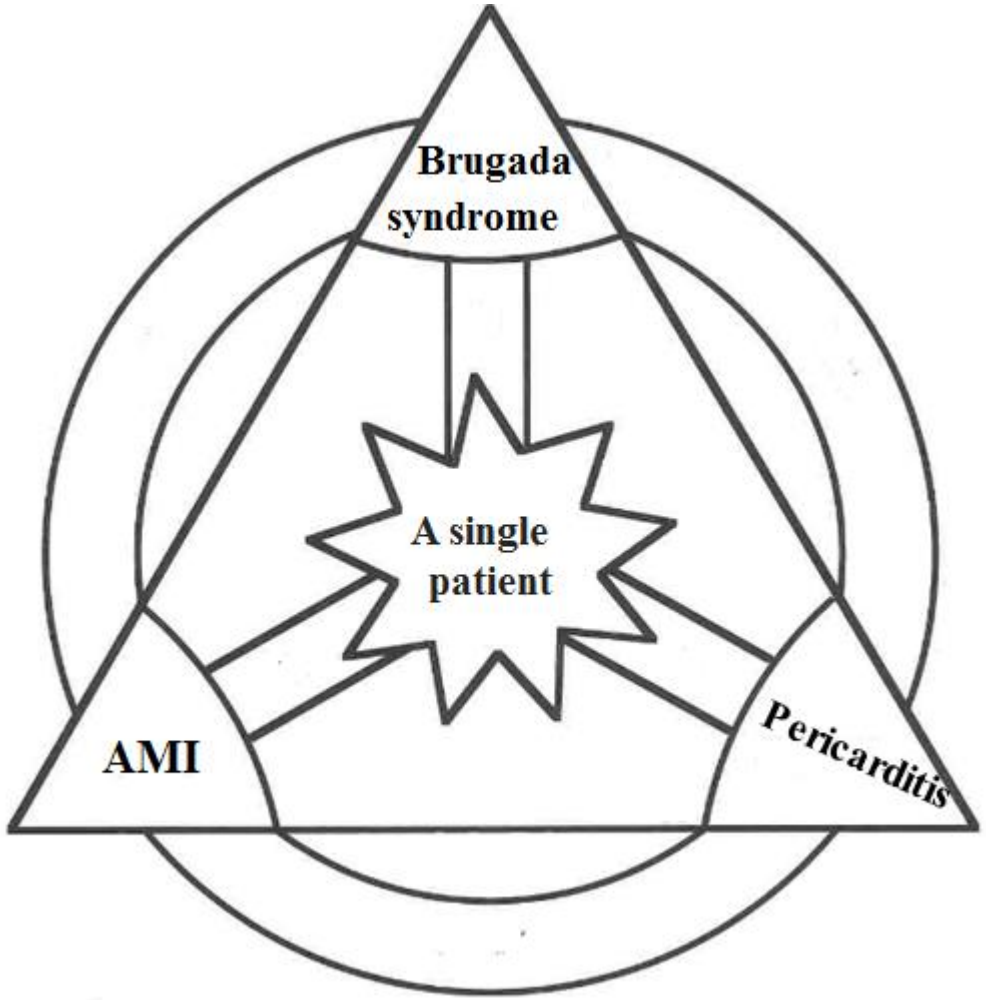
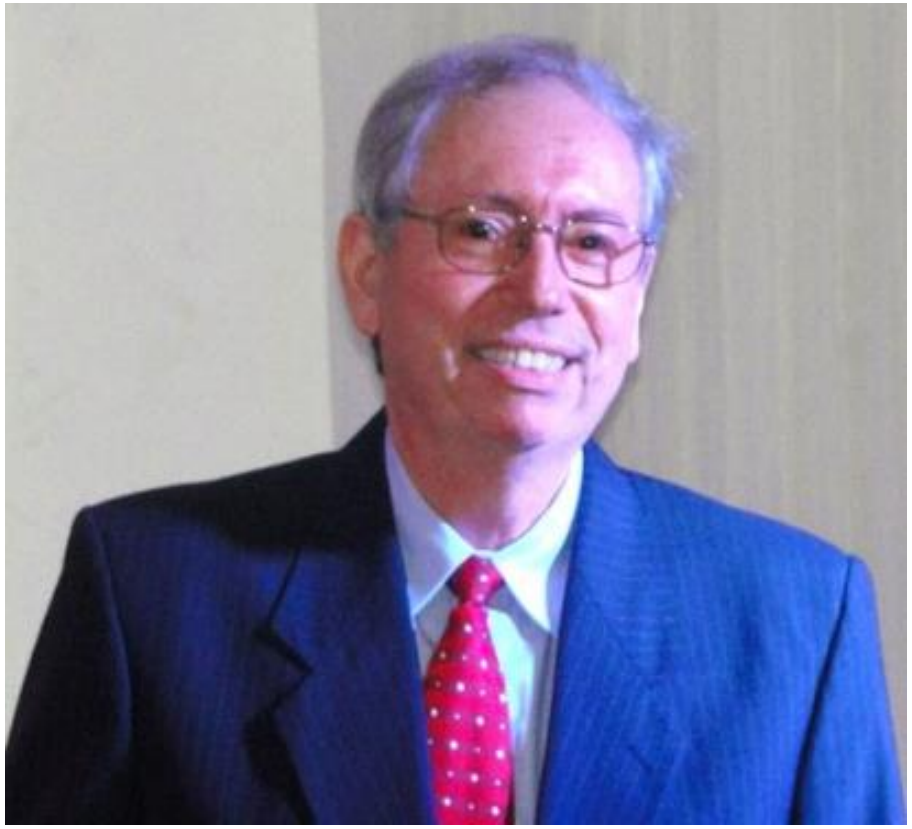
Clinical and electrocardiographic trinity at different times in a single patient

Trindade clínico-eletrocardiográfica em momentos diferentes num único paciente



AMI: Acute Myocardial Infarction



Raimundo Barbosa-Barros, MD
Chief of the Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes. Fortaleza – CE- Brazil

Case report

MJB, Caucasian, male, 31, tattooist, was admitted in our emergency room (ER) with complaint of prolonged atypical chest pain in August 23-2008 19:30 P.M.

Pathological personal antecedents: carrier of polycystic kidney disease (PKD) and hypertension (using captopril 25mg (3x/day) and hydrochlorothiazide 25mg (1 tablet daily)).

He does not refer syncope, sudden cardiac death (SCD) and heart failure (HF).

Negative familial background for syncope or SCD in firth degree relatives

Physical examination: lucid, BP = 140/100 mmHg, bradycardic (heart rate 40 bpm) regular with hyperphonetic 2nd heart sound A_2.

Laboratory: Normal biomarkers and electrolytes.

Echocardiogram: Normal.

Normal coronary angiography (unfortunately, the picture was interpreted erroneously as acute coronary syndrome (ACS).

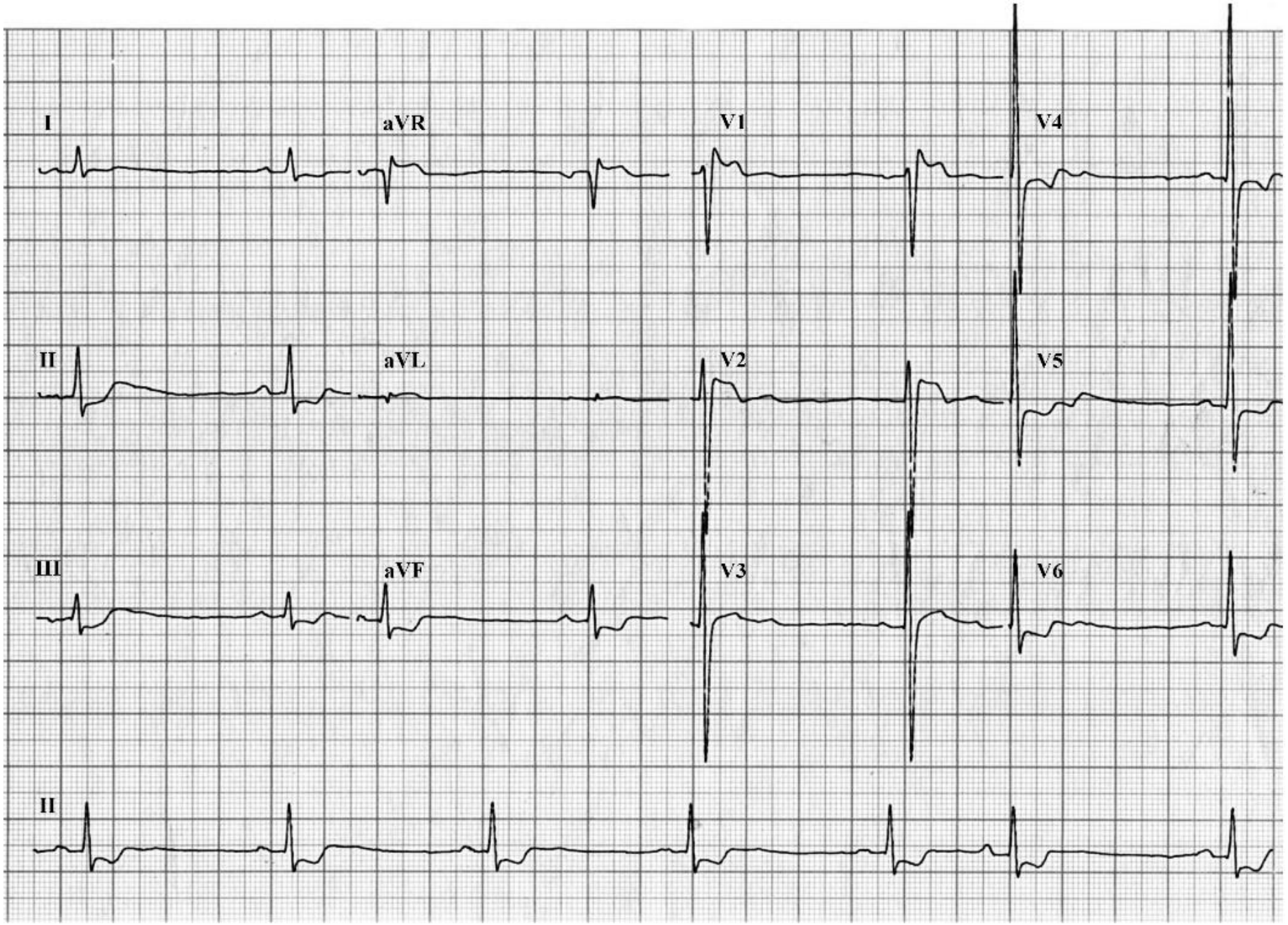
Electrophysiological Study (EPS) with Programmed Ventricular Stimulation (PVS) or Programmed Electrical Stimulation (PES) conducted to polymorphic VT that degenerated into VF.

Implanted Implantable Cardioverter Defibrillator (ICD) was indicated following the last guidelines (Class IIb indication) (Priori 2013).

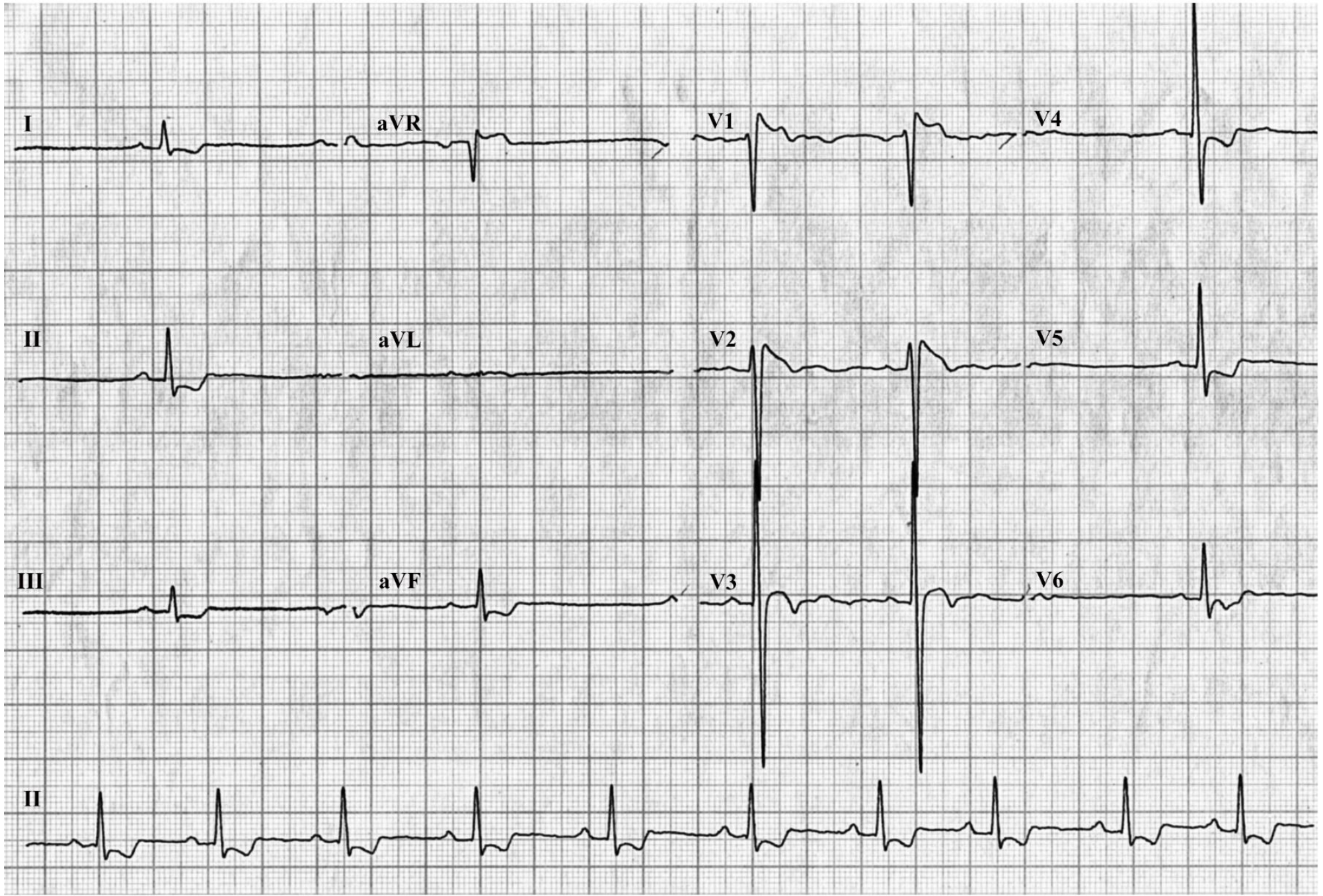
Questions:

1. Which is the ECG diagnosis of the ECG-1 performed at 1st admission?
2. Which is the ECG diagnosis of the ECG-2 performed at 2nd admission?
3. Which is the most probable cause of ST segment depression on inferior lateral wall in the ECG-1 performed during the 1st and 3rd admission?

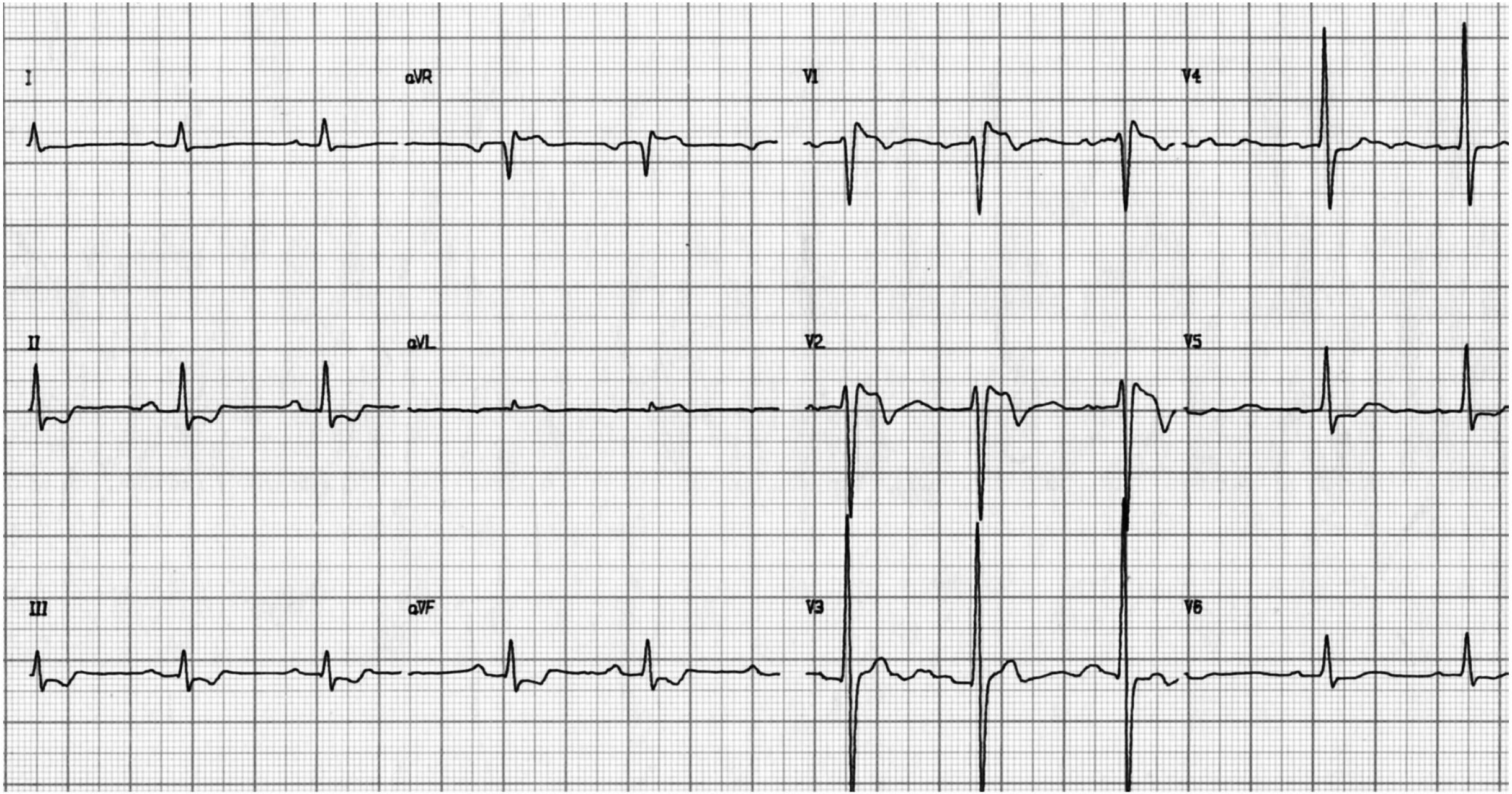
ECG-1 of the 1st admission performed on August 23-2008 19:50 P.M.



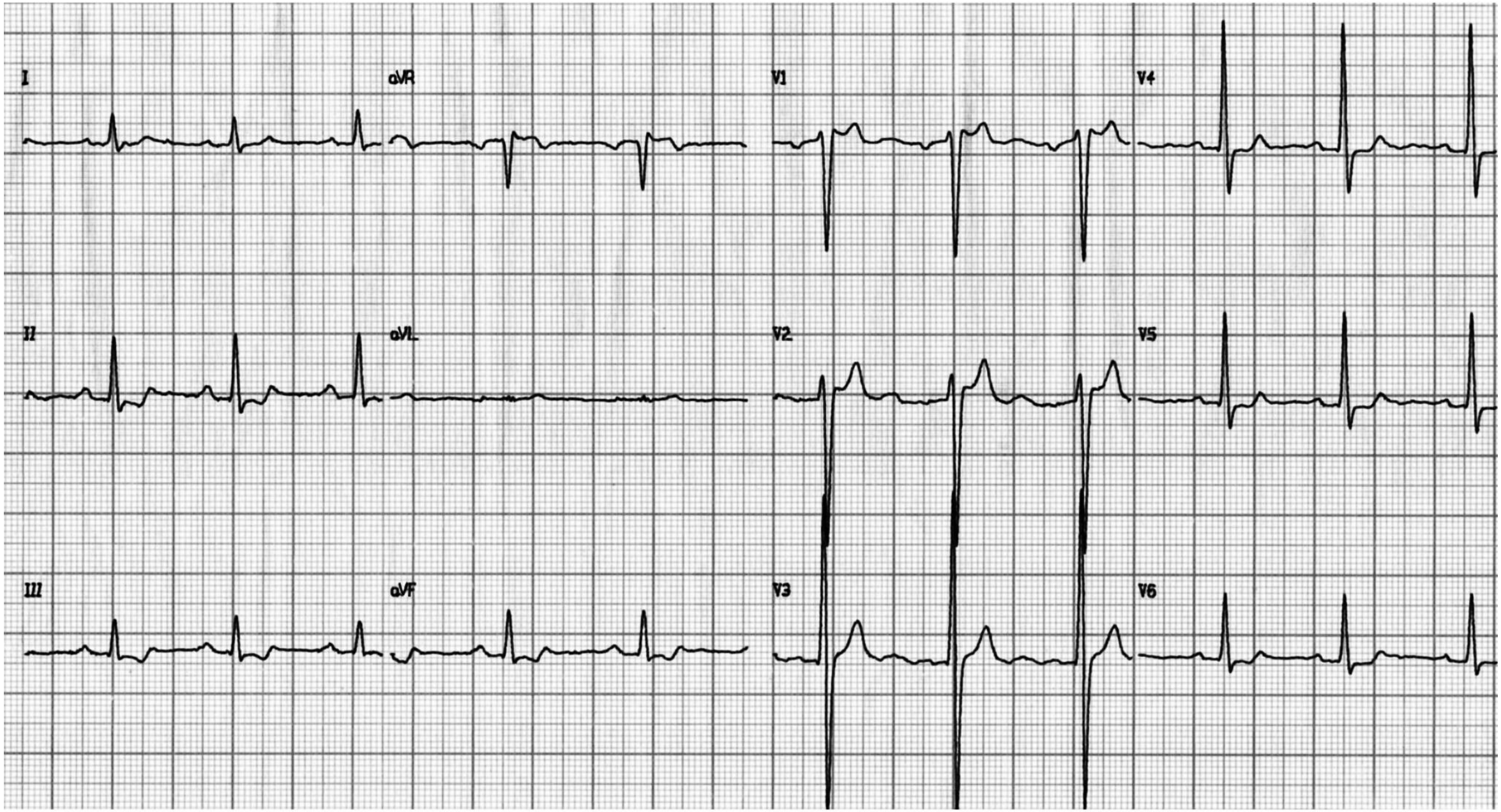
ECG-2 of the 1st admission performed immediately (5 minutes) after sublingual nitrate



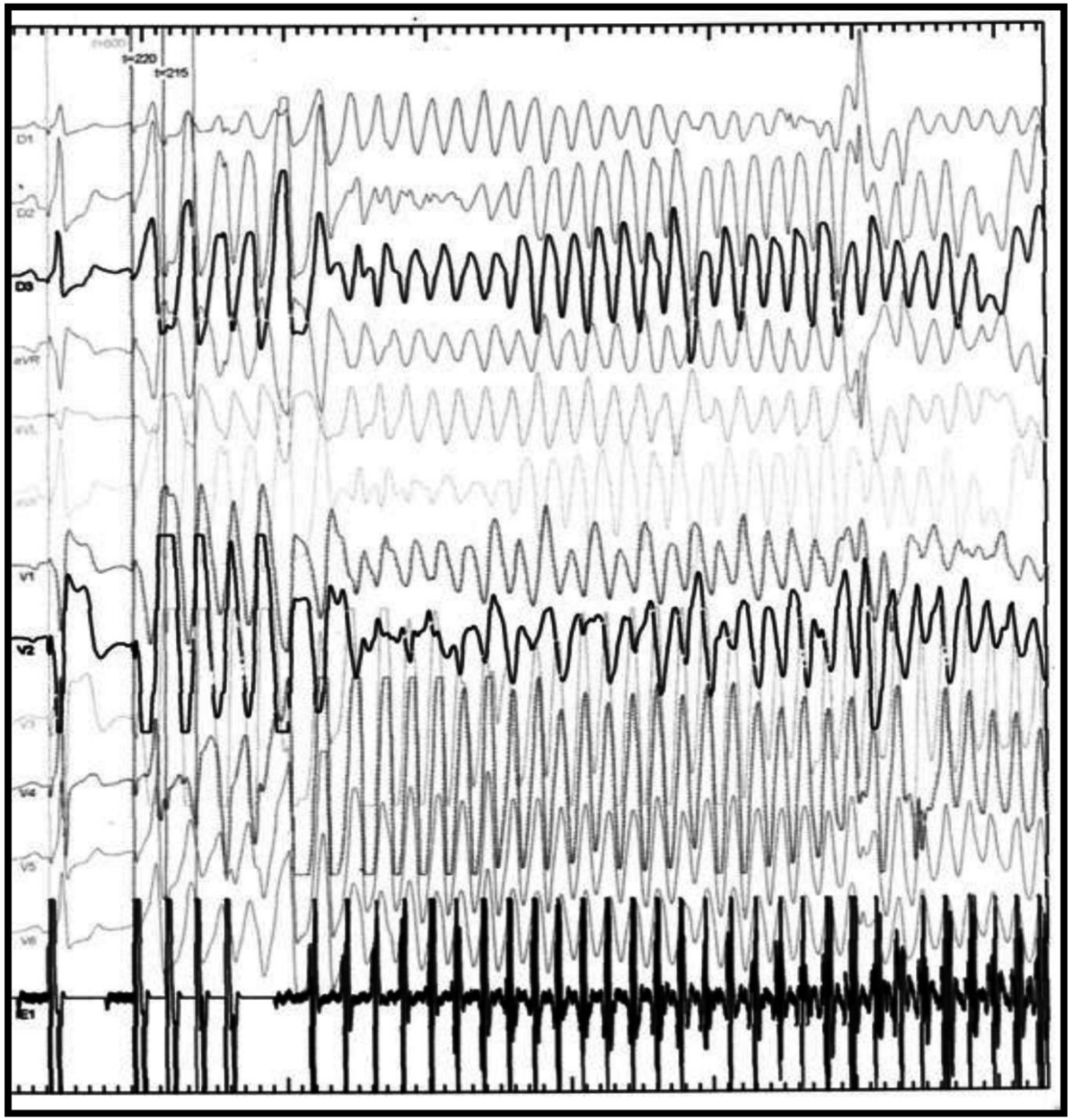
ECG-3 of the 1st admission performed after 24 hours



ECG-4 of the 1st admission performed after 48 hours



Intracardiac electrophysiological study (EPS) Programmed electrical stimulation (PES)



Programmed electrical stimulation (PES) conducted to polymorphic VT induction that degenerated into VF.

