Young man recovered from cardiac arrest

Homem caucasiano de 26 anos de idade, admitido na sala de emergência em parada cardiopulmonar, revertida com sucesso (ECG1 realizado imediatamente à ressuscitação).

Refere ter tido episódio de síncope prévio (não sabemos ainda em que circunstâncias, nem quanto tempo atrás).

Por ser filho adotivo, desconhecemos os antecedentes familiares. Segundo o padrinho, o paciente não usa drogas lícitas ou ilícitas.

Ecocardiograma normal.

Perguntas:

1. Diagnósticos do ECG1 ao ECG5
2. Possível diagnóstico
3. Conduta adequada

English: Caucasian man 26 years old, admitted to the emergency room in cardiopulmonary arrest, successfully reversed (ECG1 held immediately resuscitation).

He refers to have had previous episode of syncope (still do not know under what circumstances, or how long ago).

As an adopted son, family history is unknown. According to the godfather, the patient does not use legal or illegal drugs.

Normal echocardiogram.

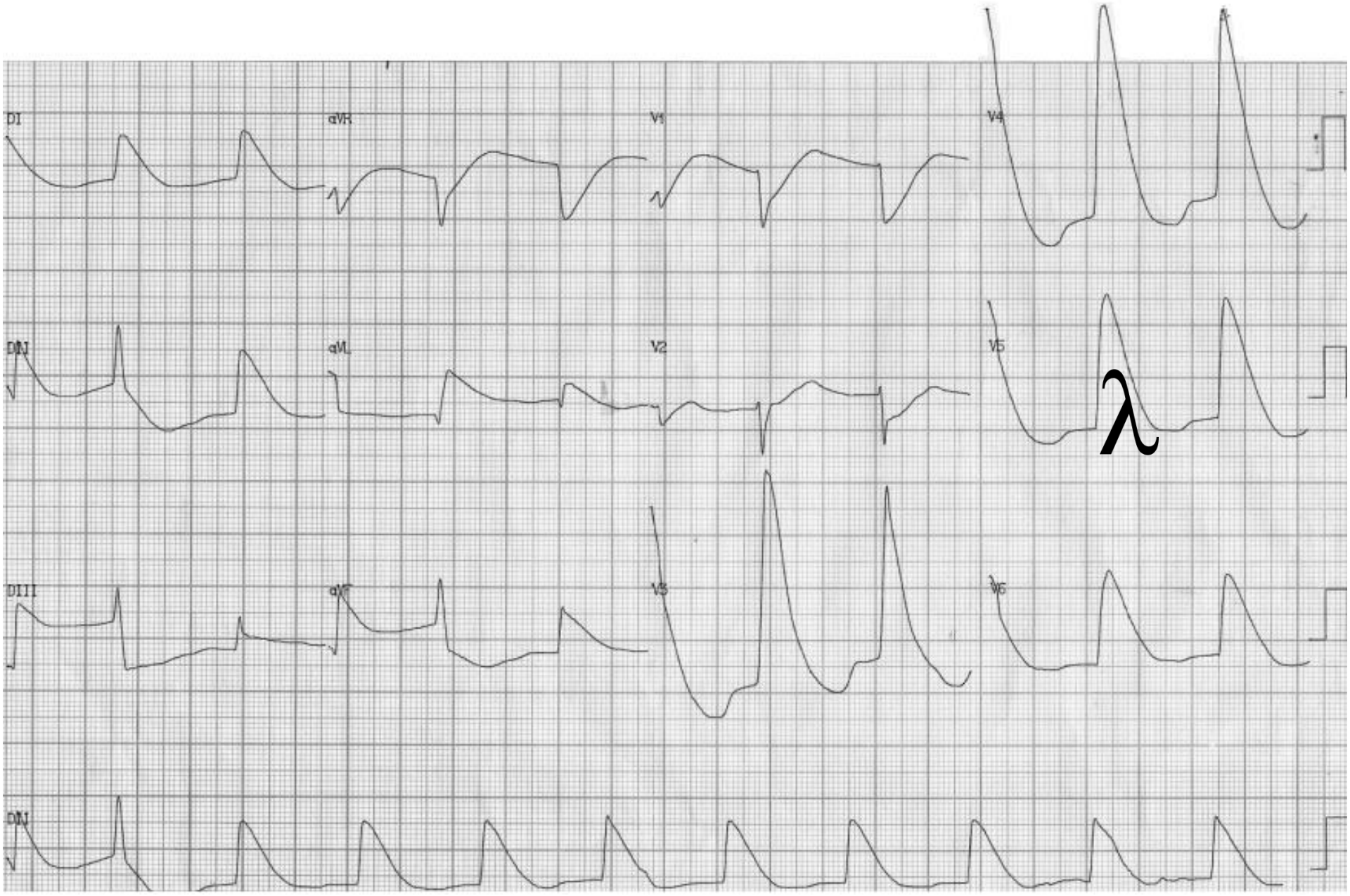
Questions:

1. Diagnostics of ECG1 to ECG5
2. Possible diagnosis
3. Proper approach

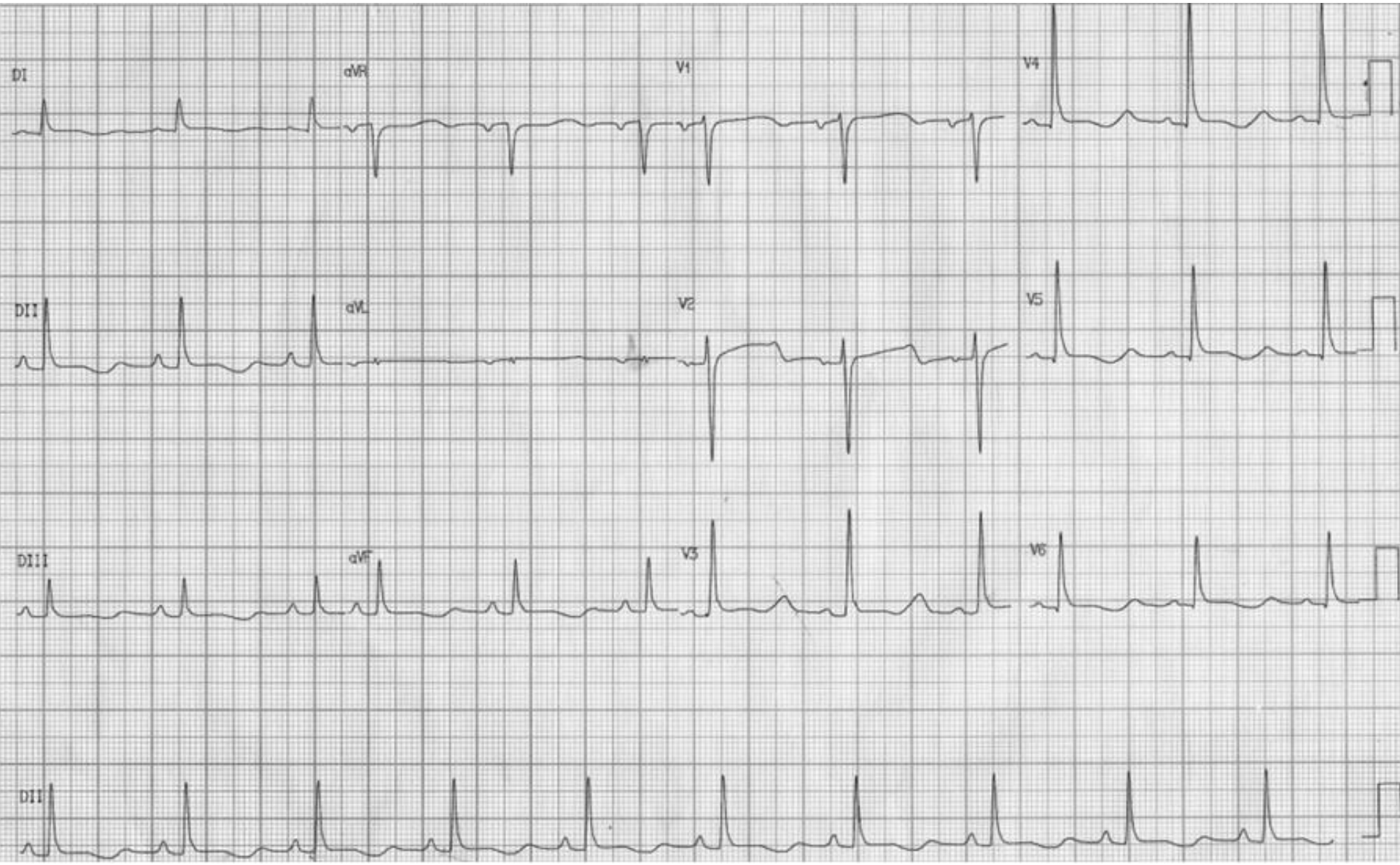
Raimundo **Barbosa-Barros**, M.D.

Chief of the Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes. Fortaleza - Brazil

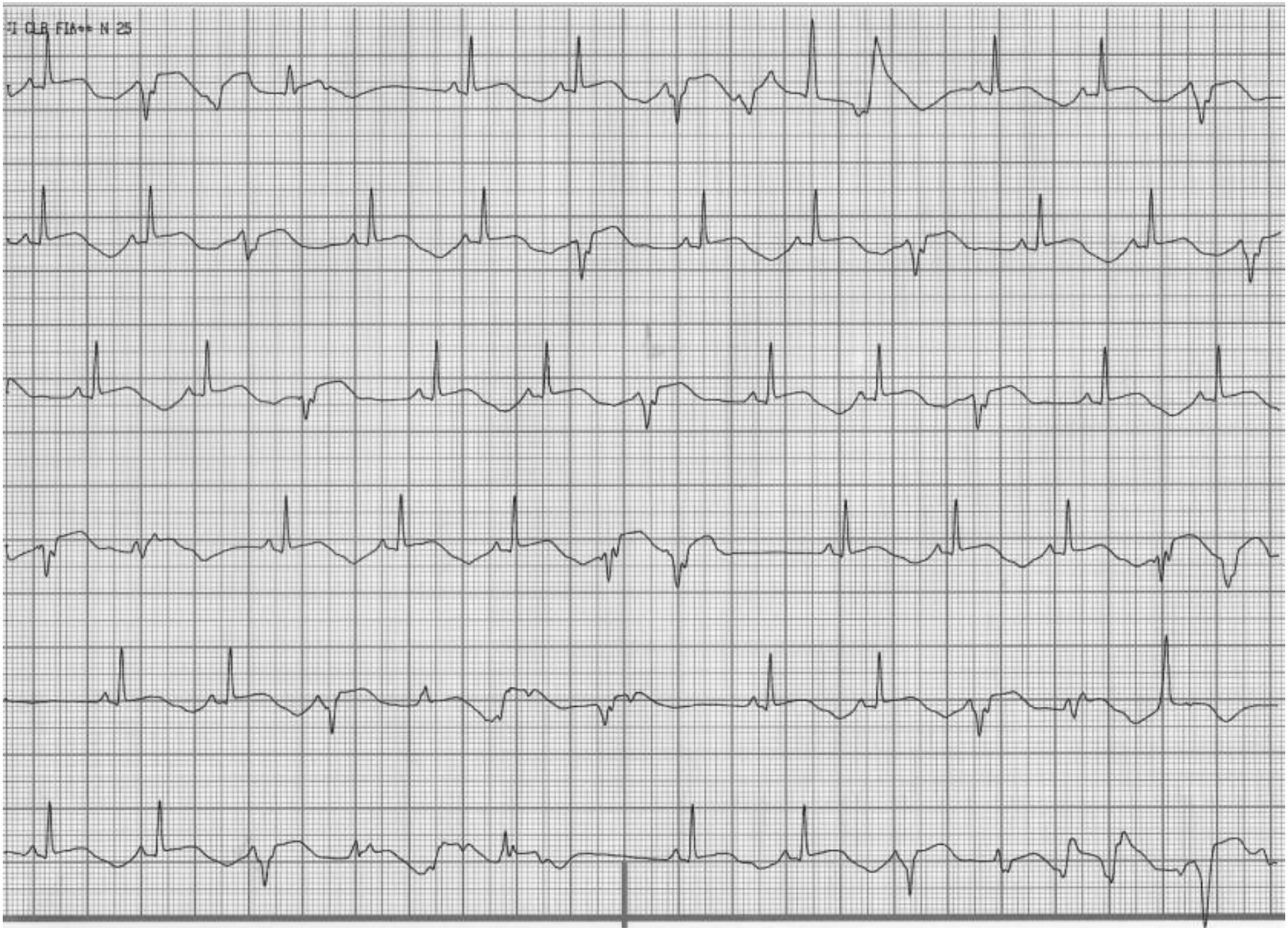
ECG1 - The 12-lead electrocardiogram performed immediately after cardiac arrest – 3 cycles



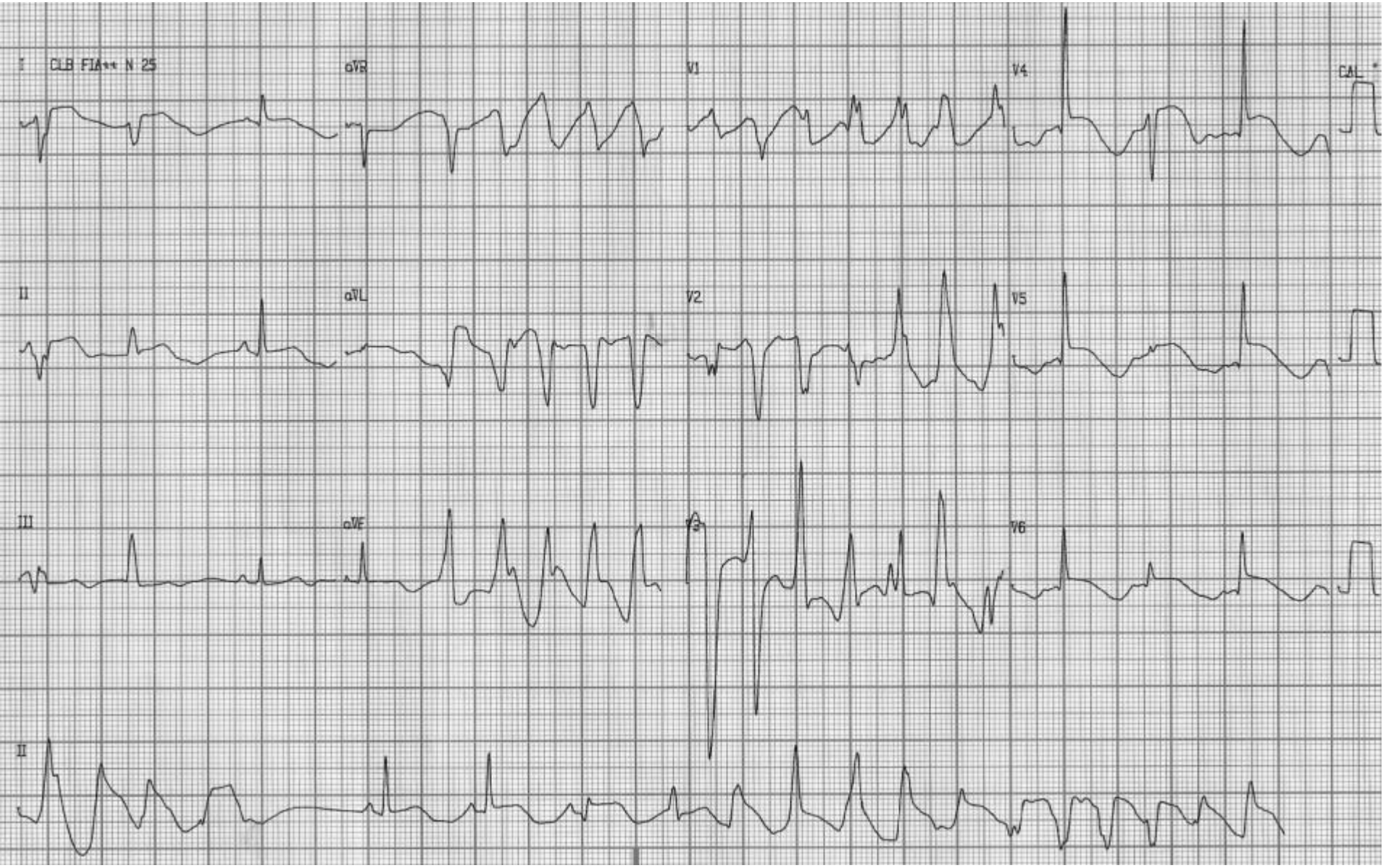
ECG2 – Basal ECG



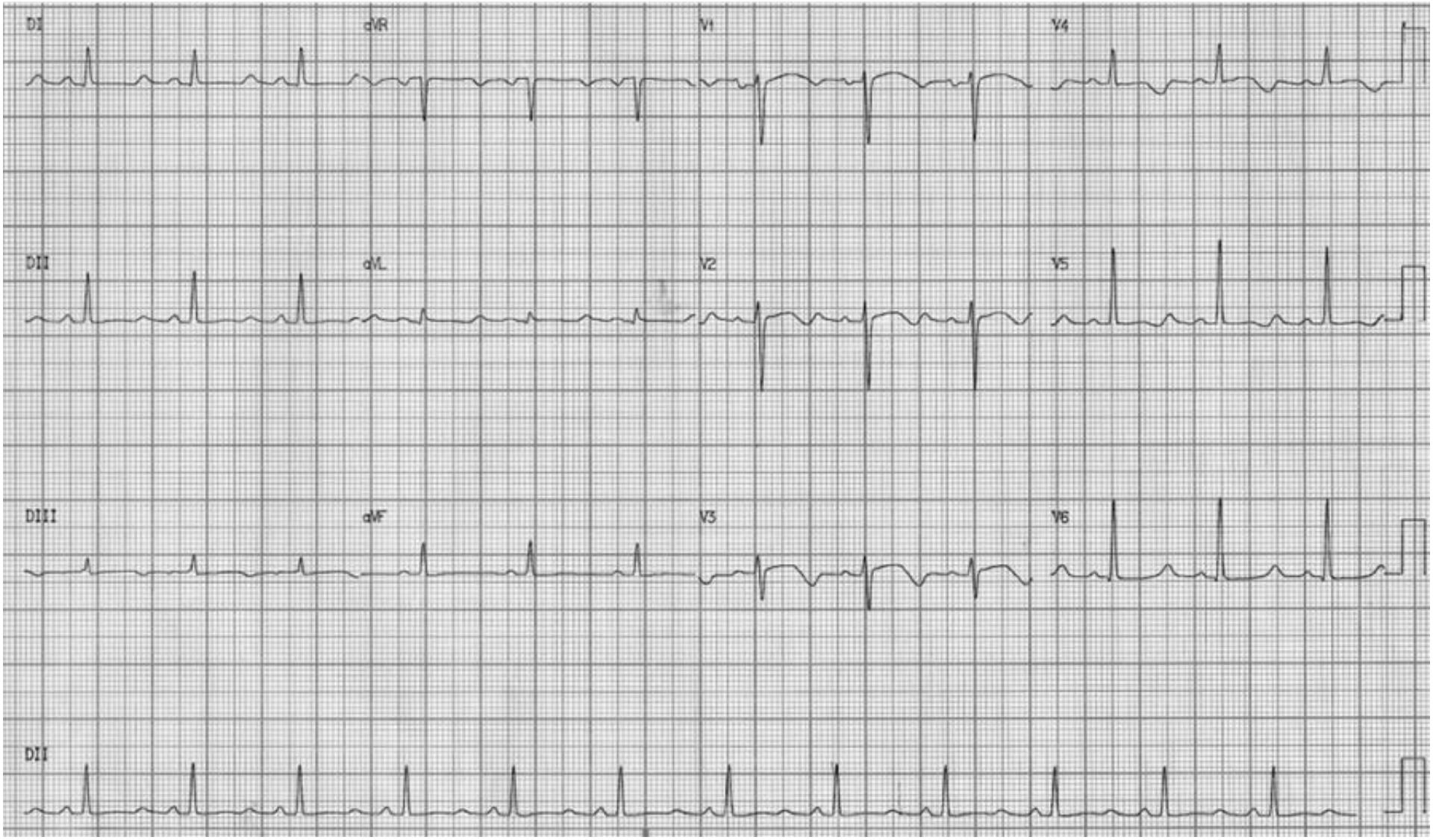
ECG3 – Continuous long lead II



ECG4 – During intermittent non-sustained events



ECG5 – After clinical and ECG stabilization



Colleagues opinions

ECG post arrest with evidence of generalized ischemia.
ECG #2 Long QT fits LQT3 pattern (mutation ofSCN5A gene)
ECG #3 frequent PVCs initiated at the end of the T wave likely EAD driven.
ECG #4 bursts of torsades.
ECG #5 clear pattern of LQT3 with long isoelectric St segment.
Management acutely atrial overdrive pacing to shorten the QT would avoid Isuprel, obtain electrolytes and correct any abnormalities found.
Consider use of Mexilitine or Ranolazine which have been shown to decrease the QT interval in LQT3.would favor ICD for this patient since there is limited experience with drug therapy and beta-blockers are less effective.
He should undergo gene testing since it may affect management of his children

Professor Melvin M. **Scheinman, MD**
Department of Cardiac Electrophysiology, University of
California San Francisco, San Francisco, California, USA. scheinman@medicine.ucsf.edu

Comments from Andrés about Dr Sheinman: **Dr**. **Melvin Scheinman**, one of the pioneers of cardiac electrophysiology, was the first to perform catheter ablation on humans. Dr. Melvin Scheinman is Professor of Medicine, Walter H. Shorenstein Endowed Chair in Cardiology, and one of the founding fathers of the field of cardiac electrophysiology. Dr. Melvin Scheinman is one of the founding pioneers of clinical cardiac electrophysiology. He grew up in Brooklyn, New York and took his undergraduate degree at Johns Hopkins University where he graduated first in his class. Postgraduate medical education included Albert Einstein College of Medicine, residency training at the University of North Carolina (Chapel Hill) and cardiology training at the University of California, San Francisco Medical Center.
Dr. Scheinman is best known as the first person to have performed catheter ablation in humans. This was done after extensive animal studies.

Dear Andrés:
I have never seen such type of tracings in the same patient. Let me start with my final diagnosis: this patient has Long QT syndrome (LQT2??) with some T alternance and torsades de pointes. The first tracing might be due to SEVERE HYPOXIC HEART just recorded after CPR. Myocardial ischemia is very unlikely.
Causes of this LQTS: "congenital" mainly but a toxic / drug origin has to be excluded.
Treatment: beta blocker (Propranolol mainly) + ICD in case we are actually dealing with idiopathic LQTS. Also familial screening+++++

I will be happy to read other specialists comments on this absolutely SUPERB case and fantastic ECG tracings (thanks a lot Dr Barbosa-Barros)

Shabbat Shalom @@@@@@@@@@

BB

BB: Bernard **Belhassen**. Cardiologist. Director, Cardiac Electrophysiology Laboratory Professor of Cardiology, Sackler School of Medicine, Tel-Aviv University. Israel.

Comments from Andrés About Shabbat Shalom:
It means peaceful/happy Sabbath (the time between Friday at sundown and Saturday at sundown.).
It basically means, have a nice weekend.

