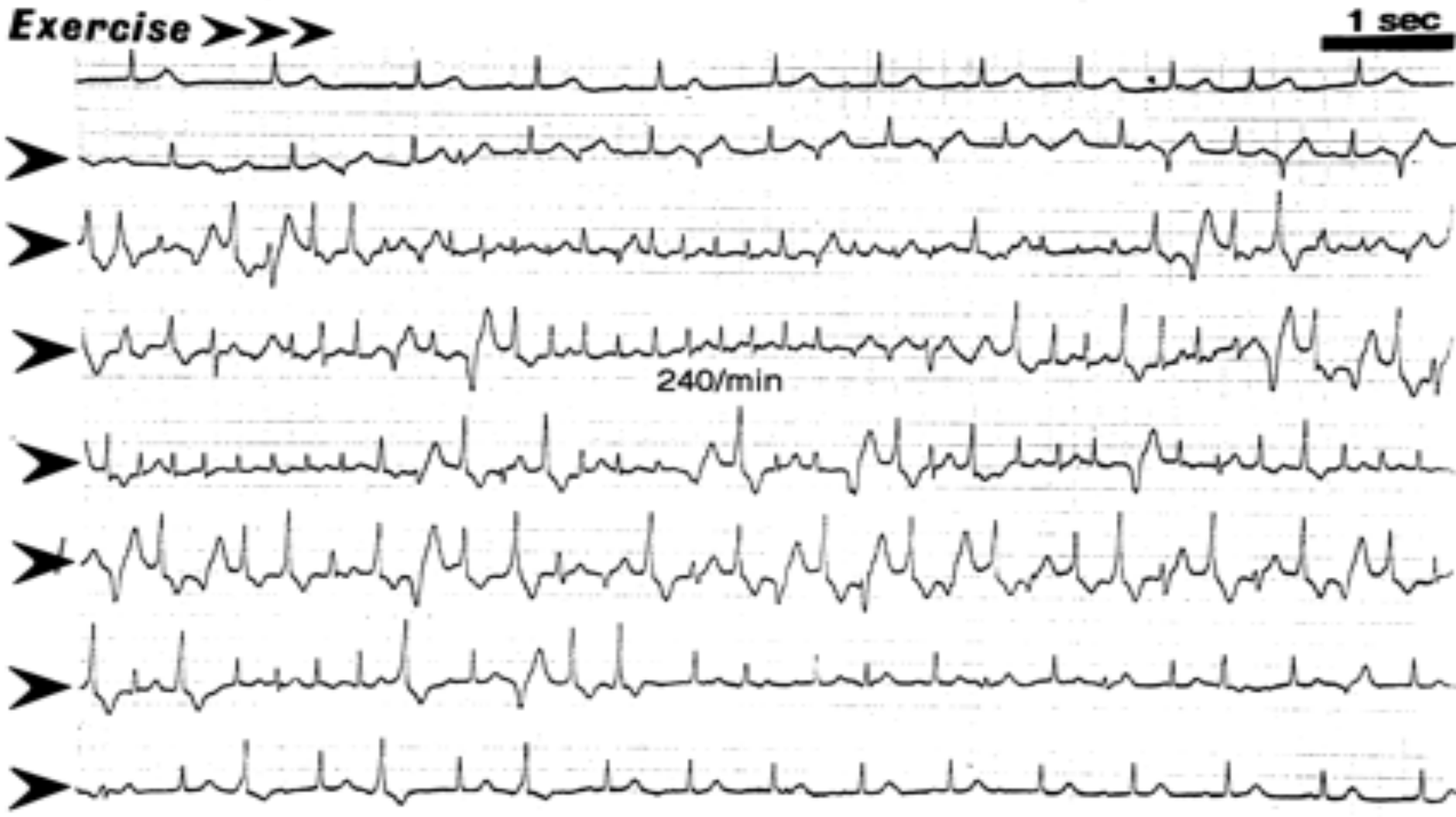
CSQ2 not only determines the $Ca^{2+}$ storage capacity of the SR but also positively controls the amount of $Ca^{2+}$ released from this organelle during excitation-contraction coupling. CSQ2 controls $Ca^{2+}$ release by prolonging the duration of $Ca^{2+}$ fluxes through the SR $Ca^{2+}$-release sites. In addition, the dynamics of functional restitution of $Ca^{++}$-release sites after $Ca^{2+}$ discharge is prolonged when CSQ2 levels is elevated and accelerated in the presence of lowered CSQ2 protein levels. Furthermore, profound disturbances in rhythmic $Ca^{2+}$ transients in myocytes undergoing periodic electrical stimulation are observed when CSQ2 levels are reduced. CSQ2 is a key determinant of the functional size and stability of SR $Ca^{++}$ stores in cardiac muscle. CSQ2 appears to exert its effects by influencing the local luminal $Ca^{2+}$ concentration-dependent gating of the $Ca^{2+}$-release channels and by acting as both a reservoir and a sink for $Ca^{2+}$ in SR. The abnormal restitution of $Ca^{++}$-release channels in the presence of reduced CSQ2 levels provides a plausible explanation for VT associated with mutations of CSQ2 (Terentyev 2003).

# Electrocardiographic characterization

- Regular VT
- Heart Rate between 140 bpm and 200 bpm
- CRBBB Pattern
- Sudden change of QRS morphology by change of SÃQRS, successively from beat to beat
- SÂQRS in the frontal plane with differences close to 180º: one beat presents ÂQRS between –60º and –90º (CRBBB + LAFB) and the following between +120º to +130º (CRBBB + LPFB).
- Eventually alternating right and left bundle branch block morphology. The origin of the tachycardia is located near the His bundle bifurcation. This suggested a single focus at the interventricular septum with two exit sites, depolarizing the right and left ventricle in an alternate fashion (Dorfman 2006). Two sets of fairly constant and alternating VA intervals are recorded. This fact is consistent with two ventricular circuits used alternatively. It is postulated that the tachycardia is due to macroreentry involving the two fascicles of the left branch. Reentry may be a possible mechanism in some cases of bidirectional tachycardia.




Female, white, 20-year-old, recurrent syncope of uncertain etiology after physical and emotional stress carrier of familial catecholaminergic cardiomyopathy. Alternans QRS complexes are observed with alternating right and left bundle branch block morphology. The QRS axis shifts from –60º to +120º.