Second admission: Two weeks after ICD implantation

History of pleuritic precordial pain referral to the left shoulder and 2 syncopal episodes.

The patient did not tolerate the supine decubitus as chest pain worsened. Pain is relieved by sitting up and leaning forward.

On physical examination drew attention by the presence of jugular venous distention, muffled heart sounds, pericardial friction (a flickering sound resembling the purr of a cat) and hypotension. Low-grade intermittent fever.

It was discarded arrhythmic event since the analysis of the device did not reveal any event.

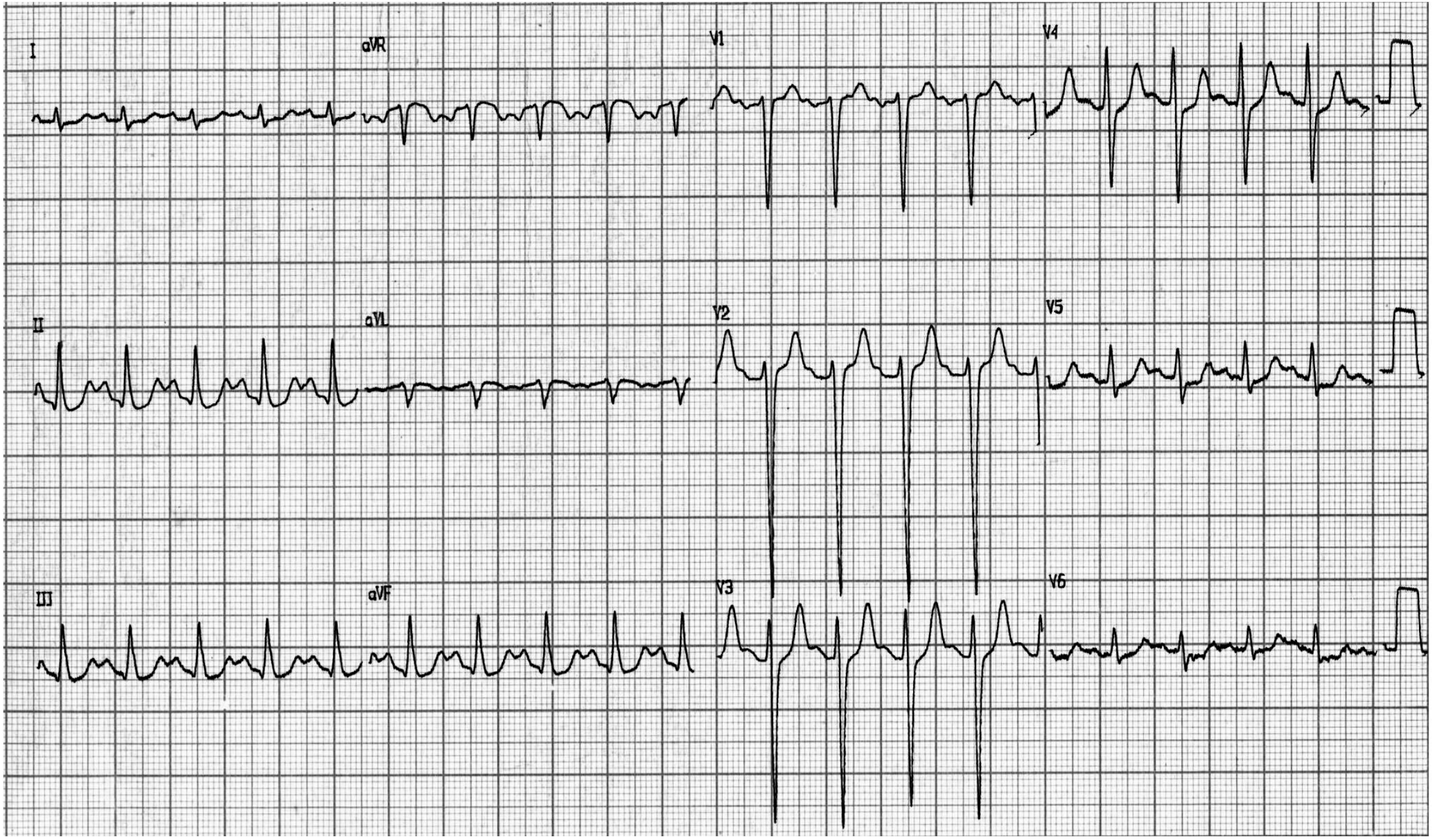
Echocardiogram revealed pericardial effusion with signs of diastolic restriction.

He underwent thoracotomy with bloody fluid. No liquid drainage had myocardial signs of perforation caused by the electrodes.

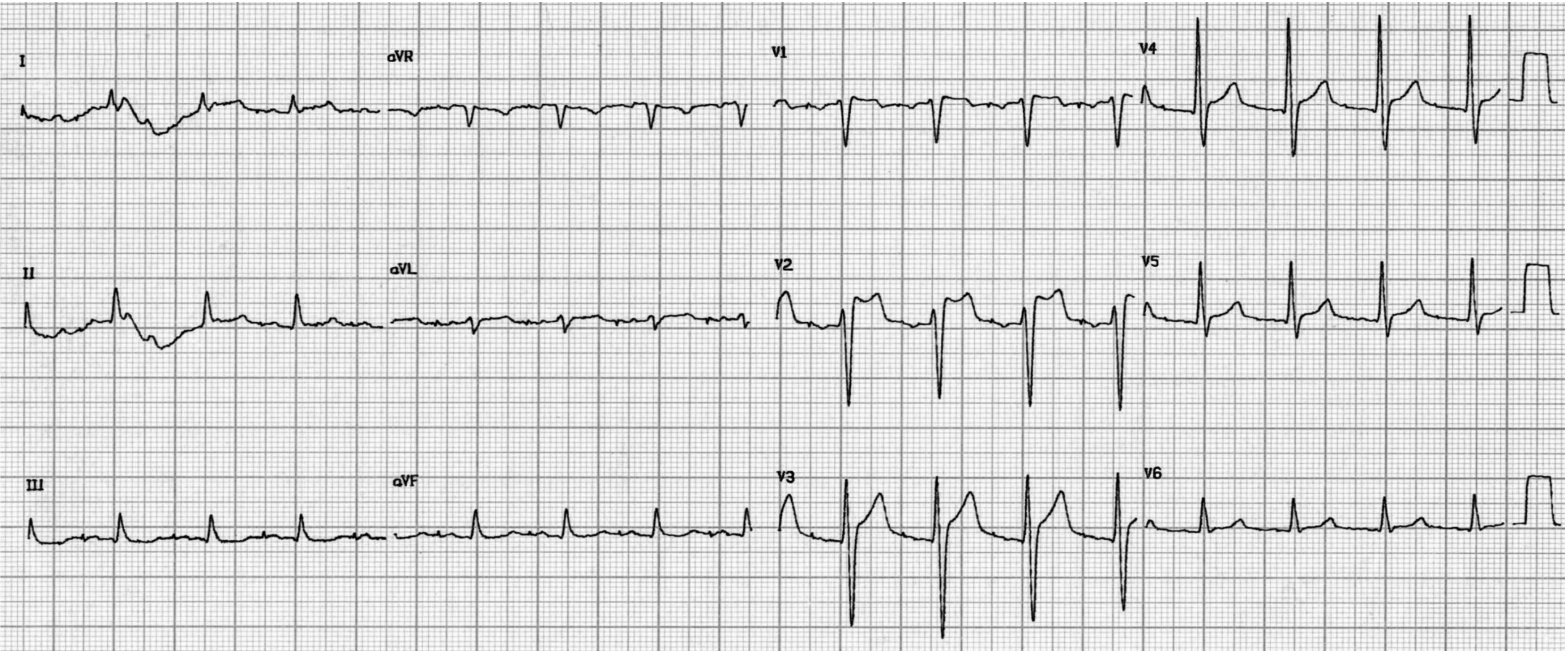
After the procedure the frame was stabilized.

He was discharged after three weeks.

ECG-1 of the 2nd admission performed two weeks after ICD implant (October 2008)



ECG2 of the 2nd admission (October 2008)



Third admission (October 2011)

Admitted at the ER with complaint of typical prolonged (> 30 minutes) constrictive retrosternal chest pain.

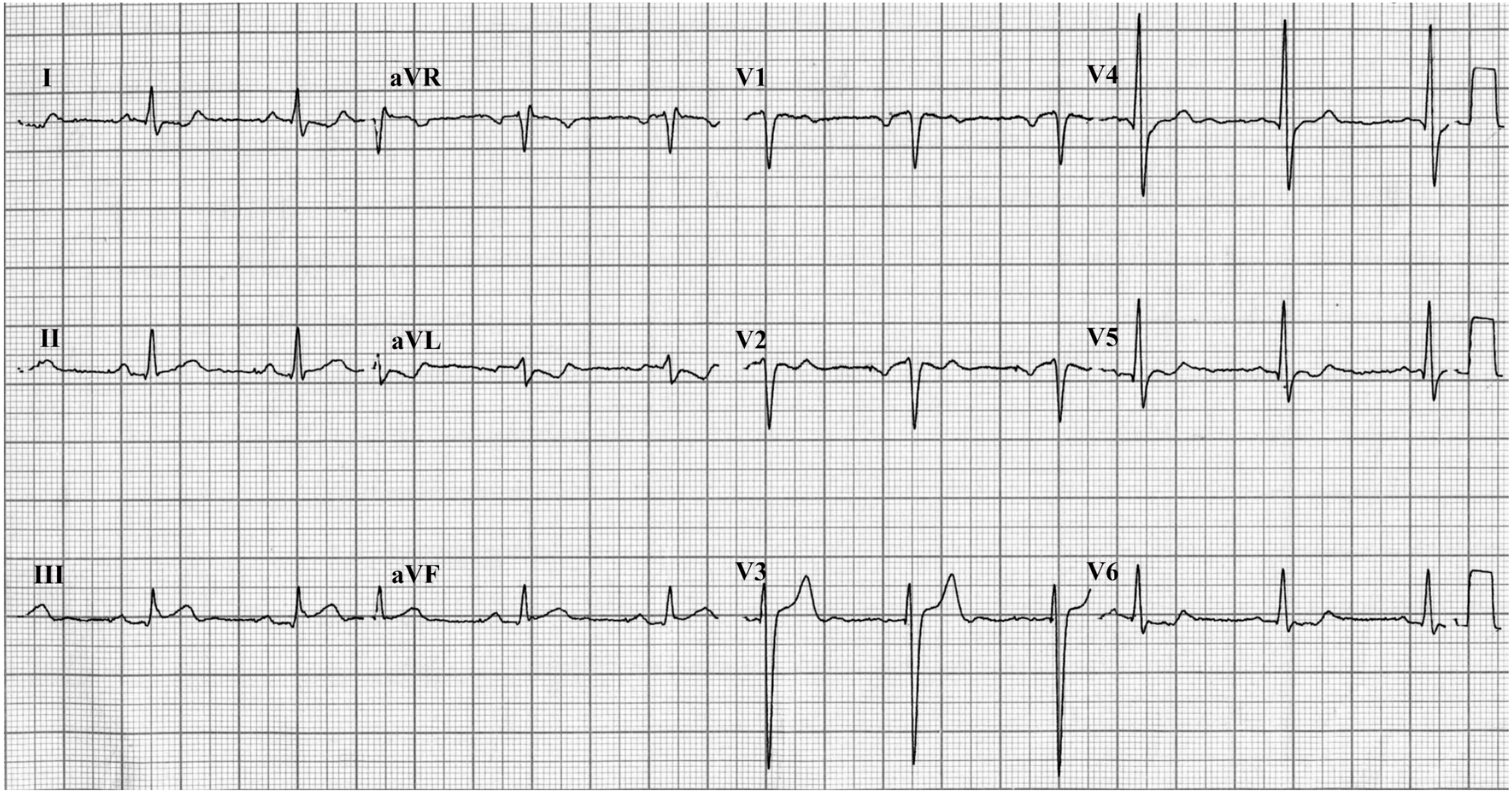
It was administered aspirin + clopidogrel.

ECG is showed in the next slide.

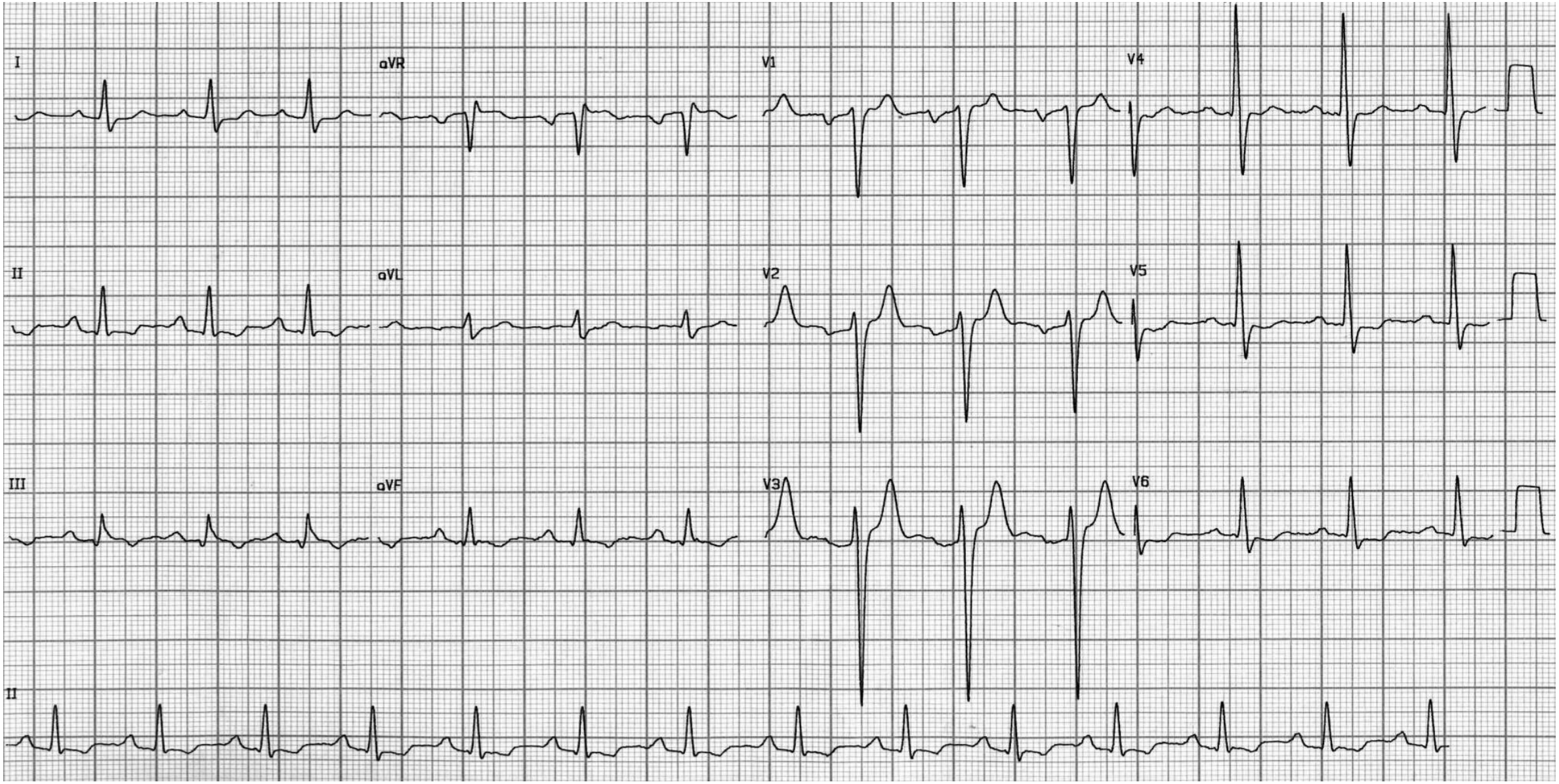
He was referred to the hemodynamics laboratory which revealed acute occlusion of the right coronary artery. He has successfully been submitted to Primary Percutaneous Coronary Intervention (PPCI) (showed in the second ECG).

He was discharged after 1 week.

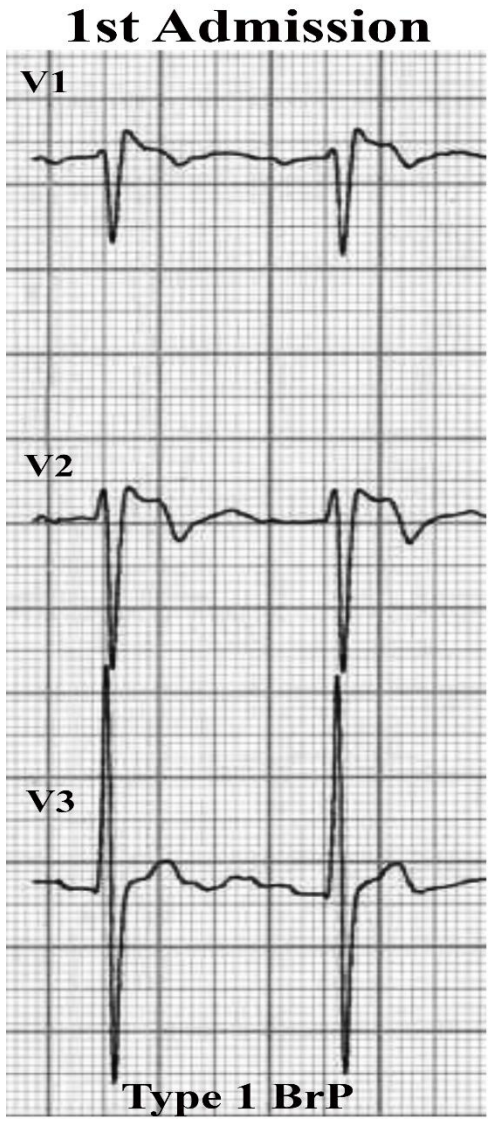
ECG-1 of the 3rd admission performed during prolonged (> 30 minutes) constrictive precordial pain in October 2011



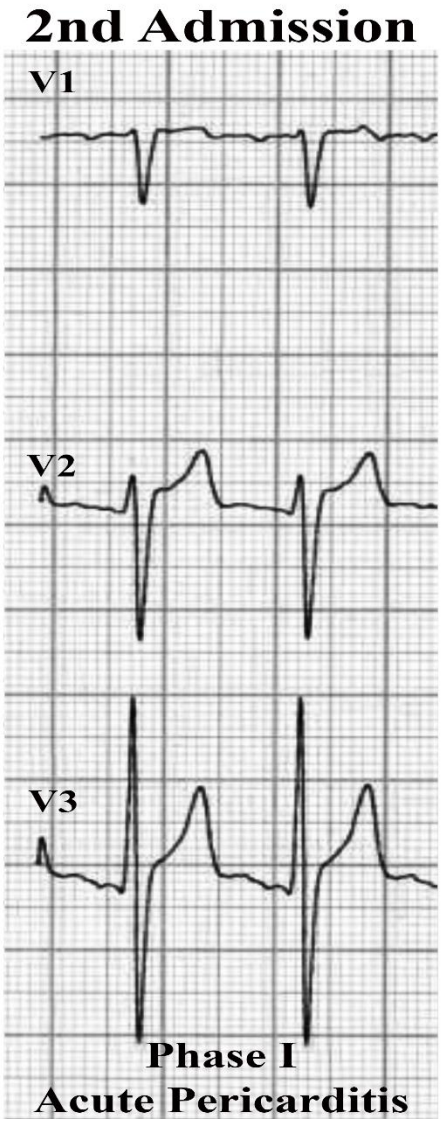
ECG-2 of the 3rd admission performed after PCI



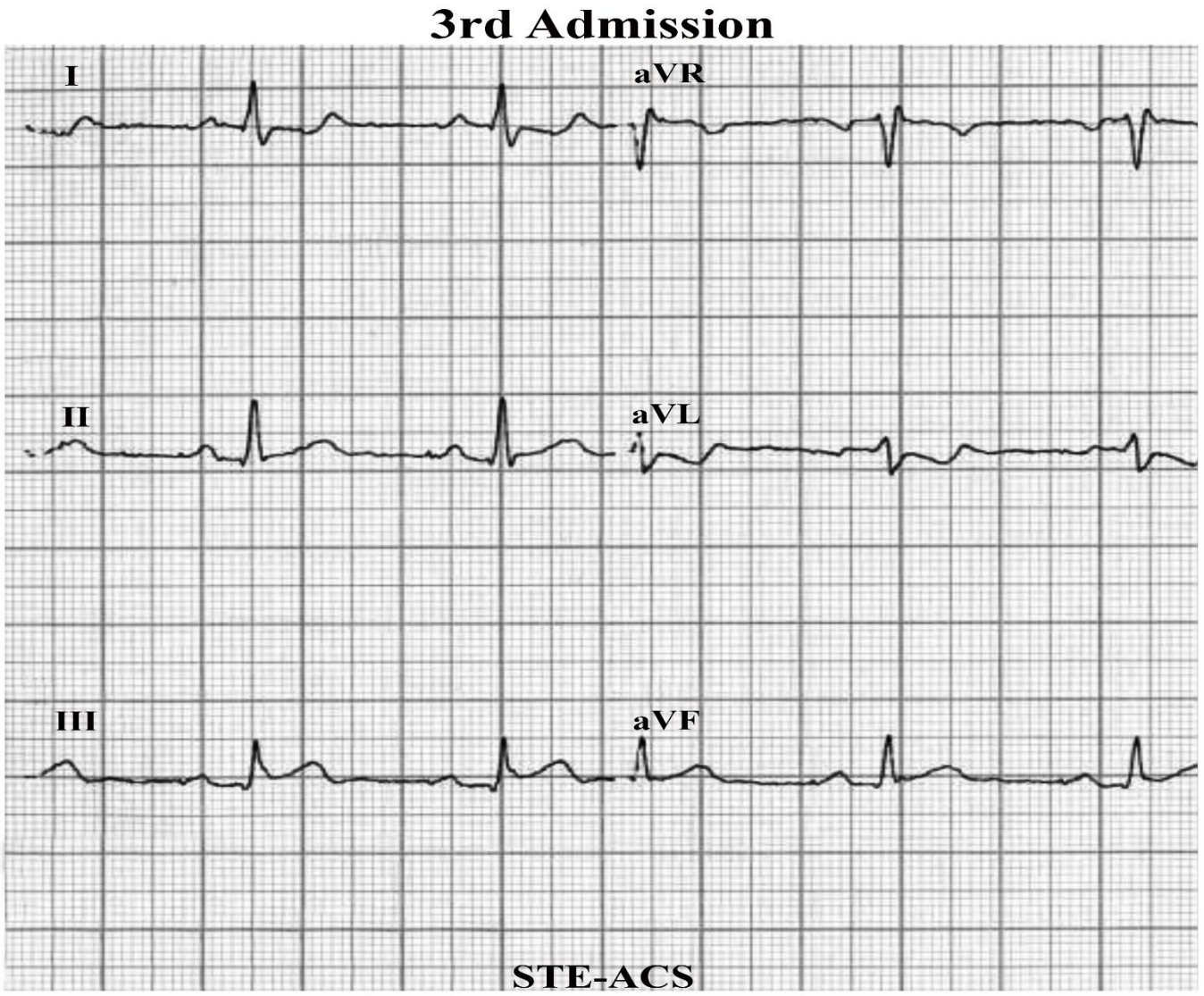
Comparative ECGs of the three admissions: ECG type 1 Brugada pattern, stage 1 of acute pericarditis and acute coronary syndrome



ECG type 1 Brugada pattern



Stage 1 ECG changes with acute pericarditis



ST Segment Elevation Acute Coronary Syndrome (STE-ACS) in the inferior leads

Colleagues opinions

I think the first ECGs are compatible with LVH + repolarization changes in addition to Brugada. I think that the echo should be reevaluated to measure LV wall thickness. The patient had hypertension and polycystic kidneys!