Dear colleagues, thank you for interesting case. By my opinion it is patient with long QT syndrome. On the ECG 1 we can see slow idioventricular rhythm that typically after cardiac arrest. On the ECG 5 QTc interval prolongation till 536 ms vs and typical ECG pattern for LQT3. But on the ECG 4 VT with nontypical pattern of the Torsades de Pointes and we need exlude LQT 7 (Tawill Anderson syndrome) with bidirectional VT by eletrolite assessment, clinical and family history (including family ECG) , molecular gene analysis, Holter monitoring and stress test. For treatment first of all need to indicate beta bockers (Nadolol), may be additional treatment Flecainide. If it will be recurrent syncope - ICD implantation.

Sincerely yours

Prof. Dr. Leonid **Makarov M.D., Ph.D**

Head of Center for Syncope and Arrhythmias in Children and Adolescents of Federal Medico-Biology Agency of Russia. President of the Russian Society for Holter Monitoring (ROHMINE). Address: Central Children Clinical Hospital FMBA of Russia. 115409 Moskvorechie str. 20. Tel. +7 (499)324-5756.

E-mail: leonidmakarov@yahoo.com

ECG I

1) Ritmo ídio ventricular / Accelerated idioventricular rhythm
2) Intervalo QT prolongado (QTc:0,68 segundos) / Long QT interval
3) Fenômeno R sobre T / R on T phenomenon
4) Extra sistolia polimórfica / Polimorphic premature ventricular contractions Torsades / Torsades de Pointes
5) QT ainda prolongado (QTc:0,49 segundos) / Long QT interval

II

Possible diagnosis: Síndrome do QT longo. Long QT syndrome.

III

Proper approach: Desfibrilador implantável Implantable Cardioverter Defibrillator (ICD)

Alexandre Teixeira Cezimbra, M.D. Rio de Janeiro, Brasil

Dear Andres,

Long time no see, it is so good to hear from you.
From ECG tracings I see at least one functional mutation occurred in KCNH2, thus this young man has type 2 LQTS. TdP must have degenerated into VF which put him into cardiac arrest...
Ischemia due to cardiac arrest and defib shocks during resuscitation can cause temp myocardial damage. As such the local hyperkalemia could suppress conduction, therefore the accelerated junctional-ventricular rhythm is shown in ECG1. It is not a Brugada syndrom, but a delayed repolarization caused by a transit increase of local [K+].
KCNH2 targeted genetic testing may find the mutation in a couple of days. Family ECG screening can identify additional affected members. Remove triggers (emotional stress, startle, QT-drugs) of cardiac event. Beta-blockers is the baseline therapy. Sodium channel blockers such as mexiletine may shorten the QT interval in severe cases regardless of genotype. Follow the guidelines for ICD recommendations.

Thanks,

Li Zhang
Director, Cardiovascular Outcomes Research, Main Line Health Heart Center, Lankenau Medical Center
Associate Professor, Lankenau Institute for Medical Research

Dear Andrés and Raimundo,
What an impressive ECGs!
The **first** post resuscitation ECG is so extreme (lambda waves) that most probably it was taken very soon after ROSC after prolonged hypoxia, possibly hypothermia and at low pH? Following his young age I presume that an acute coronary syndrome is unlikely.
The **second ECG** has a prolonged QT, type-3 LQTS like morphology, with extrasystoles from the end of the T wave or the supposed U wave in the 3rd ECG (to be able to recognize the U wave I would need 12L ECGs probably). Interestingly in the second ECG there appears to be ST elevations. Here again it is important to know when the ECG was made, was the patient still held in hypothermia for example (that can result in impressive QT prolongation / morphology changes)? Or with over electrolyte disturbances.
The 4th ECG shows non-sustained VTs polymorphic again starting with extrasystoles from the end of the prolonged T or U, not typically short-long-short
The 5th ECG finally the confirmation that this could be a type-3 LQTS

Interested in the opinion of the others

Best wishes,
Pieter G. Postema, MD, PhD
Cardiologist at Academic Medical Center (AMC)
University of Amsterdam

Dear Raimundo and Andres,

The first ECG immediately after defibrillation shows a prominent Lambda wave as you point out.
However, subsequent ECGs show a prolonged QT interval with short runs of torsade de pointes. Some ECGs suggest long QT type 3.
It is possible he could have a SCN5A mutation that could explain both the J wave syndrome and long QT3 (both sodium Chanel defects).

Very interesting! Please let me know what you find out.

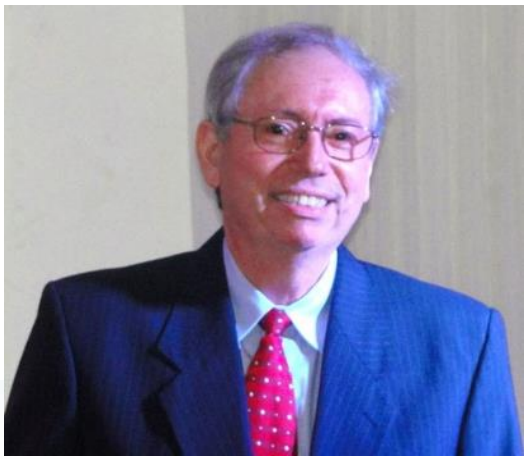
Bom final de semana!

Mario

Mario D. Gonzalez, M.D.
Professor of Medicine
Director, Clinical Electrophysiology
Penn State Heart & Vascular Institute
Milton S. Hershey Medical Center
Penn State University
500 University Drive
Hershey, PA 17033
(717) 531-3907
Fax (717) 531-4077
mgonzalez@hmc.psu.edu

Final comments by:

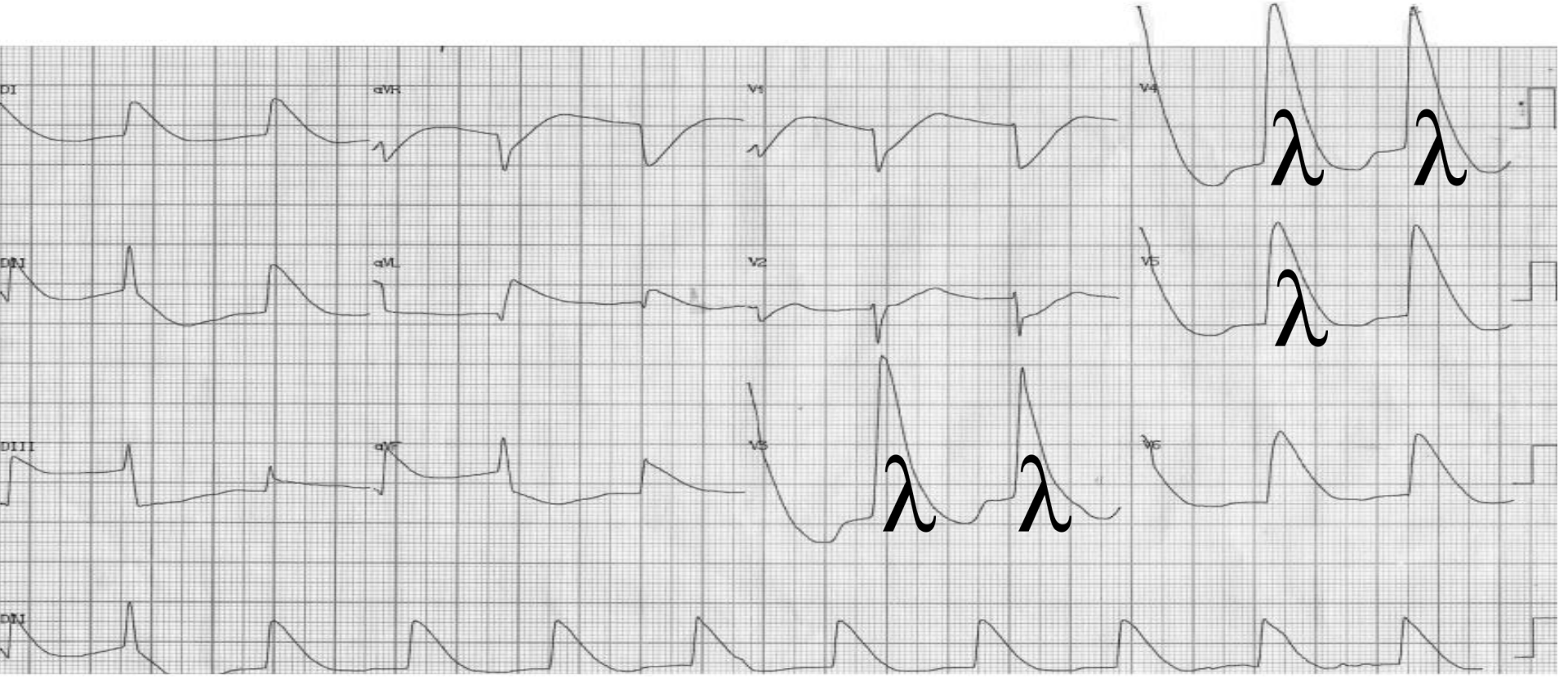
Andrés Ricardo Pérez-Riera, M.D.Ph.D.
and
Raimundo Barbosa-Barros, M.D.



Córdoba

Fortaleza

ECG1 - The 12-lead electrocardiogram performed immediately after cardiac arrest – 3 cycles



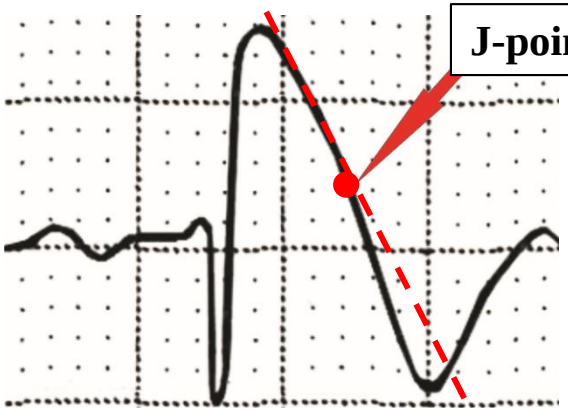
Accelerated idioventricular rhythm (HR = 65 bpm), of apparent generalized ischemia. This pattern was called lambda wave shape for the first time in 2004 by Dr Ihor Gussak (**Gussak 2004**). It was observed in atypical Brugada syndrome scenario and also in ischemic heart disease such us the lambda-like ST segment elevation of acute myocardial infarction, Prizmental angina and percutaneous ablation in hypertrophic cardiomyopathy. Kukla et al presented three cases with AMI and atypical ST segment elevation - 'lambda-wave-like' pattern, complicated with episodes of VF. This ECG pattern resembles the ST segment elevation shape in the type 1C ECG pattern in Brugada syndrome proposal by Perez-Riera in BrS (see next slide). The 'lambda-like' ST segment elevation in AMI may identify patients with increased risk of VF or SCD.

Proposal of classification of type 1 Brugada pattern

Right precordial leads

Subtype 1A

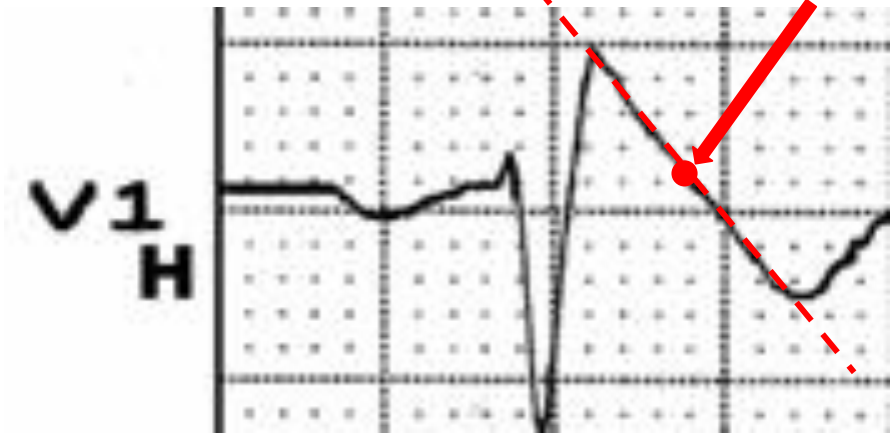
STSE convex upward



The dotted line is tangent line

Subtype 1B

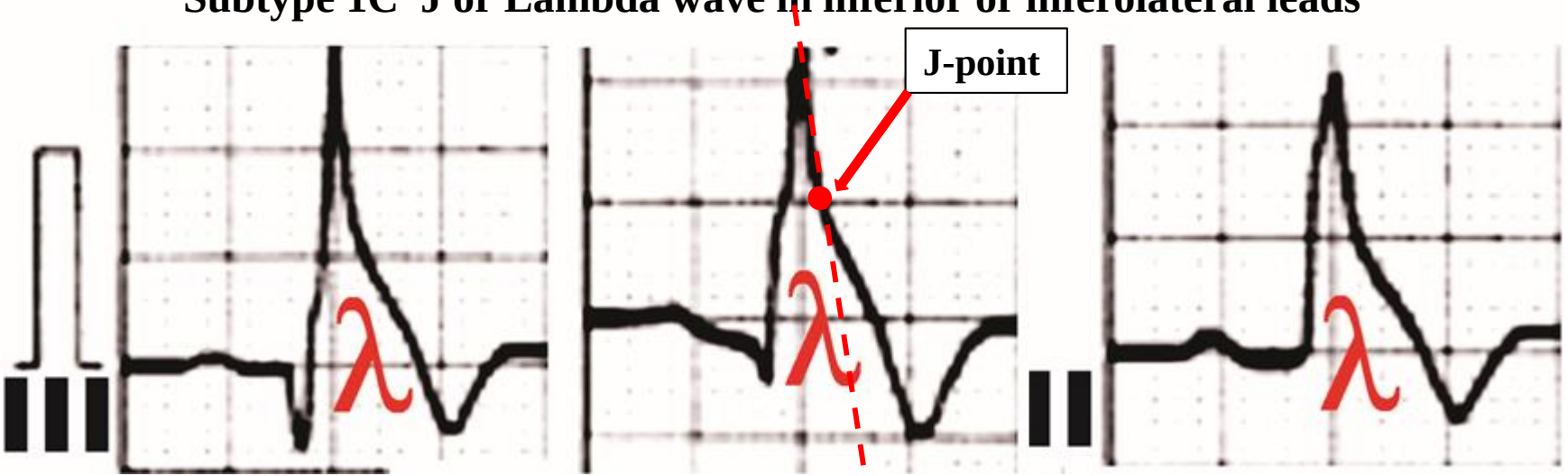
STSE rectilinear oblique descendent



The dotted line is tangent line

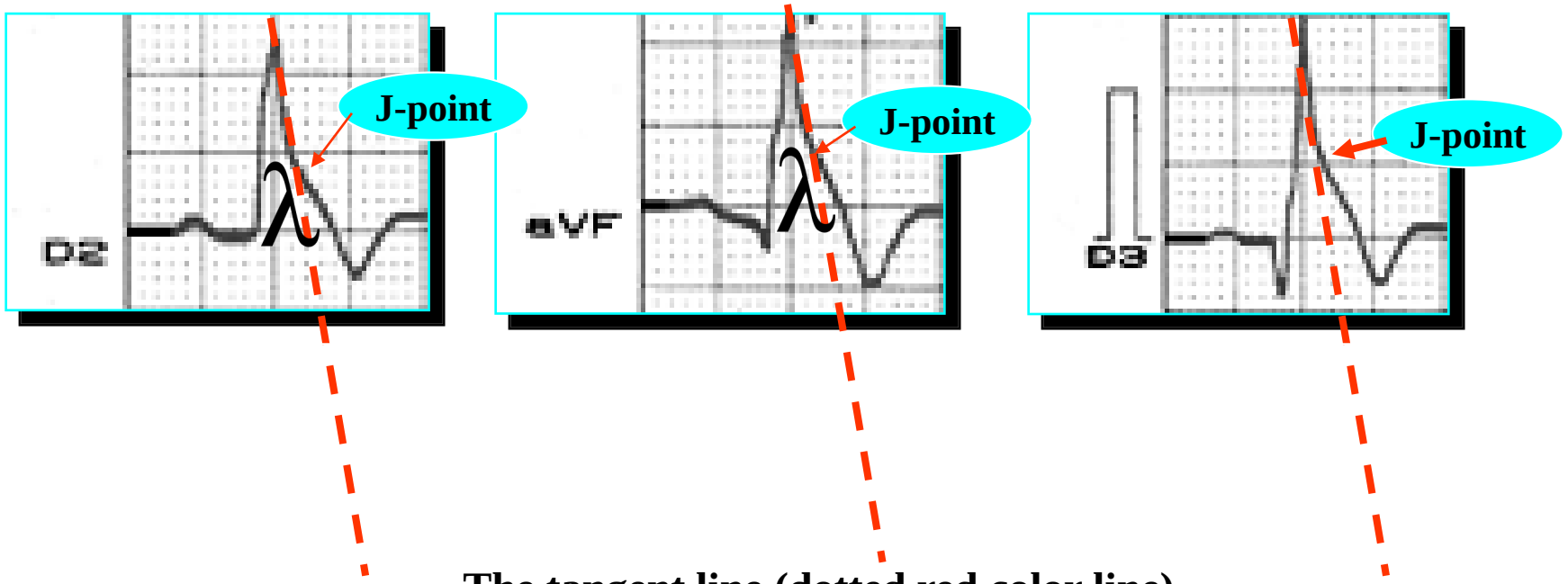
Inferior leads

Subtype 1C J or Lambda wave in inferior or inferolateral leads



ECG Subtype IC Brugada pattern was denominated “lambda” λ wave

The “tangent” line method in the case of ECG Brugada subtype 1C is very suitable for determining the exact location of the J-point (despolarization end and beginning of repolarization)



The tangent line (dotted red color line)

ECG Subtype IC Brugada pattern: It is characterized by J-point and ST-segment elevation triangular or coved to the top (“coved type”) ≥ 2mm (0.2mV), followed by negative T wave located in inferior (II, III and aVF) or inferoapical leads (II, III, aVF, V5-V6). In our opinion, the lambda wave is the J wave, however, with a particular shape that gives greater severity and poorer prognosis: “malignant” early repolarization. Additionally, it is frequently observed mirror or reciprocal image in several leads, differently from benign early repolarization pattern where mirror image is observed eventually only in aVR (**Pérez-Riera 2012**). See next 4 slides.

Case report

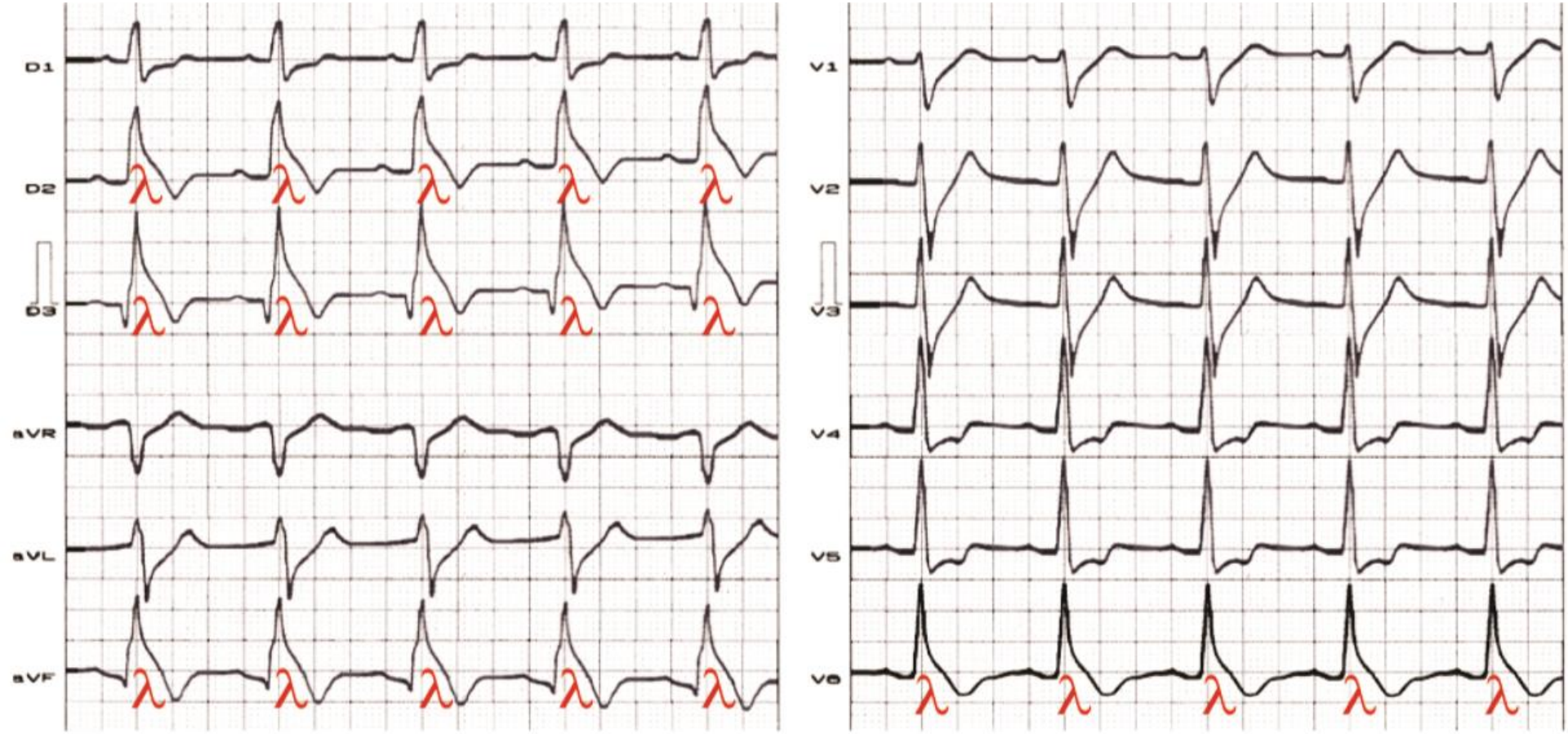
In this case report, we would like to present a 26-years-old male patient, a victim of sudden cardiac death (SCD) at night with a strong family history of SCD.

This young Thai immigrant, cook's helper in a restaurant of typical Thai food, came to our office on March 5th, 2002. The patient was accompanied by a co-worker who was also his interpreter. His main concern was a sudden and brief fainting episode associated to fecal and urinary incontinence that had occurred 2 days previously during defecation. His personal clinical history includes one additional convulsive-like episode accompanied by “agonal-type” respiration pattern that was witnessed by his roommate. It reverted spontaneously. This episode did occur at night during sleep approximately one month prior to his visit to the clinic.

The family history is remarkable for an early SCD in an older brother (died at age of 31 years) and a first-degree uncle on the father's side (died at age of 39 years). Both deaths occurred during night sleep.

Complete physical examination and extensive non-invasive diagnostic work-up (including chest X-rays and echocardiography) did not reveal any structural cardiac abnormalities that can explain his ECG abnormalities. Those include remarkable downsloping ST segment in inferior leads accompanied by horizontal ST segment depression in leads V4-V5. His ECGs were recorded twice with 2-hours interval apart. These ECGs were identical and remained unaltered after sublingual administration of isosorbide dinitrate .