ECG monitoring during a stress test (continuous strips) After an acceleration of the sinus rhythm, monomorphic ventricular premature beats appear with a bigeminy. Supraventricular tachycardia (atrial fibrillation and junctional tachycardia) with narrow QRS complexes are then recorded interfering with multiform ventricular premature beats and bidirectional ventricular tachycardia. At the end of the exercise, the arrhythmia disappears in the reverse order.

**Clue for electrocardiographic diagnosis of CPVT: association on ECG sinus bradycardia + normal QTC interval + stress-related, bidirectional VT or PVT in the absence of apparent structural heart disease (Sumitomo 2003; Priori 2002; Liu 2007)**

**Prognosis:** The mortality rate in untreated individuals is 30-50% by age 40.

**Postmortem genetic testing:** Postmortem genetic testing of RyR2 should be considered as a part of the comprehensive medicolegal autopsy investigation of a sudden unexplained death case and that this potentially heritable and often elusive arrhythmia syndrome be scrutinized carefully in family members of those who experience sudden unexplained death (Tester 2004).

**Treatment:**

Beta adrenergic blockers are the most effective pharmacological approach, unfortunately 30% of patients have recurrences. Beta-Blockers reduce arrhythmias, but in 30% of patients an implantable defibrillator may be required (Priori 2002). Implantable cardioverter defibrillator (ICD) is necessary for prophylaxis of SCD because ≈30% of patients still experience VTs (Liu 2007). may arise in certain distinct areas but the prognosis is poor. The onset of CPVT may be an indication for an ICD.

# References


1. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. Mayo Clin Proc. 1998;73:250-69.
2. Adeniran I, El Harchi A, Hancox JC, Zhang H. Proarrhythmia in KCNJ2-linked short QT syndrome: insights from modelling. Cardiovasc Res.2012 Apr 1;94(1):66-76.
3. Aizawa Y, Komura S, Okada S, Chinushi M, Aizawa Y, Morita H, Ohe T.Distinct U wave changes in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). Int Heart J. 2006; 47: 381-389.
4. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. Br Heart J 1993; 70:43.
5. Anselm D, Barbosa-Barros R, de Sousa Belém L, Nogueira de Macedo R, Pérez-Riera A, Baranchuk A. Brugada Phenocopy induced by acute inferior ST-segment elevation myocardial infarction with right ventricular involvement. Inn Card Rhythm Manag. 2013;4:1092-4.
6. Anselm DD, Evans JM, Baranchuk A. Brugada phenocopy: A new electrocardiogram phenomenon. World journal of cardiology. 2014;6(3):81.
7. Anttonen O, Vaananen H, Junttila J, Huikuri HV, Viitasalo M.Electrocardiographic transmural dispersion of repolarization in patients with inherited short QT syndrome. Ann Noninvasive Electrocardiol. 2008;13:295–300.
1. Antzelevitch Ch, Xin Yan G, Shimuzi W, et al. Electrical heterogeneity, the ECG, and Cardiac Arrhthmias. In Zipes DP, Jalife J Cardiac Electrophysiology From Cell to Bedside, Thrid Edition. W.B. Saunders Company.2000. Chaper 26 p: 222-238.
2. Antzelevitch C.; The Brugada syndrome. ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol*. 12 2001:268-272.
8. Antzelevitch C. Modulation of transmural repolarization. Ann N Y Acad Sci. 2005 Jun;1047:314-23.
9. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E,Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005 Feb 8;111(5):659-70.

10. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP Jr, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haïssaguerre M, Schimpf R, Borggrefe M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007 Jan 30;115(4):442-9.
11. Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm 2010;7:549–58.
12. Antzelevitch C, Yan GX, Viskin S. Rationale for the use of the terms J–wave syndromes and early repolarization. J Am Coll Cardiol 2011;57:1587–90.
13. Arce M, Riera AR, Femenía F, Baranchuk A. Brugada electrocardiographic phenocopy in a patient with chronic Chagasic cardiomyopathy. Cardiol J. 2010; 17(5): 525-7.
14. Awad SF, Barbosa–Barros R, de Sousa Belem L, Cavalcante CP, Riera ARP, Garcia–Niebla J, et al. Brugada phenocopy in a patient with pectus excavatum: Systematic review of the ECG manifestations associated with pectus excavatum. Annals of Noninvasive Electrocardiology. 2013;18(5):415-20.
15. Babai Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm. 2007 Aug;4(8):1009-12.
16. Baranchuk A, Nguyen T, Ryu MH, Femenía F, Zareba W, Wilde AA, et al. Brugada phenocopy: new terminology and proposed classification. Annals of Noninvasive Electrocardiology. 2012;17(4):299-314.
17. Bayés de Luna A, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, Lambiase P, Riera AP, Garcia-Niebla J, Pastore C, Oreto G, McKenna W, Zareba W, Brugada R, Brugada P. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012 Sep;45(5):433-42.
18. Bazett HC. "An analysis of the time-relations of electrocardiograms". *Heart 1920;* (7): 353–370.
19. Bellocq C, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM, Baró I, Wilde AA. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004 May 25;109(20):2394-7.
20. Bhuiyan ZA, Hamdan MA, Shamsi ETA, Postma AV, Mannens MMAM, Wilde AAM, Al-Gazali L. A novel early onset lethal form of catecholaminergic polymorphic ventricular tachycardia maps to chromosome 7p14-p22. J. Cardiovasc. Electrophysiol. 2007;18: 1060-1066.