The first ECG of the second admission is not typical for acute pericarditis. There is ST elevation in aVR with ST depression in the inferolateral leads. It is probably effusion without ECG signs of inflammation. Only after drainage (ECG2 of the second admission) we see mild ST elevation in the limb leads with minimal ST depression in aVR. Can it be that ECG1 and ECG2 of the second admission are reversed (S waves are bigger in the first ECG than the second one in V1-V3).

The first ECG of the third admission shows the importance of comparing to previous ECGs. From baseline ST depression in the inferior leads he developed mild ST elevation.

A great case!!!!

Yochai **Birnbaum**, MD, FACC, FAHA
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Spanish: Estimado Andrés. El ECG de la 1° admisión: ritmo sinusal 40 lpm, PR 240 mseg, QRS 110 mseg, QTc no mensurable a esta FC, onda U anterolateral, EE +60°, extrasistole supraventricular aislada, infraST D1, cara inferior y V4, V5 y V6 con supraST en aVR; índice de Cornell > 2440 mm/s; hipertrofia VI. patente de Brugada tipo1. Probable obstrucción de tronco de CI ó 3 vasos. Probable fenocopia de Brugada por isquemia.
2° ECG de 2° admisión: ritmo sinusal 115 lpm, PR 180 ms, QRS 110ms, QTc 470 ms , EE +80°, ondas T picudas en V2 a V4, disminución voltaje onda R en D1, V5 y V6 con rectificación del ST en V5 y V6 y rS en aVL, mínimo supraST en aVR. No hay ECG típico de pericarditis, a pesar del frote pericárdico descripto y de la posición que toma el paciente para calmar su síntomas (sentado, inclinado hacia adelante) El Ecocardiograma habla de un derrame pericárdico importante con restricción diastólica, siglos de IC derecha, febricula e hipotensión arterial. Drenan líquido sanguinolento sin relación a perforación de los electrodos. Probable neoplasia de pericardio o linfomas.
La causa más probable del infraST inferior y lateral en ECG de la 1° admisión ya la describí. Y en la 3° admisión, con angor típico > 30 min, hay supradesnivel del ST de cara inferior con infraST lateral, compatible con IAM inferior. Con CCG con oclusión de CD. Y desaparición de la patente de Brugada (fenocopia por isquemia?). Saludos afectuosos
Dr Juan Carlos **Manzzardo**, Mendoza Argentina

English: Dear Andrés,
The ECG at first admission: sinus rhythm 40 bpm, PR 240 ms, QRS 110 ms, QTc cannot be measured at this HR, anterolateral U wave, electrical axis +60°, isolated supraventricular extrasystole, ST depression in D1, inferior side and V4, V5 and V6 with ST elevation in aVR; Cornell index >2440 mm/s; LV hypertrophy. Type I Brugada pattern. Probable LCA trunk or 3 vessel obstruction. Probable Brugada phenocopy by ischemia.
2nd ECG in 2nd admission: sinus rhythm 115 bpm, PR 180 ms, QRS 110 ms, QTc 470 ms, electrical axis +80°, peaked T waves in V2 to V4, R wave voltage decrease in D2, V5 and V6 with ST straightening in V5 and V6 and rS in aVL, minimal ST elevation in aVR. There is no typical ECG of pericarditis, in spite of the pericardial rub described and the position taken by the patient to calm his symptoms (sitting, leaning forward).
Echocardiogram shows significant pericardial effusion with diastolic restriction, signs of right HF, mild fever and hypotension. Bloody liquid drained, not related to electrode perforation. Probable pericardial neoplasia or lymphomas.
I already described the most probable cause of inferior and lateral ST depression in ECG at 1st admission. And in the 3rd admission, with typical angor >30 min, there is ST elevation of inferior side with lateral ST depression, compatible with inferior MI. Coronary angiography with RCA occlusion. And disappearance of Brugada pattern (phenocopy by ischemia?). Warm regards.
Juan Carlos **Manzzardo, M.D.** Mendoza Argentina

Did you do Procaine amide or Flecainide challenge? The initial coronary angiogram is described as normal but where there any narrowing of the RCA or LAD. Am concerned that initial ECGs might have been due to coronary spasm of prox LAD with severe anterobasal ischemia. This may be difficult to dx with out provocative maneuvers i.e. Ergotamine or acetyl choline.
The 2nd admission was for pericarditis best shown on the 2nd ECG of 2nd admission and finally
3rd admission was for Right coronary occlusion.

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Portuguese/Português

Caro Dr **Pérez-Riera**

Primeiramente, é muita coisa para uma paciente apenas, ou estamos diante de uma azarada ou talvez não seja isso tudo. Vamos as respostas:

Resposta 1: Em relação ao ECG inicial observo um padrão de sobrecarga ventricular esquerda, alterações difusas da repolarização ventricular e alterações da repolarização em precordiais direitas que sugerem um Brugada tipo II. Neste caso, uma vez que a paciente não tem história de síncope, história familiar de morte súbita ou outros comemorativos que sugiram uma canalopatia, o diagnóstico diferencial com uma fenocópia de Brugada é fundamental. A realização do ECG com precordiais no segundo espaço intercostal, utilização de filtros especiais (principalmente em hipertensos) e a utilização de derivações bipolares como precordiais poderiam sensibilizar o ECG no diagnóstico de Brugada. A indicação de estudo eletrofisiológico nestes casos não está bem estabelecida. Um teste farmacológico com bloqueador de canal de sódio e a avaliação do período refratário efetivo do ventrículo tem mais valor prognóstico do que a própria indução de TV polimórfica (Estudo PRELUDE).

Resposta 2: A evolução após implante de CDI com quadro de pericardite e derrame pericárdico com sinais de restrição pode ter relação com o próprio implante do aparelho. A síndrome de Dressler é caracterizada por dor pleuropericárdica e febre, geralmente ocorre 2 a 4 semanas após IAM. Existem alguns relatos na literatura da síndrome de Dressler após implante de marcapassos/desfibriladores. (www.tsoc.org.tw/upload/journal/1/20120331/7.pdf) Acredito que essa é a hipótese mais provável para esta paciente.

Resposta 3: Já nos últimos ECGs observamos corrente de lesão na parede inferior, bastante sugestivo de evento isquêmico agudo, o que foi confirmado pela cinecoronariografia.

Um abraço cordial,

Acácio **Fernandes-Cardoso M.D**. Médico professor assistente do setor de eletrocardiologia do Hospital da Clínicas – Universidade de São Paulo. -São Paulo-Brazil.

English

Dear Dr. Pérez-Riera,

First, this is a lot for a single patient; either we are facing someone with bad luck, or maybe this is not all. Let's see the replies:

Reply 1: As to the initial ECG, I see a pattern of left ventricular enlargement, diffuse ventricular repolarization alterations and repolarization alterations in the right precordial leads, suggesting Brugada type 2. In this case, since the patient does not have a history of syncope, family history of sudden cardiac death, or another reminder that may suggest channelopathy, a differential diagnosis with Brugada phenocopy is mandatory. Performing an ECG with precordial leads in the second intercostal space, using special filters (mainly in hypertensive patients) and using bipolar leads as precordial, may add sensitivity to the ECG in the diagnosis of Brugada. The indication of electrophysiology study in these cases is not properly established. A pharmacological test with sodium channel blocker and the evaluation of ventricular effective refractory period, has more prognostic value than polymorphic VT induction proper (PRELUDE study (1)) if < 200 ms.

Reply 2: Evolution after ICD implant with symptoms of pericarditis and pericardial effusion with restriction signs could be related to the implant of the device. Dressler syndrome is characterized by pleuropericardial pain and fever, and it generally occurs 2 to 4 weeks after AMI. There are some reports in literature on Dressler syndrome after pacemaker/defibrillator implants (www.tsoc.org.tw/upload/journal/1/20120331/7.pdf). I think that this is the most likely hypothesis for this patient.

Reply 3: Already in the last ECG, we observe lesion current in the inferior wall, pretty suggestive of acute ischemic event, which was confirmed by coronary angiography.

1. **Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59(1):37-45.**

Warm regards,

Acácio **Fernandes Cardoso M.D**. Médico professor assistente do setor de eletrocardiologia do Hospital da Clínicas – Universidade de São Paulo. -São Paulo-Brazil.

Final comments by

Andrés Ricardo **Pérez-Riera, M.D. Ph.D.**

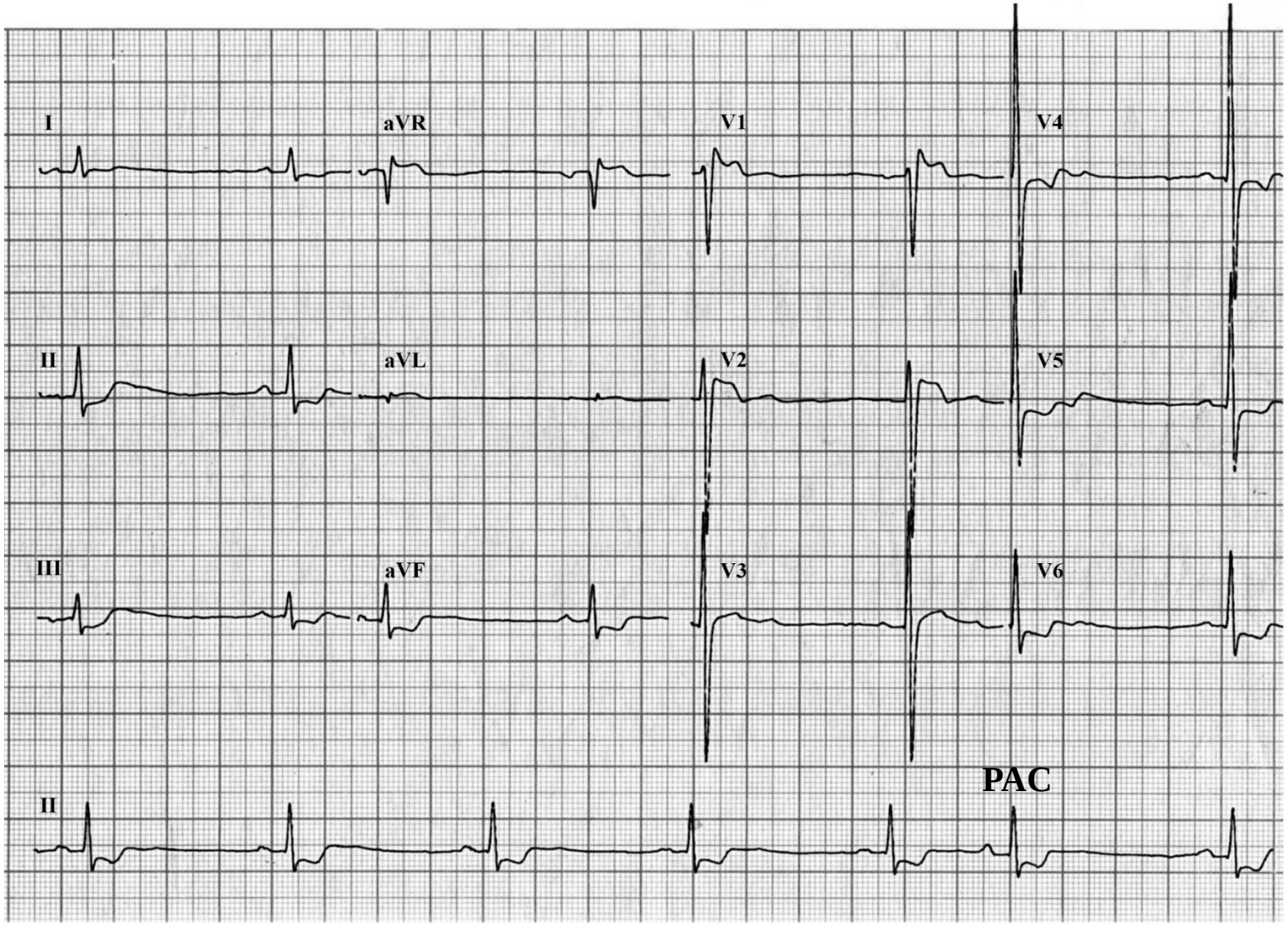
Design of Studies and Scientific Writing Laboratory in the ABC School of Medicine, Santo André, São Paulo, Brazil

https://ekgvcg.wordpress.com

Andrés about to eat a delicious "paella"

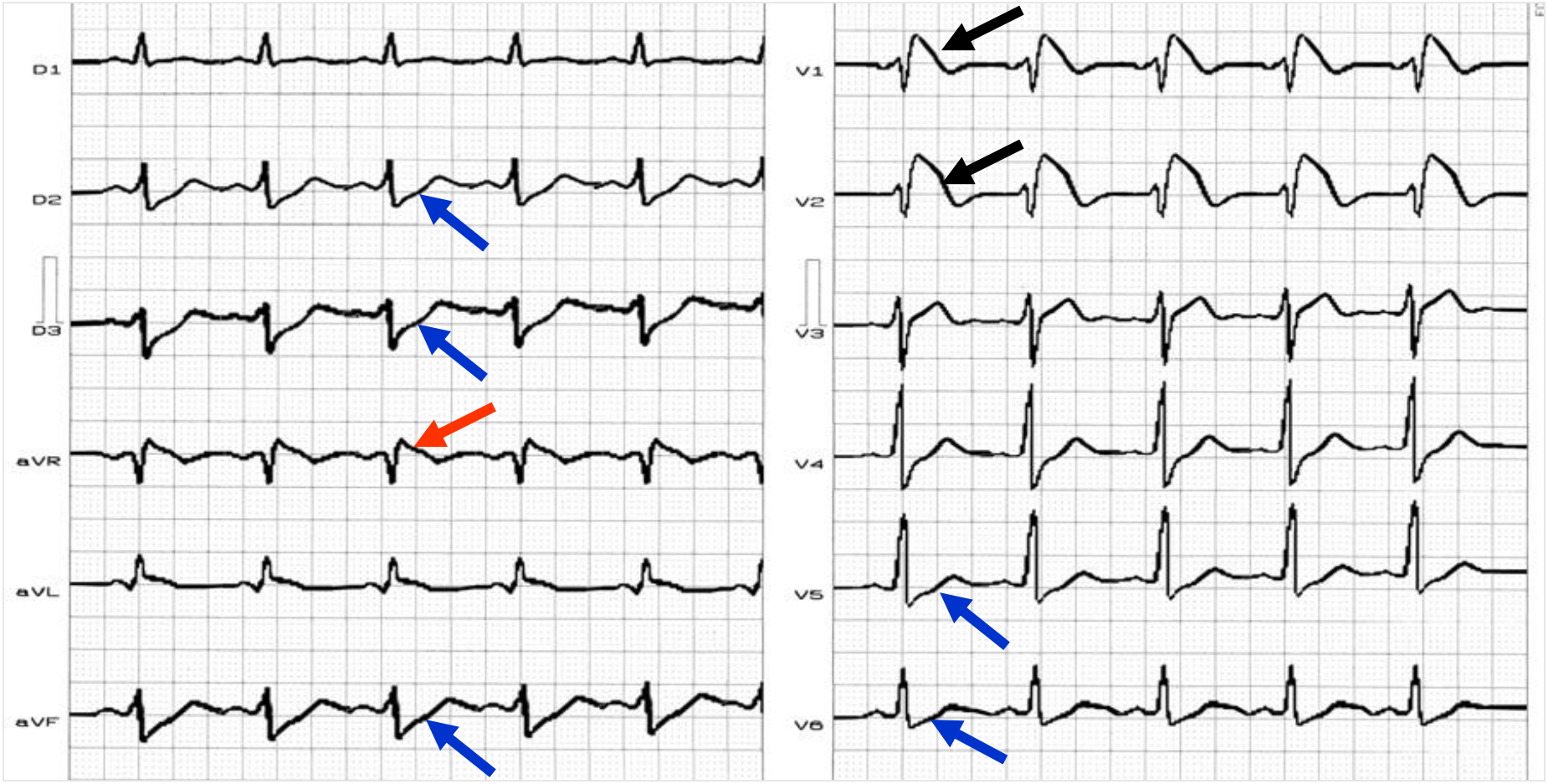
“Simplicity may be beauty in art, but Science is complex beauty that cannot be reduced into simplicity.”
Pedro Brugada

First ECG (ECG-1) performed at first admission on August 23-2008 19:50 P.M.



ECG: sinus bradycardia (HR= 38bpm), ST segment depression in inferolateral leads, ST segment elevation saddleback type followed by positive T wave in leads V1- aVR and type 1 Brugada pattern (BrP) ST segment elevation > 2mm convex to the top followed by negative T-wave in V2.
Conclusion: sinus bradycardia, concomitant type 2 and type 1 BrP, premature atrial contraction (PAC) and ST segment depression in inferolateral walls: Possible cause? See next slide……..

Typical type 1 ECG BrP in a symptomatic patient with reciprocal changes in inferolateral leads



ECG diagnosis: J point and ST segment elevation, convex to the top followed by negative T wave in right precordial leads from V_1 to V_2 (**black arrows**): Type 1 BrP, Brugada sign or idiopathic J wave. Unipolar aVR lead that heads toward the RV epicardium above the RVOT , which shows subtle ST segment and J point elevation (**red arrows**).

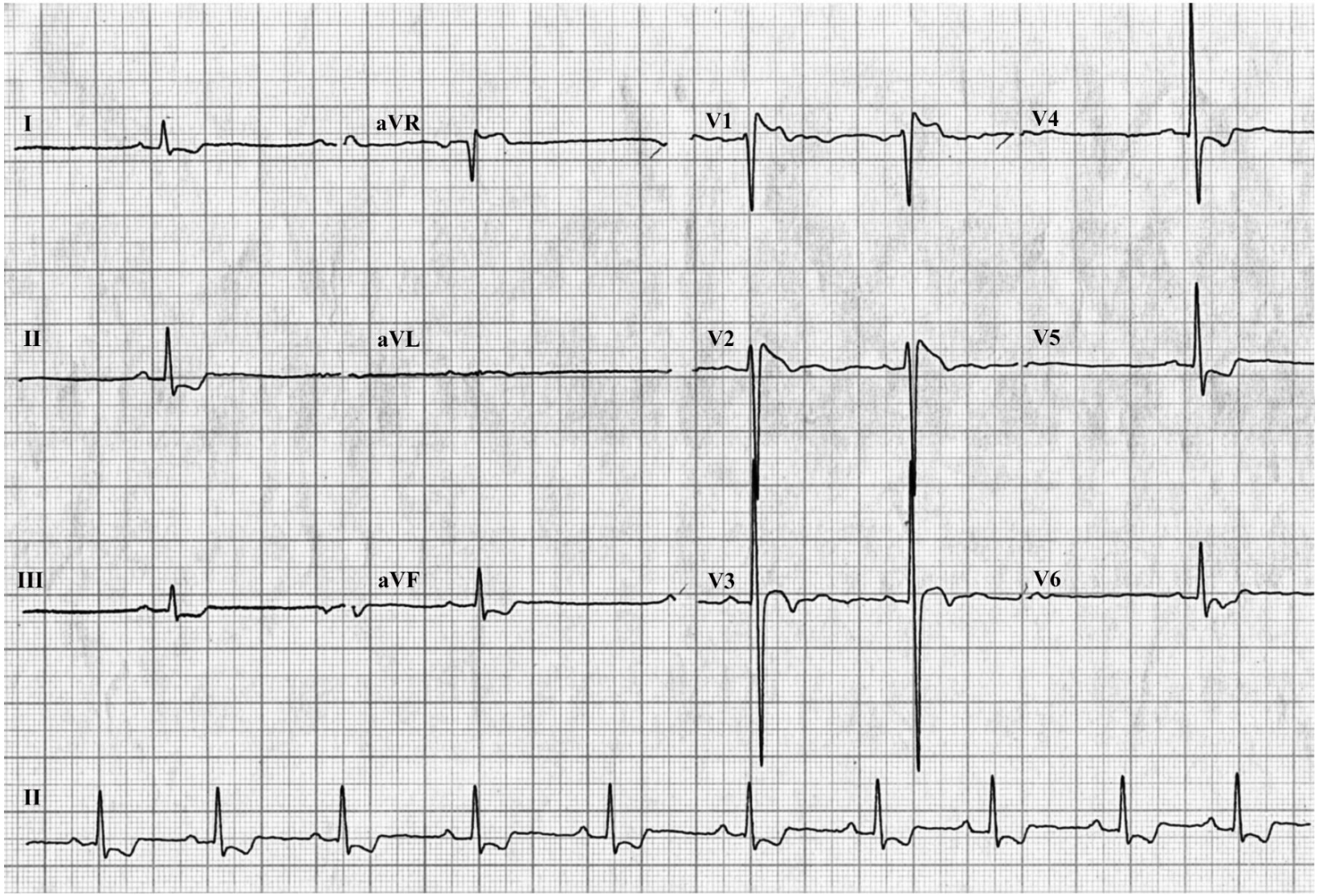
Inferolateral leads show reciprocal changes or mirror images of V1-V2 and aVR (**blue arrows**).