Name: Y. A. S.; **Sex:** Male**; Age:** 26 years old; **Ethnic group:** Asian; **Weight:** 64 Kg; **Height:** 1,68 m.
Date: 03/05/2002**.**



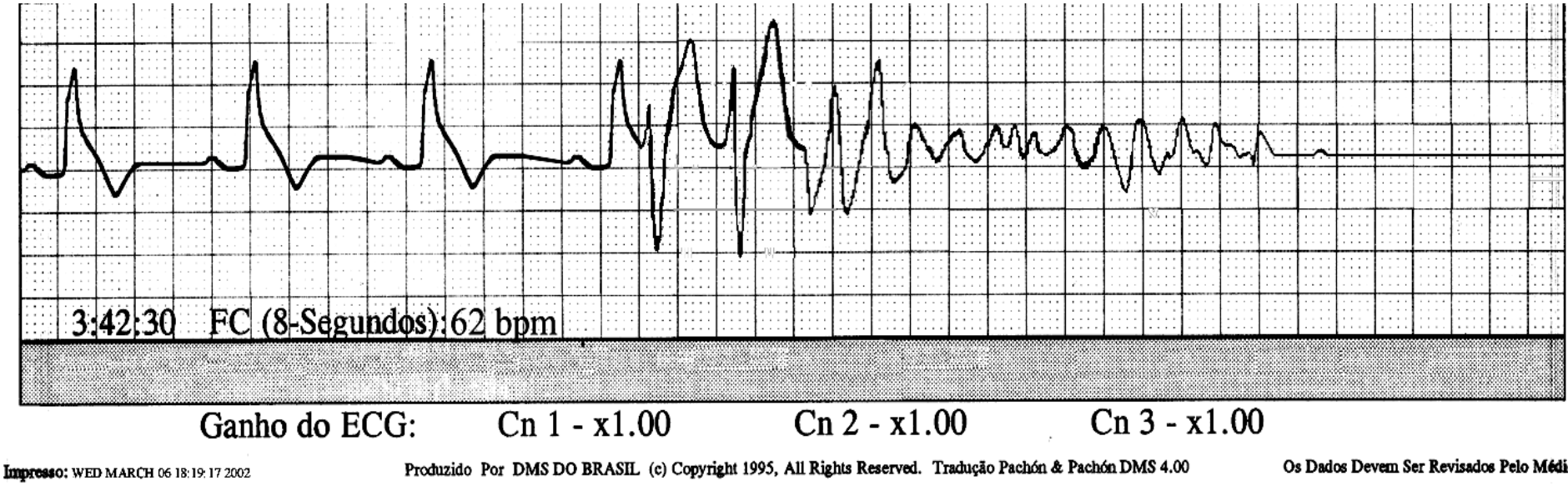
The ECG shows persistent ST segment elevation in the inferior and apical leads, associated to concomitant reciprocal or mirror image in the anterior wall from V1 to V5 that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia.

Downsloping ST segment elevation is present in inferior leads (Idiopathic J waves, lambda waves or Osborn wave). Reciprocal or mirror image is seeing in anterior wall from V1 to V5 and I, aVL and aVR. On the other hand, in “benign” early repolarization pattern, mirror image is only possible in aVR (**Riera 2004**).

The patient refused hospitalization stating as reasons his status of illegal immigrant and lack of medical insurance but except a 24-hours Holter monitoring. On the next morning, the patient was found dead in his bed. Autopsy was not performed.
Holter monitoring revealed a short episode of very fast polymorphic ventricular tachycardia with initial short coupling extra-systole that degenerates into short ventricular fibrillation followed by asystole.

Name: Y. A. S.; **Sex**: Male; **Age**: 26 years old; **Ethnic group:** Asian; **Weight:** 64 Kg; **Height**: 1,68 m;
Date: 03/05/2002; **Time**: 3:42:30 AM Patient Sleeping.

Long-term electrocardiographic recording (Holter)



Sudden Cardiac Death by IPVT/IVF with short coupling ending in cardiac arrest.

Discussion

Studies showed that Sudden, Unexplained Nocturnal Death Syndrome (SUNDS) and BrS are phenotypically, genetically and functionally the same entity. Among 27 Thai men, Nademanee et al (**Nademanee 1997**) reported as many as 16 had the ECG pattern of BrS. Several works show, through spontaneous or drug induced ECG, the possibility of recording type 1 Brugada ECG pattern (Brugada sign) or idiopathic J wave in inferior wall and not in the V_1- V_2- V_3. This concept has been confirmed by employing neurocardiac image techniques, with 123metaiodobenzylguanindine (**Furuhashi 2002; Kawaguchi 2006**), which proves an abnormal 123I-MIBG uptake in patients with BrS, indicating presynaptic sympathetic dysfunction of the heart with potential impact on arrhythmogenesis in these patients. Ultra-fast computed tomography or electron-beam computed tomography, in a lesser percentage of cases, displays alterations in inferior wall dynamics and not in the right ventricle outflow tract. ST segment elevation in inferior wall leads, II, III and aVF, has been proved to be caused by a G752R mutation in the SCN5A gene. **Although we did not have the chance to gather blood samples for genetic typification or to conduct a necropsy, we believe we are facing a case of SUNDS due to the clinical features:**

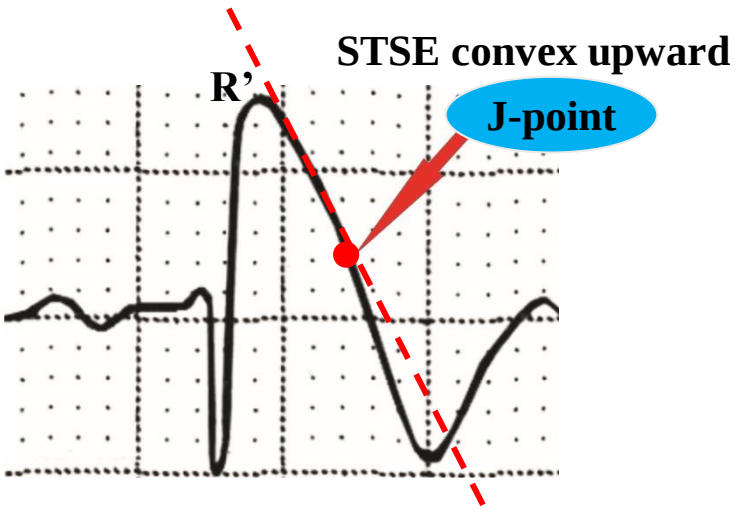
- Strong SCD background in first-degree relatives under 45 years of age;
- Origin of the patient from an endemic area: South Asian Patient (Thailand);
- Documented SCD at rest and during sleep at night;
- Occurrence of syncope with episode of agonal respiration during sleep;
- Presence of Brugada sign in inferior wall in absence of ischemia or electrolytic disorders, which remains unaltered with sublingual isosorbide dinitrate (dismissing the possibility of Prinzmetal's variant angina;
- Absence of structural heart disease by echocardiogram and chest X-rays;
- Documentation of short terminal burst of very fast PVT with short initial coupling extra-systole that degenerates into VF followed by asystole.

We believe that this case supports the hypothesis that BrS could have an electrophysiological substrate in inferior wall. Additionally, this case suggests the advisability of cataloguing the repolarization pattern as type 1C to differentiate it from the current type 1A (convex upward) and 1B (rectilinear oblique) that occurs in right precordial leads.

Proposal of classification of type 1 Brugada pattern

Right precordial leads

Subtype 1A

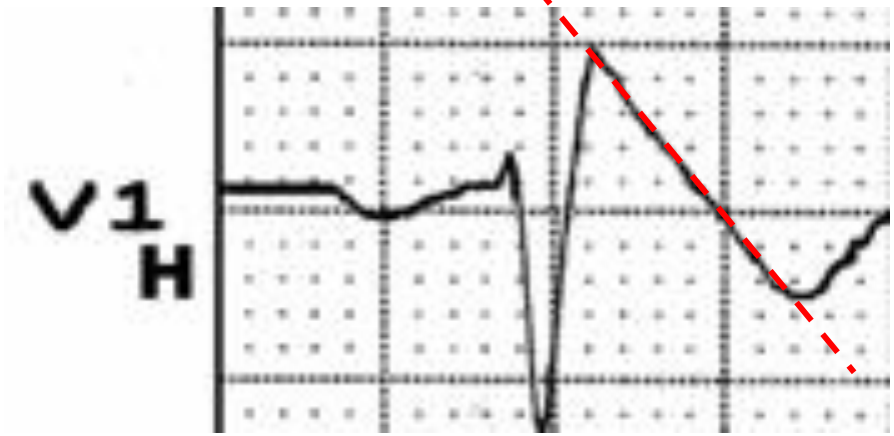


The dotted line is tangent line

In 1A subtype, the J point is located where the downward ramp R' moves away from the tangent line.

Subtype 1B

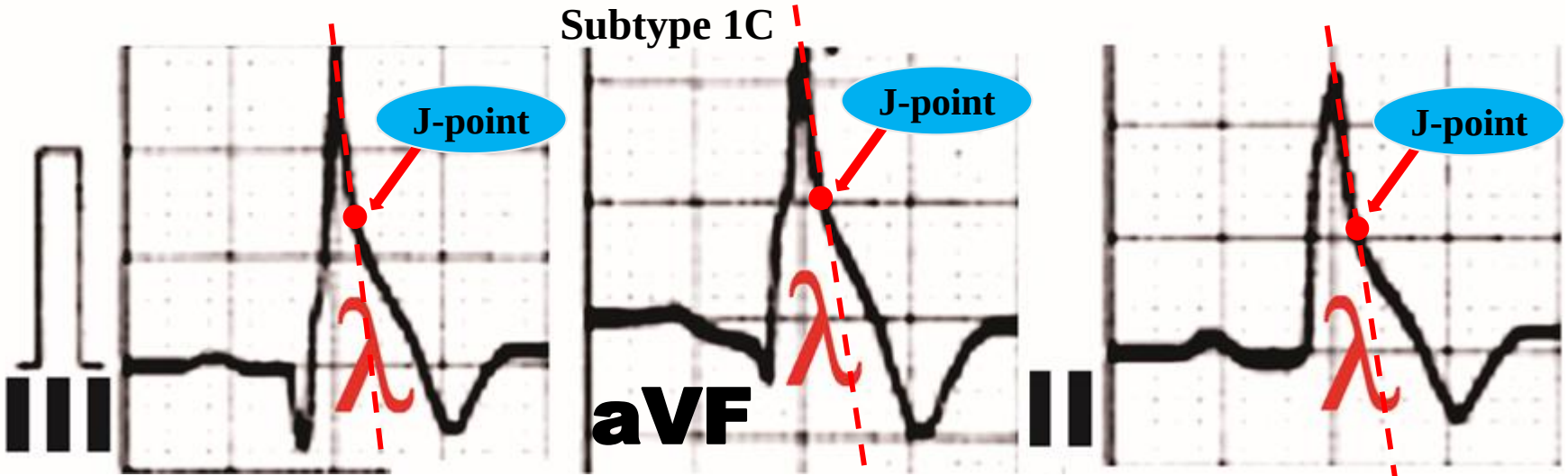
STSE rectilinear oblique descendent



The dotted line is tangent line

It is impossible to determinate the exact location of J-point with tangent line method

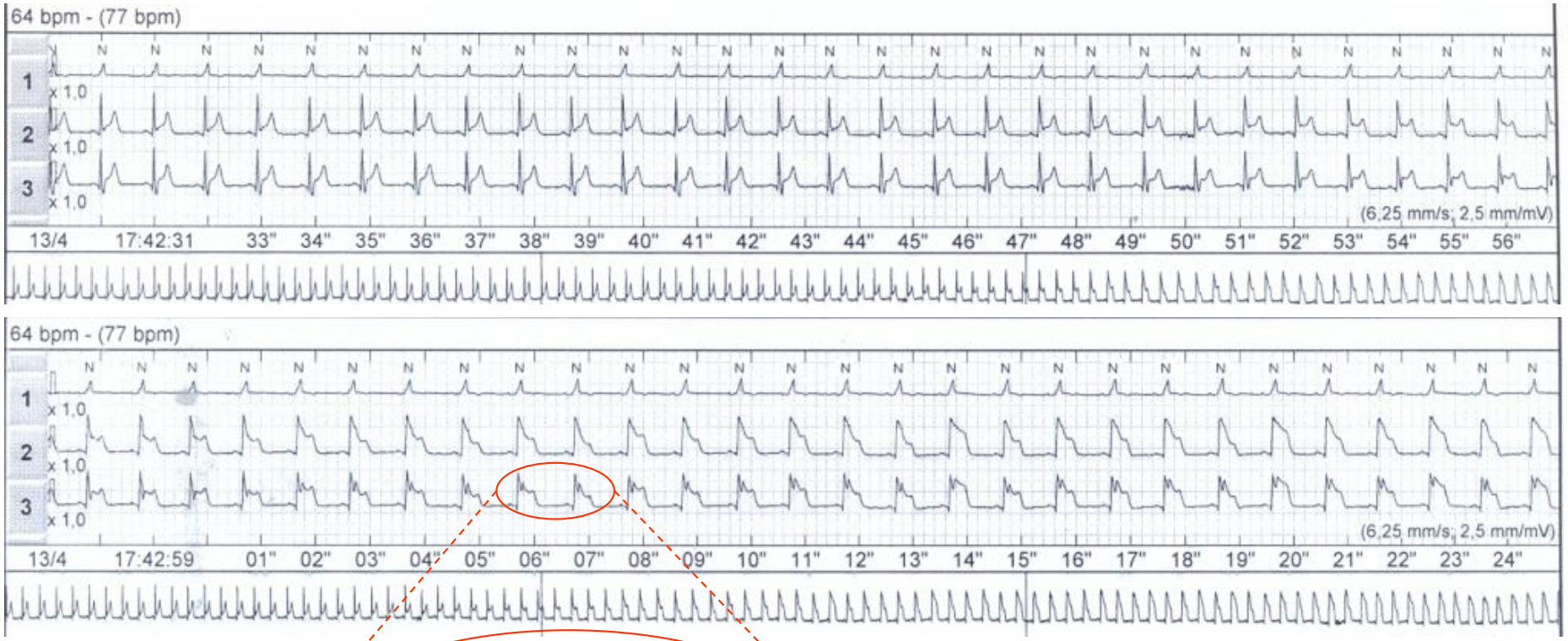
Subtype 1C

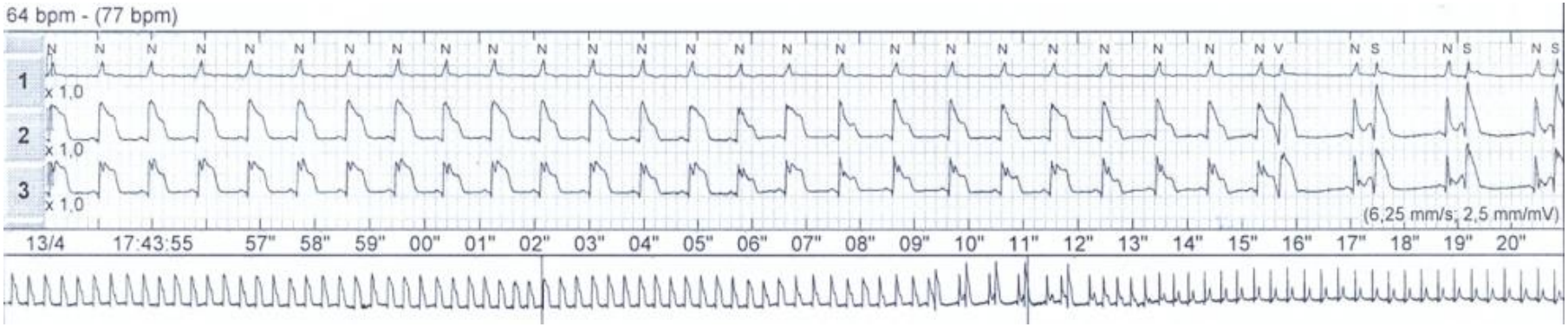


Lambda wave registered in variant angina scenario (Prinzmetal)

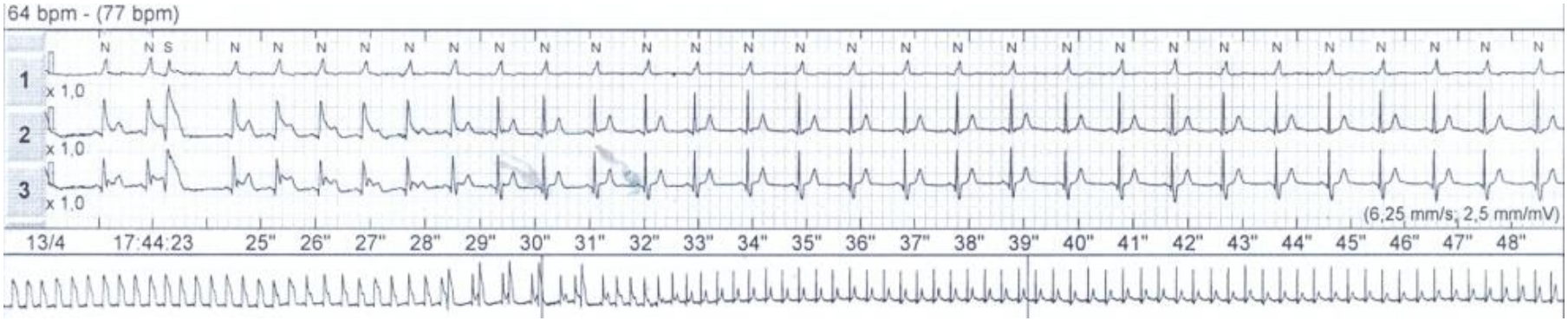
Man who had coronary revascularization a time ago.

Continuous Holter monitoring during an episode of angina and concomitant ST segment elevation and ischemic giant J-wave "lambda-like type" associated with Premature Ventricular Contractions with Bigeminy sequence and very short coupling. The PVCs disappear immediately after cessation of vasospastic ischemia with administration of sublingual nitrate

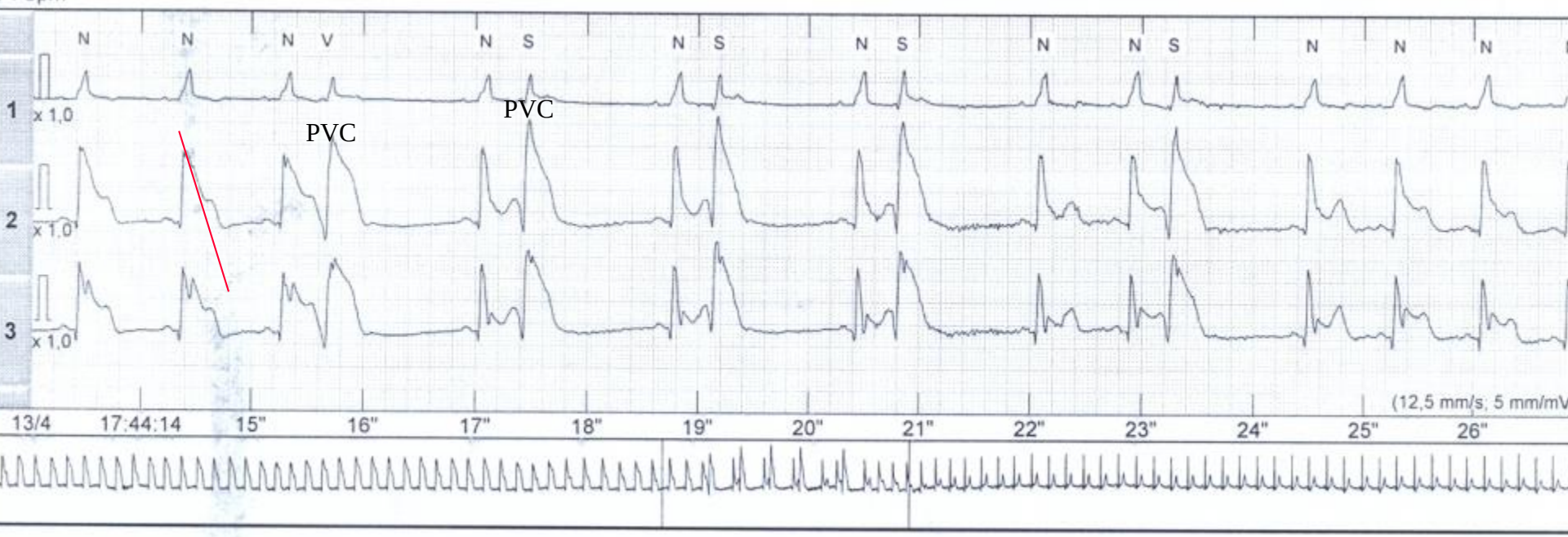




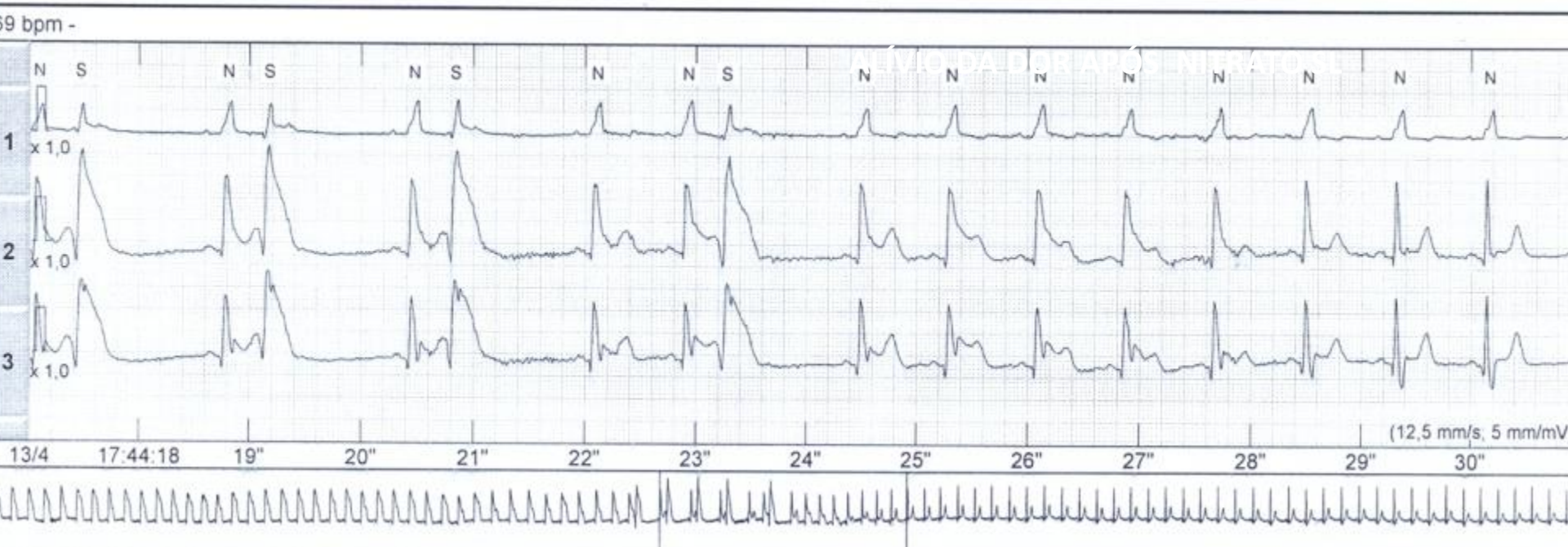
Holter monitoring shows STSE with lambda wave pattern during Prinzmetal angina. The last 4 group of beats are formed by sinus beat followed by premature ventricular contractions.