19. Bhuiyan ZA, van den Berg MP, van Tintelen JP, Bink-Boelkens MT, Wiesfeld AC, Alders M, Postma AV, van Langen I, Mannens MM, Wilde AA. Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. Circulation. 2007;116:1569-1576.
20. Bianco M, Bria S, Gianfelici A, Sanna N, Palmieri V, Zeppilli P. Does early repolarization in the athlete have analogies with the Brugada syndrome? Eur Heart J. 2001 March 22(6):504-10.
21. Bieganowska K, Sawicka-Parobczyk M, Bieganowski M, Piskorski J. Tpeak -tend interval in 12-lead electrocardiogram of healthy children and adolescents tpeak -tend interval in childhood. Ann Noninvasive Electrocardiol. 2013 Jul;18(4):344-51.
22. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. Europace. 2007 Oct;9(10):947-50.
23. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391−6.
24. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS,Guerchicoff A, Bianchi F, Giustetto C, Schimpf R, Brugada P, Antzelevitch C. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004 Jan 6;109(1):30-5.
25. Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpón E, Hu D, Desai M, Borggrefe M, Häissaguerre M, Kanter R, Pollevick GD,Guerchicoff A, Laiño R, Marieb M, Nademanee K, Nam GB, Robles R, Schimpf R, Stapleton DD, Viskin S, Winters S, Wolpert C,Zimmern S, Veltmann C, Antzelevitch C. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. Heart Rhythm. 2010 Dec;7(12):1872-82.
26. Butz T, Vogt J, Vielhauer C, Wetzel U, Langer C, Horstkotte D. Detection of a type 1 Brugada ECG by ECG recording at a higher intercostal space of leads V(1) and V (2). Herz. 2010 Mar; 35(2):112.
27. Campbell TJ. Characteristics of cardiac action potentials in marsupials. J Comp Physiol B. 1989;158(6): 759-62.

19. Carpenter E, Peers C. Swelling- and cAMP-activated Cl- currents in isolated rat carotid body type I cells. J Physiol. 1997 Sep 15; 503: 497-511.
20. Carturan E, Basso C, Thiene G. Molecular investigation of sudden death G Ital Cardiol (Rome). 2007;8:752-759.
29. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, Quiñones Pérez MA, Fayad Rodríguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006 May 2;47(9):1828-34.
30. Cerrone M, Noujaim SF, Tolkacheva EG, Talkachou A, O'Connell R, Berenfeld O, Anumonwo J, Pandit SV, Vikstrom K, Napolitano C, Priori SG, Jalife J. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. Circ Res. 2007;101:1039-1048.
31. Cheng TO. Digitalis administration: an underappreciated but common cause of short QT interval. Circulation. 2004 Mar 9;109(9):e152.
32. Chevallier S, Forclaz A, Tenkorang J, Ahmad Y, Faouzi M, Graf D, Schlaepfer J, Pruvot E. New electrocardiographic criteria for discriminating between Brugada types 2 and 3 patterns and incomplete right bundle branch block. J Am Coll Cardiol. 2011 Nov 22;58(22):2290-8.
33. Chinushi M, Sato A, Izumi D, Furushima H. Nifekalant enlarged the transmural activation-recovery interval difference as well as the peak-to-end interval on surface ECG in a patient with short-QT syndrome. J Cardiovasc Electrophysiol. 2012 Aug;23(8):877-80.
34. Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJ, Verkerk AO, de Groot JR, Bhuiyan Z, Bezzina CR, Veldkamp MW, Linnenbank AC, van der Wal AC, Tan HL, Brugada P, Wilde AA, de Bakker JM. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation. 2005 Nov 1;112(18):2769-77.
35. Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Right bundle branch block, right precordial st-segment elevation, and sudden death in young people.Circulation. 2001 Feb 6;103(5):710-7.

29. Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, Ackerman MJ. Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3. Heart Rhythm. 2007; 4: 161-166.
30. Cui C, Yan G. Update of the J wave syndrome and acute ischemia J wave (in Chinese). Chin J Cardiol 2010;38:299−300.
31. Daccarett M, Freih M, Machado C. Acute cannabis intoxication mimicking Brugada-like ST segment abnormalities. International journal of cardiology. 2007;119(2):235-6. Darbar D, Roden DM, Ali MF, Yang T, Wathen MS. Images in cardiovascular medicine. Himalayan T waves in the congenital long-QT syndrome. Circulation. 2005 Mar 22;111(11):e161.
38. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. Heart Rhythm. 2009 Mar; 6 (3 Suppl): S8-14.
39. Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. Curr Opin Cardiol. 2010 Jan; 25: 59-64.
40. Das MK, Maskoun W, Shen C, et al. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm. 2010 Jan; 7:74-80.
41. Davey P, Bateman J. Heart rate and catecholamine contribution to QT interval shortening on exercise. Clin Cardiol. 1999 Aug;22(8):513-8.
42. Deo M., Ruan Y., Pandit S. V., Shah K., Berenfeld O., Blaufox A, Cerrone M, Noujaim SF, Denegri M, Jalife J, Priori SG. KCNJ2 mutation in short QT syndrome3 results in atrial fibrillation and ventricular proarrhythmia. Proc Natl Acad Sci U S A. 2013 Mar 12;110(11):4291-6.
43. Dogan M, Ertem A, Cimen T, Yeter E. Type-1 Brugada-like ECG pattern induced by adrenal crisis. Herz. 2013:1-3.
44. Doi A, Takagi M, Maeda K, Tatsumi H, Shimeno K, Yoshiyama M. Conduction delay in right ventricle as a marker for identifying high-risk patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2010 Jun 1;21(6):688-96.
45. Dorfman FK, Mesas CE, Cirenza C, de Paola AA. Bidirectional ventricular tachycardia with alternating right and left bundle branch block morphology in a patient with metastatic cardiac tumors. J Cardiovasc Electrophysiol. 2006;17:784-785.

38. Dreyfuss D, Jondeau G, Couturier R, Rahmani J, Assayag P, Coste F. Tall T waves during metabolic acidosis without hyperkalemia: a prospective study. Crit Care Med. 1989 May;17(5):404-8.
39. Eldar M, Pras E, Lahat H.A Missense Mutation in the CASQ2 Gene Is Associated with Autosomal-Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia. Trends Cardiovasc Med 2003; 13: 148-151.
49. Faber GM, Rudy Y. Calsequestrin mutation and catecholaminergic polymorphic ventricular tachycardia: A simulation study of cellular mechanism.Cardiovasc Res. 2007;75: 79-88.
50. Farwell D, Gollob MH. Electrical heart disease: Genetic and molecular basis of cardiac arrhythmias in normal structural hearts. Can J Cardiol. 2007; 23 Suppl A:16A-22A.
51. Fazelifar AF, Nikoo MH, Haghjoo M, Emkanjoo Z, Alizadeh A, Bonakdar HR, Sdr-Ameli MA. A patient with sick sinus syndrome, atrial flutter and bidirectional ventricular tachycardia: Coincident or concomitant presentations? Cardiology Journal 2007 6: 585-588.
52. Fridericia LS. "The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease". *Acta Medica Scandinavica* 1920;(53): 469–486.
53. Gaita, F., Giustetto, C., Bianchi, F., Wolpert, C., Schimpf, R., Riccardi, R., Grossi, S., Richiardi, E., Borggrefe, M. Short QT syndrome: a familial cause of sudden death. Circulation 2003;108: 965-970.
54. Garberoglio L, Giustetto C, Wolpert C, Gaita F. Is acquired short QT due to digitalis intoxication responsible for malignant ventricular arrhythmias? J Electrocardiol. 2007;40:43–46.
55. Garnett CE, Zhu H, Malik M, Fossa AA, Zhang J, Badilini F, Li J, Darpö B, Sager P, Rodriguez I. Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects. Am Heart J. 2012 Jun;163(6):912-30.
56. Garson A Jr. How to measure the QT interval – what is normal? Am J Cardiol 1993; 72:14B–16B.
57. Garson A Jr, Dick M 2nd, Fournier A, Gillette PC, Hamilton R, Kugler JD, van Hare GF 3rd, Vetter V, Vick GW 3rd. The long QT syndrome in children. An international study of 287 patients. Circulation. 1993 Jun;87(6):1866-72.