Conclusion: Type 1 BrP. We speculate that it could be reciprocal changes or mirror image on ECG as well.

Crea et al observed ST segment depression ≥ 0.1 mV with duration ≥ 0.08 s in the inferior leads in 24% of cases with type 1 BrP (**Crea 2015**).

Reciprocal changes are the mirror image of the indicative changes and are often seen in leads recording from the opposite area of the heart, picked up on the ECG as ST depression. For this reason, ST depression does not always mean myocardial injury…it could just mean that those ECG leads are picking up on a large surge of energy from the indicative changes occurring in the opposite ECG leads.
Reciprocal changes may include taller than normal R waves (mirror image of Q waves), ST depression (mirror image of ST elevation), and tall T waves (mirror image of T wave inversion). Reciprocal changes tend to be seen in up to 70% of inferior infarctions and 30% of anterior infarctions.
It is important to note the following:
Reciprocal changes only potentially apply if there is ST depression evident on an ECG
If ST depression is evident on the ECG without any sign of concurrent ST elevation, it should be treated as an ECG change consistent with ischaemia/injury in the area of the heart that the affected leads are viewing
If ST depression is evident on the ECG in the presence of concurrent ST elevation, it may merely reflecting a reciprocal change – however, myocardial injury in that area cannot be completely ruled out!
Benign early repolarization pattern does not have mirror image.
Classical early repolarization pattern (ERP) is a benign phenomenon observed predominantly in teenagers, young adults, male athletes and the black race. The universally old accepted criterion for its diagnosis is the presence, in at least two adjoining leads, of ≥ 1 mm or 0.1 mV ST segment elevation. In benign ERP reciprocal ST segment changes are possible only in lead aVR. In contrast, reciprocal ST segment changes can be observed in several leads in idiopathic VF (IVF) and ACS. In benign ERP the ST segment and T wave patterns have a relative temporal stability. IVF is an entity with low prevalence, possibly familiar, and characterized by the occurrence of VF events in a young person. More frequently this occurs in male subjects without structural heart disease and with otherwise with normal ECG even using high right accessory leads and/or after ajmaline injection. Several clinical entities cause ST segment elevation include asthenic habitus, acute pericarditis, STEMI, BrS, congenital SQTS, and IVF. In these circumstances clinical and ECG data are most important for differential diagnosis. In IVF the modifications could be dramatic and predominantly at night during vagotonic predominance when J waves > 2 mm in amplitude. The ST/T abnormalities are dynamic, inconstant, and reversed with isoproterenol. Convex upward J waves, with horizontal/descending ST segments or "lambda-wave" ST shape are suggestive of IVF with early repolarization abnormalities. PVCs with very short coupling and "R on T" phenomenon are characteristics with two pattern: When originate from RVOT LBBB morphology and from peripheral Purkinje network, LBBB pattern. The inherited-familial forms are not frequent in IVF; however mutations were identified in the genes KCNJ8, DPP6, SCN5A, SCN3B, CACNA1C, CACNB2, and CACNA2D1. The management of IVF has class I indication for ICD implantation. Ablation therapy is considered additional to ICD implantation in those patients with repetitive ventricular arrhythmia. Quinidine is a highly efficient drug that prevents recurrence (**Pérez-Riera 2012**).

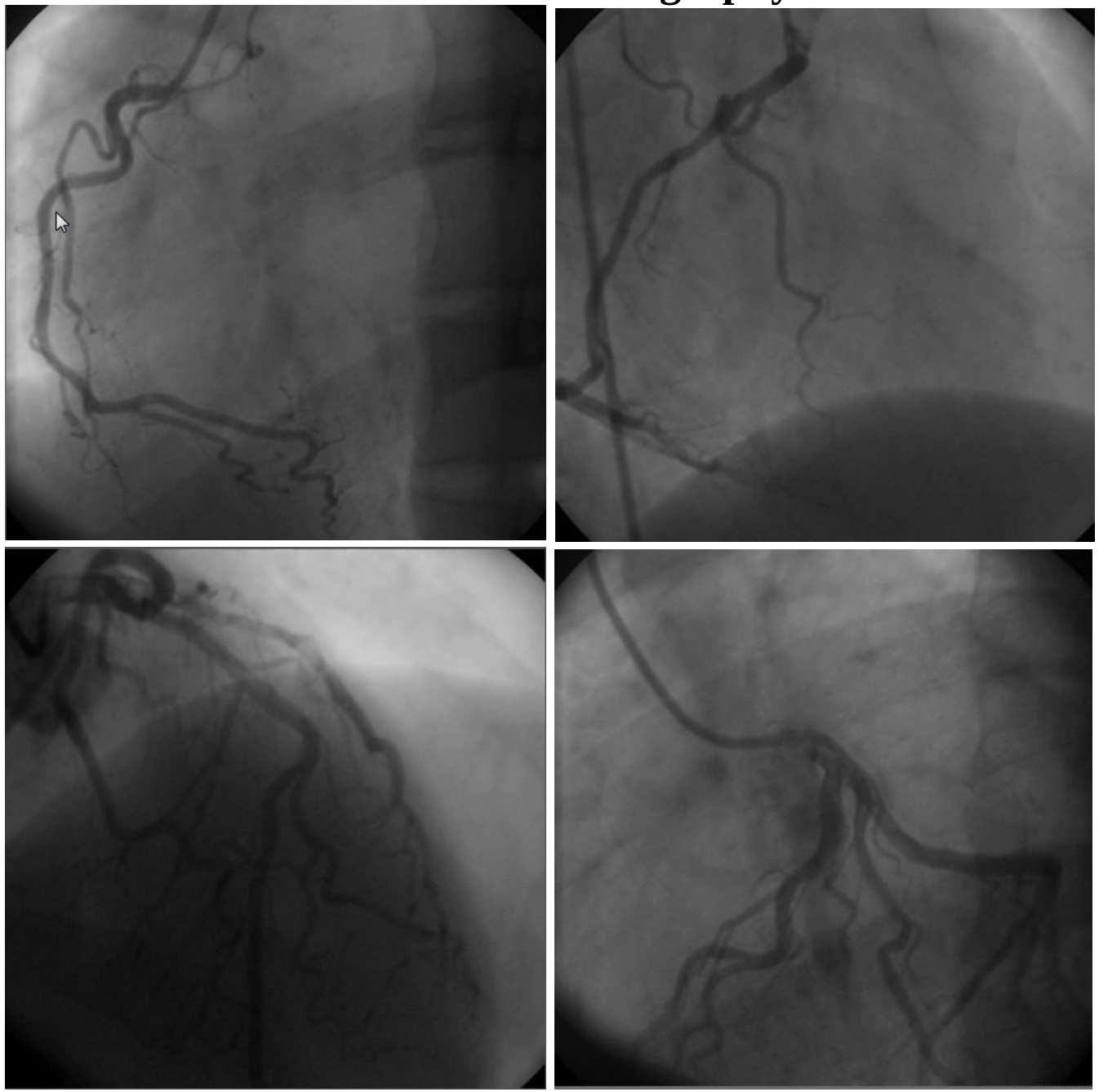
Second ECG (ECG-2) performed immediately (5 minutes) after sublingual nitrate



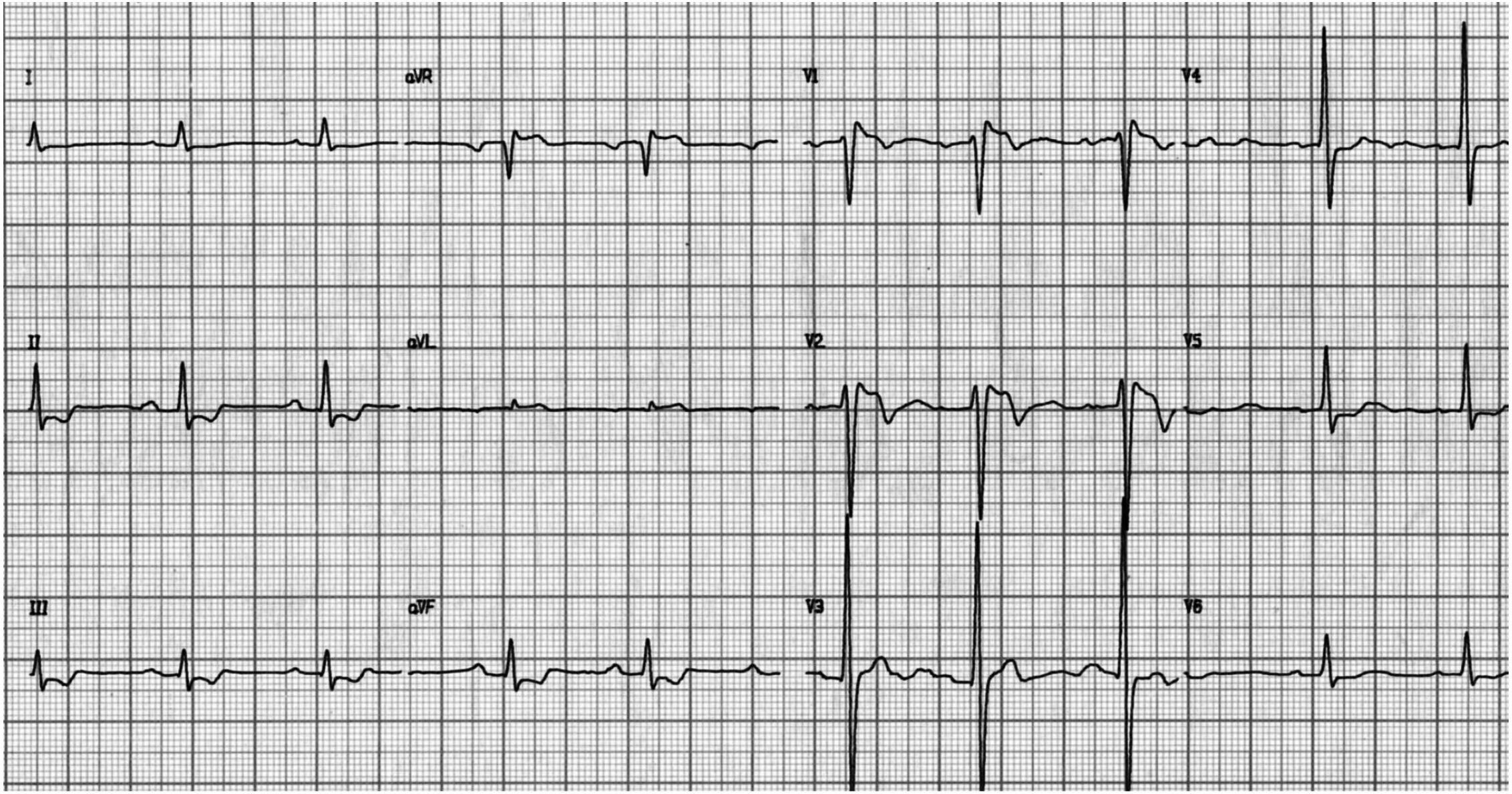
ECG diagnosis: sinus rhythm, HR= 65bpm, ST segment depression in inferolateral leads, ST segment elevation saddleback type followed by positive T wave in leads aVR and ST segment elevation ≥ 2mm convex to the top followed by negative T-wave in V2.

Conclusion: concomitant type 2 and 1 Brugada pattern, ST segment depression on inferolateral wall: cause? What means ST depression in inferolateral leads? Answer: Probably reciprocal changes or mirror image.

Normal coronariography

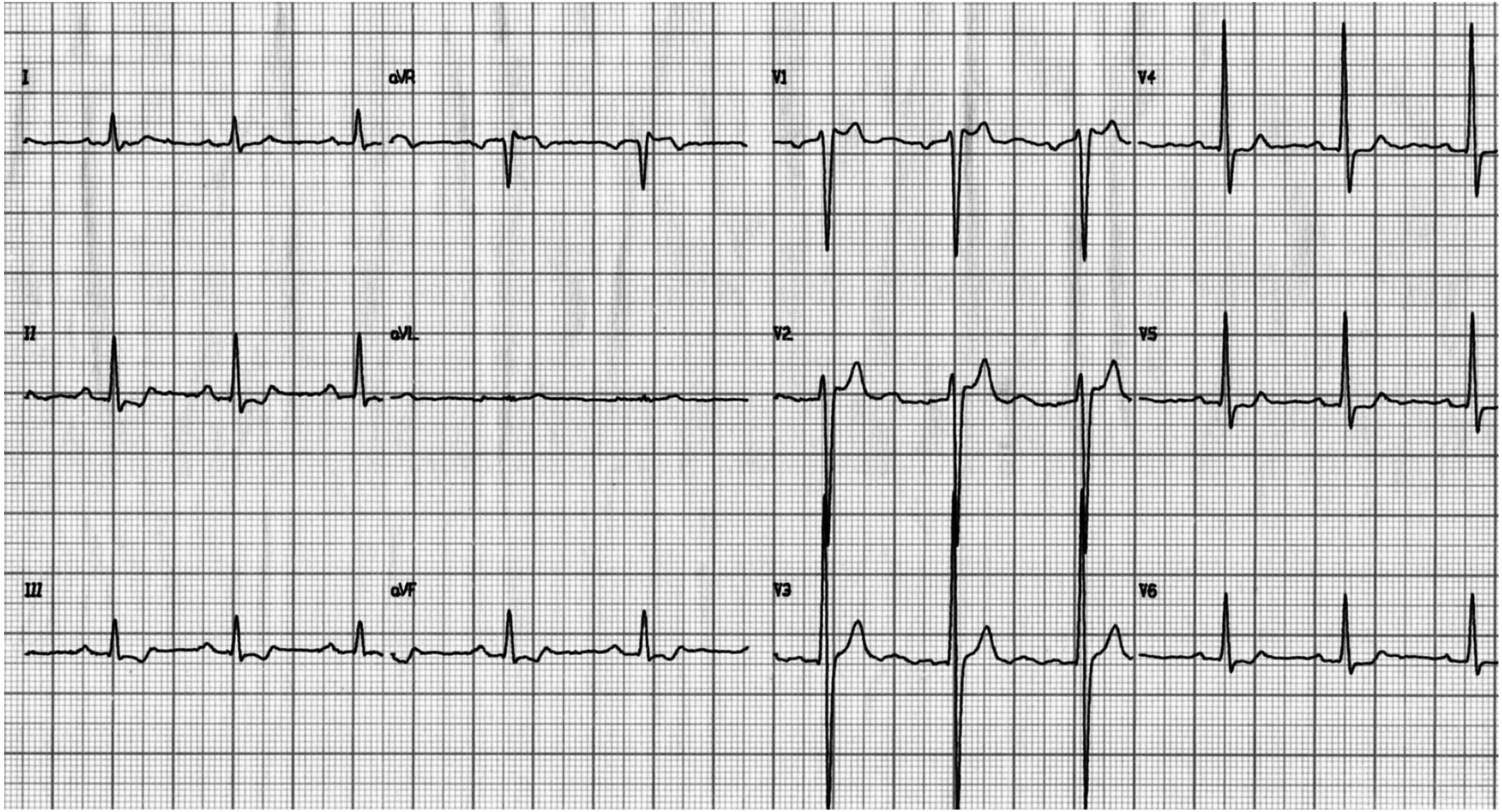


Third ECG (ECG-3) performed after 24 hours

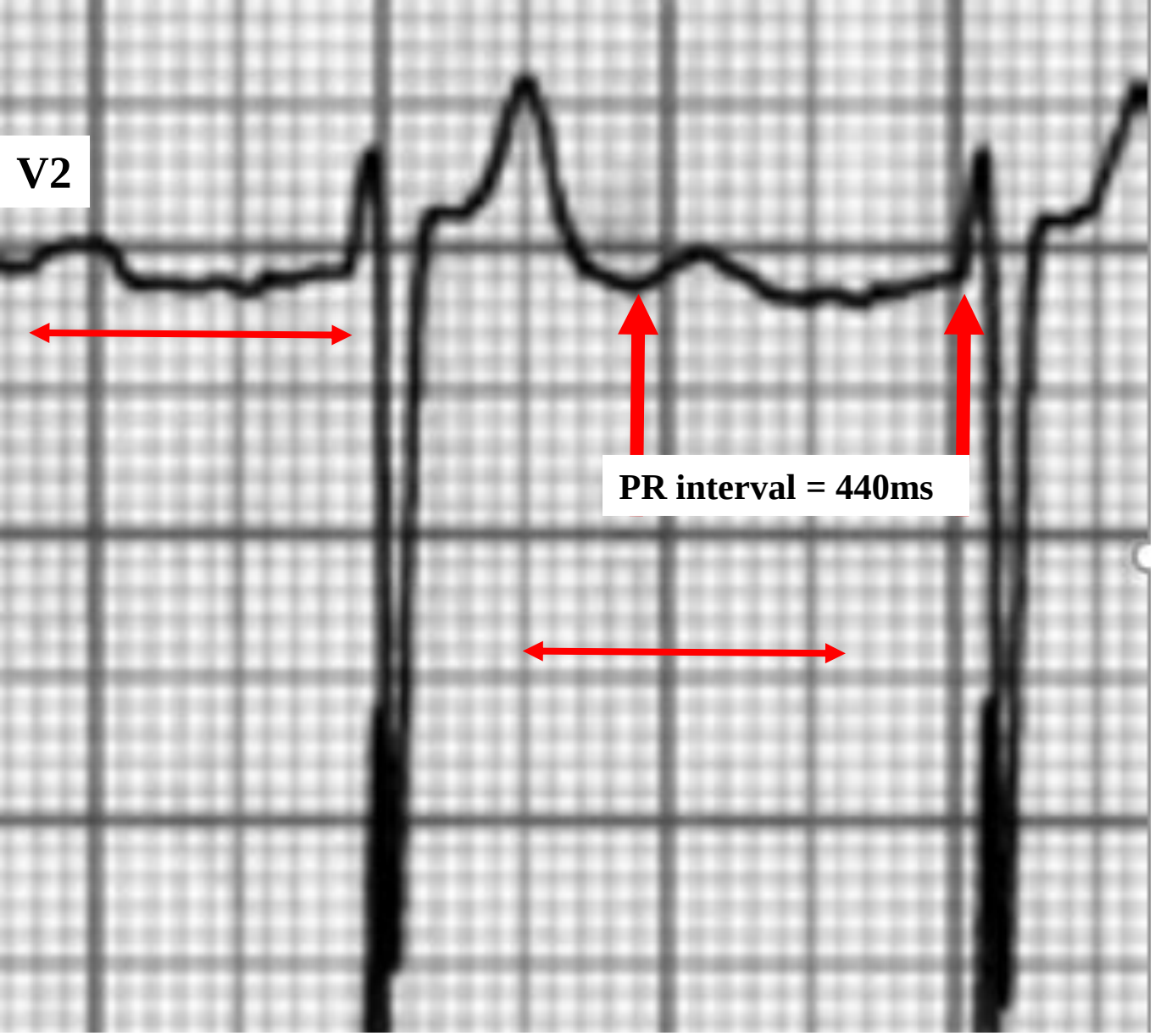


ECG diagnosis: Spontaneous type 1 BrP: ST segment elevation ≥ 2mm (≥ 0.2 mV) followed by negative T wave in V1-V2 “coved-type”. Concomitant ST segment depression in II, III and aVF and minimal ST depression in lateral wall.

ECG performed after 48 hours



ECG diagnosis: variables degree of PR interval prolongation, sometimes very prolonged(440ms): first degree AV block. QRS duration in V2 > 120ms, ST segment elevation with saddle back appearance followed by positive T wave. See V2 lead in next two slides.

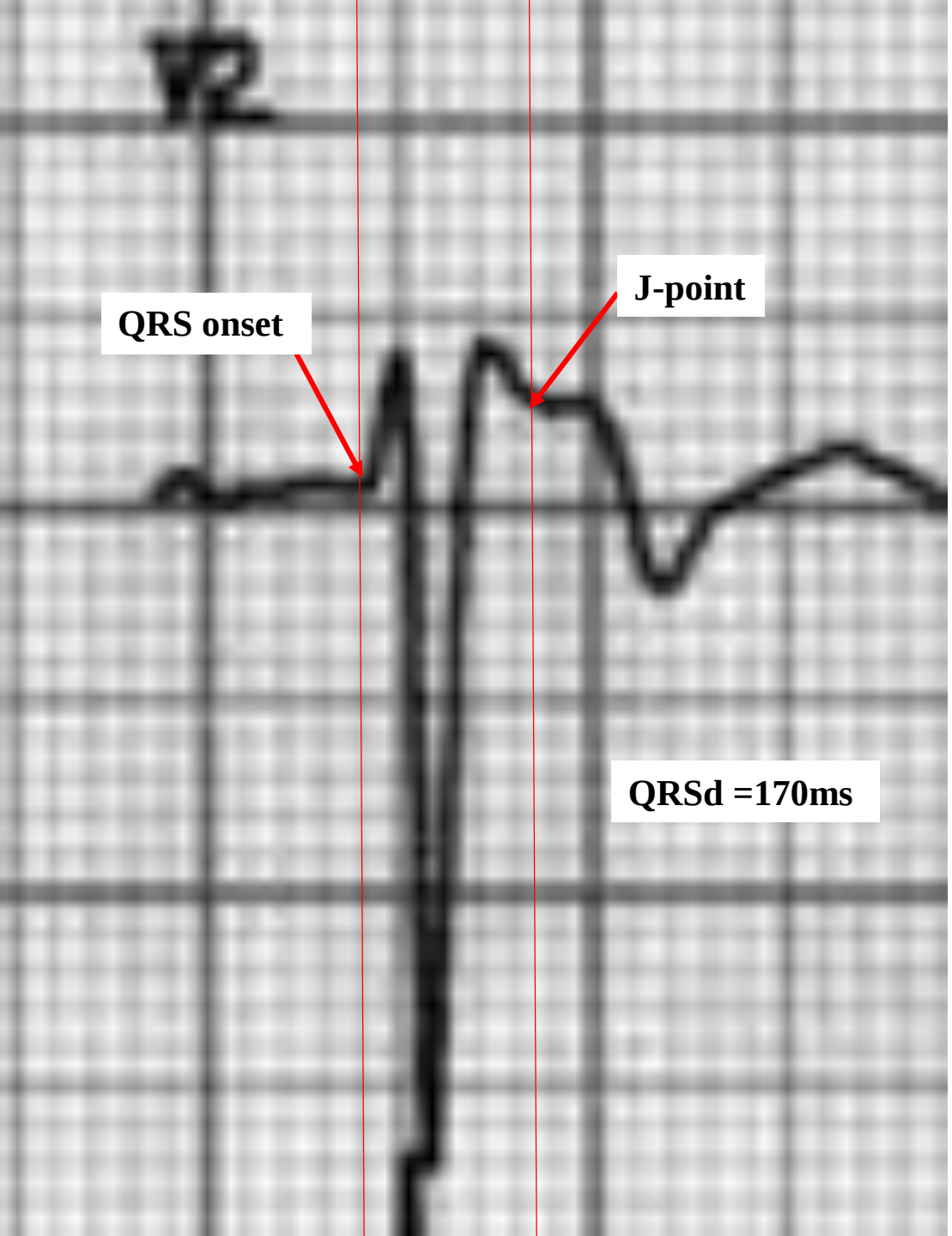


Very prolonged PR interval. This feature is a risk marker factor in BrS

Comments: In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes 100 ms (**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 prolonged 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**).