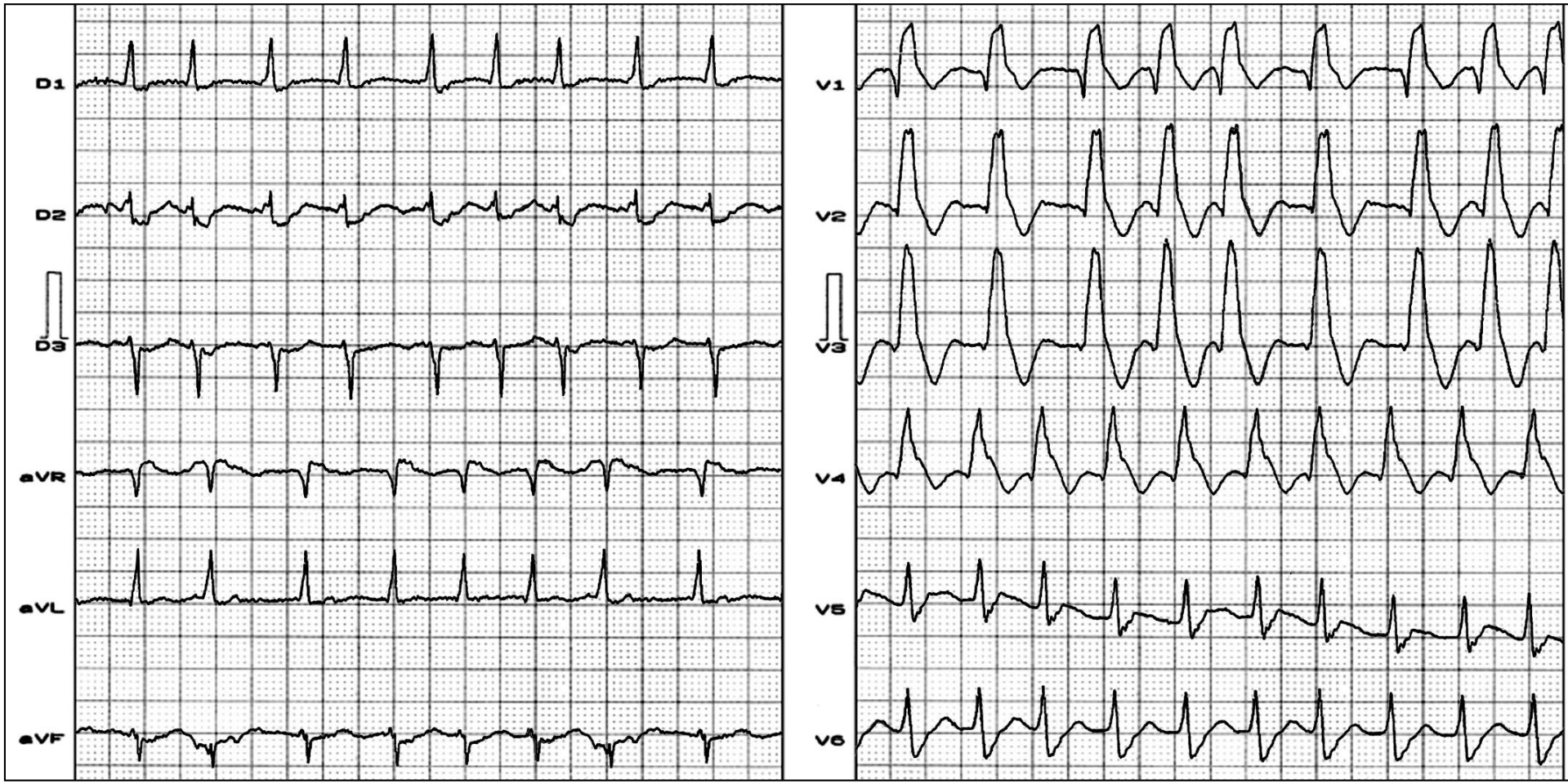
The first beat is sinus rhythm with minimal STSE. The second one has drastical augmentation of STSE followed by short coupled PVC. From third to eighth beat there are minimal STSE. The remaining trace has normal ST segment level.



Premature ventricular contractions (PVCs) occurring after each sinus beat (bigeminy) with lambda wave shape.

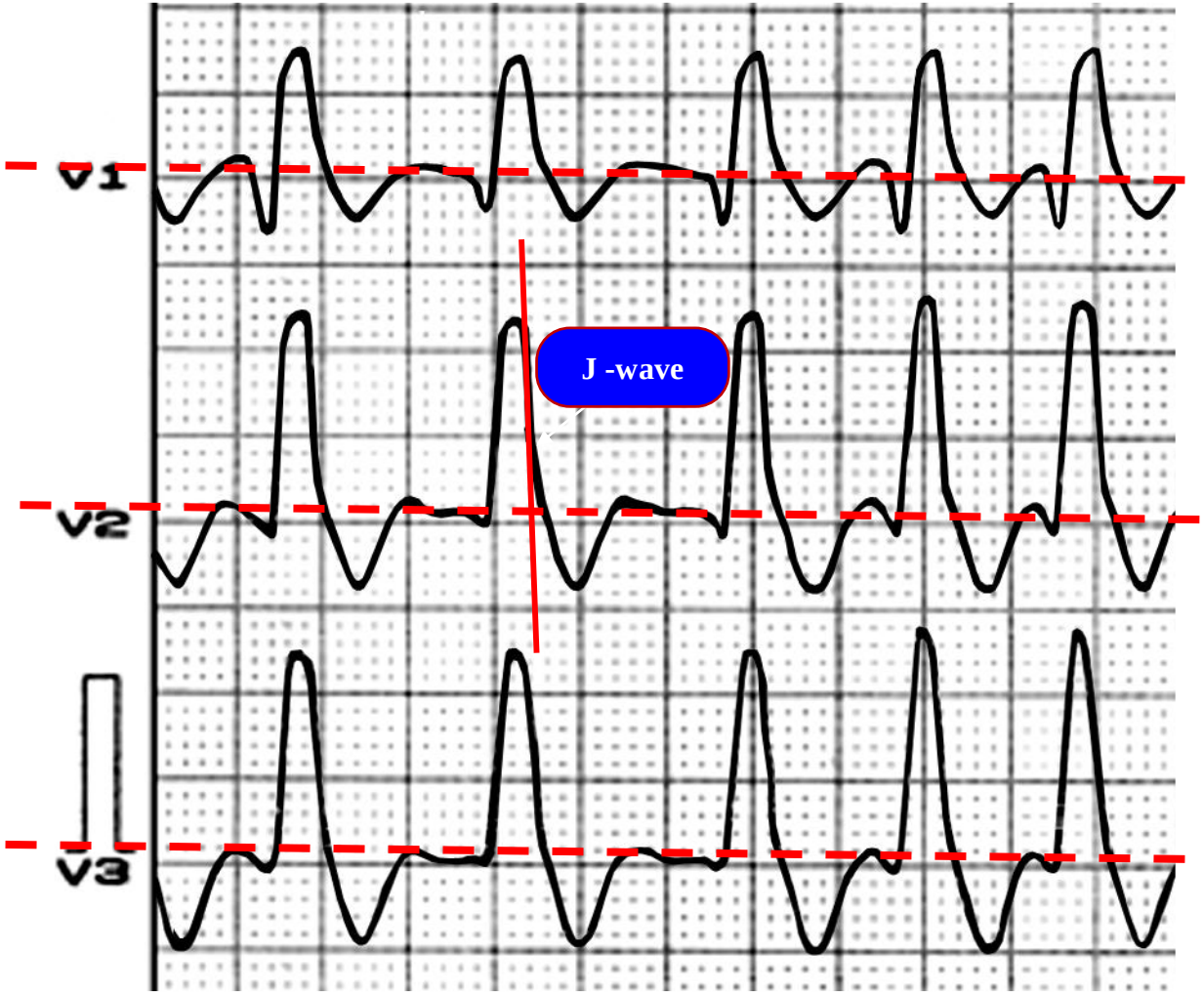


Lambda wave in acute AMI scenario complicated with RBBB



This 12-lead ECG shows acute anterior STEMI in the presence of right bundle branch block, but you really need a trained eye to see it.

We talk a lot about the “rule of appropriate T-wave discordance” with bundle branch blocks. What makes this case difficult is the fact that the T-waves are appropriately discordant. However, the J-points are concordant in leads V1-V4! Why? The answer is in the next slide.

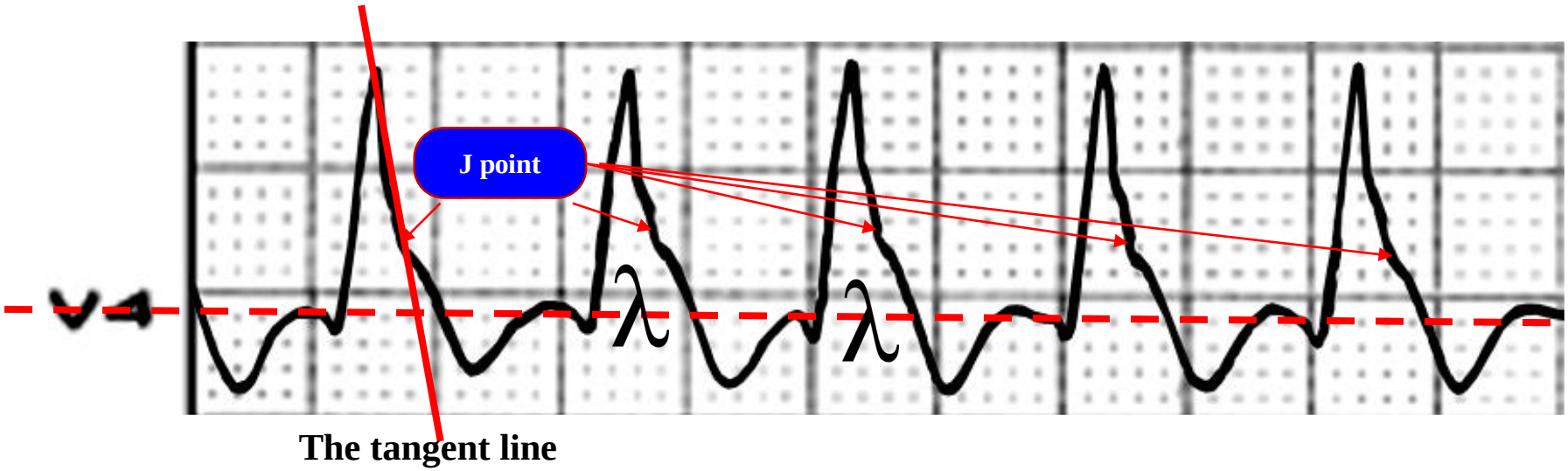


In leads V1-V3 the T-waves are appropriately discordant.

However, the J-points are inappropriately concordant.

This is normal and suggestive of acute STEMI.

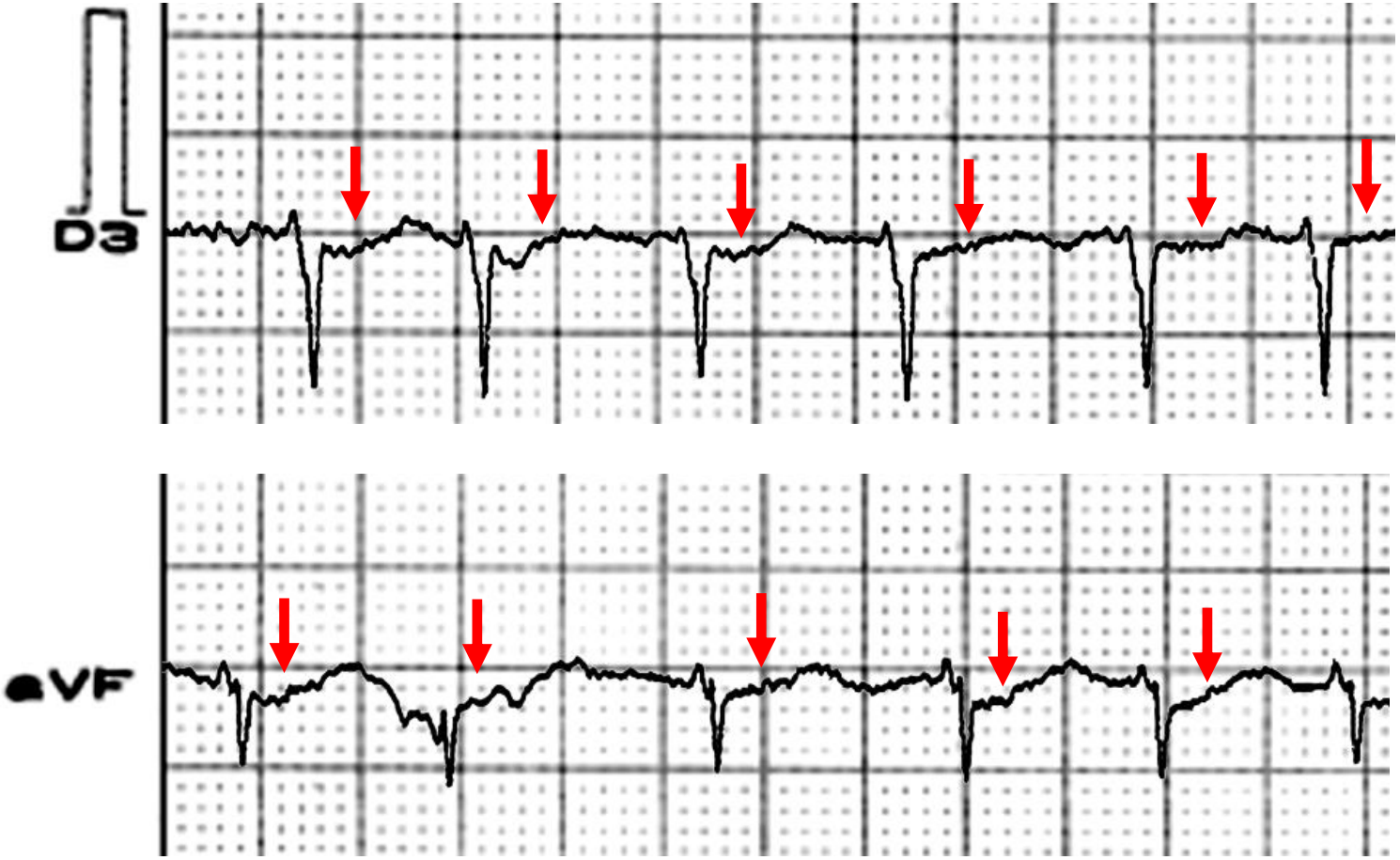
If you look carefully you will see that the point at which the QRS complex turns into the ST-segment (the J-point or “junction” point) is elevated above the isoelectric line.
That’s abnormal for right bundle branch block. In fact, if the J-point isn’t isoelectric in the right precordial leads it should be slightly depressed (in the same direction as the T-waves).



In lead V4, once again the trick is to accurately locate the J-point. Once that is accomplished it becomes obvious that ST-elevation is present.

The T-waves are appropriately discordant.

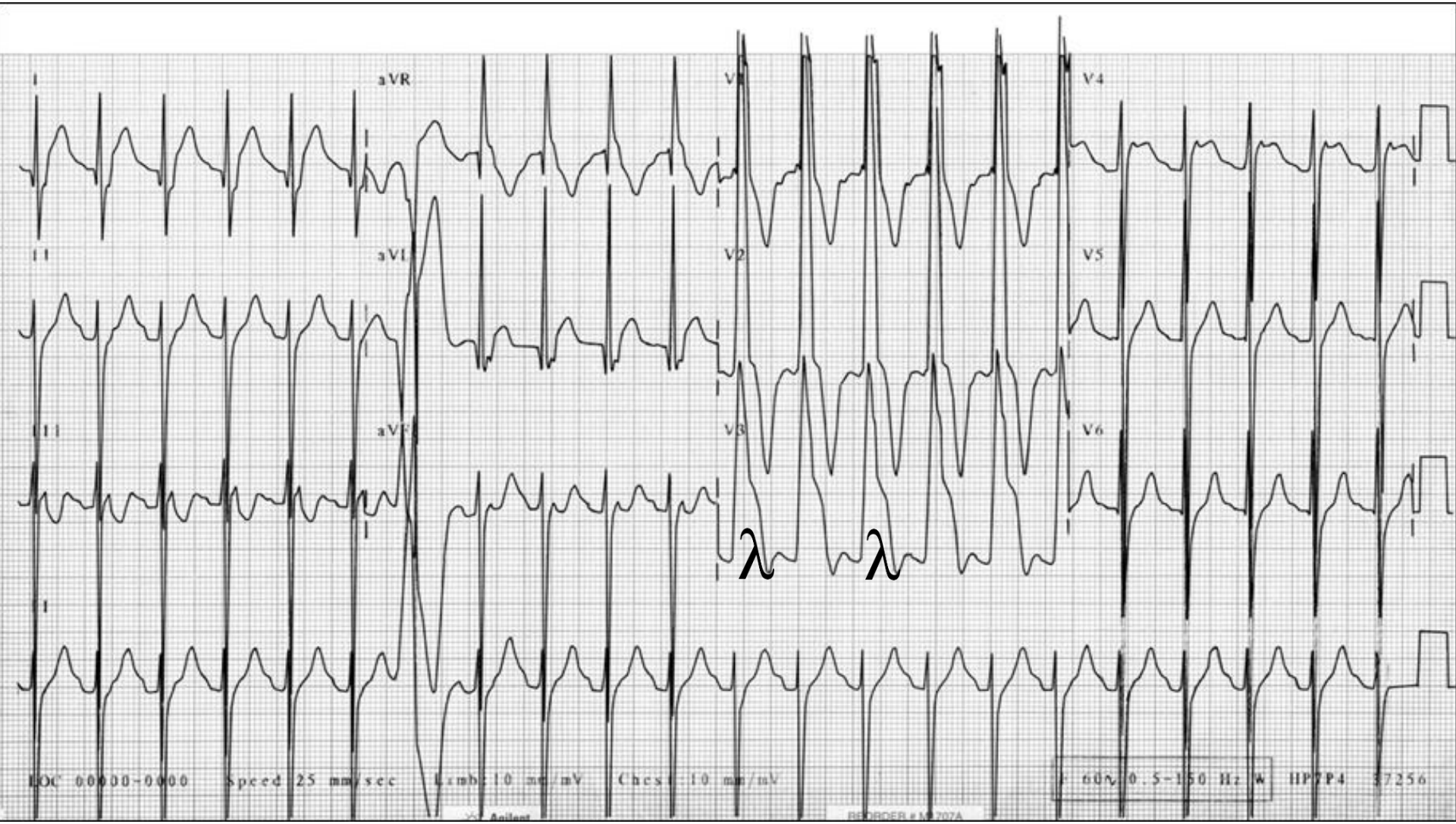
If you're still having doubts, consider that initial Q-waves are present in leads V1-V4.
to "consider the company" that any ECG abnormality keeps.
Finally, let's look at leads III and aVF.



In the context of J-point elevation in the anterior leads, the ST-depression in leads III and aVF must be presumed to be reciprocal changes. We are forced to assume that these are reciprocal changes. Once again, it's the sum of all these abnormalities that is significant. They are more than the sum of their parts.
This patient was in fact diagnosed with an acute anteroseptal ST-elevation myocardial infarction.

Lambda wave immediatly percutaneous transluminal alcohol septal ablation

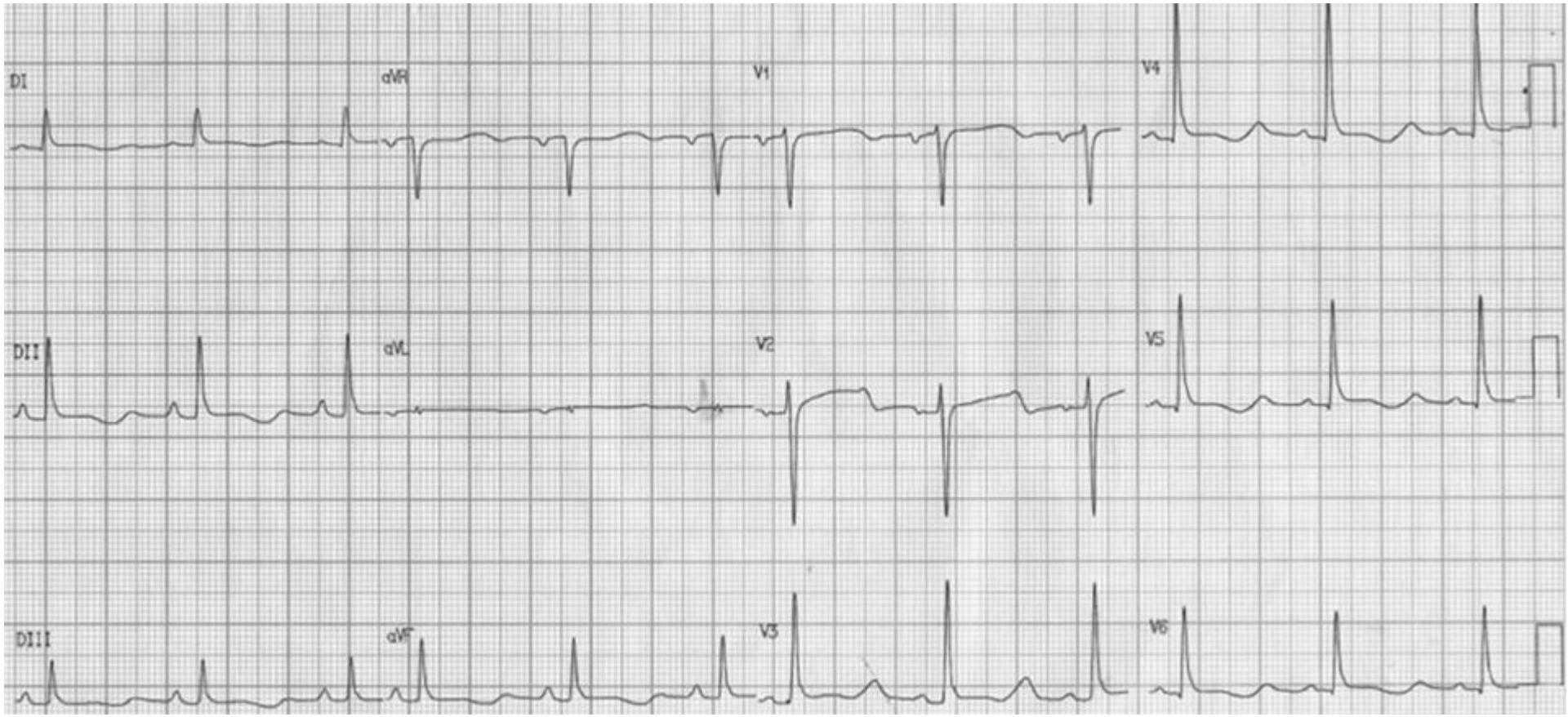
Sex: F; **Ethnic group**: Caucasian; **Age**: 13 y/o; **Weight**: 50 kg; **Height**: 1.60 m; **Date**: Jan 23, 2003.