49. Gazzoni GF, Borges AP, Bergoli LC, Soares JL, Kalil C, Bartholomay E. Brugada-like electrocardiographic changes induced by hypokalemia. Arquivos Brasileiros de Cardiologia. 2013;100(3):e35-7.
50. Genaro NR, Anselm DD, Cervino N, Estevez AO, Perona C, Villamil AM, Kervorkian R, Baranchuk A. Brugada phenocopy clinical reproducibility demonstrated by recurrent hypokalemia. Ann Noninvasive Electrocardiol. 2014 Jul;19(4):387-90.
60. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, Leone G, Maury P, Anttonen O, Haissaguerre M, Gaita F. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J. 2006 Oct;27(20):2440-7.
61. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, ProbstV, Blanc JJ, Sbragia P, Dalmasso P,Borggrefe M, Gaita F.Long-term follow-up of patients with short QT syndrome. J AmColl Cardiol 2011;58:587–595.
62. Gollob MH, Redpath CJ, Roberts JD. The Short QT syndrome Proposed Diagnostic Criteria. J Am Coll Cardiol; 2011; 57: 802-812.
63. Guo DL, Zhao XJ, WuY, Liu TX, Kowey PR, Yan GX. L−type calcium current reactivation contributes to arrhythmogenesis associated with action potential triangulation. J Cardiovasc Electrophysiol 2007;18:196−203.
64. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, Yan GX. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol. 2008 Nov-Dec;41(6):567-74.
65. Gurabi Z, Koncz I, Patocskai B, Nesterenko VV, Antzelevitch C. Cellular mechanism underlying hypothermia−induced ventricular tachycardia/ventricular fibrillation in the setting of early repolarization and the protective effect of quinidine, cilostazol, and milrinone. Circ Arrhythm Electrophysiol 2014;7:134−42.
66. Gussak, I., Brugada, P., Brugada, J., Wright, R. S., Kopecky, S. L., Chaitman, B. R., Bjerregaard, P. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000;94: 99-102.
67. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016−23.
68. Haraoka K, Morita H, Saito Y, et al. Fragmented QRS is associated with torsades de pointes in patients with acquired long QT syndrome. Heart Rhythm. 2010 Dec;7:1808-1814.
69. Hattori T, Makiyama T, AkaoM, Ehara E, Ohno S, Iguchi M, Nishio Y, Sasaki K, Itoh H, Yokode M, Kita

60. Hayashi H, Sumiyoshi M, Yasuda M, Komatsu K, Sekita G, Kawano Y, Tokano T, Nakazato Y, Daida H. Prevalence of the Brugada-type electrocardiogram and incidence of Brugada syndrome in patients with sick sinus syndrome. Circ J. 2010 Feb;74(2):271-7.
61. Hersch C. Electrocardiographic changes in head injuries. Circulation 1961;23:853−60.
62. Hiss RG, Lamb LE. Electrocardiographic findings in 122.043 individuals. Circulation 1962; 25: 947-61.
60. Homsi M, Alsayed L, Safadi B, et al. Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Ann Noninvasive Electrocardiol. 2009 Oct;14:319-326.
61. Hong, K., Bjerregaard, P., Gussak, I., Brugada, R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J. Cardiovasc. Electrophysiol. 2005;16: 394-396.
69. Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E, Santos-de-Soto J, Grueso-Montero J, Diaz-Enfante E, Brugada P, Sachse F,Sanguinetti MC, Brugada R. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovasc Res. 2005 Dec 1;68(3): 433-40.
70. Ikeda T, Sakurada H, Sakabe K, Sakata T, Takami M, Tezuka N, Nakae T, Noro M, Enjoji Y, Tejima T, Sugi K, Yamaguchi T. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. J Am Coll Cardiol. 2001 May;37(6):1628-34.
71. Inagaki N, Gonoi T, Clement JP, Namba N, Inazawa J, Gonzalez G, Aguilar-Bryan L, Seino S, Bryan J. "Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor". Science 270 (5239): 1166–70.
72. Iribarren C, Round AD, Peng JA, Lu M, Klatsky AL, Zaroff JG, Holve TJ, Prasad A, Stang P. Short QT in a cohort of 1.7 million persons: prevalence, correlates, and prognosis. Ann Noninvasive Electrocardiol. 2014 Sep;19(5):490-500.
73. Iyer V, Hajjar RJ, Armoundas AA. Mechanisms of abnormal calcium homeostasis in mutations responsible for catecholaminergic polymorphic ventricular tachycardia. Circ Res. 2007;100: 22-31.
74. Jastrzebski M, Kukla P. Ischemic J wave: Novel risk marker for ventricular fibrillation? Heart Rhythm 2009;6:829−35.

1. Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: A Brugada syndrome variant? J Cardiovasc Electrophysiol 2000;11:95−8.
2. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, Shimizu W, Kurita T, Suyama K, Noda T, Satomi K, Okamura H, Tomoike H; Brugada Syndrome Investigators in Japan. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol. 2009 Oct; 2(5):495-503.
3. Kaneko Y, Nakajima T, Irie T, Kurabayashi M. Brugada-type ST-elevation Associated with Writhing of a Reconstructed Esophagus. Internal medicine (Tokyo, Japan). 2013;52(19):2287.
4. Kannankeril PJ, Mitchell BM, Goonasekera SA, Chelu MG, Zhang W, Sood S, Kearney DL, Danila CI, De Biasi M, Wehrens XH, Pautler RG, Roden DM, Taffet GE, Dirksen RT, Anderson ME, Hamilton SL. Mice with the R176Q cardiac ryanodine receptor mutation exhibit catecholamine-induced ventricular tachycardia and cardiomyopathy. Proc Natl Acad Sci U S A. 2006; 103: 12179-12184.
5. Kataoka H. Electrocardiographic patterns of the Brugada syndrome in 2 young patients with pectus excavatum. J Electrocardiol. 2002 Apr; 35(2): 169-71.
6. Ki CS, Jung CL, Kim HJ, Baek KH, Park SJ, On YK, Kim KS, Noh SJ, Youm JB, Kim JS, Cho H. A KCNQ1 mutation causes age-dependant bradycardia and persistent atrial fibrillation. Pflugers Arch. 2014 Mar;466(3):529-40.
7. Kilicaslan F, Tokatli A, Ozdag F, Uzun M, Uz O, Isilak Z, Yiginer O, Yalcin M, Guney MS, Cebeci BS. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with moderate and severe obstructive sleep apnea. Pacing Clin Electrophysiol. 2012 Aug;35(8):966-72.
8. Kobza R, Roos M, NiggliB, AbacherliR, Lupi GA, Frey F, Schmid JJ, Erne P. Prevalence of long and short QT in a Young population of 41,767 predominantly male Swiss conscripts. Heart Rhythm 2009;6:652–657.
9. Kovacic JC, Kuchar DL. Brugada pattern electrocardiographic changes associated with profound electrolyte disturbance. Pacing and clinical electrophysiology. 2004;27(7):1020-3.
10. Kraus F. Concerning the effect of calcium on the circulation (in German). Dtsch Med Wochenschr 1920;46:201−3.
11. Kukla P, Jastrzebski M, Bacior B, Gomuła P, Grodecki J, Kawecka-Jaszcz K. Variant Brugada syndrome--

69. Jim MH, Siu CW, Chan AO, Chan RH, Lee SW, Lau CP. Prognostic implications of PR-segment depression in inferior leads in acute inferior myocardial infarction. Clin Cardiol. 2006 Aug;29(8): 363-8.
70. Jørgensen IN, Skakkebaek A, Andersen NH, Pedersen LN, Hougaard DM, Bojesen A, Trolle C, Gravholt CH. Short QTc Interval in Males with Klinefelter Syndrome-Influence of CAG Repeat Length, Body Composition, and Testosterone Replacement Therapy. Pacing Clin Electrophysiol. 2015 Jan 23. doi: 10.1111/pace.12580. [Epub ahead of print]
71. Junttila MJ, Brugada P, Hong K, Lizotte E, DE Zutter M, Sarkozy A, Brugada J, Benito B, Perkiomaki JS, Mäkikallio TH, Huikuri HV, Brugada R. Differences in 12-lead electrocardiogram between symptomatic and asymptomatic Brugada syndrome patients. J Cardiovasc Electrophysiol. 2008 Apr;19(4): 380-3.

86. Kummer JL, Nair R, Krishnan SC. Images in cardiovascular medicine. Bidirectional ventricular tachycardia caused by digitalis toxicity. Circulation. 2006; 113 (7):e156-157.
87. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, Morita H, Nishii N, Watanabe A, Tada T, Murakami M, Miyaji K, Hiramatsu S, Nakagawa K,Tanaka M, Miura A, Kimura H, Fuke S, Sumita W, Sakuragi S, Urakawa S, Iwasaki J, Ohe T. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. J Am Coll Cardiol. 2008 Mar 25;51(12):1169-75.
86. Laitinen PJ, Swan H, Piippo K, Viitasalo M, Toivonen L, Kontula K.Genes, exercise and sudden death: molecular basis of familial catecholaminergic polymorphic ventricular tachycardia.Ann Med. 2004; 36 Suppl 1:81-86.
88. Lepeschkin E. Components of Q-T and Q-U intervals of the electrocardiogram in normals. J Appl Physiol. 1956 Nov;9(3):443-6.
89. Lepeschkin E.:The U wave of the electrocardiogram. Mod Concepts Cardiovasc Dis 1969;38:39.
90. Lepeschkin E.: Physiologic basic of the U wave. In Advances in Electrocardiography. Edited by Schlant RC, and Hurst JW. New York, Grune & Stratton 1972;pp 431-447.
91. Letsas KP, Weber R, Astheimer K, Mihas CC, Stockinger J, Blum T, Kalusche D, Arentz T. Predictors of atrial tachyarrhythmias in subjects with type 1 ECG pattern of Brugada syndrome. Pacing Clin Electrophysiol. 2009 Apr;32(4):500-5.
92. Li H, Wang D, Yang H, Gong C, Cui C, Yan G. Clinical characteristics of ST elevation acute myocardial infarction with J wave syndrome (in Chinese). Chin J Card Arrhythm 2009;13:357−60.
93. Lien WC, Huang CH, Chen WJ. Bidirectional ventricular tachycardia resulting from digoxin and amiodarone treatment of rapid atrial fibrillation. Am J Emerg Med. 2004; 22: 235-236.
94. Liu CK, Greenspan G, Pilccirillo RT. Atrial infarction of the heart. Circulation. 1961 Mar;23:331-8.
95. Loussouarn G, Baró I, Escande D. KCNQ1 K+ channel-mediated cardiac channelopathies. Methods Mol Biol. 2006;337:167-83.
96. Liu N, Colombi B, Raytcheva-Buono EV, Bloise R, Priori SG.Catecholaminergic polymorphic ventricular tachycardia. Herz. 2007;32:212-217.
97. Luna Filho B, Bocanegra JA, Pfeferman A, et al. Fascicular block of the His bundle: critical approach for its identification. Arq Bras Cardiol 1989 Nov; 53(5): 261-65.