Spontaneous and exercise-induced type 1 BrP, fragmented QRS complex, prolonged PR interval (> 200 ms), QRS prolongation in V2 (≥ 120 ms) are markers of an increased heterogeneity of ventricular repolarization and associated with an increased arrhythmic risk. Conduction disturbances are frequent and sometimes diffuse in patients with BrS. First degree AVB is independently linked to outcome and may be proposed to be used for individual risk stratification (**Maury 2013**).

Loss-of-function sodium channelopathies manifest as a spectrum of diseases including BrS, progressive cardiac conduction defects (PCCD), also known as Lenègre disease. Conduction delay is the commonest finding on ECG. In loss-of-function SCN5A channelopathies, patients carrying mutations leading to premature truncation of the protein. T and missense mutations M (inactive) develop a more severe phenotype than those with M (active) mutations. This mutation is associated with more severe conduction disorders (**Meregalli 2009**).



The QRS interval measured from QRS onset to the J point in leads II and V2. The only significant difference between the symptomatic and asymptomatic patients is the QRS duration measured from lead V2. The mean QRS interval is 129.0 ± 23.9 ms in symptomatic patients versus 108.3 ± 15.9 ms in asymptomatic patients (**Ohkubo 2011**).

Prolonged QRS duration, measured in V2 and II from standard 12-lead ECG, is associated with symptoms and could serve as a simple noninvasive risk marker of vulnerability to life-threatening ventricular arrhythmias in BrS (**Junttila 2008**).

Genes associated with Brugada syndrome and allelic disorders with their mutations (Brugada R 2014)

Diagnosis is based on clinical findings. Mutations in 17 genes have been associated with BrS *SCN5A, SCN1B, SCN2B, SCN3B, GPD1L, CACNA1C, CACNB2, CACNA2D1, KCND3,KCNE3, KCNE1L (KCNE5), KCNJ8, HCN4, RANGRF, SLMAP, TRPM4 and HEY2* (**Bezzina 2013**). ≈ 25%-30% of BrS is accounted for by pathogenic variants in this 16 genes mentioned. (BrS is a rare cardiac rhythm disorder associated with SCD. Mutations in the Na^+ channel gene SCN5A are found in ~20% (**Kapplinger 2010**) of cases while mutations in other genes collectively account for <5%. Although BrS is considered a mendelian disorder with autosomal dominant transmission, studies in families harboring SCN5A mutations have demonstrated low disease penetrance (**Priori 2000; Probst 2009**) and, in some instances, absence of the familial SCN5A mutation in some affected family members. Also, many cases are sporadic (**Schulze-Bahr 2003; Hermida 2010**), and familial linkage analyses have largely been unsuccessful in uncovering new disease-causing genes. These observations suggest a more complex inheritance model. Identifying new genetic risk factors could assist in further diagnosis, provide new insights into underlying molecular mechanisms and yield new information relevant to the broader problem of SCD. Average prevalence of 5:10,000 worldwide. 5/1,000 (Caucasians) to 14/1,000 (Asian). Currently, more than 180 mutations in 17 genes have been associated with BrS.

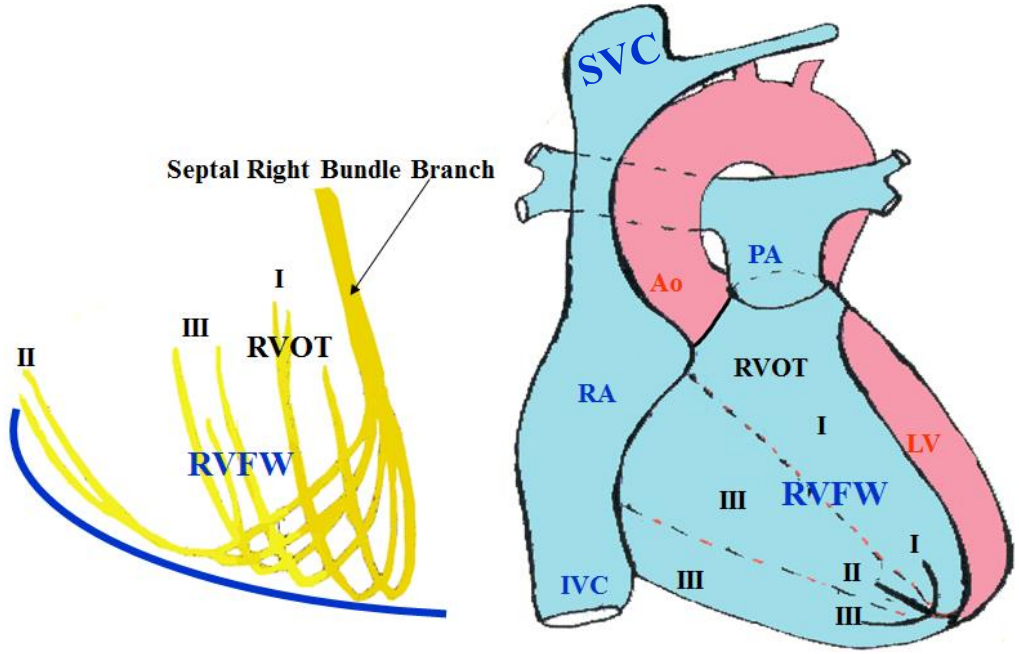
Type	OMIM	Mutation	Notes
BrS1 (15-30%)	601144	SCN5A (**Chen 1998**)	α subunit of the Na^+. (I_{Na}.) Loss of function in this channel leads to an unopposed I_{to} current (KCND2)
BrS2 (<1%)	611778 M	GPD1L. Cytogenetic Location: 3p22.3 (**London 2007**)	Glycerol-3-phosphate dehydrogenase like peptide
BrS3 (<1%)	114205	CACNA1C (**Splawski 2004**) (**Antzelevitch 2007**).	α-subunit of cardiac L-type calcium channel
BrS4 (<1%)	600003	CACNB2 ((**Antzelevitch 2007**).**Taviaux 1997; Burashnikov 2010**)	β-2 subunit of the voltage dependent L-type calcium channel
BrS5 (<1%)	604433	KCNE3 which coassembles with KCND3 (**Delpón 2008**)	β subunit to KCND3. Modulates the I_{to} potassium outward current
BrS6 (<1%)	600235	SCN1B (**Scheffer 2007; Watanabe 2009**)	β-1 subunit of the sodium channel SCN5A (**Watanabe 2008**)
BrS7		SCN10A	(**van den Boogaard 2014;Hu 2014; Behr 2015;Fukuyama 2016**)
BrS8		KCNJ8, IVF, ERS, BrS	Kv6.1 Kir6.1 (**Medeiros-Domingo 2010:Barajas-Martínez 2012**)
		HEY2 (**Bezzina 2013**)	

Channel	Type	Gene	Protein
Sodium	BrS1	SCN5A(**Chen 1998**)	Nav1.5 at chromossome 3p21
	BrS2	GPD1L(**London 2007**)	Glycerol-3-P-DH-1
	BrS5	SCN1B(**Watanabe 2008**)	Navβ1
	BrS7	SCN3B (**Wang 2010; Ishikawa 2013**)	Navβ3
	BrS16	SCN2B (**Haug 2000**)	Navβ2
	BrS10	RANGRF (**Campuzano 2014**)	RAN-G-release factor (or MOG1)
	BrS14	SLMAP (**Bönnemann 2002**)	Sarcolemma associated protein
Potassium	BrS6	KCNE3 (**Sternberg 2003**)	MiRP2
	BrS8	KCNJ8 (**Medeiros-Domingo 2010:Barajas-Martínez 2012**) IVF, ERS, BrS	Kv6.1 Kir6.1
	BrS9	HCN4(sinus node dysfunction, LQTS, BrS)	Hyperpolarization cyclic nucleotide-gated 4
	BrS11	KCNE1L (**Ravn 2008**)	K voltage-gated subfamily E member 1 like
	BrS12	KCND3 (**Raudenská 2008**)	Kv4.3 Kir4.3
Calcium	BrS3	CACNA1C (**Antzelevitch 2007**)	Cav1.2
	BrS4	CACNB2B(**Antzelevitch 2007**)	Voltage-dependent β-2
	BrS13	CACNA2D1 (**Templin 2011; Burashnikov 2010**)	Voltage-dependent α2/δ1
	BrS15	TRPM4 (**Kruse 2009**)	Transient receptor potential M4

The Brugada Syndrome (BrS) is a channelopathy, characterized by ion channel dysfunction (sodium, calcium, and potassium) and typical ECG alterations, originally described by Osher and Wolff in 1953 (**Osher 1953**) and further elucidated by Josep and Pedro Brugada in 1991. Osher and Wolff speculated that the ECG pattern "simulating acute myocardial injury" is apparently due to prolongation of the depolarization process by

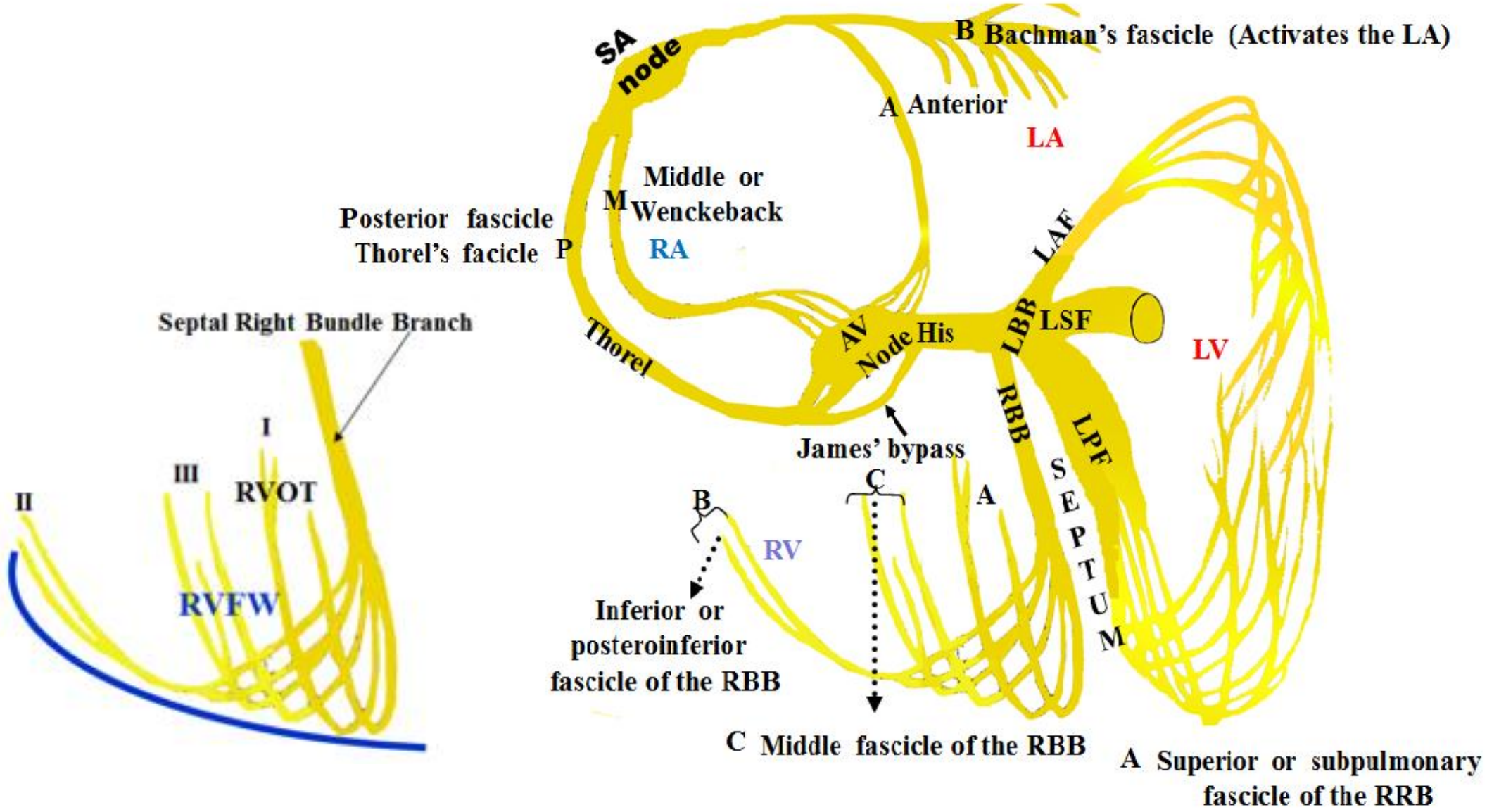
RBBB or possibly **focal block with delayed activation of a portion of the right ventricle (Antzelevitch 2002)**. Surprisingly fifty-one years later we verified that Osher and Wolff were right!!!! This verification of focal block with delayed activation of a portion of the RV we denominate **R**ight **E**nd **C**onduction **D**elay (**RECD**) located in free wall of RV at the region of the right ventricular outflow tract (**RVOT**) best registered in unipolar aVR lead. Ours II guidelines on analysis and issuance of electrocardiographic reports of the Brazilian Society of Cardiology call this focal block **Right Superior Divisional Block (Luna Filho 1989), superior or subpulmonary fascicular block** (**Pastore 2016**) or **Right anterior subdivision block (RASB)**. This fascicle is located inside of RVOT in front of aVR lead and consequently better recorded in this lead: "The forgotten lead"

Distribution of the three fascicles of the right bundle branch of the His bundle in the right ventricle free wall (Pérez-Riera 2005)



I - Territory of superior or subpulmonary fascicle(Right superior division or subpulmonary fascicle inside of RVOT
II – Territory of inferior or posteroinferior fascicle
III – Territory of middle fascicle: Do it exist?
RVFW: Right Ventricular Free Wall; **SVC:** Superior Vena Cava; **IVC:** Inferior Vena Cava; **RVOT:** Right Ventricular Outflow Tract; PA: Pulmonary Artery; **Ao:** Aorta; **RA:** Right Atrium; LV: Left Ventricle.

The cardionector system and the hexafascicular concept of intraventricular Hisian system demonstrated by Vectorcardiography



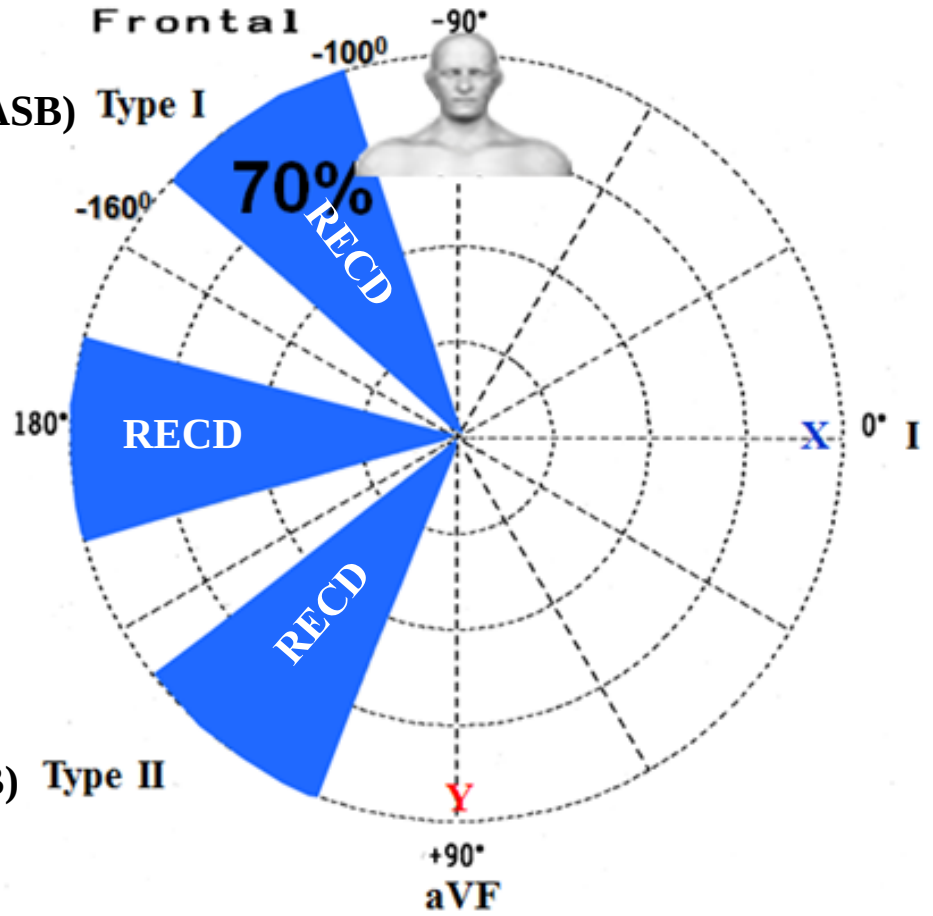
Right End Conduction Delay (RECD) concept: These are the electrovectorcardiographic conduction changes, secondary to physiological delay or to true dromotropic disturbance in the territory of one of the three hypotetical fascicles(or contingents) of the right bundle branch (right fascicular block of the His bundle or right anterior subdivision block (RASB) (**de Micheli 1988**), in isolation in right ventricular free wall. We divided the right divisional blocks according the location of the **RECD** in the frontal plane in three types: **Type I (right anterior subdivision block (RASB)), Type II (Right posteroinferior subdivision block (RPSB)) and Type III (right middle fascicle block (RMFB). Does it exist?).** The type I is the variant observed in the Brugada syndrome (**Pérez Riera 2008**) and in concealed forms of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (**Corrado 1996; Corrrado 2001**).

Classification of right divisional blocks according the location of the RECD in the Frontal Plane

Right Anterior Subdivision Block (RASB) **Type I**

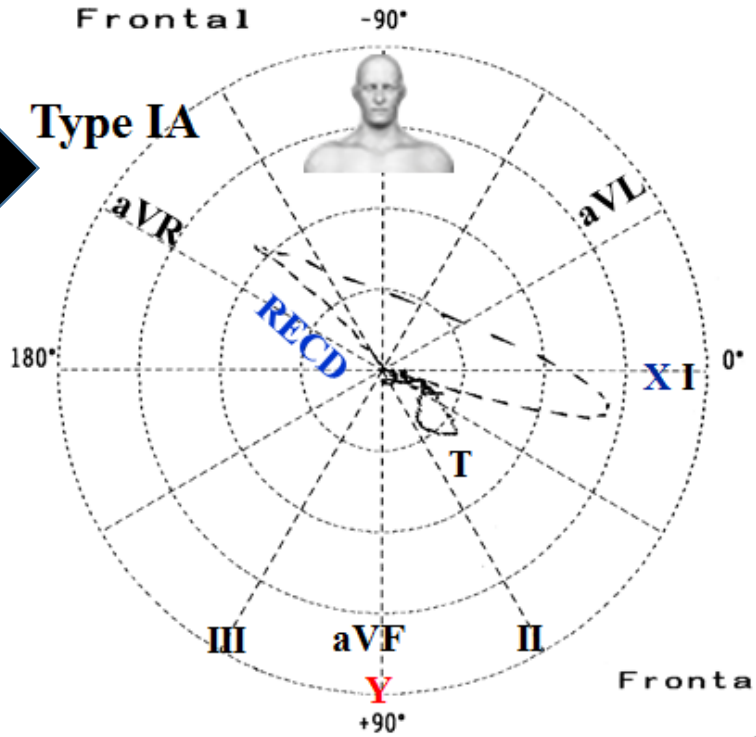
Right Middle Fascicle Block (RMFB) **Type III**

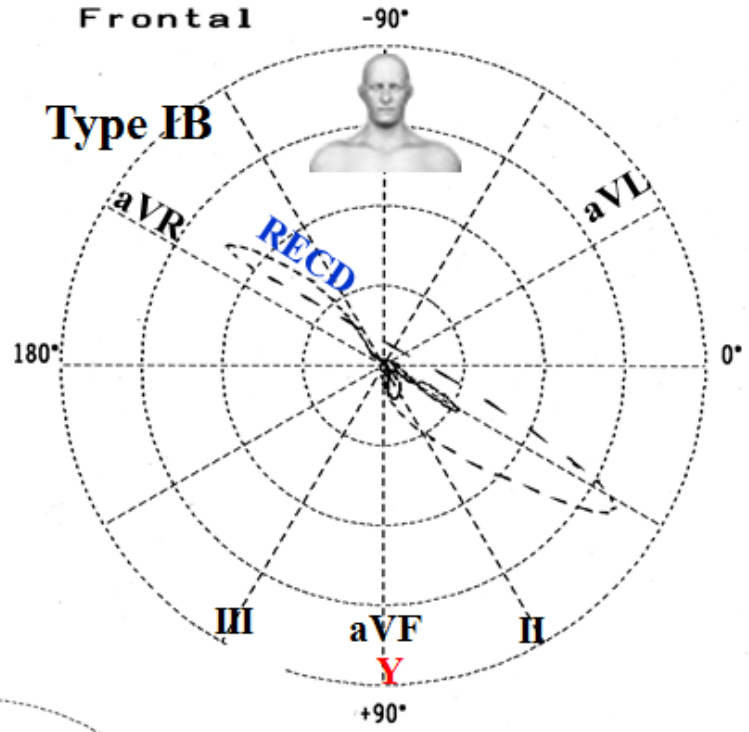
Right Posteroinferior Subdivision Block (RPSB) **Type II**

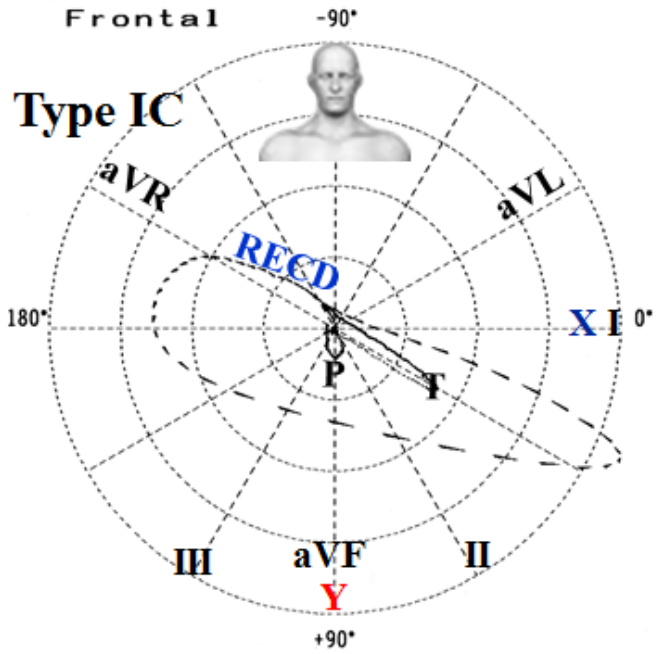


I) Right anterior subdivision block (RASB) or type I: Vectorcardiographic types (following the QRS rotation in the FP

Only type I has differential diagnosis with LAFB







I) Right anterior subdivision block (RASB)

Type I: It is the variant observed in Brugada syndrome and concealed forms of ARVC. **RECD** near -150° (aVR) "the forgotten lead"

- **Type IA:** QRS loop predominantly located in the left superior quadrant, (SÂQRS with extreme deviation to the left), counterclockwise rotation and **RECD** located in the right superior quadrant. Very similar to LAFB;
- **Type IB:** QRS loop pointed, clockwise or in eight, with the initial portion located in the left inferior quadrant and **RECD** located in the right superior quadrant. SAQRS difficult to determine or shifted to the right;
- **Type IC:** QRS loop of clockwise rotation with SAQRS with no deviation or with a mild shift to the right.

In the three types I the **RECD** is located in the right upper quadrant.