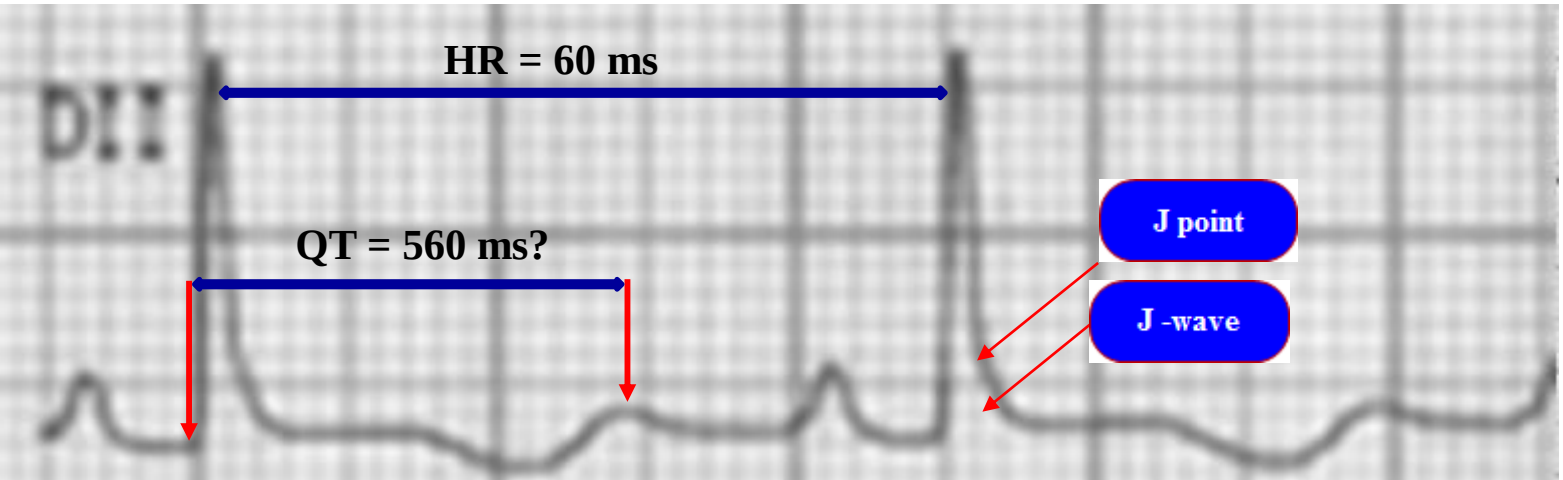


Severe obstructive hypertrophic cardiomyopathy: immediately ECG post percutaneous transluminal alcohol septal ablation. Ventricular fibrillation occurred.

Clinical result: Unsuccessful. Class II to III NYHA.

ECG2 – Basal ECG

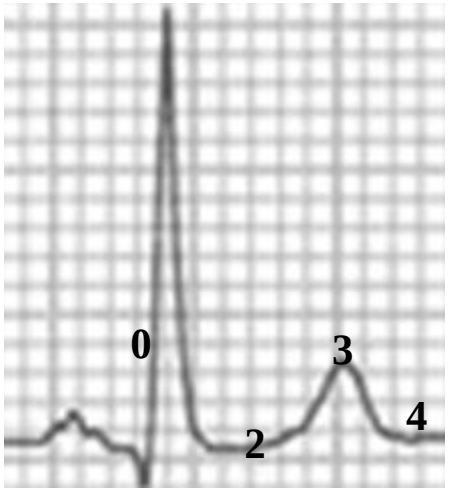




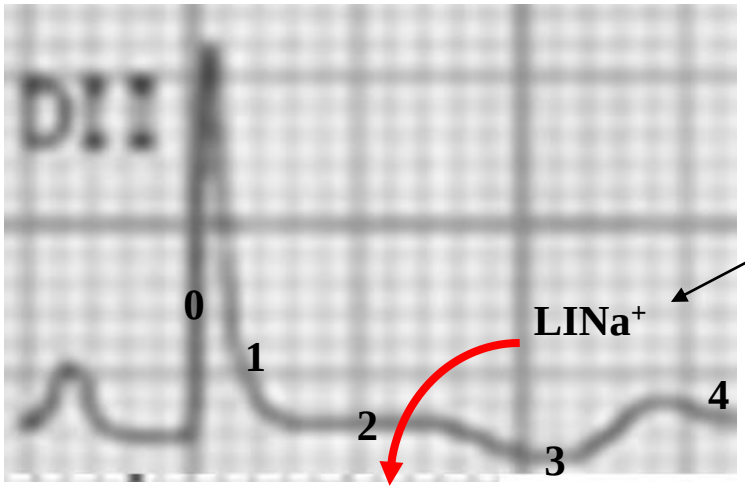
Characteristics of LQT3 variant, SCN5A mutation

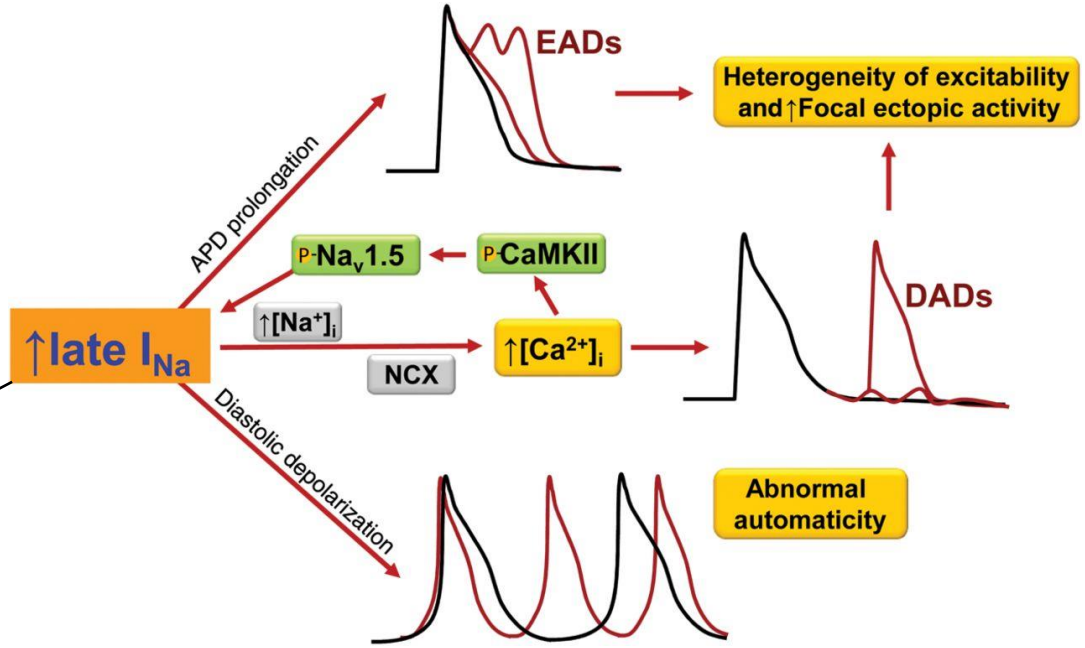
Long QT interval by ST segment prolongation. Delayed appearance of T wave. Significant dependence on heart rate of QT interval Affected gene: SCN5A, p21-24 mutation in chromosome 3, TAP phase: plateau, dome or phase 2 by persistent sodium(Na^+) inflow.

≈ 80% of events during sleeping or at rest



Normal





ST segment prolongation and delayed appearance of T wave

Male sex has higher risk This is the mirror image of Brugada syndrome (allele entities)

Congenital LQT3 variant

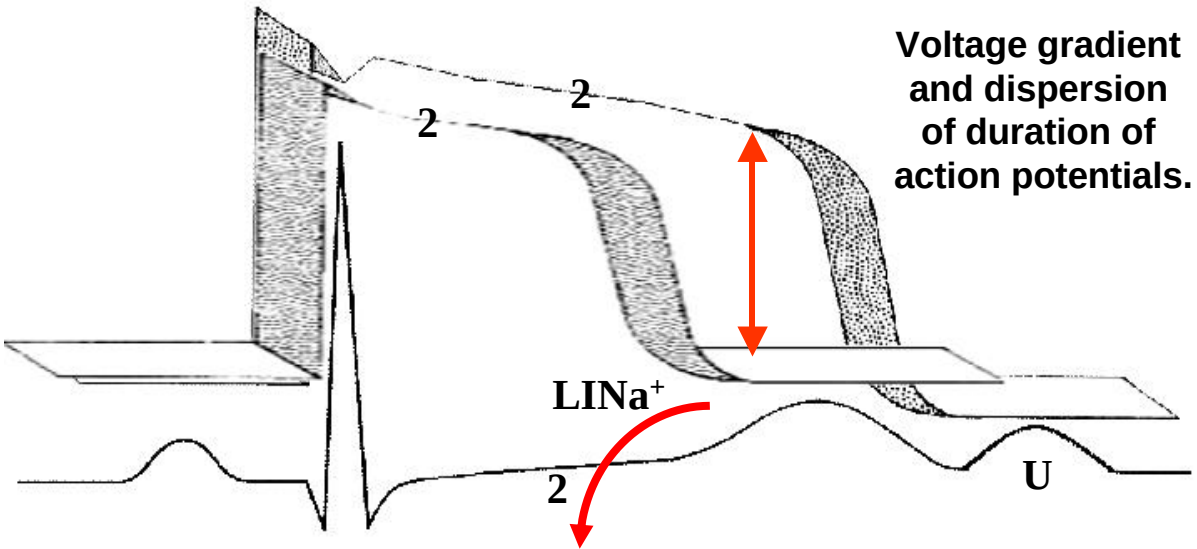
Jiang et al mapped the LQT3 variant for the first time in 1994 (**Jiang 1994**). One year later, Wang et al detected in the SCN5A gene of the Na^+ current a p21-24 mutation in chromosome 3, in patients with LQT3 variant (**Wang 1995**)**.** It is considered an allelic entity to Brugada syndromt; it is the mirror image.

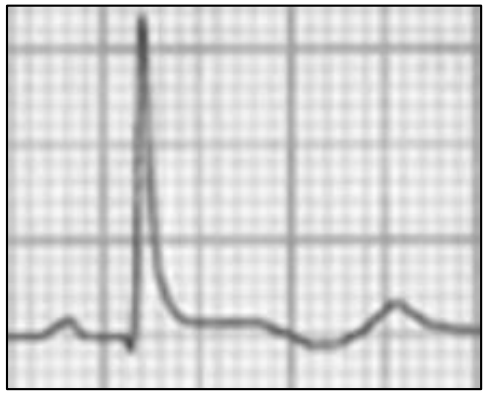
It is identified as a dominant autosomal entity (**A dominant allele whose gene is located on an autosome. Autosome**: **Any of the "numbered" chromosomes -- not the X, Y, or mitochondrial chromosomes. Each human has two copies of each; one inherited from the mother and one from the father**), or Romano Ward without deafness, much more frequent than the form with deafness of Jervel-Lange-Nielsen, which affects the SCN5A gene of chromosome 3p21-p24.

Priori et al showed the first evidence that the Romano-Ward variant can be transmitted recessively (**Priori 1998**)**.**

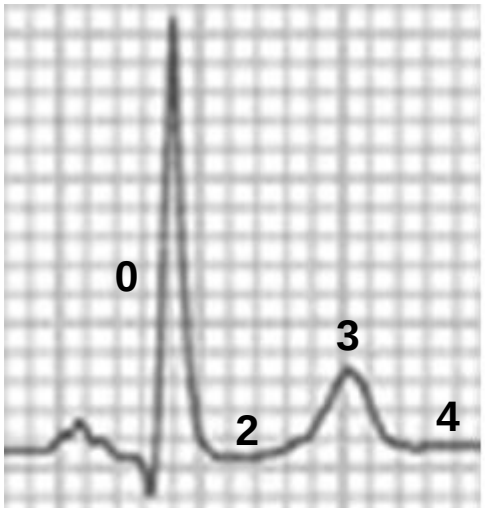
The place of mutation in the SCN5A gene is different from BrS and produces a phenotype characterized by QT interval prolongation at the expense of ST segment and late appearance of T wave, prominent U wave, and high tendency and triggering of atypical polymorphic ventricular tachycardia bursts, known as TdP.

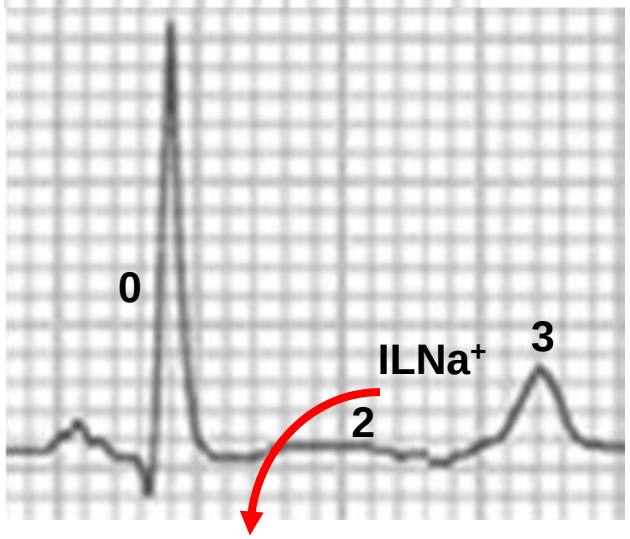
The diagram of figures below exemplifies the electrocardiographic characterization of the LQT3 variant.



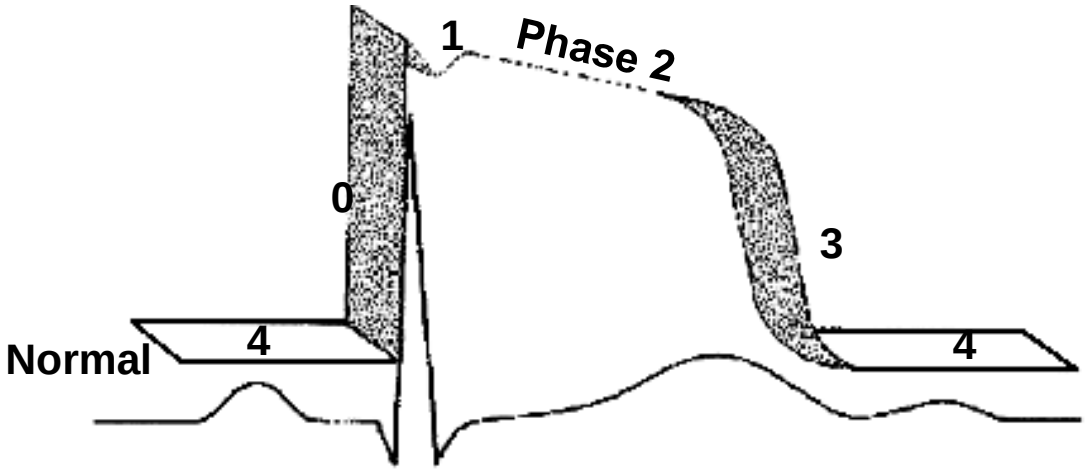


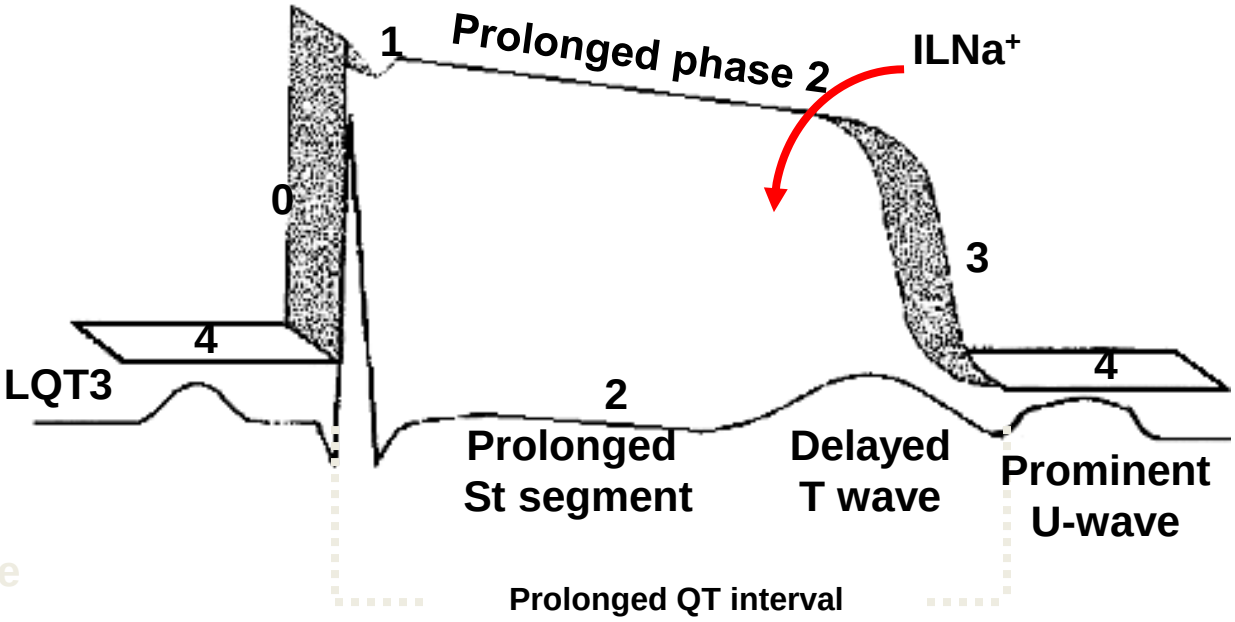
Normal ECG and action potential versus LQT3 ECG and action potential





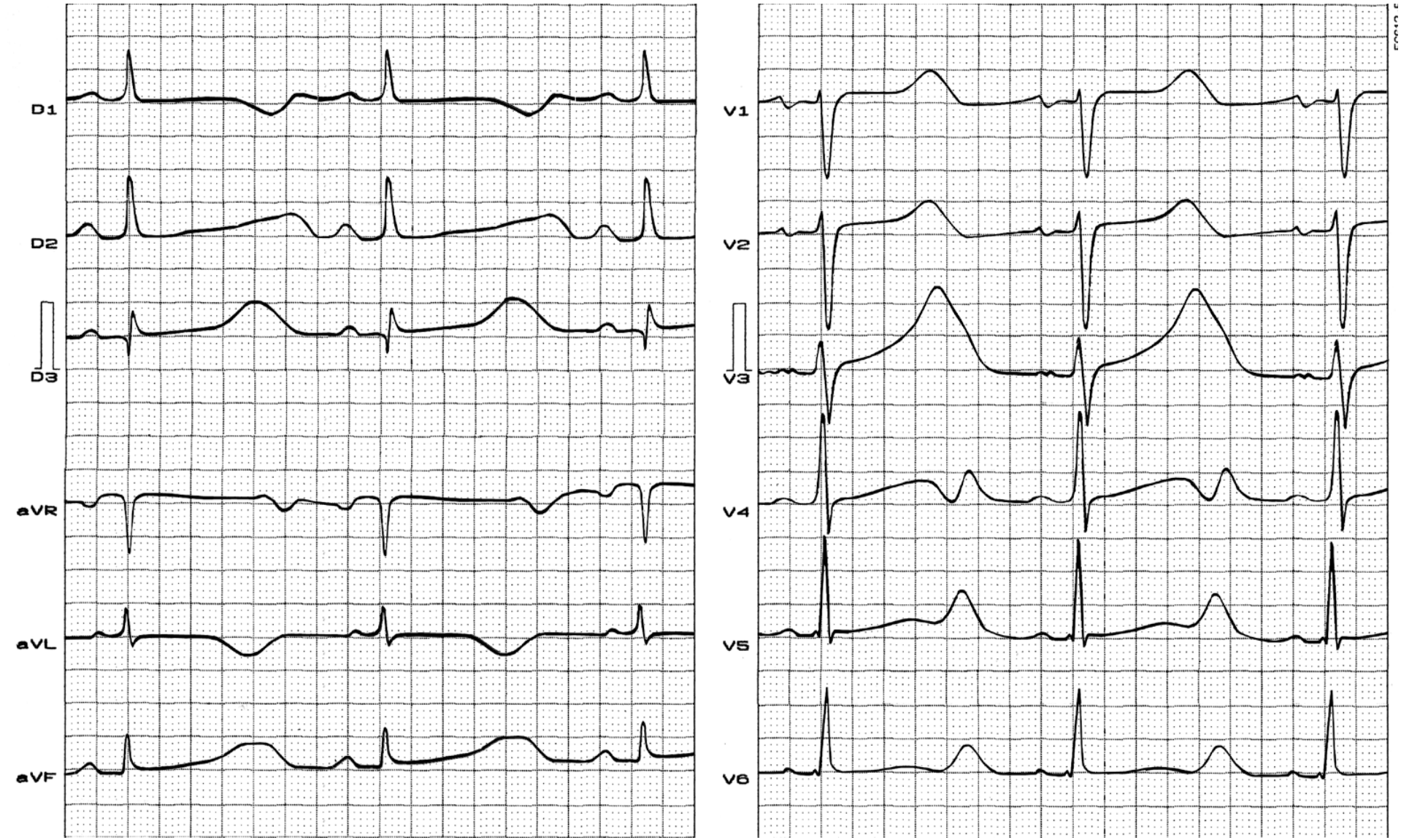
Delayed appearance of T wave





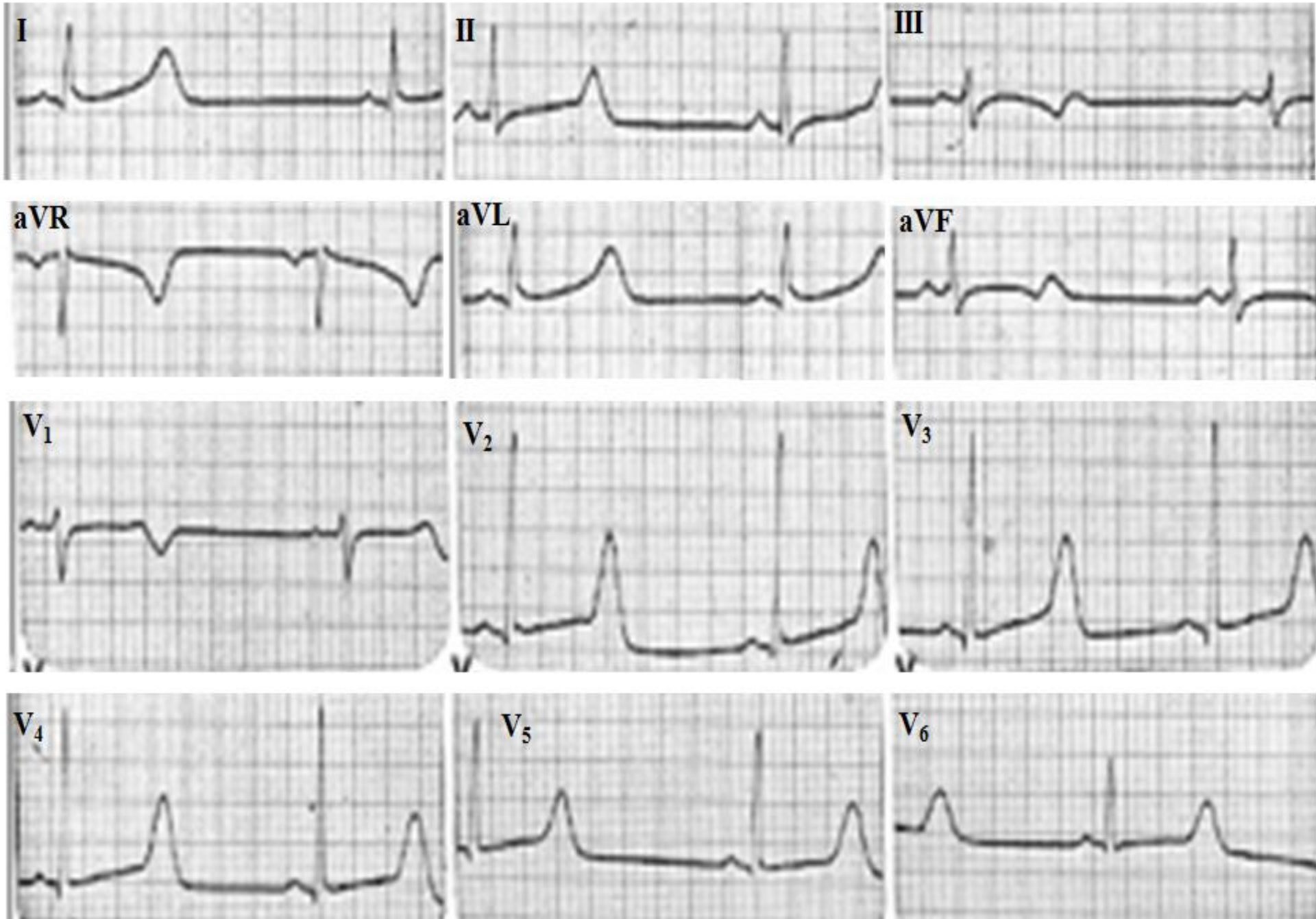
Characteristics of LQT3 variant, SCN5A mutation