97. Luo S, Tompkins WJ. Parameter evaluation of the inverse power-law spectrum of heart rate. A quantitative approach for ECG arrhythmia evaluation.J Electrocardiol, 27 (1994), pp. 46–52.
98. Macfarlane P, Antzelevitch C, Haissaguerre M, Huikuri HPMRR, Sacher F, Tikkanen J, Wellens H, Yan G-X. Consensus paper: early repolarization pattern. J Am Coll Cardiol 2015 J Am Coll Cardiol. 2015;66(4): 470-477.
99. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T, Satomi K, Suyama K, Aihara N, Kurita T, Kamakura S, Shimizu W. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol. 2010 Nov 2;56(19): 1576-84.
100. Makita N, Tsutsui H. Genetic polymorphisms and arrhythmia susceptibility. Circ J. 2007;71 Suppl A:A54-60.
97. Massin M, Leroy P, Misson JP, Lepage P. Catecholaminergic polymorphic ventricular tachycardia in a child: an often unrecognized diagnosis Arch Pediatr. 2003; 10: 524-526.
101. McIntyre WF, Pérez-Riera AR, Femenía F, Baranchuk A. Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities. J Electrocardiol. 2012 May-Jun;45(3): 195-8.
102. Mehta SR, Eikelboom JW, Natarajan MK, Diaz R, Yi C, Gibbons RJ, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. J Am Coll Cardiol 2001;37:37−43.
103. Miyamoto A, Hayashi H, Makiyama T, Yoshino T, Mizusawa Y, Sugimoto Y, Ito M, Xue JQ, Murakami Y, Horie M. Risk determinants in individuals with a spontaneous type 1 Brugada ECG. Circ J. 2011;75(4): 844-51.
104. Mohamed U, Napolitano C, Priori SG.Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. J Cardiovasc Electrophysiol. 2007; 18: 791-797.
105. Mok NS, Tong CK, Yuen HC. Concomitant−Acquired Long QT and Brugada Syndromes Associated with Indapamide−Induced Hypokalemia and Hyponatremia. Pacing and clinical electrophysiology. 2008;31(6): 772-5.
106. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation. 2008 Oct 21;118(17):1697-704.

106. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol, 72 (1993), pp. 23B–25B.
107. Moss AJ. Fragmented QRS: the new high-risk kid on the block in acquired long QT syndrome. Heart Rhythm.2010 Dec;7:1815-18166.
108. Näbauer M, Beuckelmann DJ, Uberfuhr P, Steinbeck G. Regional differences in current density and rate−dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. Circulation 1996;93:168−77.
109. Nam GB, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. N Engl J Med 2008;358:2078−9.
110. Napolitano C, Priori SG. Role of standard resting ECG in the assessment of sudden cardiac death risk. G Ital Cardiol (Rome). 2014 Dec;15(12):670-7.
111. Naschitz J, Fields M, Isseroff H, Sharif D, Sabo E, Rosner I. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. J Electrocardiol. 2006 Oct;39(4):389-94.
112. Nayyar S, Nair M. Brugada pattern in toxic myocarditis due to severe aluminum phosphide poisoning. Pacing and Clinical Electrophysiology. 2009;32(11):e16-e7.
113. Nguyen T, Smythe J, Baranchuk A. Rhabdomyoma of the interventricular septum presenting as a Brugada phenocopy. Cardiol Young. 2011 Oct;21(5):591-4.
114. Niwa N, Nerbonne JM. Molecular determinants of cardiac transient outward potassium current (I (to)) expression and regulation. J Mol Cell Cardiol 2010;48:12−25.
115. Nyegaard, M., Overgaard, M. T., Sondergaard, M. T., Vranas, M., Behr, E. R., Hildebrandt, L. L., Lund, J., Hedley, P. L., Camm, A. J., Wettrell, G., Fosdal, I., Christiansen, M., Borglum, A. D. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. Am. J. Hum. Genet. 91: 703-712, 2012.
116. Ogawa Y. Distinct mechanisms for dysfunctions of mutated ryanodine receptor isoforms. Biochem Biophys Res Commun. 2008 Apr 25;369(1):208-12.
117. Ohkubo K, Watanabe I, Okumura Y, Ashino S, Kofune M, Nagashima K, Nakai T, Kunimoto S, Kasamaki Y, Hirayama A. A new criteria differentiating type 2 and 3 Brugada patterns from ordinary incomplete right bundle branch block. Int Heart J. 2011;52(3):159-63.

106.Ortega-Carnicer J, Benezet J, Ruiz-Lorenzo F, Alcázar R. Transient Brugada-type electrocardiographic abnormalities in renal failure reversed by dialysis. Resuscitation. 2002;55(2):215-9.
107. Osborn JJ. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. Am J Physiol 1953;175:389−98.
108.Ozeke O, Selcuk M, Topaloglu S, Maden O, Aras D. Brugada-like early repolarisation pattern associated with acute pericarditis. Emergency Medicine Journal. 2006;23(12):e64-e.
117.Pastore CA, Moffa PJ, Spiritus MO, Tobias NM, de Moraes AP, Del Nero Júnior E, Dècourt LV, Pillegi F. Fascicular blocks of the right branch. Standardization of vector electrocardiographic findings. Arq Bras Cardiol 1983 Sep; 41(3): 161-66.
118.Pérez MV, Friday K, Froelicher V. Semantic confusion: the case of early repolarization and the J point. Am J Med. 2012 Sep;125:843-844.
119.Pérez Riera AR, Ferreira C, Schapachnik E. Value of 12 leads electrocardiogram and derived methodologies in the diagnosis of Brugada disease. In The Brugada Syndrome From Bench to Bedside. Editor Antzelevitch C. Blackwell Futura. 2005 Chapter 7, pp: 87-110.
120.Peréz-Riera AR, Ferreira Filho C, de Abreu LC, Ferreira C, Yanowitz FG, Femenia F, Brugada P, Baranchuk A; International VCG Investigators Group. Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study. Europace. 2012 Jun;14(6):889-97.
121.Pérez Riera AR, Paixão-Almeida A, Barbosa-Barros R, Yanowitz FG, Baranchuk A, Dubner S, Palandri Chagas AC. Congenital_short QT syndrome: landmarks of the newest arrhythmogenic cardiac channelopathy. Cardiol J. 2013;20(5):464-71.
122.Peters S, Trümmel M, Koehler B. QRS fragmentation in standard ECG as a diagnostic marker of arrhythmogenic right ventricular dysplasia-cardiomyopathy. Heart Rhythm. 2008 Oct;5:1417-1421.
123.Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP Jr, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haïssaguerre M, Schimpf R, Borggrefe M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007 Jan 30;115(4):442-9.
124.Pitzalis MV, Anaclerio M, Iacoviello M, Forleo C, Guida P, Troccoli R, Massari F, Mastropasqua F, Sorrentino S, Manghisi A, Rizzon P. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42(9):1632-7.