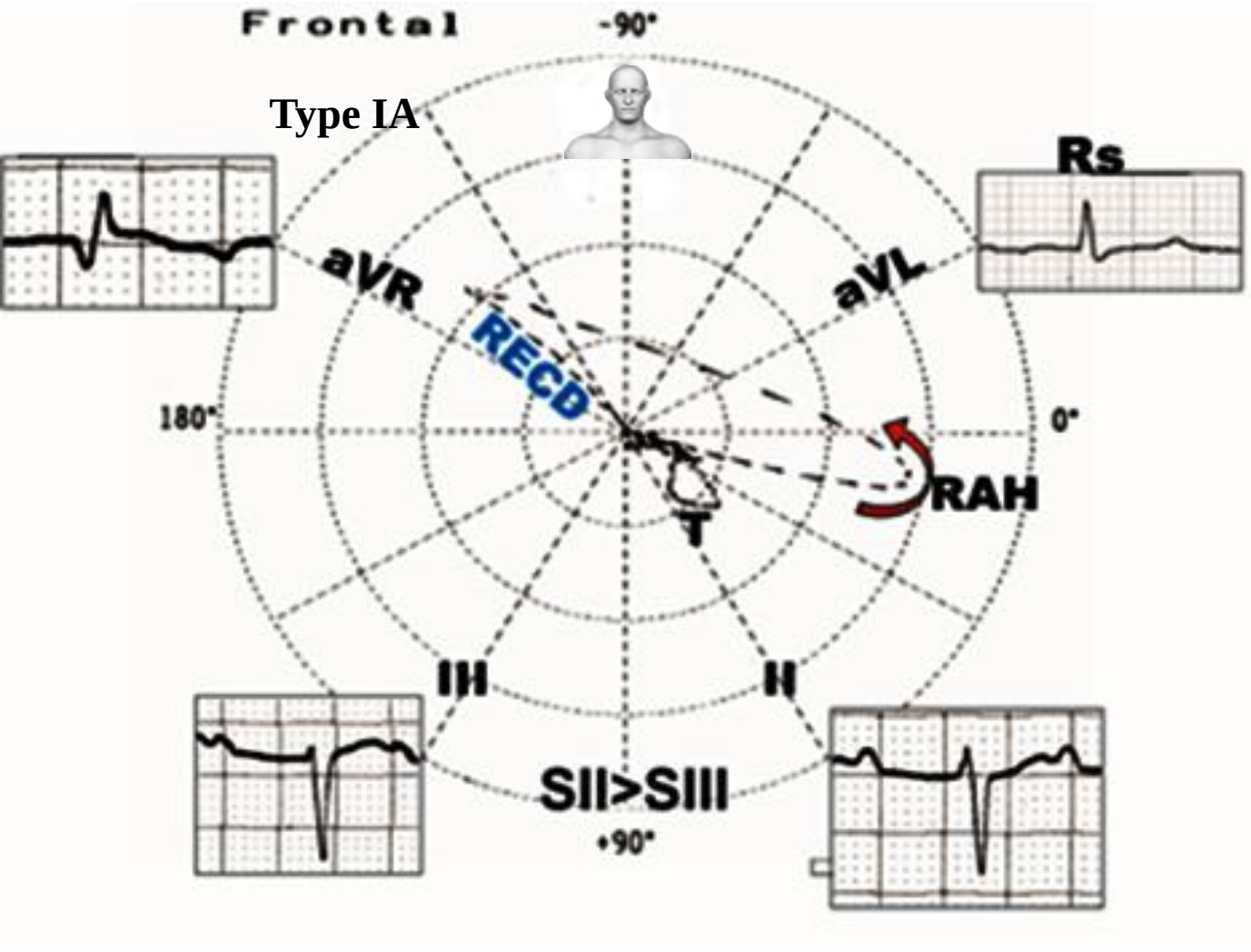
When the anterosuperior subdivision of the right bundle branch, (located in the region of the pulmonary artery infundibulum (RVOT)), is injured, the corresponding unipolar epicardial leads point out the existence of regional delay in the right ventricular activation process, limited to the structures of the ventricular outflow chamber: anterosuperior areas of the right septal mass and high right anterior paraseptal areas. In such areas, R-peak time(or intrisecoide deflextion) could be prolonged by 10 ms in average. Additionally the last ≥ 30ms of the QRS loop of vectorcardiogram shows conduction delay "Right End Conduction Delay (**RECD**)". In the presence of RASB, the resulting vector of depolarization of the basal regions of the right ventricle (3d vector) is essentially heading upward and right or leftward, from -90°, according to the position and rotation of the heart. The electrocardiographic diagnosis of RASB could yield the pattern: S_I S_{II} S_{III} and $AQRS_F$, with the latter shifted upward from the transversal axis between ±180° and 0° (**Type IA**), at the right or left from -90°, with R wave vortex slurring and R-peak time prolongation in I, aVR, V_{3R}, and sometimes in V1, and in the right chest unipolar leads of V_{4R} through V_{9R}, and slurred S waves in V_6, aVF, II and III.

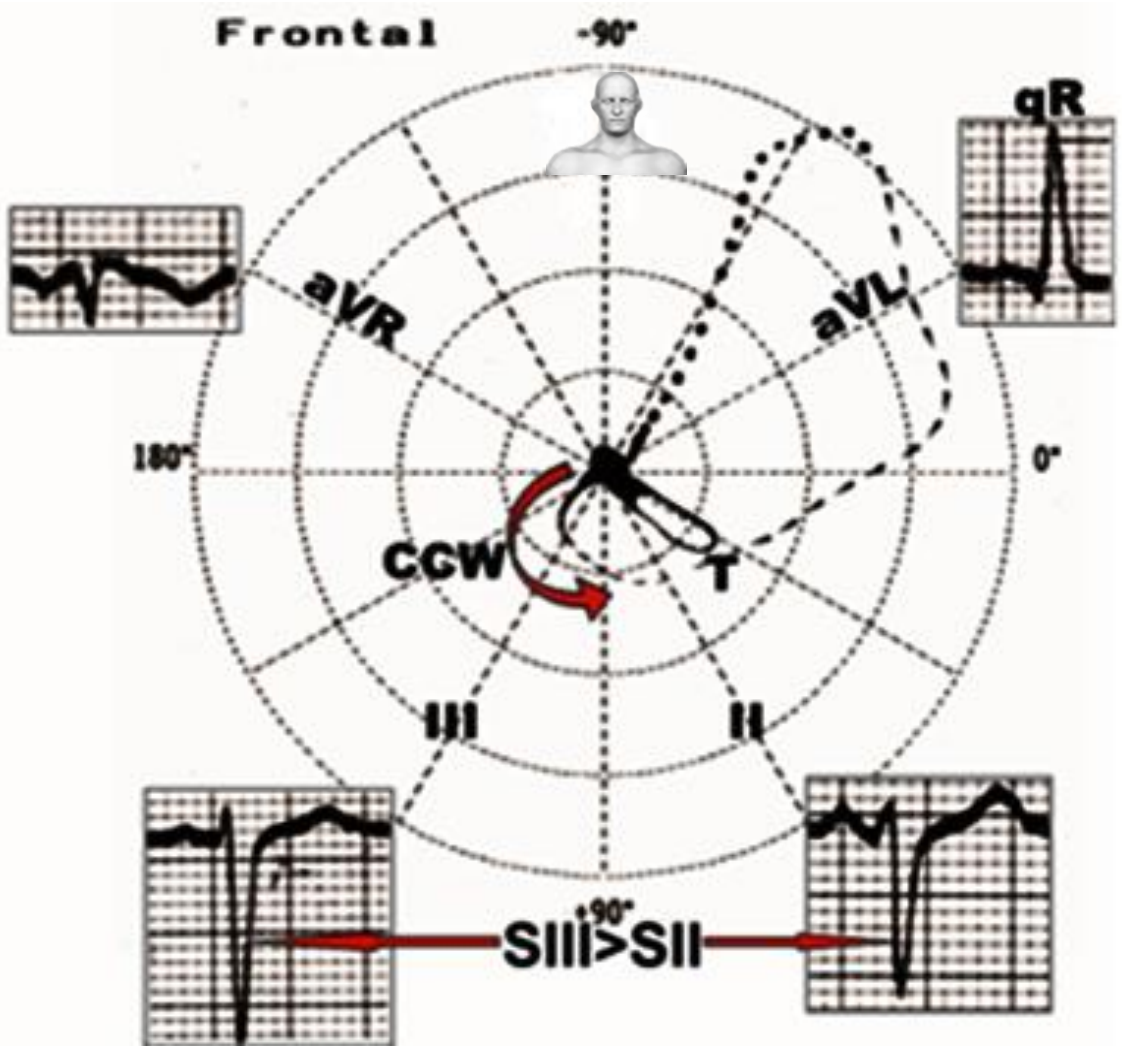
Observation: The loops (P, QRS and T) are fragmented by the action of an oscillator – which cuts the current intermittently for a known period of time, usually each dash has 2 ms (0.0002 s). The goal of this intermittent cut is to know the total duration of the loop in study, which may be estimated by multiplying the number of fragments (in the form of dashes) for the time selected (in our case 2 ms). Additionally , The greater or the lesser distance between dashes indicates the greater or the lesser conduction velocity in the area. Each dash represents a time of 2 ms or 2.5 ms, depending on the calibration of the device. Thus, when they are very close to each other, it indicates the presence of **conduction delay**. To consider the phenomenon as true, it is necessary for it to be evident in at least 2 planes.

Differential diagnosis between Right Superior Divisional Block (RSDB) type IA and Left Anterior Fascicular Block

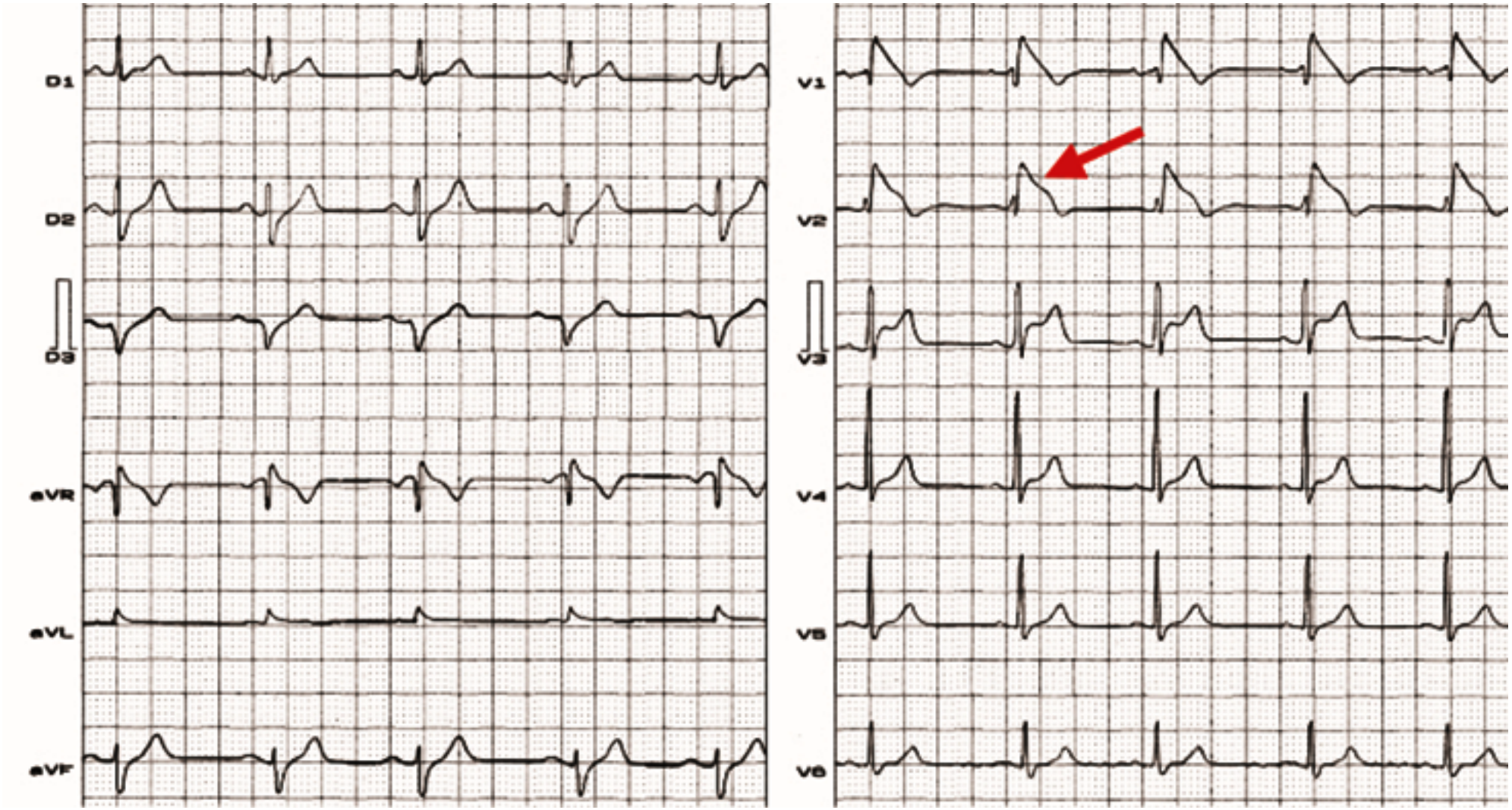
	RSDB Type IA	LAFB
10 to 20ms initial forces	Directed to left and downward	Directed to right and downward
SIII/SII ratio	SII>SIII	SIII>SII
Final R wave in aVR	Prominent	Maybe low or absent
I and aVL pattern	R or Rs	qR
QRS loop rotation in the frontal plane	Counterclockwise	Counterclockwise
Final 30 to 60 ms of QRS loop	Located on upper right quadrant near -150° with RECD very close dashes = less dromotropism*	Located on upper left quadrant
QRS loop rotation in the frontal plane	Counterclockwise rotation	Counterclockwise rotation ECD on upper left quadrant

Differential diagnosis between Right Superior Divisional Block (RSDB) type IA and Left Anterior Fascicular Block





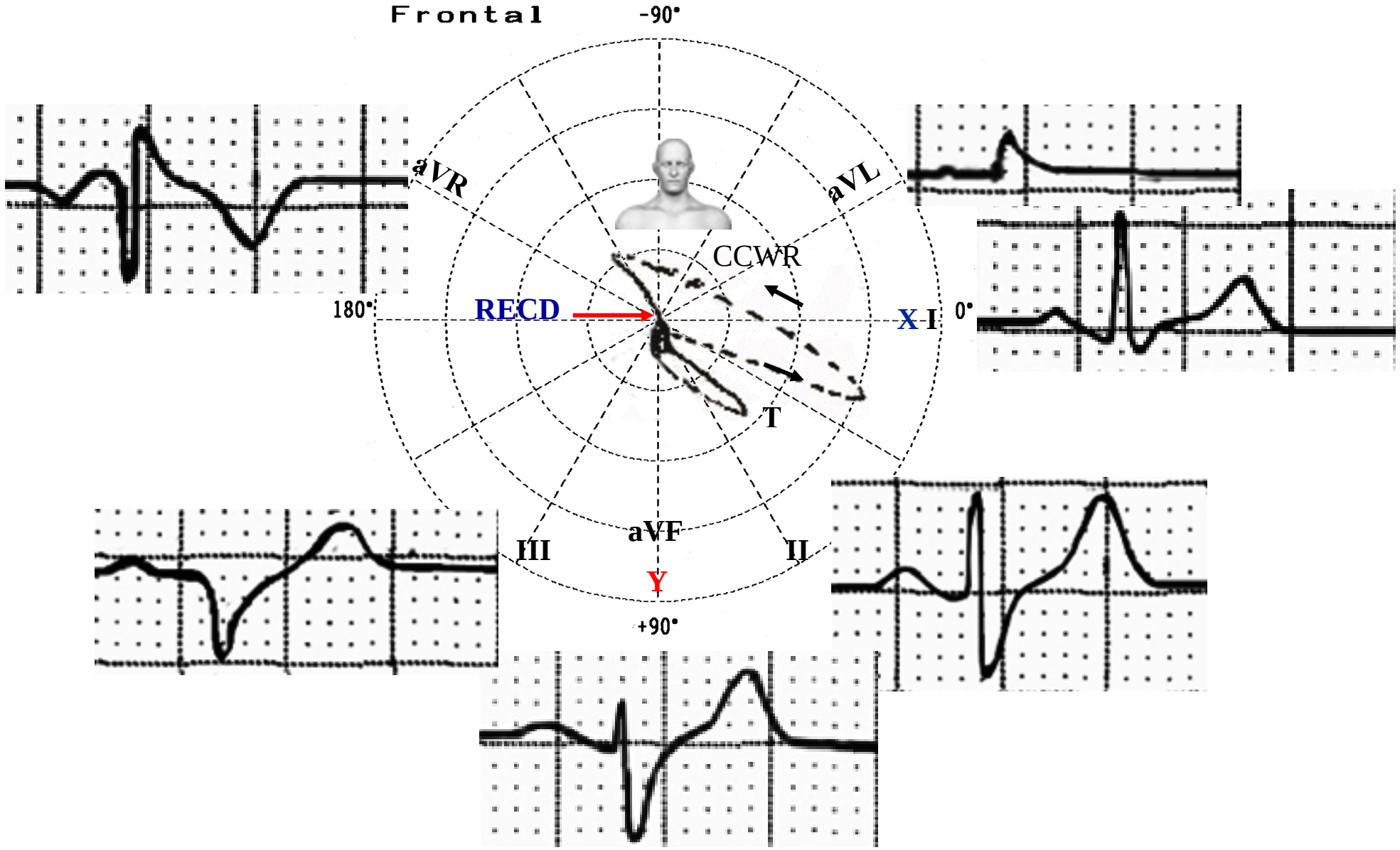
Typical example of Brugada type I and Block of Superior Division of Right Bundle-Branch (BSDRBB) Type IA (pseudo LAFB)



12-lead surface ECG shows a marked axis deviation to the left; SII > SIII and a prominent final R wave of unipolar aVR limb lead and typical type 1 BrP.

Conclusion:

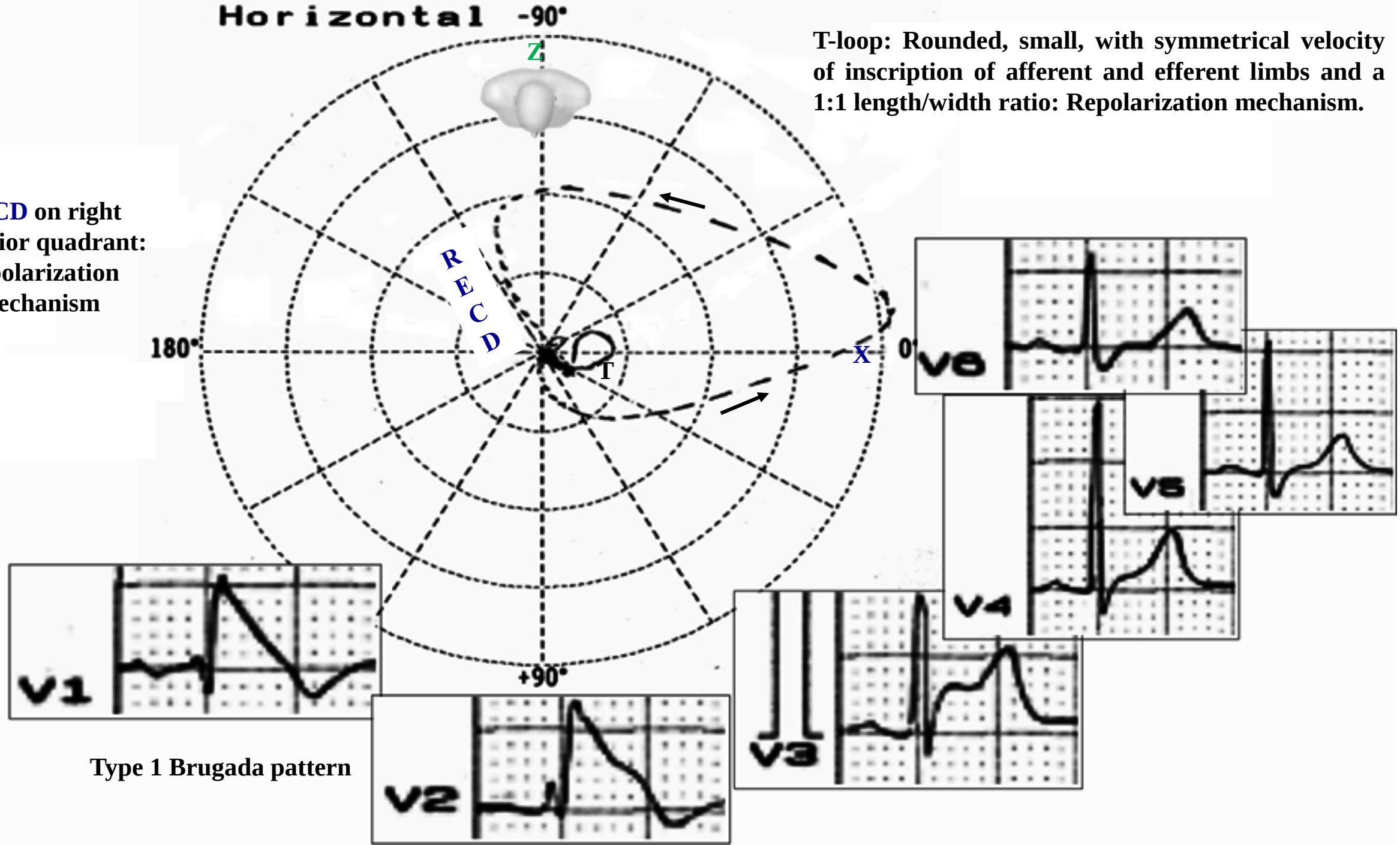
1) Block of Superior Division of Right Bundle-Branch (BSDRBB) Type IA: pseudo LAFB (see explanation in the next example)
2) Type 1 Brugada Pattern.