Name: B.A.S.; **Age:** 8y; **Sex:** Female; **Race:** Caucasian; **Date**: 03/12/1998; **Weight**: 25 Kg
Height: 1,25m; **Drugs in Use:** Nadolol (Corgard) 120 mg/day

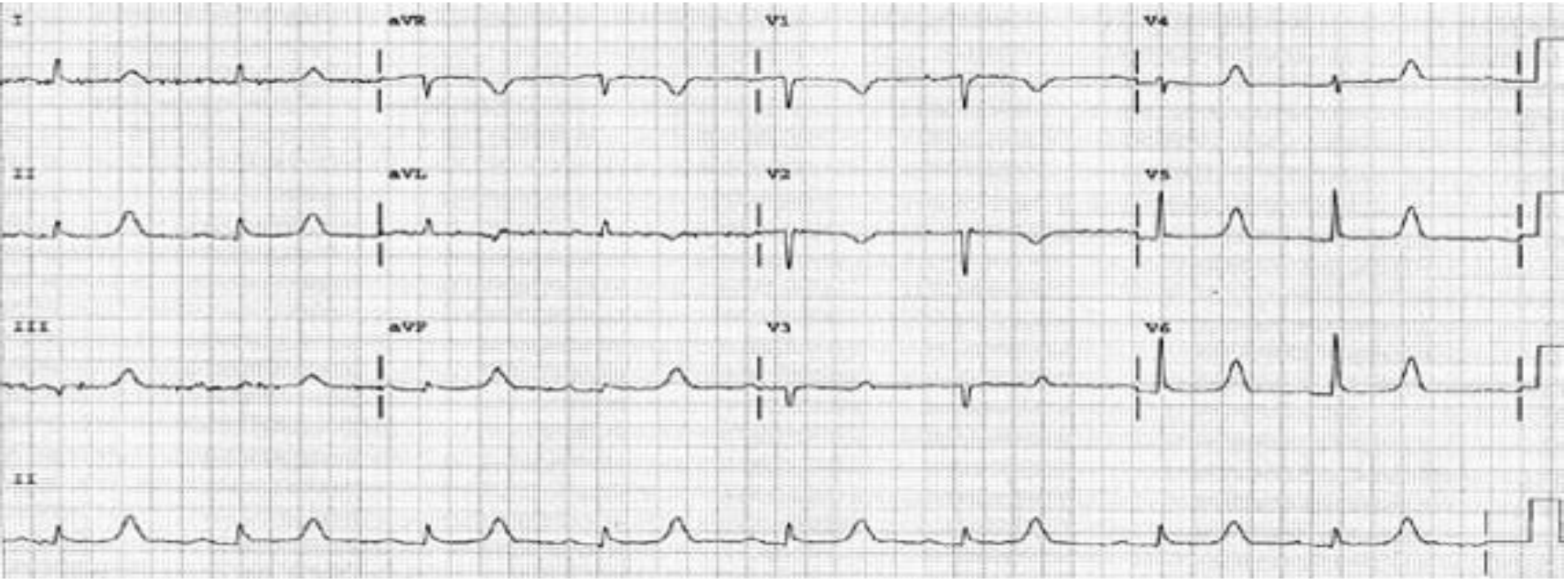


Clinical diagnosis: LQT3 variant.
ECG diagnosis: Sinus rhythm; HR: 36 bpm: Sinus Bradichardia QT interval : 110 msec. Long ST segment, Bifid and prominent T wave.

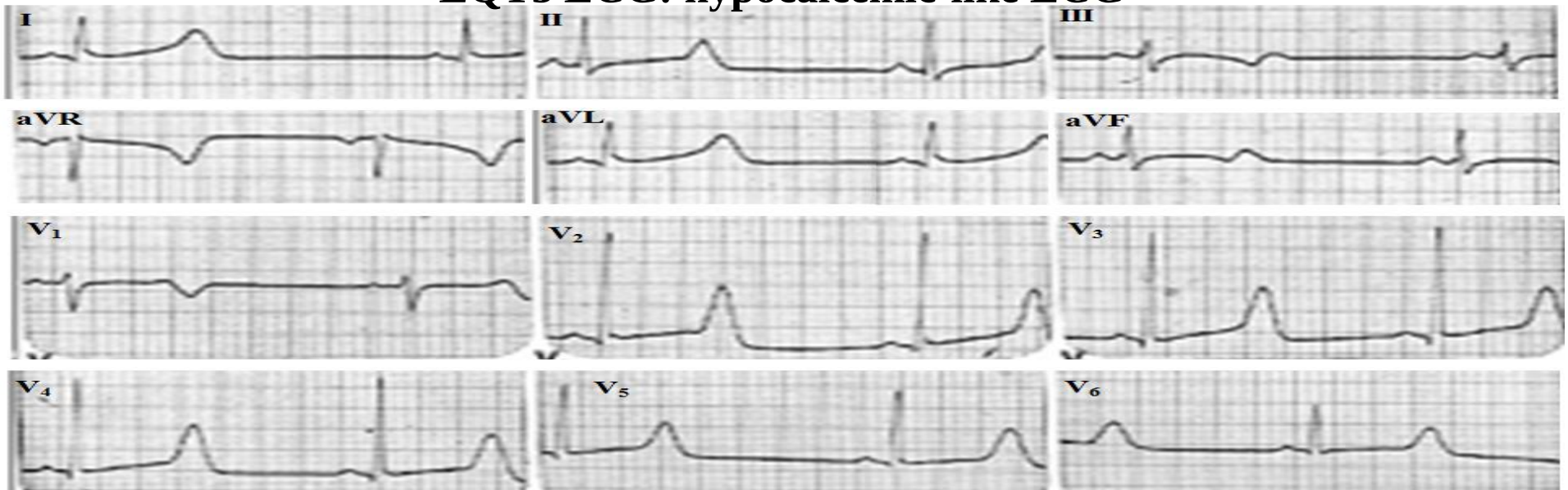
LQT3 ECG



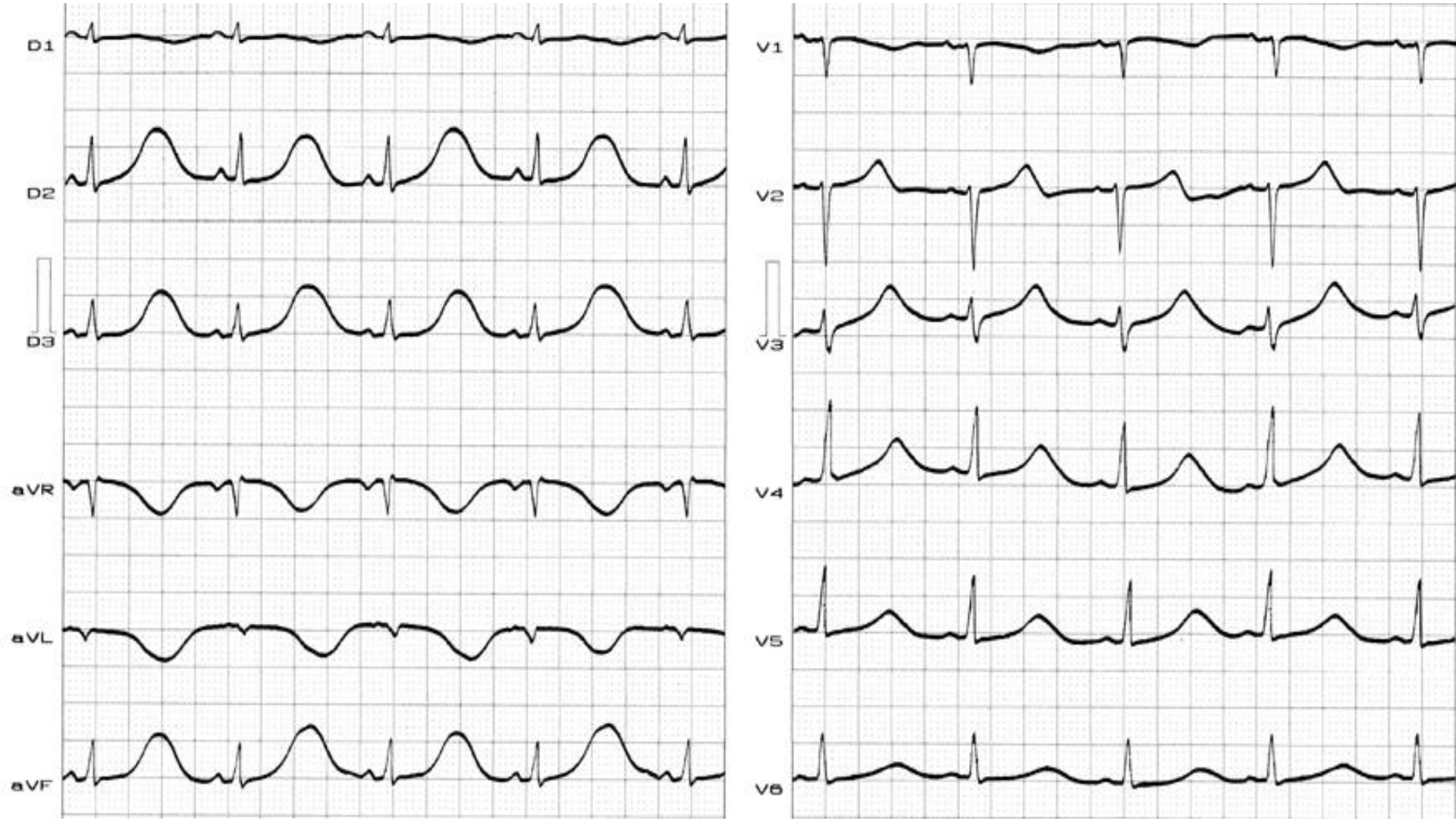
Hypocalcemia ECG



LQT3 ECG: hypocalcemic-like ECG



Typical ECG of congenital long QT syndrome Romano-Ward LQT3 variant



A seven year old boy without sensorineural deafness. LQT3 affects SCN5A gene on chromosome 3p21-24.
The channel affected is the Na+ current on the alpha-subunit.
There is a bizarre QT interval prolongation (620 ms) with late initiation of the T wave.
This patient had repetitive syncope.
LQT3 patients tend to have more events during sleep.

Characterization of the LQT3 variant

- **Presentation:** Syncope, aborted cardiac arrest, SCD more frequent during the night or rest;
- **Triggering factors:** sound, night vagotony;
- **Phenotypic characteristics**: In LQT3 there is a report of association with syndactyly (**Marks 1995**).
- **Predominant age for events:** for LQT1 and LQT2, events are observed since birth until adolescence. LQT3 has a later peak such us the present case;
- **Dependence of heart rate on QT interval** Increase of HR causes shortening of QT interval in LQT3, but it does not in LQT2 (**Priori 1996**). LQT3 variant has significant dependence of heart rate on QT interval;
- In LQT3, there is a mutation in the sodium channel gene (SCN5A) which causes the channel to inactivate incompletely; the persistent inward current carried by Na+ ions also prolongs the action potential.
- In LQT3, various mutations in SCN5A were identified, which produce a gain of sodium channel function (**Janse 1998; Benhorin 1998; Wei 1999; Keller 2003**).
- In the LQT3 variant the E1784K mutation in the SCN5A gene causes a gain in function with slow and persistent inward late movement of Na^+, a hyperpolarization of the balanced state, and a fast recovery from the inactivation state (**Deschenes 2000**).
- In LQT3, there is a tendency to bradycardia by age in some cases. Sympathetic hypotonia in right stellar ganglion has been suggested as responsible;
- Long QT interval occur at expense of ST segment prolongation;
- Late appearance of T wave due to ST segment prolongation;
- Prominent U waves are frequent
- Tendency to appearance of PVT bursts of the TdP type with initial telediastolic coupling, bradycardia-dependent, triggered by pauses or bradyarrhythmias with frequent indication of permanent pacemaker at a higher rate;.
- Frequency of tachyarrhythmic events when the mutation is present: 18%
- Risk of death in each tachyarrhythmic event: 20% (**Zareba 1998**)

Management of LQT3

Drugs

- **Mexiletine,** an antiarrhythmic agent of the 1B class, "lidocaine-like", shortens QTc interval only in the LQT3 variant, preventing appearance of TdP. The drug does not shorten the long QT interval of congenital LQT2, which affects the K^+ current (HERG defect of the K^+ current) (**Moss 1995; Shimizu 1997; Priori 1997**). The rationale for using Na+ channel blockers in LQT3 is based on the experimental evidence that mexiletine reduces the AP prolongation produced by delayed inactivation of the Na+ current and the persistent inward current associated with 3 mutations (ΔKPQ, R1644H, and N1325S). Indeed, acute oral testing with mexiletine shortened the QT interval in LQT3 patients
- **Oral flecainide** has shortened the QT interval in LQT3 patients. leading to the suggestion of using it as a specific long-term treatment for LQT3. Benhorin et al reported that oral flecainide significantly shortened the QT interval in 8 asymptomatic members of one LQT3 family. The response to flecainide could be either gene-specific or mutation-specific. In fact, the picture could be even more complex. Like the puzzling issue of incomplete penetrance, with some family members carrying the mutation but not manifesting QT prolongation, it may also be true that the response to Na+ channel blockade shows individual variability or that it lacks reproducibility within the same patient. This raises uncertainties about the negative predictive value of the lack of ST segment elevation after the IV administration of flecainide and questions the overall safety of long-term treatment with flecainide in LQT3. These findings prompt 2 considerations relevant to clinical practice. The similar response of LQT3 and BrS patients to flecainide challenge, combined with the common clinical features of the 2 diseases (suspected or certain lack of therapeutic efficacy of β-blockers, high lethality of cardiac events, and arrhythmias occurring at rest or sleep), demonstrates that the phenotypic overlapping of LQT3 and BrS is larger than commonly appreciated.The evidence that flecainide may provoke ST segment elevation calls for caution in initiating long-term flecainide treatment in LQT3 patients.Kilinc et al.(**Kikinc 2011**) presented a case report, of a patient with congenital LQT3 (Y1795C mutation) presenting with ICD storm. Patient's arrhythmia burden was eliminated following successful treatment with flecainide.

- **Ranolazine:** Ranolazine is a Na(V)1.5 antagonist with antianginal and antiarrhythmic properties. Consequently the drug is used to treat chronic angina (**Kloner 2013**). In clinical trials ranolazine slightly increased QT interval in some patients Ranolazine selectively inhibits late I(Na), reduces [Na(+)](i)-dependent calcium overload and attenuates the abnormalities of ventricular repolarization and contractility that are associated with ischaemia/reperfusion and heart failure (**Belardinelli 2006**). Thus, inhibition of late I(Na) can reduce [Na(+)](i)-dependent calcium overload and its detrimental effects on myocardial function. Ranolazine inhibits the late Na^+ current (I_{NaL}) and is effective against arrhythmias in LQT3 despite its blocking properties of the rapid component of delayed rectifying potassium current. The late Na current is of pathophysiological importance for the heart. Ranolazine is an innovative anti-ischemic and antianginal agent thatinhibits the late Na current, thereby reducing the Na-dependent Ca-overload, which improves diastolic tone and oxygen handling during myocardial ischemia. In addition, ranolazine seems to exert beneficial effects on diastolic cardiac function. Moreover, there are experimental and clinical data about its antiarrhythmic properties. A beneficial atrial selectivity of ranolazine has been suggested that may be helpful for the treatment of atrial fibrillation (**Maier 2012**). .Actually, researches from the Tel-Aviv Sourasky Medical Center are studying this drugs with the purpose of to determine whether ranolazine will reduce the risk of arrhythmic events in patients with LQT3. The study is actually in phase 2. Ranolazine effectively inhibits mechanosensitivity of Na(V)1.5. The block of Na(V)1.5 mechanosensitivity by ranolazine does not utilize the established binding site and may require bilayer partitioning. Ranolazine block of Na(V)1.5 mechanosensitivity may be relevant in disorders of mechanoelectric dysfunction.(**Beyder 2012**) Additionaly, ranolazine decreased reverse Na(+)/Ca(2+) exchange current (INCX) by inhibiting INa.L in normoxia, concentration-dependently attenuated the increase of late sodium current (INa.L), which thereby decreased the reverse INCX, and obviously relieved EADs during hypoxia.(**Wang 2014**). Finally, ranolazine attenuates the electrophysiological effects responsible for the acceleration and increase in complexity of ventricular fibrillation produced by myocardial stretch.(**Chorro 2015**).

- **β-blockers** have a protective effect in LQT1 and LQT2; however, they can trigger TdP in LQT3. A refractory set of symptoms can occur in 3-4% of patients, in response to antiadrenergic treatment (β-blockers and thoracic sympathectomy), then pacemaker could be indicated. On the other hand recent experimental study indicate that, contrary to previous reports, β-blockade effectively prevents VT/VF in a validated LQT3 model. Together with the most recent clinical data, these findings indicate that there is no reason for not initiating protective therapy with β-blockers in LQT3 patients.(**Calvillo 2014**). LQT3 patients respond less well to β-blockers, but the available, albeit limited, data suggest that the worst response to medical therapy concerns mainly the patients with cardiac events in the first year of life and that the remaining patients fare rather well with β-blockers and/or LCSD (**Schwartz 2009**).

- **Pacemaker:** The implantation of a permanent pacemaker at higher rates could yield a higher benefit in patients carriers of LQT3 than in those with other variants, because these have a higher risk of arrhythmias at low rates. In symptomatic patients of LQT3 in whom the TdP is bradycardia-dependent or pause-dependent, a pacemaker could be used to avoid bradycardia and pauses.

- **Implantable cardioverter-defibrillator ICD:** is indicated where arrhythmia is not controlled with pacemaker and β-blockade. However, the combination of new devices with pacemaker and ICD capabilities appear promising in these patients warranting further study (**Khan 2004**). In pediatric population, none of the 14 patients who underwent primary prevention, ICD implantation received appropriate shocks in 41 patient-years of follow-up, while 2 of 6 patients who underwent secondary prevention ICD implantation received appropriate shocks in 30 patient-years of follow-up. Half of patients who underwent ICD implantation experienced inappropriate shocks or ICD-related complications. (**Blaufox 2012**). LQT3 patients had a disproportionately high probability of being implanted with an ICD; and during an average follow-up of <5 years, adverse events, major and minor, occur in 25% of the patients excluding inappropriate shocks and in 31% including inappropriate shocks. It is likely that many of the appropriate shocks received by 28% of the patients might have been avoided by different programming designed to allow short runs of TdP VT to self-terminate.

- These data should call attention to the appropriateness of the decision to implant an ICD in a significant number of LQTS patients and definitely mandate a reassessment of the ICD programming for LQTS patients. LQT3 patients represent only 7% to 10% of the overall genotyped LQTS patients, they make up 22% of the genotyped LQTS patients receiving an ICD. Here, the explanation is likely to reflect the idea, accepted rather uncritically until a few years ago that non device therapies are ineffective in preventing deaths and the fact that ACA/SCD may often be their first clinical manifestation. As a consequence, there is the risk that once physicians are informed by the genetic laboratory that that their patient carries a *SCN5A* mutation (most of the time even without any evidence that this is a disease-causing mutation), they are concerned with the presumed lack of effective therapies and may decide to proceed with an ICD implantation. This interpretation has the dramatic support of the percentage of asymptomatic patients who received an ICD based on genotype. Whereas this number ranged 45% for LQT3 patients. This tendency has had some justification until a few years ago, but recent data and the argue strongly for assessing the pros and cons of an ICD on the basis of the actual clinical risk of the individual patient. The present data and of the previous data on the therapy of genotype-positive LQTS patients suggests a more cautious approach before jumping from an *SCN5A* mutation to an ICD implantation in an asymptomatic individual and might also lead, after a full disclosure of the data available to the patients, to first implementing a preventive strategy based on β-blockade and possibly LCSD. This approach would still leave open the option of implanting an ICD if deemed appropriate. Zareba al. indicated the absence of ICD shocks during follow-up in LQT3 patients who received an ICD because of their genotype (**Zareba 2007**) The same absence of shocks, but in a larger group of LQT3 patients, has been observed by Ackerman (personal communication)

Mixed forms or overlapping arrhythmia phenotypes on SN5Amutations

- BrS and LQT3 variant
- BrS and progressive dromotropic disorders of the His Purkinje system: "Lenègre disease";
- BrS and Sinus Node Dysfunction(SND)
- BrS and Idiopathic VF

Brugada Syndrome and LQT3 variant

The defects on the SCN5A gene that encode the α-subunit of the cardiac Na^+ current may cause both the LQT3 and BrS. Both are allelic disorders with a common genotype. Evidence shows the existence of an overlapping of phenotypes between BrS and LQT3 variant. Bezzina et al (**Bezzina 1999**) described a large family that displays an SCN5A mutation, where in all the members a mixed ECG pattern was observed, characterized by Brugada ECG pattern in V_1 to V_2, and long QT interval with high tendency to nocturnal SCD. The genotype study of these patients revealed the insertion of 3 nucleotides (TGA) in the 5537 position, which would cause an insertion of aspartic acid (1795insD) in the C-terminal domain of the protein of the SCN5A gene**.** Some class I antiarrhythmic agents have been used to differentiate these diseases. Intravenous flecainide can cause ST segment elevation in some patients carriers of the LQT3 variant (**Cerrone 2001; Khan 2004**). An SCN5A mutation (1795insD) in the C terminus results in a clinical phenotype combining QT prolongation and ST segment elevation, indicating a close interrelationship between BrS and the LQT3. Two novel mutations on the same codon, Y1795C (LQT-3) and Y1795H (BrS), have marked and opposing effects on channel gating consistent with activity associated with the cellular basis of each clinical disorder. Y1795H speeds and Y1795C slows the onset of inactivation. The Y1795H, but not the Y1795C, mutation causes a marked negative shift in the voltage dependence of inactivation, and neither mutation affects the kinetics of the recovery from inactivation. Interestingly, both mutations increase the expression of sustained Na^+ channel activity compared with wild type channels, although this effect is most pronounced for the Y1795C mutation, and both mutations promote entrance into an intermediate or a slowly developing inactivated state. This data confirms the key role of the C-terminal tail in cardiac Na^+ channel gating, illustrates how subtle changes in channel biophysics can have significant and distinct effects in human disease, and, additionally, provides further evidence of the close interrelationship between BrS and LQT3 at the molecular level (**Rivolta 2001**).