126. Portugal G, Martins Oliveira M, Silva Cunha P, Ferreira F, Lousinha A, Fiarresga A, Nogueira da Silva M, Cruz Ferreira R. Short QT syndrome presenting as syncope: how short is too short? Rev Port Cardiol. 2014 Oct;33(10):649.e1-6.
127. Postma AV, Denjoy I, Hoorntje TM, Lupoglazoff JM, Da Costa A, Sebillon P, Mannens MM, Wilde AA, Guicheney P. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. Circ Res 2002; 91:e 21-26.
128. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, Wilde AA.Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. J Med Genet. 2005; 42: 863-870.
129. Primeau R. Peaked, symmetrical T waves, an early sign of myocardial infarct. Union Med Can. 1969 Jan; 98(1):104-5.
130. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2002; 106: 69-74.
131. Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, Napolitano C, Anumonwo J, di Barletta MR, Gudapakkam S,Bosi G, Stramba-Badiale M, Jalife J. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res. 2005 Apr 15;96(7):800-7.
132. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012 Jan 3;59(1):37-45.
133. Radojevic N, Savic S, Aleksic V, Cukic D. Unusual case of right atrial reinfarction. J Forensic Leg Med. 2012 Feb;19(2):105-8.
134. Recasens L, Meroño O, Ribas N. Hyperkalemia mimicking a pattern of Brugada syndrome. Revista Española de Cardiología. 2013;66(04):309.
135. Riera AR, Ferreira C, Schapachnik E, Sanches PC, Moffa PJ. Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. J Electrocardiol. 2004 Apr; 37(2): 101-4.

136. Riera AR, Uchida AH, Schapachnik E, Dubner S, Filho CF, Ferreira C. Propofol infusion syndrome and Brugada syndrome electrocardiographic phenocopy. Cardiol J. 2010; 17(2): 130-5.
137. Roberts R, Brugada R. Genetics and arrhythmias. Annu Rev Med. 2003; 54:257-267.
138. Robinson RL, Curran JL, Ellis FR, Halsall PJ, Hall WJ, Hopkins PM, Iles DE, West SP, Shaw MA. Multiple interacting gene products may influence susceptibility to malignant hyperthermia. Ann Hum Genet.2000;64:307–20.
139. Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999 Dec;10(12):1664-83.
140. Rollin A, Maury P, Guilbeau−Frugier C, Brugada J. Transient ST elevation after ketamine intoxication: a new cause of acquired brugada ECG pattern. Journal of cardiovascular electrophysiology. 2011;22(1): 91-4.
141. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol. 1992 Sep 15;70(7):797-801.
142. Sangawa M, Morita H, Nakatsu T, Nishii N, Miura D, Miura A, Tada T, Murakami M, Hiramatsu S, Nagase S, Nakamura K, Oka T, Toyonaga S, Mashima K, Kusachi S, Yamamoto K, Ohe T, Kusano KF. Abnormal transmural repolarization process in patients with Brugada syndrome. Heart Rhythm. 2009 Aug; 6(8):1163-9.
143. Schimpf R, Wolpert C, Gaita F, Giustetto C, Borggrefe M. Short QT syndrome. Cardiovasc Res. 2005 Aug 15;67(3):357-66.
144. Schimpf R, Veltmann C, Papavassiliu T, Rudic B, Göksu T, Kuschyk J, Wolpert C, Antzelevitch C, Ebner A, Borggrefe M, Brandt C. Drug-induced QT interval shortening following antiepileptic treatment with oral rufinamide. Heart Rhythm. 2012 May;9(5):776-81.
145. Schulze-Bahr E, Haverkamp W, Borggrefe M, Wedekind H, Mönnig G, Mergenthaler J, Assmann G, Funke H, Breithardt G. Molecular genetics of arrhythmias--a new paradigm. Z Kardiol. 2000;89 Suppl 4:IV12-22.
146. Shamroth, L.: An introduction to Electrocardiography. Backwell Scientific Publications, 1971.

147. Shipley RA, Hallaran WR. The four lead electrocardiogram in two hundred normal men and women. Am Heart J 1936;11:325−45.
148. Shu J, Zhu T, Yang L, Cui C, Yan GX. ST−segment elevation in the early repolarization syndrome, idiopathic ventricular fibrillation, and the Brugada syndrome: Cellular and clinical linkage. J Electrocardiol 2005;38 4 Suppl: 26−32.
149. Smith SW, Shah RR, Hunt JL, Herzog CA.Bidirectional ventricular tachycardia resulting from herbal aconite poisoning. Ann Emerg Med. 2005;45:100-101.
150. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K, Tager-Flusberg H, Priori SG, Sanguinetti MC, Keating MT. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell. 2004;119:19–31.
151. Sridharan, MR, Horan, LG. Electrocardiographic J wave of hypercalcemia. Am J Cardiol 1984;54,672-673.
152. Srivathsan K, Steven J. Lester SJ, Appleton CP, ScottLRP, Thomas M. MungerTMVentricular Tachycardia in the Absence of Structural Heart Disease Indian Pacing Electrophysiol. J. 2005; 5: 106-121.
153. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, Ushinohama H, Shibata T, Niimura I. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003; 89:66-70.
154. Swan H, Laitinen P, Kontula K, Toivonen L. Calcium Channel Antagonism Reduces Exercise-Induced Ventricular Arrhythmias in Catecholaminergic Polymorphic Ventricular Tachycardia Patients with RyR2 Mutations. J Cardiovasc Electrophysiol. 2005; 16: 162-166.
155. Takagi M, Aonuma K, Sekiguchi Y, Yokoyama Y, Aihara N, Hiraoka M; Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: multicenter study in Japan. Heart Rhythm. 2013 Apr;10(4):533-9.
156. Take Y, Morita H, Wu J, Nagase S, Morita S, Toh N, Nishii N, Nakamura K, Kusano KF, Ohe T, Ito H, Zipes DP. Spontaneous electrocardiogram alterations predict ventricular fibrillation in Brugada syndrome. Heart Rhythm. 2011 Jul;8(7):1014-21.