The 10 to 20ms initial forces are directed to left and downward (in LAFB this forces are directed to right and downward). Counterclockwise rotation(CCWR) with extreme left axis deviation, SII>SIII, prominent final R wave in aVR and prolonged R-peak time in this led ,

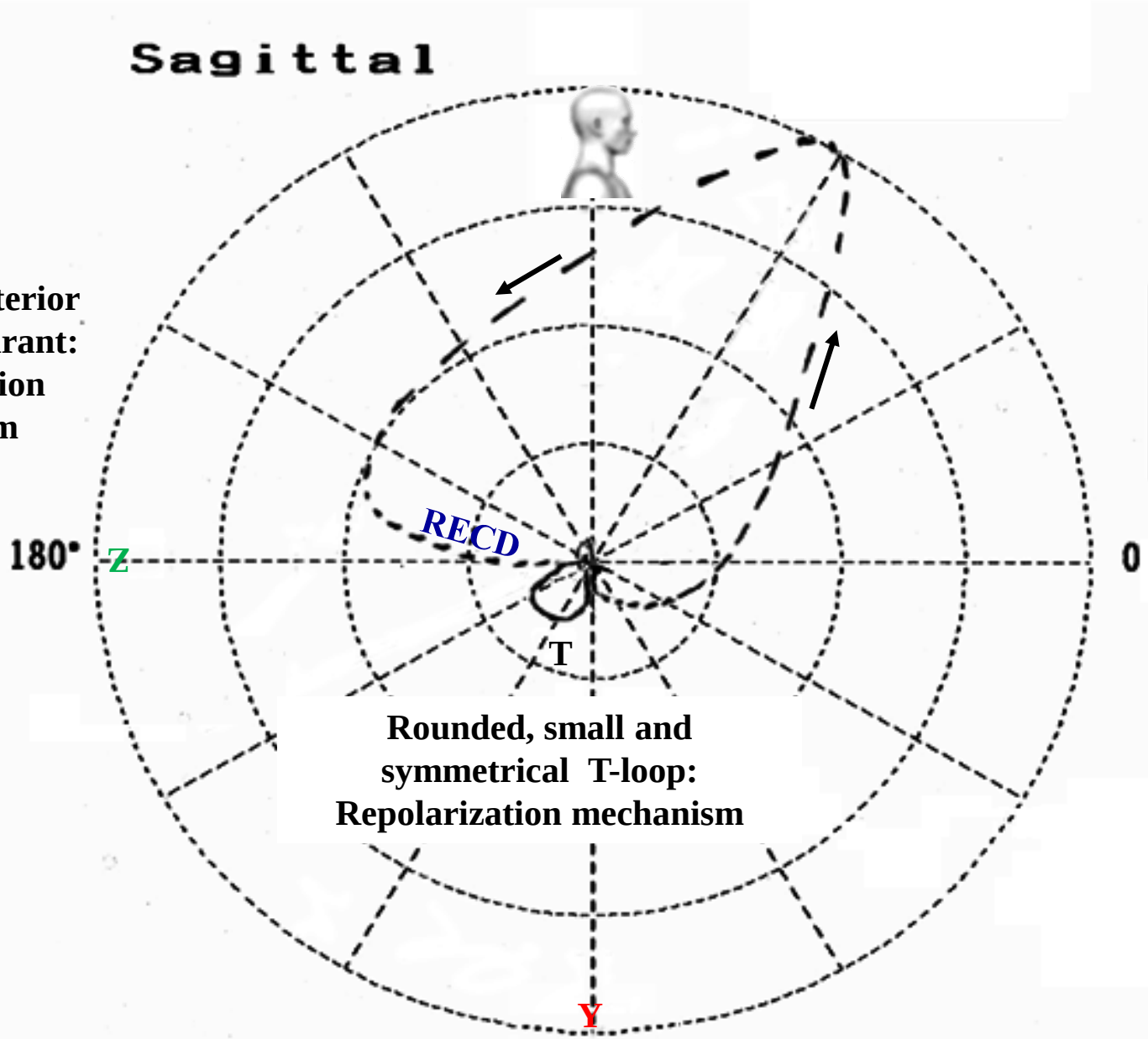
T-loop: Rounded, small, with symmetrical velocity of inscription of afferent and efferent limbs and a 1:1 length/width ratio: Repolarization mechanism.

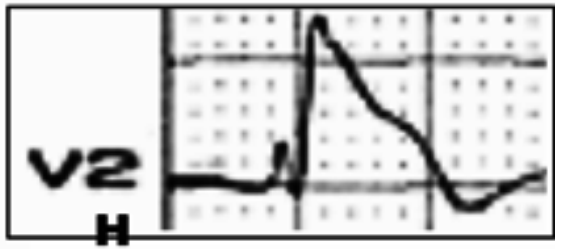
RECD on right posterior quadrant: Depolarization mechanism



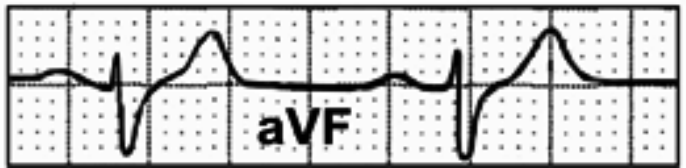
Type 1 Brugada pattern

RECD on posterior superior quadrant: Depolarization mechanism





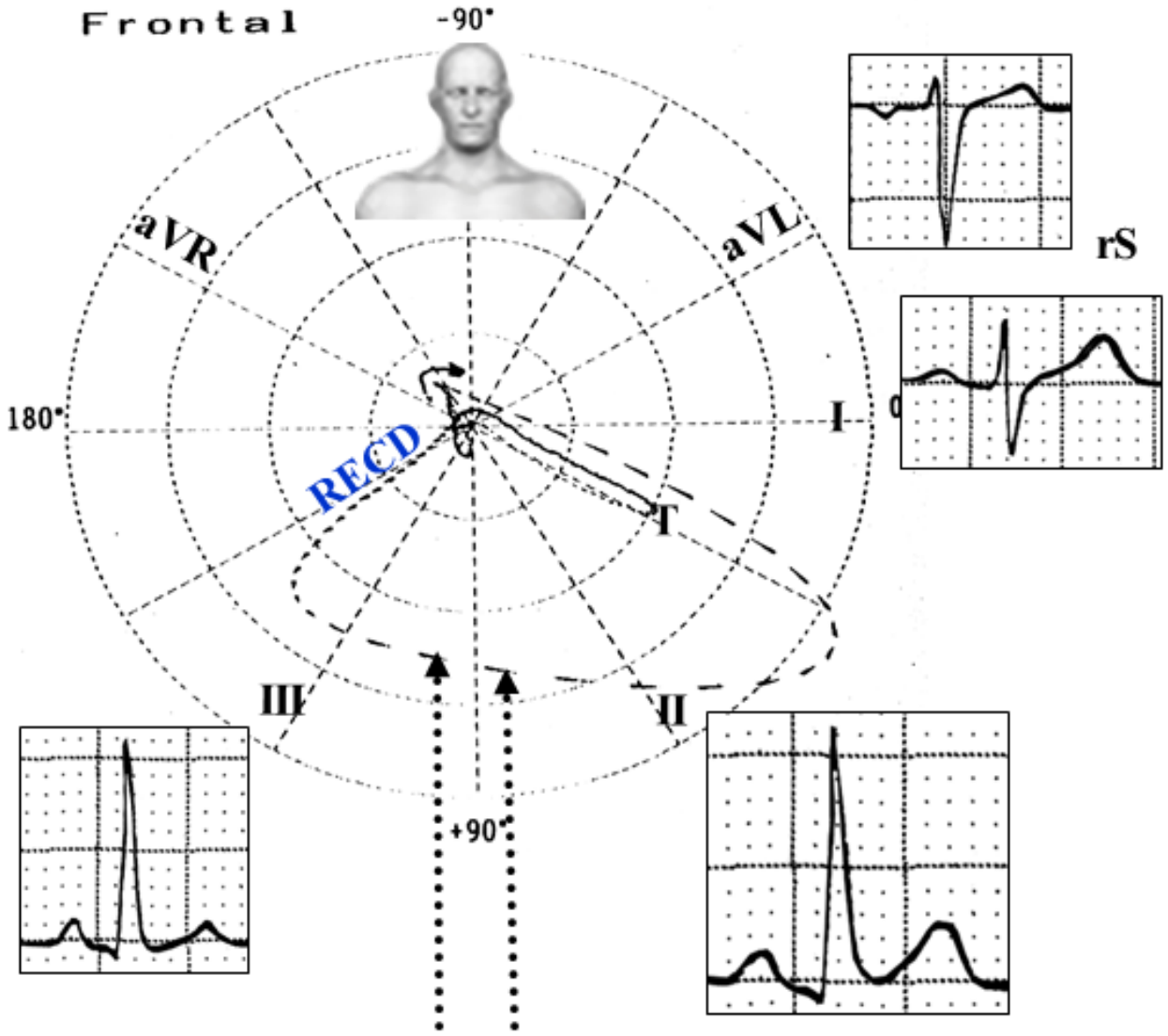
Rounded, small and symmetrical T-loop: Repolarization mechanism



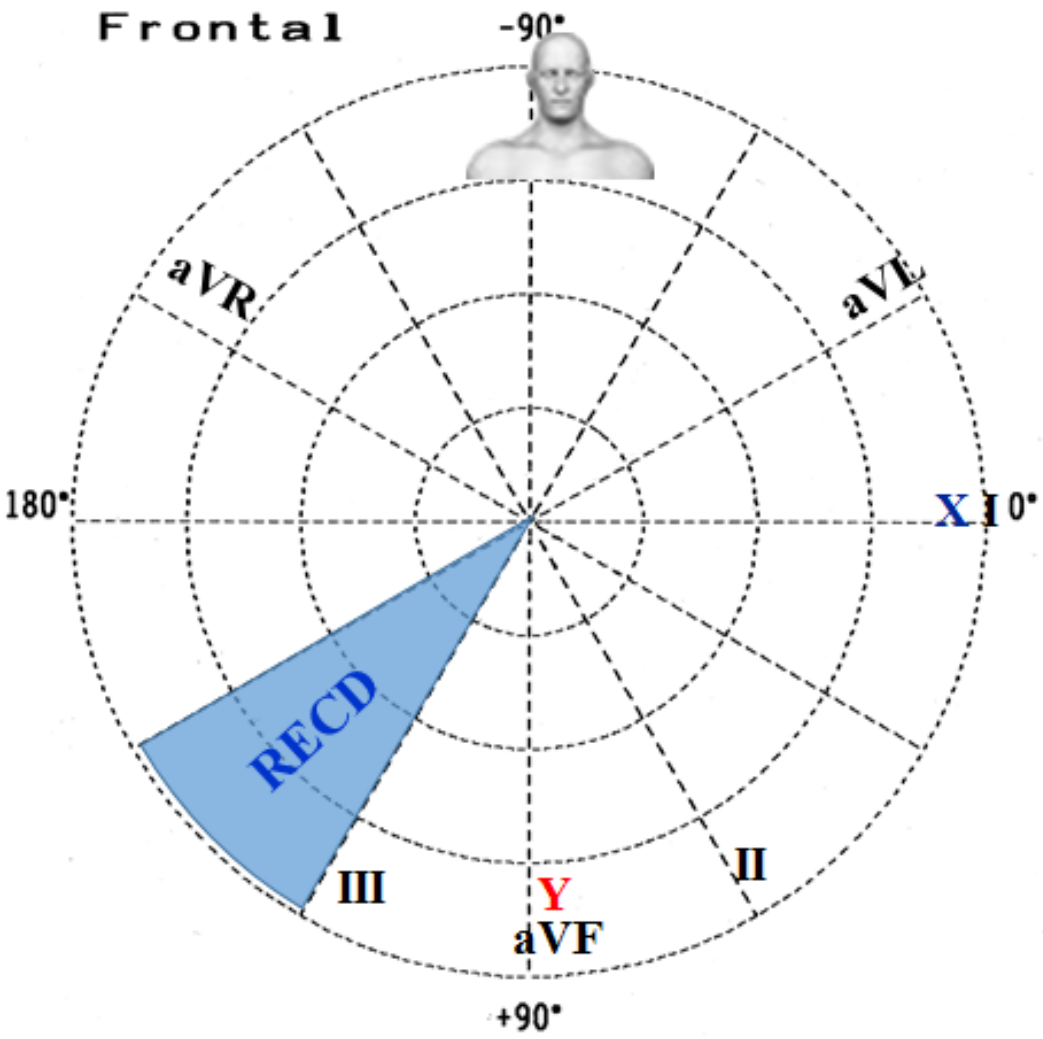
Type II RECD or Right Posteroinferior Subdivision Block (RPSB)

In this variant the **RECD** is located in the right inferior quadrant, in the territory of the inferior fascicle of the right bundle branch or right posterior subdivision block (RPSB) (**de Micheli A 1988**). SÂQRS$_{FP}$: +95°. SI-RII-RIII pattern (RIII < 15 mm). I and aVL: rS, II and III: qR. The descending ramp of R wave is slightly slow. It may present differential diagnosis with LPFB. Surface ECG suggests RPSB or type II RECD when delay and slowness of right ventricular myocardial depolarization signs (R-wave slurring and R-wave peak time prolongation) become evident only in the leads exploring the posterior and mid-inferior lateral regions of the free right ventricular wall. In this case, the resulting vector of homolateral ventricular activation is heading to the right, below and back from its origin point. There is QRS complex slurring in V_{3R} and V_1, also in aVF and in the high right abdominal lead MD, if the cardiac position is horizontal. Likewise, S wave slurring is observed in V_5 and V_6. Further, there should be a significant difference between R-wave peak time from the affected regions and that from the right anteroinferior septal mass (R-wave peak time in V_3 and/or V_4). In absence of right ventricular hypertrophy, such difference should be ≥ 30 ms. This is considered even more significant when the manifestation time of vector 2s is normal: between 20 and 25 ms (healthy hearts or with a single right ventricular dilatation) (**Medrano 1978**). Usually, right chest leads V_{5R}, V_{4R} and V_{3R} explore the posterolateral portions of the right ventricular free wall; while V_3 and V_4 remain facing the interventricular septum (intermediate cardiac position). But in horizontal hearts, it is the low leads (particularly aVF) that explore the low posterolateral regions of the right ventricular free wall. The resulting vector from ventricular activation manifests around 60 ms after the activation starts, and heads ≈+125° in the frontal plane.

Type II RECD or Right Posteroinferior Subdivision Block (RPSB) ECG/VCG correlation on frontal Plane



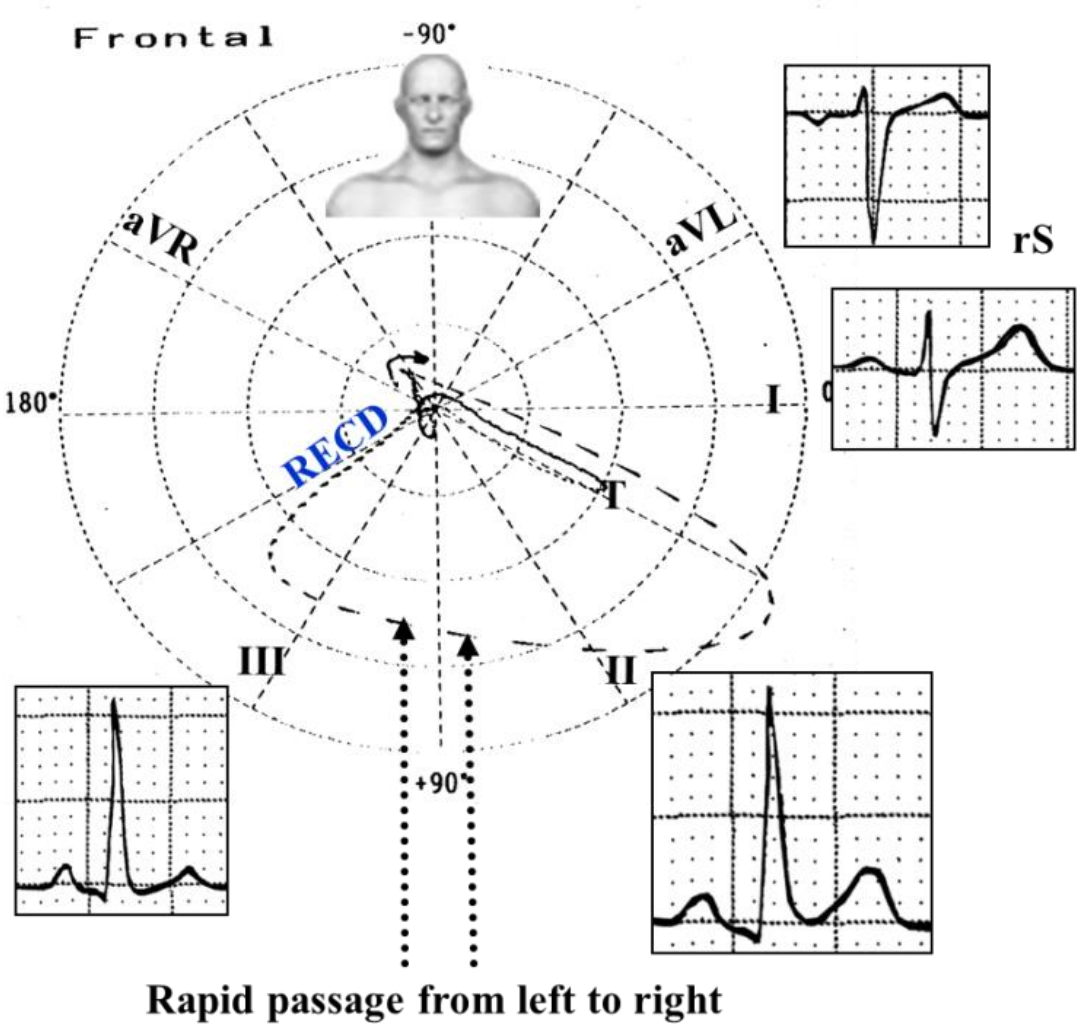
Location of RECD in RPSB



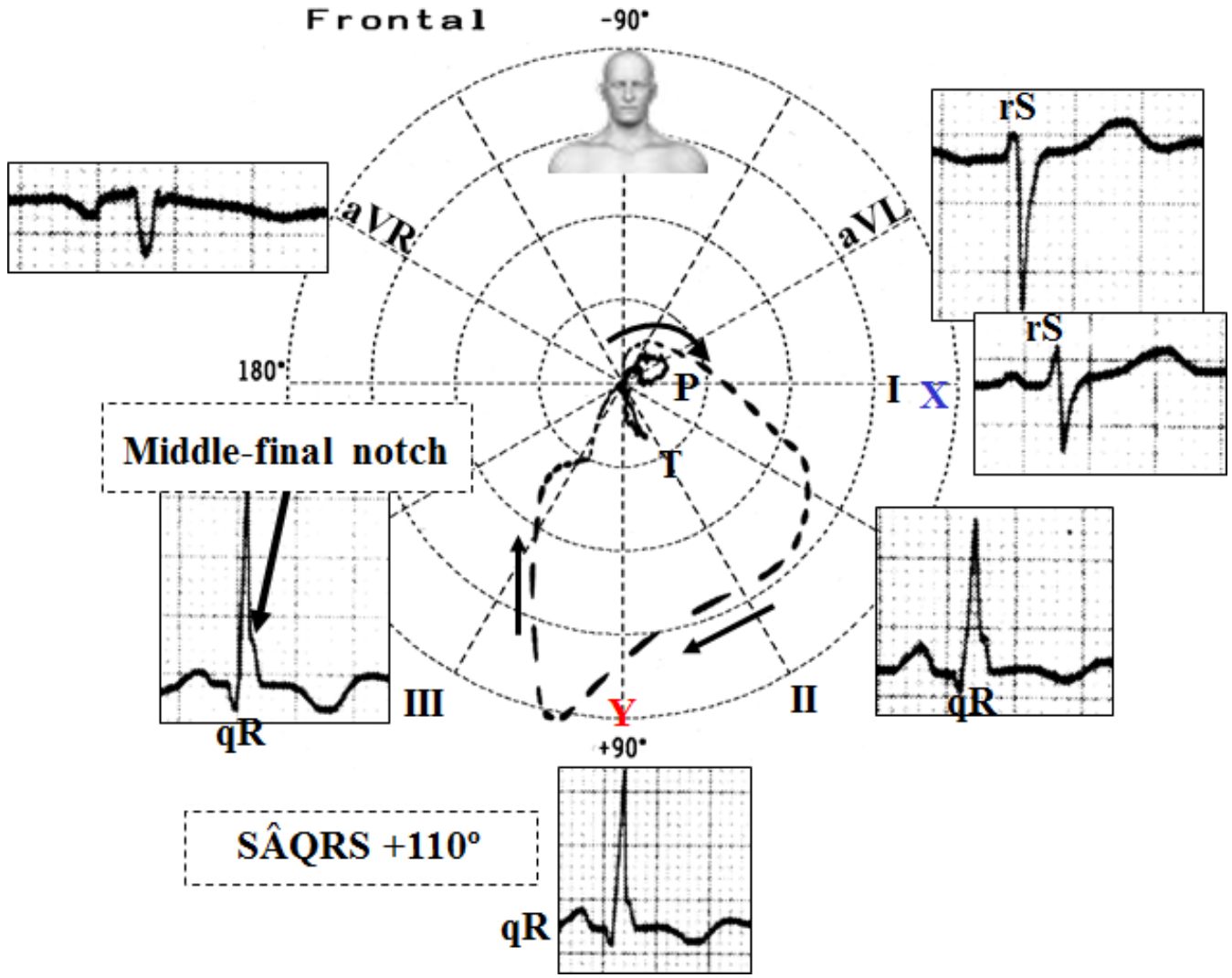
ECG/ VCG features are very similar with the LPFB: See differential diagnosis in next slide table

	Type II RECD or RPSB	LPFB
R-peak time in aVF, V5 and V6	Normal	Increased: > 35 ms (**Rusconi 1980**)
R-peak time in aVL	Normal	Decreased: up to 15 ms.
Aspect of QRS loop in the frontal plane	CWR and with characteristic rapid passage from left to right between 30 and 50 ms.	CWR, aspect of "fat" loop and maximal vector close to + 120°.
Clinical factors that should be excluded	Not stated.	Vertical heart, RVH and lateral infarction.
Association with RBBB		It is the rule
Notch in the descending limb of the R wave in III	No	Characteristic
Middle-final notch in RIII	No	Yes
RII/RIII voltage ratio	RII > RIII	RIII > RII
The q wave in III/ q wave in II ratio	qIII > qII	qIII < qII

Type II RECD or RPSB

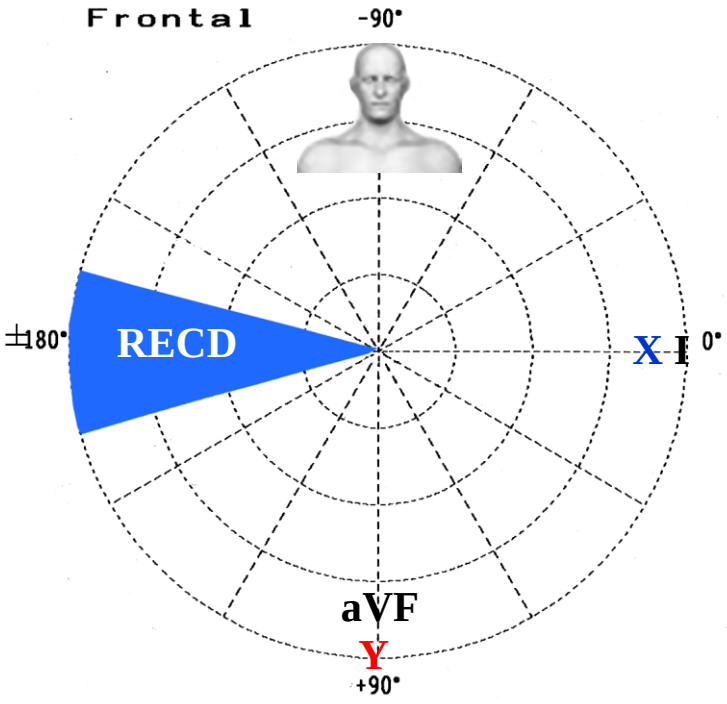


LPFB

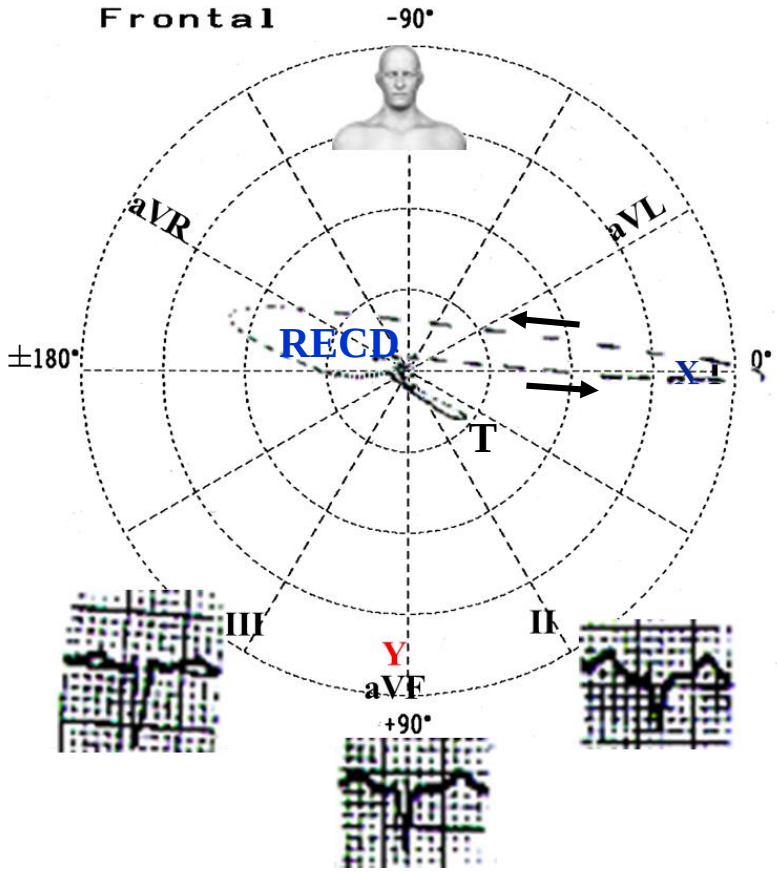


Type III, does it exist?: **RECD** located on the right portion of the 0±180° line, corresponding to the territory of distribution of the hypothetical middle fascicle of the right bundle branch. **RECD** located in the territory of the middle or anterosuperior fascicle of the right bundle branch, i.e. very close of ±180° on X orthogonal lead. It may be called Right Middle Fascicle Block (RMFB). Type III existence is polemic.