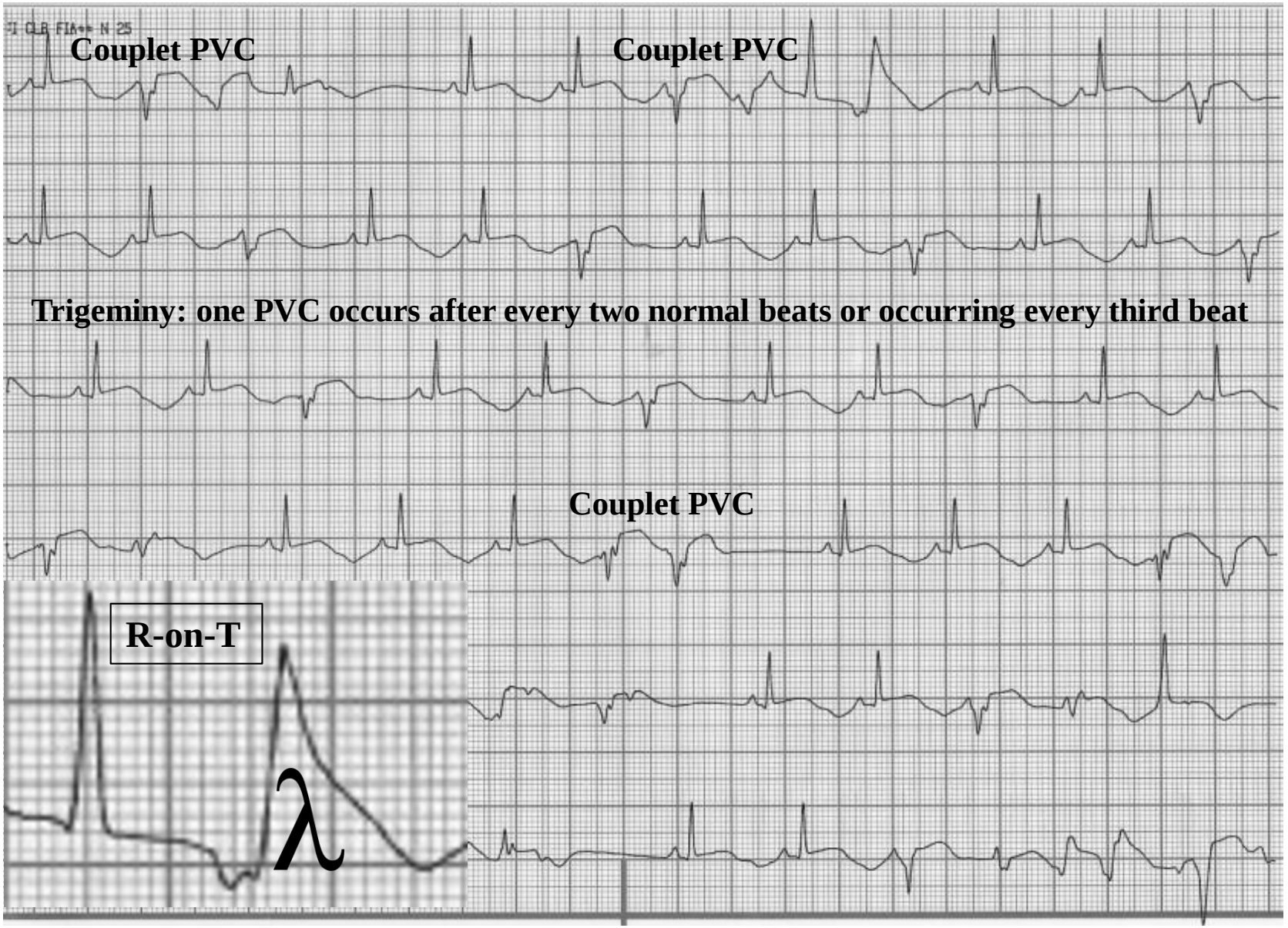
The differences in clinical facts that result from LQT3 variant and BrS are due to discrete modifications in amino acid residues within the Na^+ current. Unlike BrS, the LQT3 variant presents a late, slow and persistent inward movement of the Na^+ cation during the plateau or dome of the monophasic action potential (MAP) (**Brugada 2001**) extending the ST segment.

Pfahnl et al (**Pfahnl 2007**) identified a threonine-to-isoleucine missense mutation at position 353 (T353I) adjacent to the pore-lining region of domain I of the cardiac sodium channel (SCN5A) in a family with BrS. Both male and female carriers are symptomatic at young ages, have typical Brugada-type ECG changes, and have relatively normal QTc. The clinical presentation of patients carrying the T353I mutation is that of BrS and could be explained by a cardiac Na(+) channel trafficking defect. However, when the defect was ameliorated with mexiletine, a Na(+) channel blocking agent the mutated channels had biophysical properties consistent with LQTS. The lack of phenotypic changes associated with the LQTS could be explained by a T353I-induced trafficking defect reducing the number of mutant channels with persistent currents present at the sarcolemma.

. IV flecainide, was used as a provocative test to unmask the type 1 ECG phenotype of BrS. If these seemingly differential responses of LQT3 and BrS patients to flecainide are indeed specific, then this drug might represent a tool to better distinguish the 2 diseases.

In 13 LQT3 patients who carry 7 different mutations, Priori et al evaluated the response to IV flecainide at a dose of 2 mg/kg over 10 minutes and found that flecainide elicited the ECG type 1 Brugada pattern in 6 of the 13. This finding raises concerns about the safety of flecainide therapy in LQTS and demonstrates the existence of an intriguing overlap between the 2 diseases. Ajmaline and flecainide are diagnostic test for the identification of concealed forms or type 2 of BrS. (**Priori 2000**)

ECG3 – Continuous long lead II

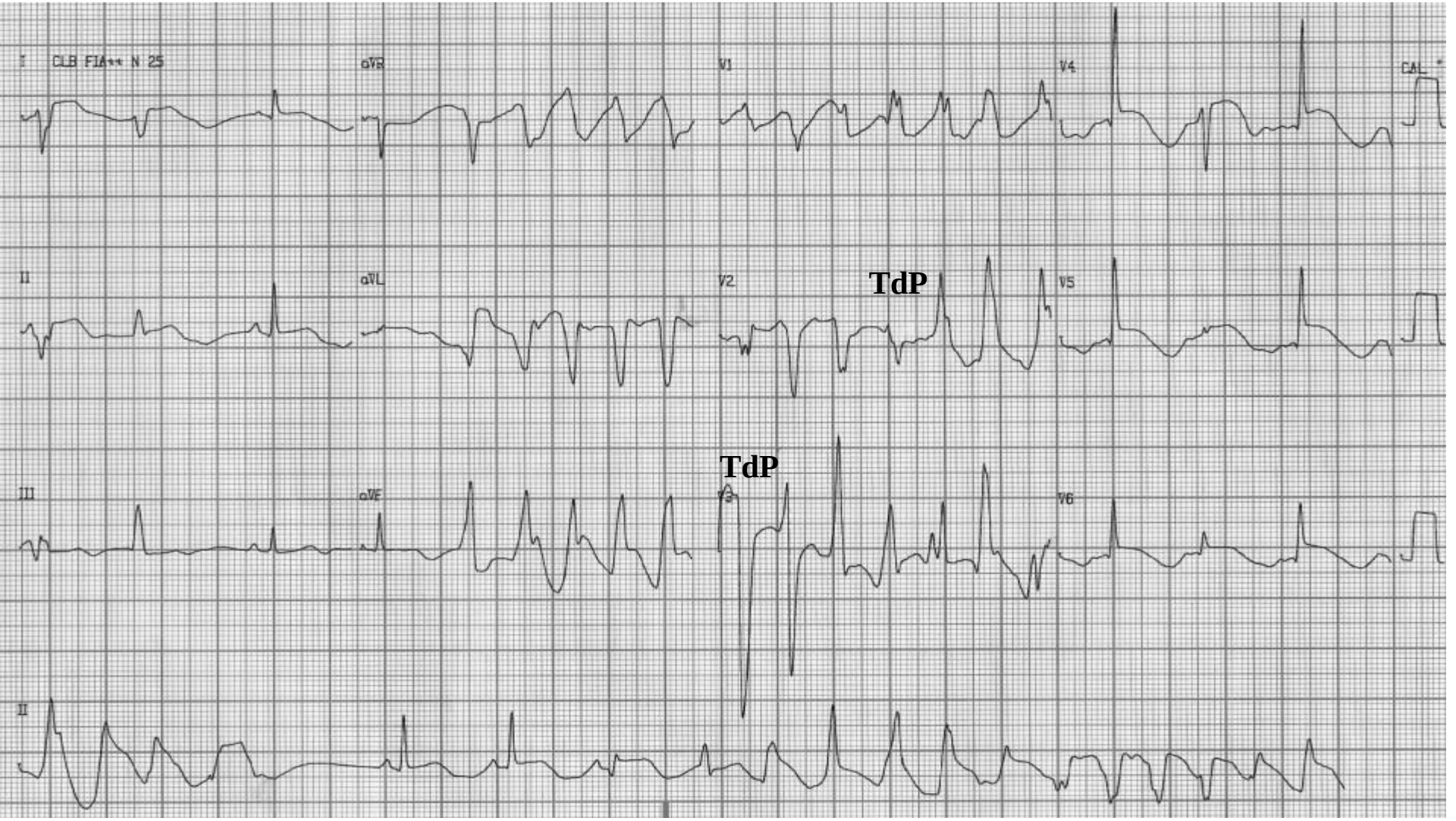


Premature ventricular contraction with telediastolic or end-diastolic couplet but with R-on-T phenomenon because QT interval prolongation, different from truly polymorphic ventricular tachycardia. See next slide.

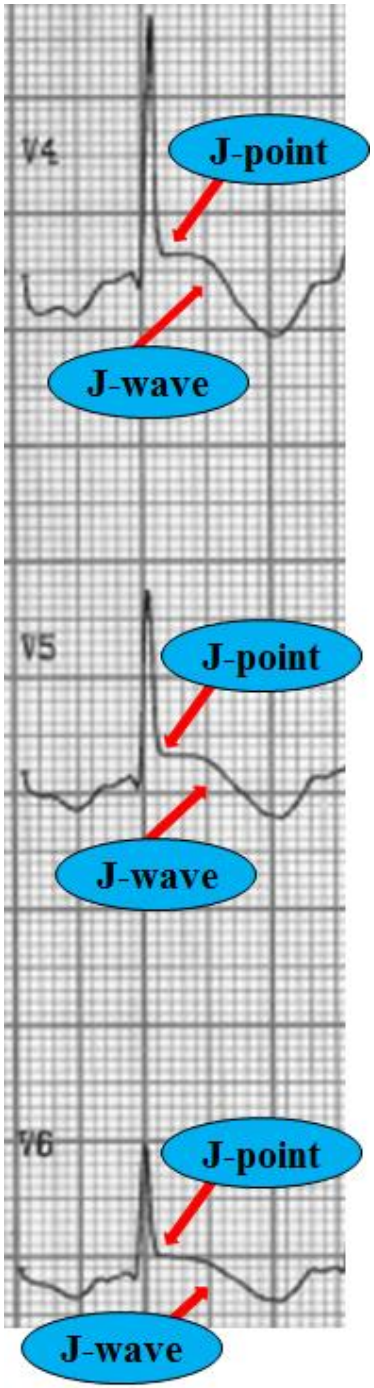
Differential diagnosis between Torsade de Pointes and true polymorphic VT

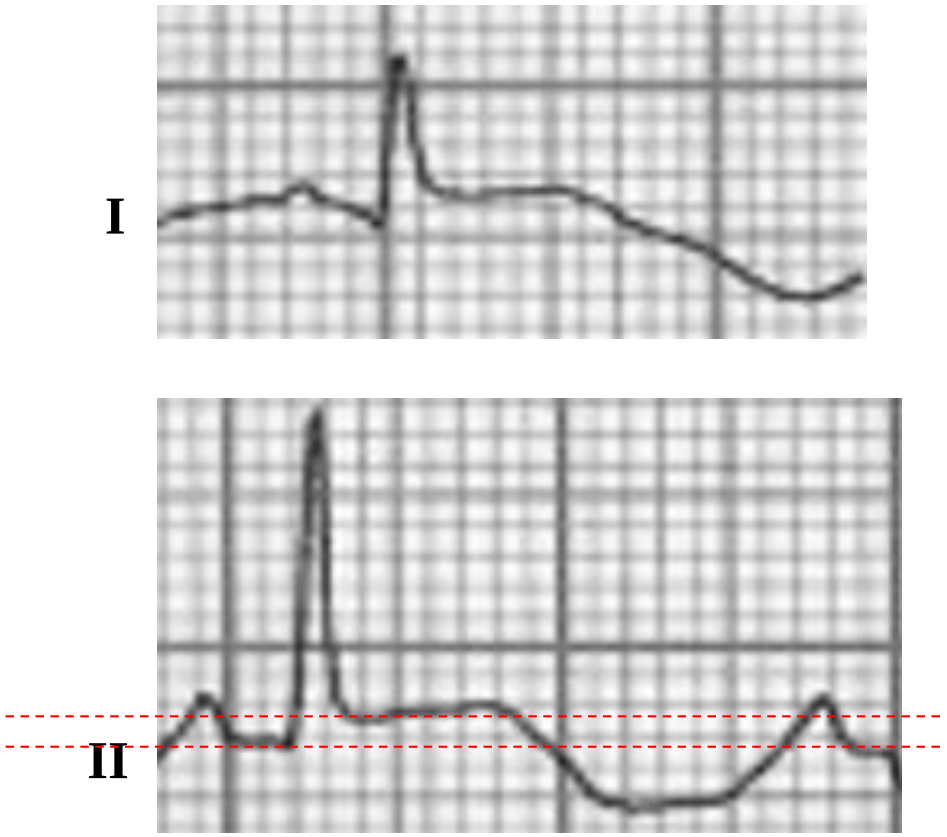
	TdP	True PVT
Related to sinus bradycardia	Yes	No
Events that precede pauses: "pause-dependent" onset of arrhythmia or "long-short" sequences	Yes	No
HR:	200-250/bpm.	Between 260 and 352 bpm in Brugada disease.
Associated electrolytic anomalies	Frequent	No
Coupling of initial PVC	Delayed or telediastolic: 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". Beta blocker: CPVT or ICD.

ECG4 – During intermittent non-sustained events



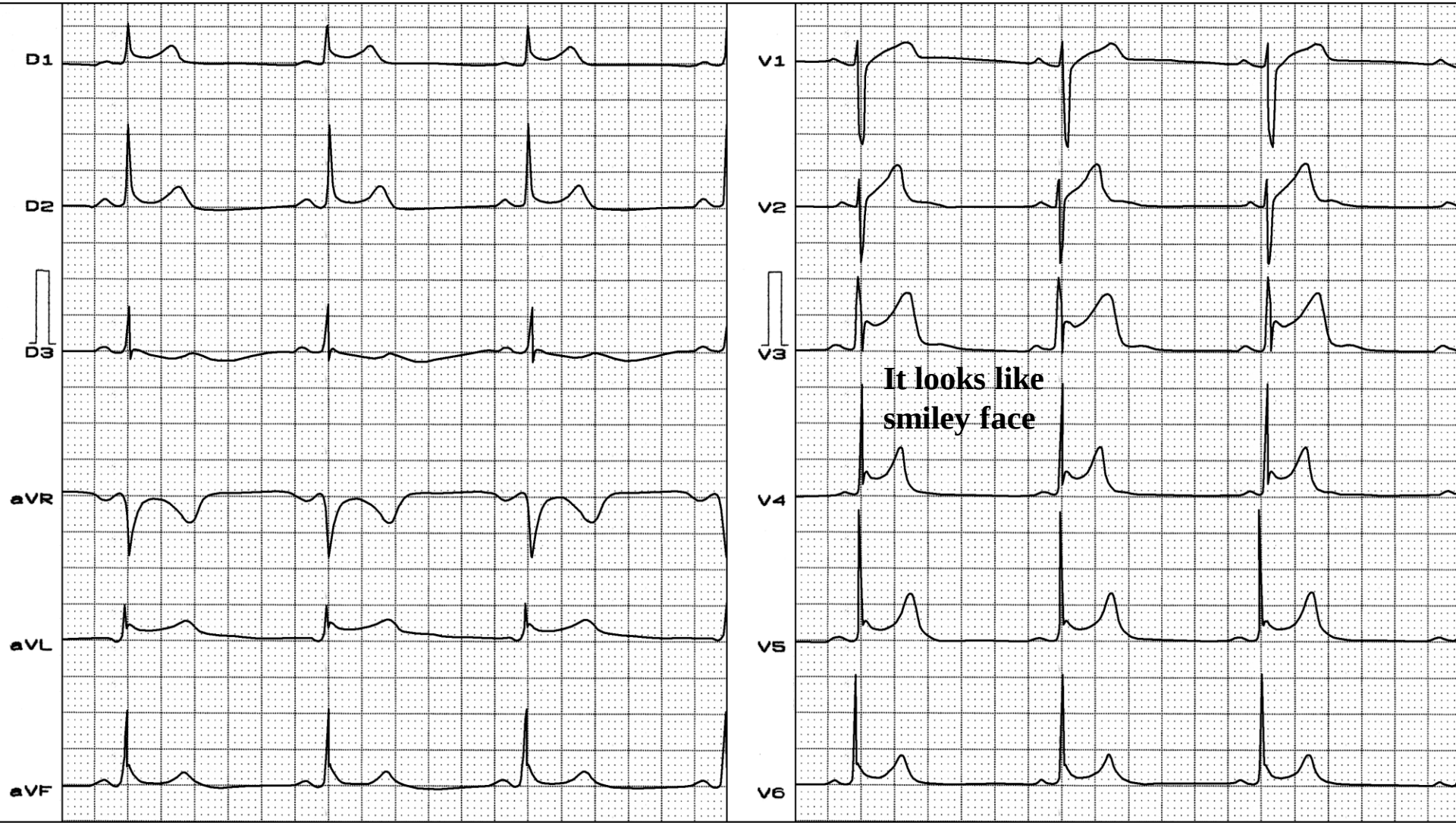
Rotation of the apex of QRS along the baseline. “swinging pattern” or “twisting appearance”: TdP.
Runs of NS-VT more than three consecutive ventricular depolarizations with a rate above 100 bpm and with a duration lower than 30 seconds. ST segment elevation convex to the top from V4 to V6.





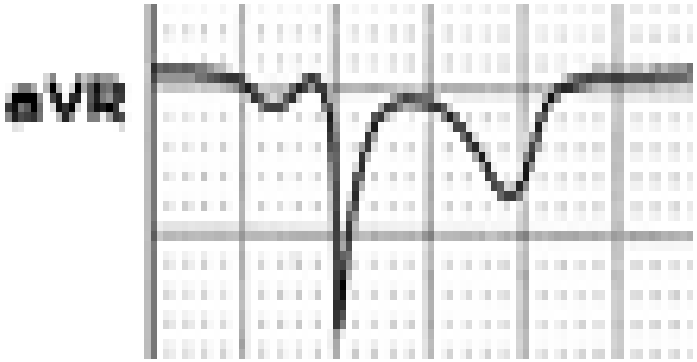
"Malignant" early repolarization in anterolateral and inferior leads: J-point and ST segment elevation convex to the top followed by negative T-wave

Name: DAS; **Age:** 24y/o; **Sex:** Male; **Ethnic group:** Afro-descendant; **Weight:** 82 kg; **Height:** 1.91 m;
Biotype: Athletic; **Profession:** professional basketball player

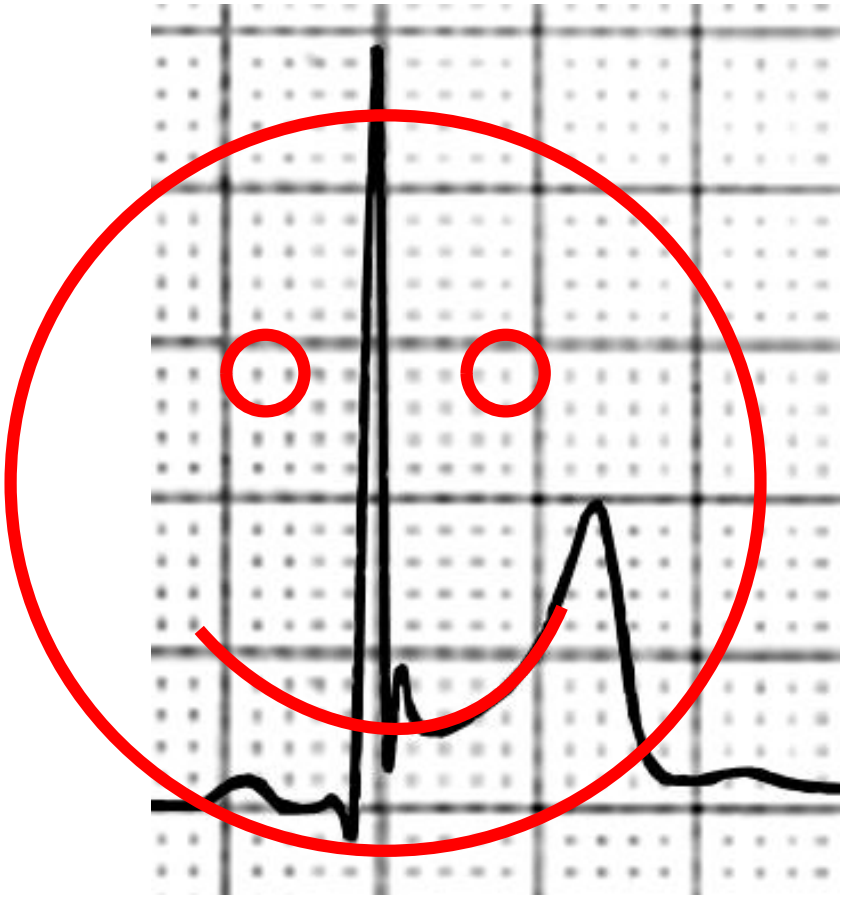


ECG diagnosis: Sinus bradycardia, (HR 50 bpm). J point and ST segment with elevation > 4 mm in precordial leads from V_3-v_5 of superior concavity. Notch or slurring of terminal portion of the QRS complex (J point). ST segment elevation > 4mm in precordial leads V_3, V_4 and V_5.
Conclusion: sinus bradycardia, benign early repolarization pattern.