155. Templin C, Ghadri JR, Rougier JS, Baumer A, Kaplan V, Albesa M, Sticht H, Rauch A, Puleo C, Hu D, Barajas-Martinez H, Antzelevitch C, Lüscher TF, Abriel H, Duru F. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). Eur Heart J. 2011 May;32(9): 1077-88.
156. Terentyev D, Viatchenko-Karpinski S, Gyorke I, Volpe P, Williams SC, Gyorke S. Calsequestrin determines the functional size and stability of cardiac intracellular calcium stores: Mechanism for hereditary arrhythmia. Proc Natl Acad Sci U S A. 2003; 100:11759-11764.
157. Tester DJ, Spoon DB, Valdivia HH, Makielski JC, Ackerman MJ. Targeted mutational analysis of the RyR2-encoded cardiac ryanodine receptor in sudden unexplained death: a molecular autopsy of 49 medical examiner/coroner's cases. Mayo Clin Proc. 2004;79:1380-1384.
158. Tigen K, Karaahmet T, Gurel E, et al. The utility of fragmented QRS complexes to predict significant intraventricular dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. Can J Cardiol. 2009 Sep;25:517-522.
159. Tomaszewski W. Electrocardiographic changes observed in a man frozen to death (in French). Arch Mal Coeur 1938;31:525−8.
160. Tsai C-F, Wu D-J, Lin M-C, Ueng K-C, Lin C-S. A Brugada-pattern electrocardiogram and thyrotoxic periodic paralysis. Annals of internal medicine. 2010;153(12):848-9.
161. Tülümen E, Giustetto C, Wolpert C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Scrocco C, Rudic B, Veltmann C, Sun Y, Gaita F, Antzelevitch C, Borggrefe M, Schimpf R. PQ segment depression in patients with short QT syndrome: a novel marker for diagnosing short QT syndrome? Heart Rhythm. 2014 Jun;11(6):1024-30.
162. Vatta, M, Ackerman MJ, Ye, B, Makielski JC, Ughanze EE, Taylor EW, Tester DJ, Balijepalli RC, Foell J D, Li Z, Kamp TJ, Towbin JA. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. Circulation 2006; 114: 2104-2112.
163. Viatchenko-Karpinski S, Terentyev D, Gyorke I, Terentyeva R, Volpe P, Priori SG, Napolitano C, Nori A, Williams SC, Gyorke S. Abnormal calcium signaling and sudden cardiac death associated with mutation of calsequestrin. Circ Res. 2004;94:471-477.
164. Villafañe J , Fischbach P, Gebauer R. Short QT syndrome manifesting with neonatal atrial fibrillation and bradycardia. Cardiology. 2014;128(3):236-40.

1. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med, 327 (1992), pp. 846–852.
2. Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D, Tekes-Manova D, Belhassen B. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. Heart Rhythm. 2004 Nov;1(5):587-91
3. Viskin S. The QT interval: Too long, too short or just right. Heart Rhythm 2009; 6: 711–715.
4. Wang DQ, Su XM, Li HB, Ma Y, Yang HT, Yu ZX, et al. The clinical characteristics of J wave syndrome during early ischemia in acute myocardial infaction (in Chinese). Chin J Card Pacing Electrophysiol 2008;22:31−3.
5. Wang J, Xu H, Sun X, Niu W. Pharmacological and biophysical properties of swelling-activated chloride channel in mouse cardiac myocytes. Chin J Physiol. 2006 Jun 30; 49: 126-131.
6. Wang JG, McIntyre WF, Kong W, Baranchuk A. Electrocution-induced Brugada phenocopy. International journal of cardiology. 2012;160(3):e35-e7.
7. Watanabe H, Makiyama T, Koyama T, Kannankeril PJ, Seto S, Okamura K, Oda H, Itoh H, Okada M, Tanabe N, Yagihara N, Kamakura S, Horie M, Aizawa Y,Shimizu W. High prevalence of early repolarization in short QT syndrome. Heart Rhythm. 2010 May;7(5):647-52.
8. Wettwer E, Amos G, Gath J, Zerkowski HR, Reidemeister JC, Ravens U. Transient outward current in human and rat ventricular myocytes. Cardiovasc Res 1993;27:1662−9.
9. Wettwer E, Amos GJ, Posival H, Ravens U. Transient outward current in human ventricular myocytes of subepicardial and subendocardial origin. Circ Res 1994;75:473−82.
10. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA, Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002 Nov 5; 106(19): 2514-19.
11. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J. 2002 Nov;23(21):1648-54.
12. Wolpert C, Schimpf R, Giustetto C, Antzelevitch C, Cordeiro JM, Dumaine R, Brugada R, Hong K, Bauersfeld U, Gaita F, Borggrefe M. Further insights into the effect of quinidine in short QT syndrome

174. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST−segment elevation. Circulation 1999;100:1660−6.
175. Yan GX, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: Cellular basis and clinical significance. J Am Coll Cardiol 2003;42:401−9.
176. Yan GX, Yao QH, Wang DQ, Cui CC. J wave and J wave syndromes (in Chinese). Chin J Card Arrhythm 2004;8:360−5.
177. Yan GX, Joshi A, Guo D, Hlaing T, Martin J, Xu X, et al. Phase 2 reentry as a trigger to initiate ventricular fibrillation during early acute myocardial ischemia. Circulation 2004;110:1036−41.
178. Yokokawa M, Noda T, Okamura H, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Shimizu W. Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. Am J Cardiol. 2007 Aug 15;100(4):649-55.
179. Yuce M, Davutoglu V, Ozbala B, et al. Fragmented QRS is predictive of myocardial dysfunction, pulmonary hypertension and severity in mitral stenosis. Tohoku J Exp Med. 2010; 220: 279-283.
180. Zhao X, Xie Z, Chu Y, Yang L, Xu W, Yang X, Liu X, Tian L. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol. 2012 Sep;35(9):559-64.
181. Zhao Z, Yuan Z, Ji Y, Wu Y, Qi Y. Left ventricular hypertrophy amplifies the QT, and Tp-e intervals and the Tp-e/ QT ratio of left chest ECG. J Biomed Res. 2010 Jan;24(1):69-72.