The “smiley face” sign of benign early repolarization pattern

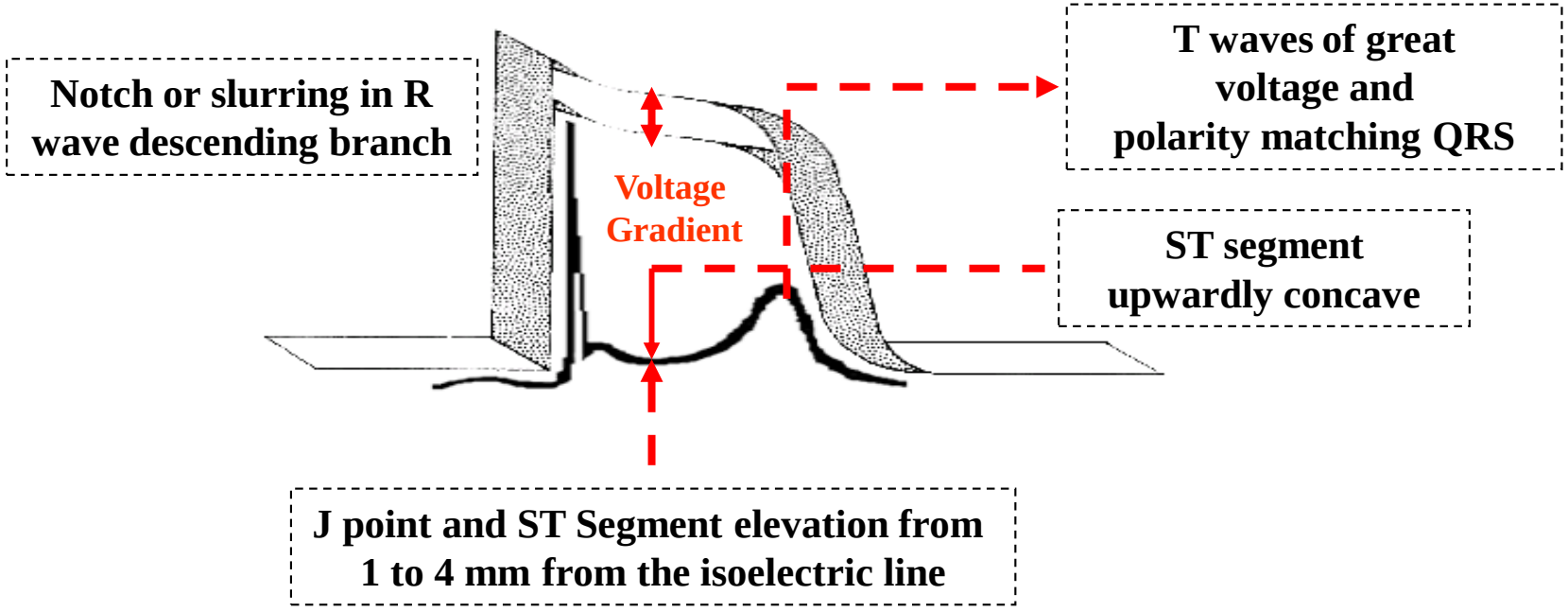


Mirror image or reciprocal changes only in aVR lead



The figure shows in lead V4 the “upwardly concave” followed by tall positive T wave the classic “hooked J-point” in lead V4 typical of benign early repolarization pattern. ST-elevation looks like a “smiley face”.

In “benign” early repolarization, there is a voltage gradient, however, no dispersion of duration of action potentials in ventricular wall thickness. For this reason, these patients showed ST segment elevation with no tendency to develop arrhythmias.

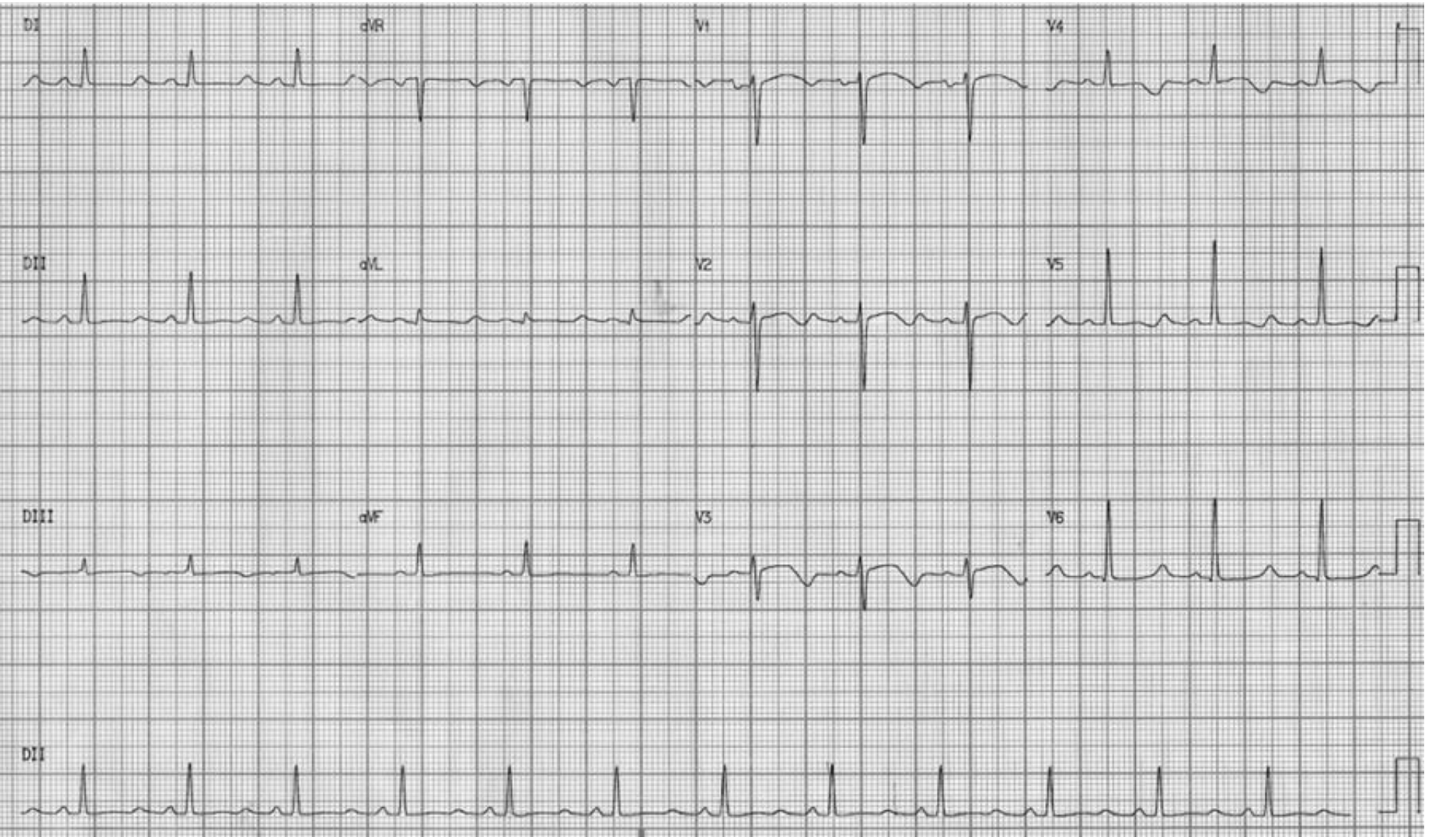


Theoretical electrophysiological explanation for ST segment elevation in ECGs in athletes.

ECG criteria that suggest benign Early Repolarization Pattern (ERP)

- HR: sinus bradycardia is frequent;
- QRS axis, ST segment and T wave, are oriented in the same direction in the FP;
- Deep and narrow Q waves followed by R wave of great voltage in left precordial leads;
- Notch or slurring of R wave descending branch;
- Transition area in precordial leads of sudden occurrence;
- J point and ST segment elevation, usually < 2 mm (exceptionally it may be > 5 mm) of superior concavity in middle and/or left precordial leads and possibly in inferior leads;
- Possible reduction in J point and ST segment elevation by sympathetic action and sympathomimetic drugs;
- Absence of reciprocal or mirror image (exception in aVR lead);
- Pseudo symmetrical tall T waves, with matching QRS.

ECG5 – After clinical and ECG stabilization

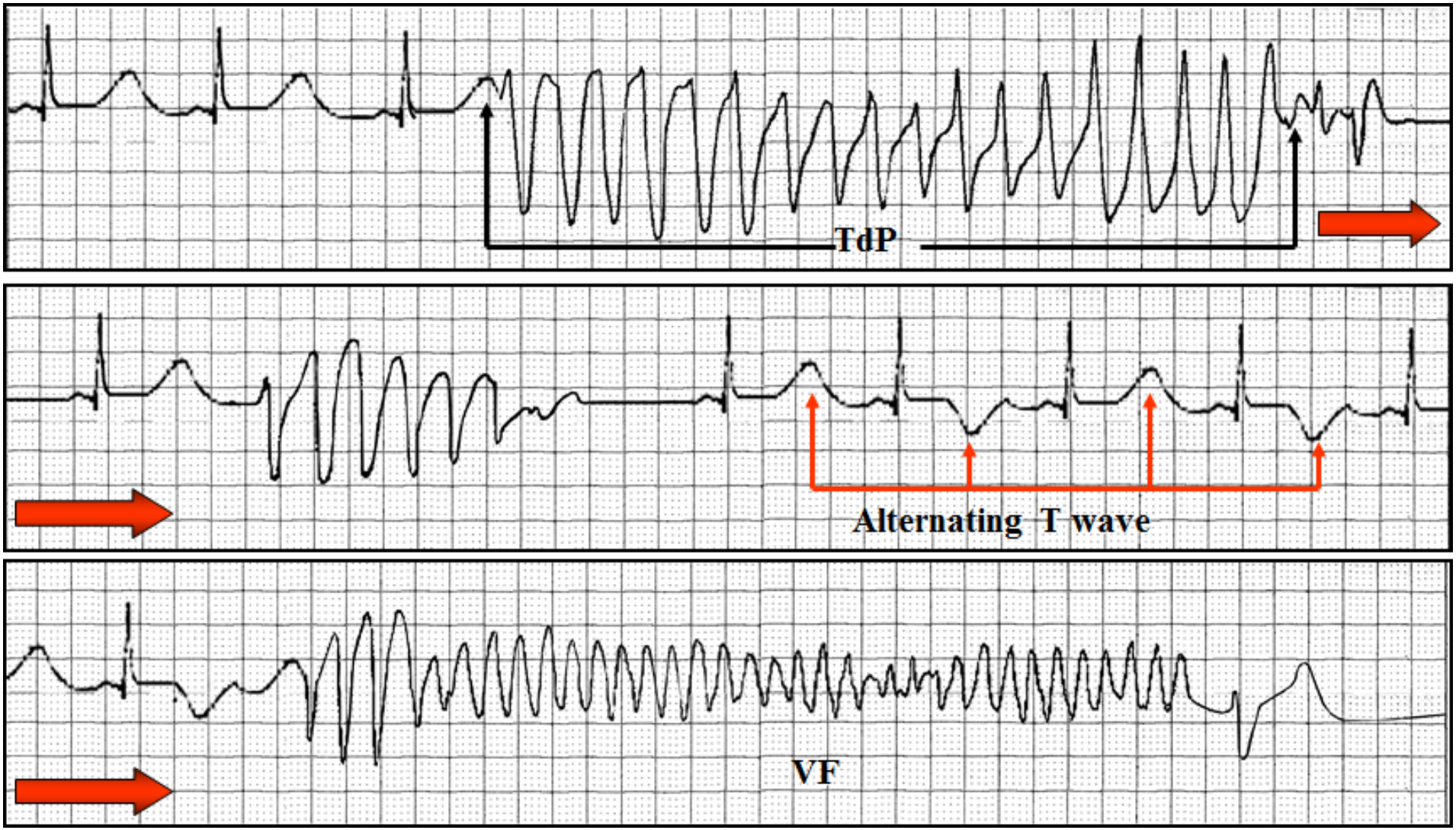


Prolonged QT interval consequence of ST segment prolongation and delayed T-wave, suggesting LQT3.

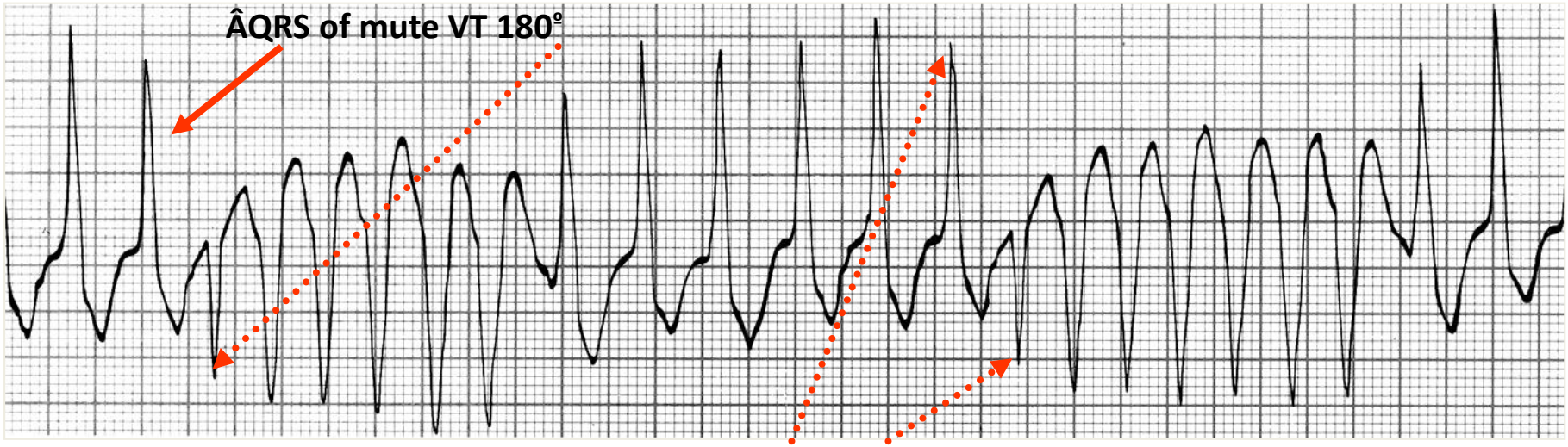
T-Wave Alternans trigged TdP

6 y/o Caucasian female

Diagnosis: Congenital LQTS - QT: 670 ms



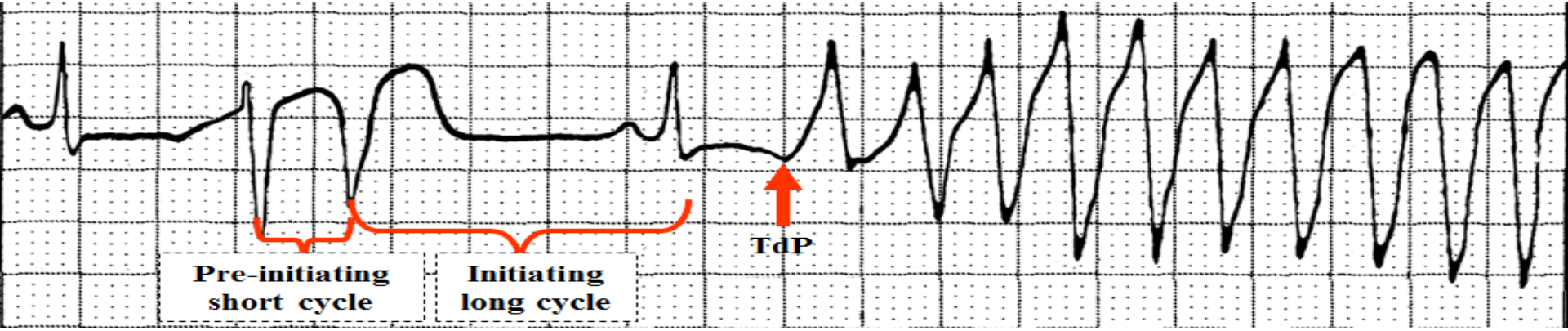
Typical example of Torsade de Pointes (TdP)



“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.



References

1. Beyder A, Strege PR, Reyes S, et al. Ranolazine decreases mechanosensitivity of the voltage-gated sodium ion channel Na(v)1.5: a novel mechanism of drug action. Circulation. 2012 Jun 5;125(22):2698-706.
2. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium currentinhibitor ranolazine. Heart. 2006 Jul;92 Suppl 4:iv6-iv14.
3. Benhorin J, Goldmit M, MacCluer JW, et al. Identification of a new SCN5A mutation, D1840G, associated with the long QT syndrome. Mutations in brief no. 153. Online. Hum Mutat. 1998; 12:72.
4. Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999 Dec 3-17;85:1206-1213.
5. Blaufox AD, Tristani-Firouzi M, Seslar S, et al**Congenital long QT 3 in the pediatric population.** Am J Cardiol. 2012 May 15;109(10):1459-65.
6. Brugada J, Brugada P, Brugada R. Brugada Syndrome: The Syndrome of Right Bundle Branch Block, ST segment Elevation in V1 to V3 and Sudden Death Indian. Pacing and Electrophysiology Journal. 2001; 1:6-11.
7. Calvillo L, Spazzolini C, Vullo E, et al. Propranolol prevents life-threatening arrhythmias in LQT3 transgenic mice: implications for the clinical management of LQT3 patients. Heart Rhythm. 2014 Jan;11(1):126-32.
8. Cerrone M, Crotti L, Faggiano G, De Michelis V, Napolitano C, Schwartz PJ,et. al. Long QT syndrome and Brugada syndrome: 2 aspects of the same disease? Ital Heart J 2001; 2(3 Suppl):253-257.
9. Chorro FJ, Del Canto I, Brines L, et al. Ranolazine Attenuates the Electrophysiological Effects of Myocardial Stretch in Langendorff-Perfused Rabbit Hearts. Cardiovasc Drugs Ther. 2015 Jul 3. [Epub ahead of print]
10. Deschenes I, Baroudi G, Berthet M, et. al. Electrophysiological characterization of SCN5A mutations causing long QT (E1784K) and Brugada (R1512W and R1432G) syndromes. Cardiovasc Res 2000; 46:55-65.

11. Furuhashi M, Uno K, Tsuchihashi K. Myocardial iodine-123-metaiodobenzylguanidine (123I-MIBG) imaging in Brugada syndrome. Circulation. 2002 Sep 24;106(13):e59-60.
12. Gussak I, Bjerregaard P, Kostis J. Electrocardiographic "lambda" wave and primary idiopathic cardiac asystole: a new clinical syndrome?J Electrocardiol 2004;37:105-107.
13. Janse MJ, Wilde AA. Molecular mechanisms of arrhythmias.Rev Port Cardiol. 1998; 17:41-46.
14. Jiang C, Atkinson D, Towbin JA, Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity. Nat Genet. 1994 Oct;8(2):141-7.
15. Kawaguchi T, Nomura M, Tujikawa T, Nakaya Y, Ito S. 123I-metaiodo-benzylguanidine myocardial scintigraphy in the Brugada-type ECG. J Med Invest. 2006 Feb;53(1-2):95-102.
16. Keller DI, Acharfi S, Delacretaz E, et al. A novel mutation in SCN5A, del QKP 1507-1509, causing long QT syndrome: role of Q1507 residue in sodium channel inactivation. J Mol Cell Cardiol. 2003; 35:1513-1521. Khan IA, Nair CK. Brugada and long QT-3 syndromes: two phenotypes of the sodium channel disease. Ann Noninvasive Electrocardiol. 2004; 9: 280-299.
17. Kilinc OU, Tuzcu VSuccessful elimination of significant arrhythmia burden with flecainide in an adolescent with long QT syndrome type 3. Congenit Heart Dis. 2012 Jul-Aug;7(4):E42-5..
18. Kloner RA, Hines ME, Geunes-Boyer S. Efficacy and safety of ranolazine in patients with chronic stable angina. Postgrad Med. 2013 Nov;125(6):43-52. doi: 10.3810/pgm.2013.11.2711.
19. Marks, M. L.; Whisler, S. L.; Clericuzio, C. et. al.: A new form of long QT syndrome associated with syndactily. J Am Coll Cardiol.1995; 25:59-61.
20. Maier LS. New treatment options for late Na current, arrhythmias, and diastolic dysfunction. Curr Heart Fail Rep. 2012 Sep;9(3):183-91
21. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave pattern in genetically distinct forms of the hereditary long QY síndrome Circulation 1995; 92:2929-2934.
22. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation. 1997;96:2595-2600.

23. Pérez-Riera AR, Abreu LC, Yanowitz F, Barros RB, Femenía F, McIntyre WF, Baranchuk A. "Benign" early repolarization versus malignant early abnormalities: clinical-electrocardiographic distinction and genetic basis. Cardiol J. 2012;19(4):337-46.
24. Pfahnl AE, Viswanathan PC, Weiss R, Shang LL, Sanyal S, Shusterman V, Kornblit C, London B, Dudley SC Jr. A sodium channel pore mutation causing Brugada syndrome. Heart Rhythm. 2007; 4: 46-55
25. Priori SG, Napolitano C, Schwartz PJA. molecular basis for the therapy of the long QT syndrome. Arch Mal Coeur Vaiss. 1996; 89:1185-1187.
26. Priori SG, Napolitano C, Paganini V, et al: molecular biology of QT long syndrome; Inpact on management Pacing Clin Electrophysiol 20:2052-2057-1997.
27. Priori SG, Schwartz PJ, Napolitano C, et al. A ressecive variant of the Romano-Ward long QT syndrome? 1998; 97:2420-2425.
28. Priori SG, Napolitano C, Schwartz PJ, et al. The elusive link between **LQT3** and Brugada syndrome: the role of flecainide challenge. Circulation. 2000 Aug 29;102(9):945-7.
29. 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
30. Rivolta I, Abriel H, Tateyama M, Liu H, Memmi M, Vardas P,. et al. Inherited Brugada and long QT-3 syndrome mutations of a single residue of the cardiac sodium channel confer distinct channel and clinical phenotypes. J Biol Chem 2001; 276: 30623-30630.
31. Schwartz PJ, Spazzolini C, Crotti L. All LQT3 patients need an ICD: true or false? Heart Rhythm. 2009;6:113–120.
32. Shimizu W, Antzelevitch C: Sodium channel block wit mexiletine is effective in reducing dispersión of repolarization and preventig torsade de pointes in LQT2 and LQT3 models of long QT síndrome 1997; 33:307-313.
33. Wang Q, Shen J, Splawski I et al. SCN5A mutation associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995; 80:805-811.

34. Wang XJ, Wang LL, Fu C, et al. Ranolazine attenuates the enhanced reverse Na^{+}-Ca^{2+} exchange current via inhibiting hypoxia-increased late sodium current in ventricular myocytes. J Pharmacol Sci. 2014;124(3):365-73.
35. Wei J, Wang DW, Alings M, et al. Congenital long-QT syndrome caused by a novel mutation in a conserved acidic domain of the cardiac Na+ channel. Circulation. 1999; 99:3165-3171.
36. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med 1998;339:960-965.
37. Zareba W, Goldenberg I, Moss AJ, Implantable cardioverter-defibrillator therapy by genotype in long QT syndrome patients. Heart Rhythm 2007;4(suppl):S131.