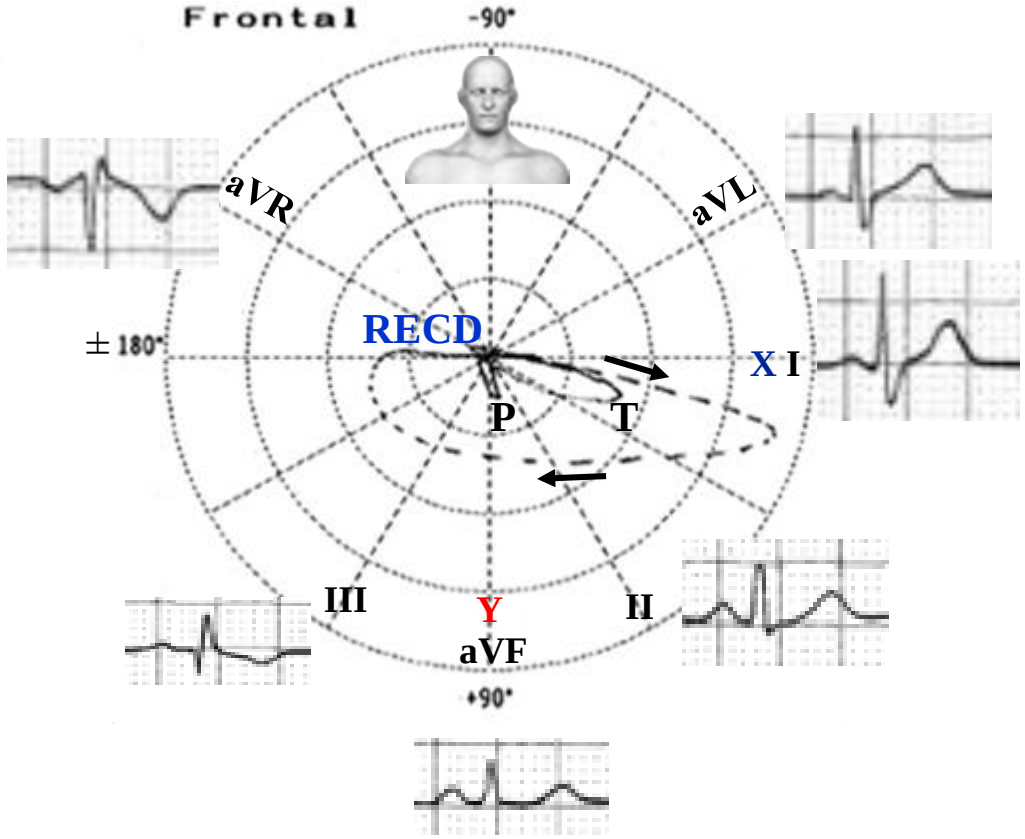
Type III



Subtype IIIA: CCWR



Subtype IIIB: CWR



Pseudo inferior myocardial infarction

CCWR: QRS loop with counterclockwise rotation. This subtype has a pattern very similar with myocardial inferior infarction CWR: QRS loop with clockwise rotation

The clinical significance and interest of right divisional or fascicular peripheral right bundle block

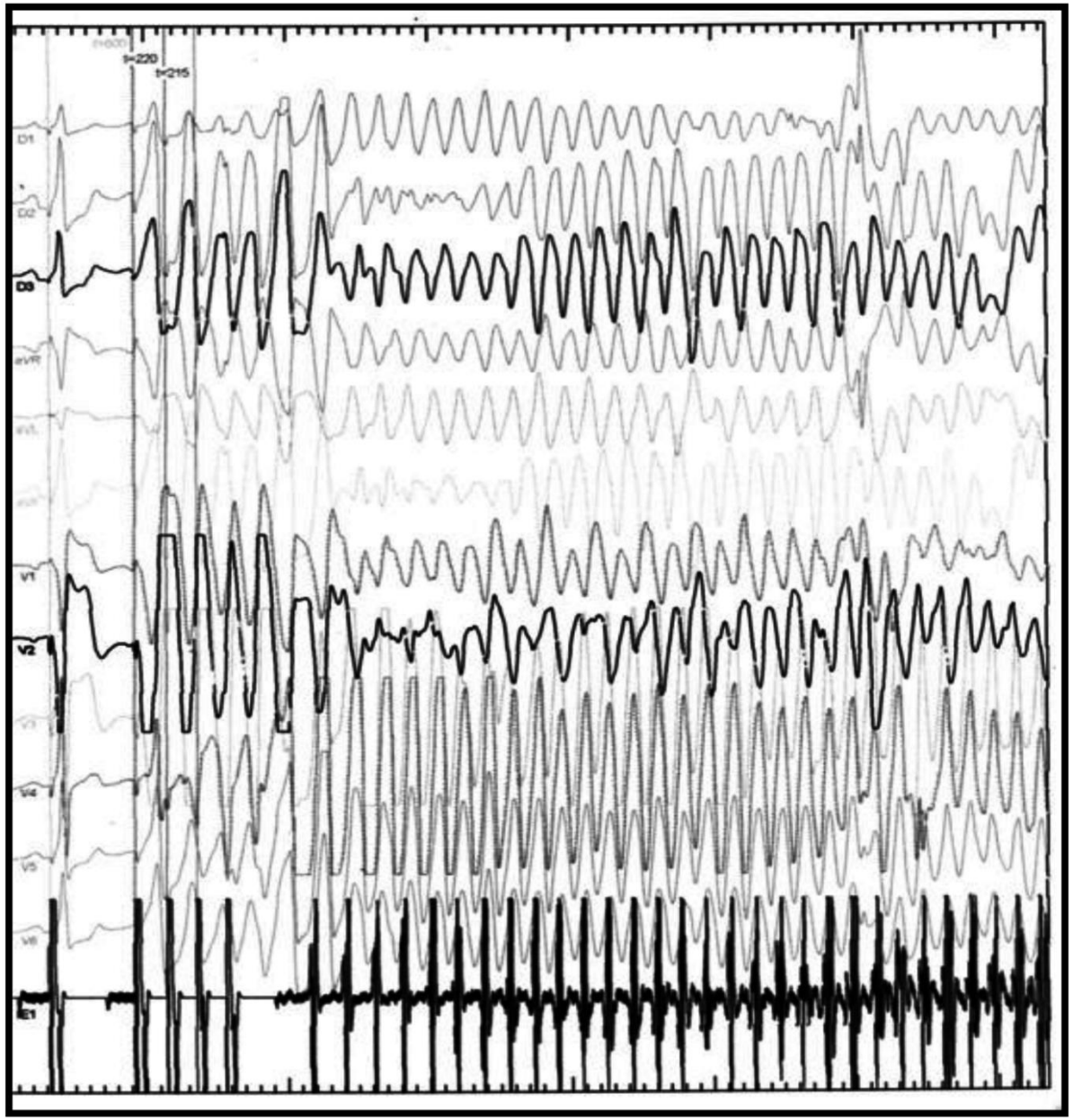
I. They may be confused with left fascicular blocks:
   - *Left Anterior Fascicular Block: with the type IA or right superior divisional/fascicular block (RSDB) with counter clock wise rotation on frontal plane) and*
   - *Left Posterior Fascicular Block: with the type II or right inferior divisional/fascicular block (RSDB) on frontal plane.*

II. They may be confused with electrically inactive areas (pseudo electrically inactive areas or pseudo myocardial infarction) both in the anterior and the inferior walls.

III. They may represent the ECG/VCG pattern of Brugada syndrome (**Pérez-Riera 2008**), of one subpopulation of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia(ARVC/D (the so called concealed forms) (**Corrado 1996; Corrado 2001**) and also observed in chronic chagasic cardiomyopathy (**Vichi 1982; Tobias 1986**). Corrado et al investigated members of a single family who possessed the type 1 ECG BrP. Cardiac histopathological examination in the proband revealed myocardial atrophy, transmural fatty replacement, interstitial fibrosis (including fibrosis involving the specialised conducting tissue), although no wall thinning or inflammatory infiltrates associated with classical ARVC were seen. An older sibling had moderate RV dilatation, apical trabecular changes and his right endomyocardial biopsy showed moderate fibrofatty replacement. Some other members of the pedigree had mild to moderate RV and/or RVOT dilatation, wall motion abnormalities and a trabecular pattern on echocardiography. The findings in this family, although not typical of classical ARVC, possess enough pathological features to suggest that there may be a relationship between BrS and ARVC, illustrating the issue of diagnostic classification in the presence of both a typical type 1 ECG and marked structural abnormalities. The suggestion that BrS may actually be a form of ARVC in view of the increasing evidence of structural abnormalities, has been raised. Significant overlap between the two conditions does exist: ajmaline has provoked type 1 changes in ARVC patients (**Peters 2004**), and fibrofatty replacement of cardiac myocytes has been reported in patients diagnosed with BrS (**Zumhagen 2009**).

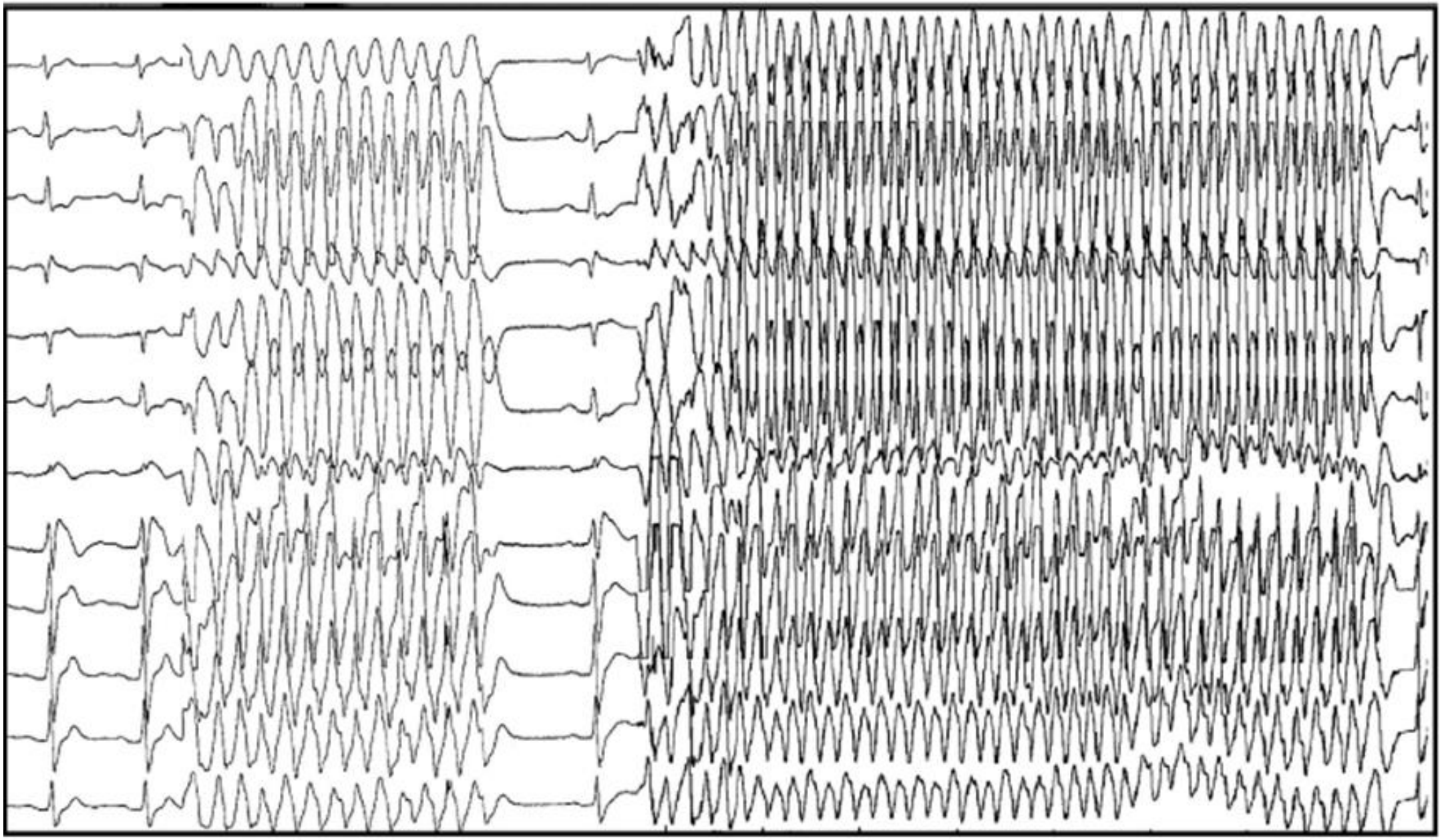
Intracardiac electrophysiological study (EPS)

Electrophysiological study (EPS) included basal measurements of conduction intervals and programmed ventricular stimulation (PVS).



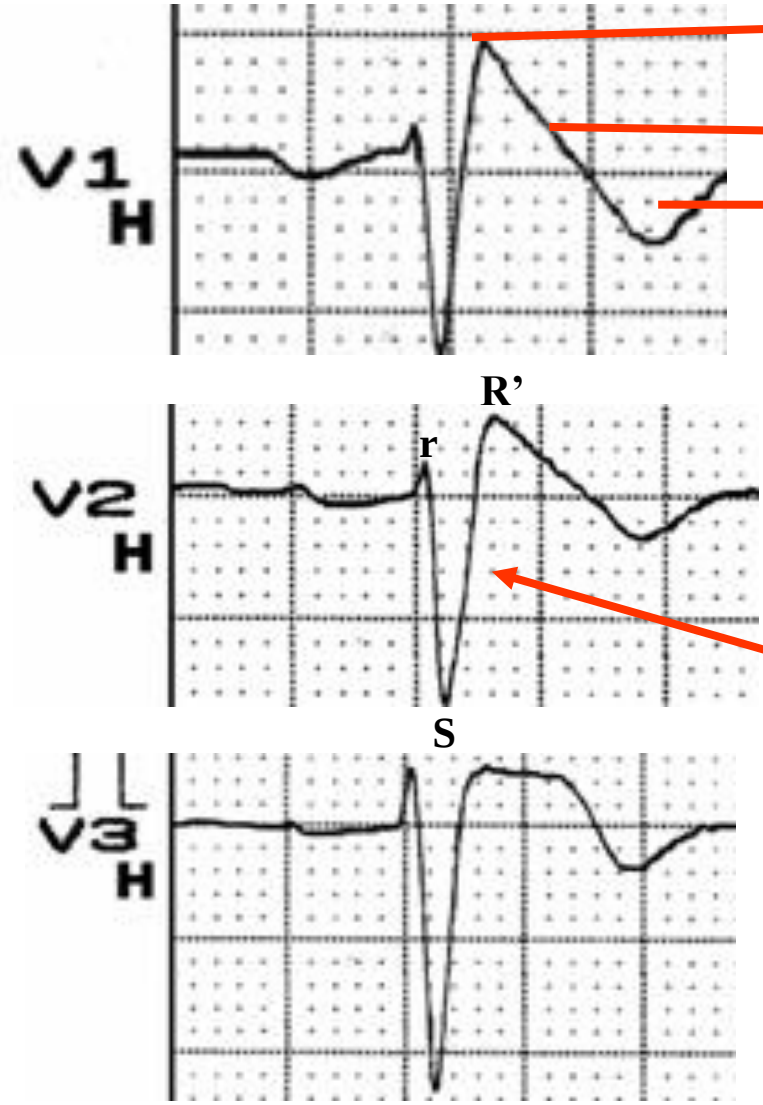
ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during PES(inducible patients). Class IIb

Programmed ventricular stimulation (PVS) conducted to polymorphic VT induction that degenerated into VF.



The trace shows two non-sustained episodes of very fast monomorphicventricular tachycardia (NS-MVT) triggered by premature ventricular contractions (PVCs) with the same morphology and equal very short-coupled interval approximately 360ms (R on T phenomenon). The PVCs fall at the relative refractory period (end of phase 3 of the monophasicaction potential.).

Signature ECG-changes in Brugada syndrome



High take-off

J point ST Segment Elevation ≥ 2mm

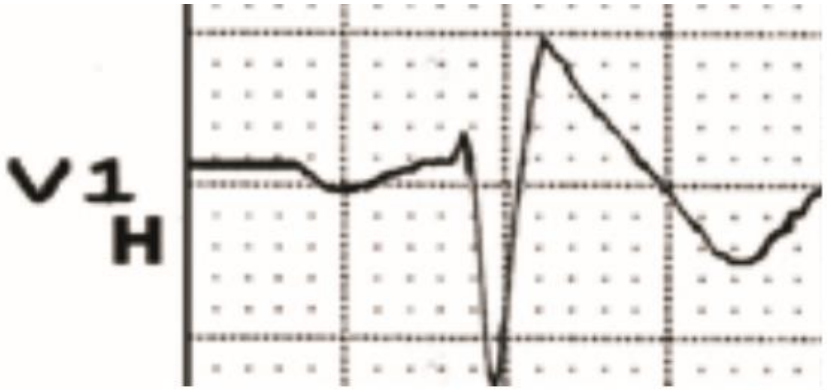
negative T wave

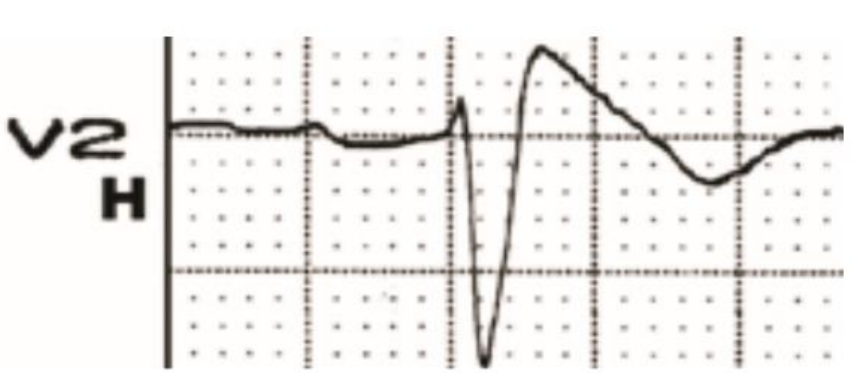
Type 1 ECG
Brugada patten

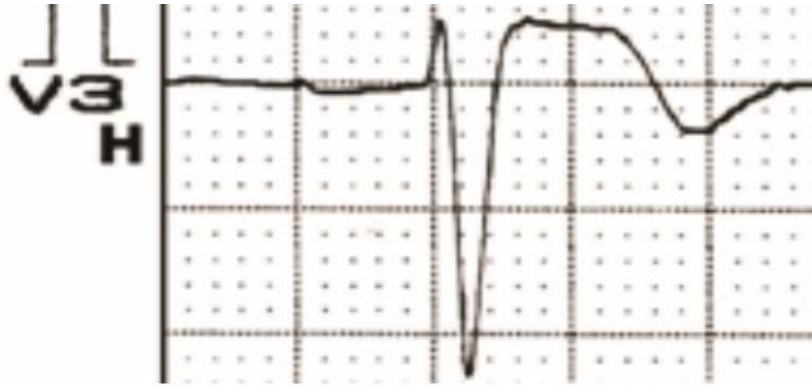
Triphasic QRS complex
rSR'

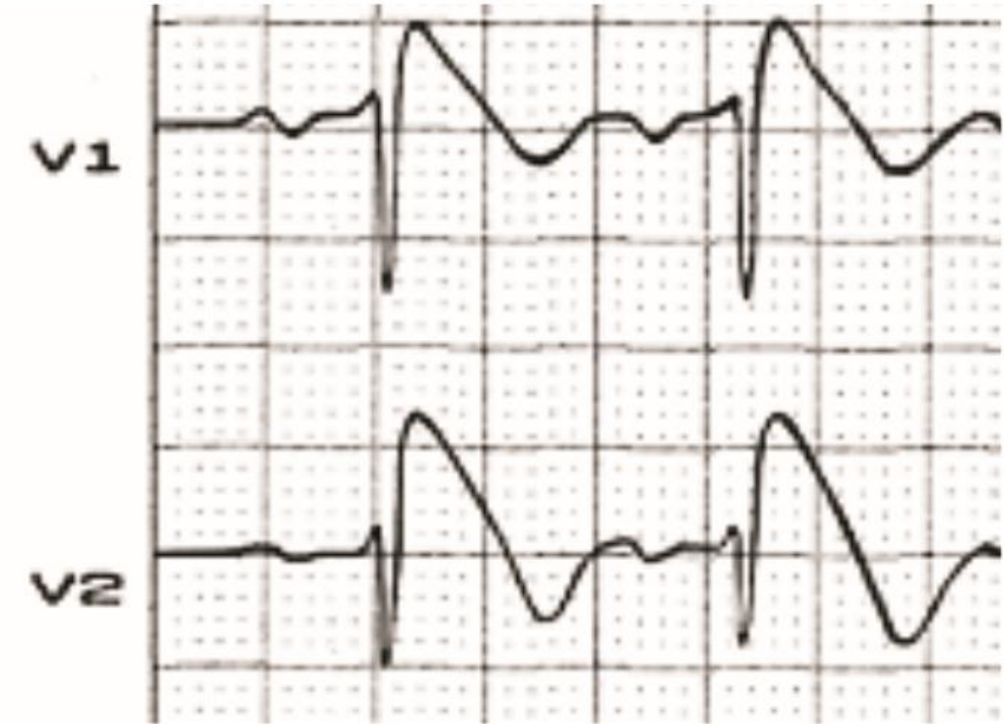
RBBB?

Shape of Type 1 Brugada ECG pattern









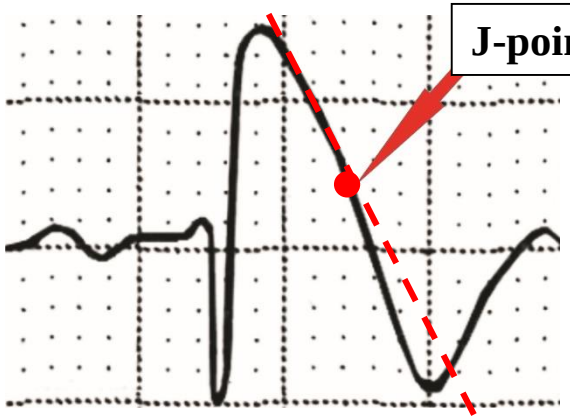
Type-1 electrocardiographic (ECG) Brugada pattern: J point and ST segment elevation ≥2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on right precordial leads (V_1-V_2 or from V_1 through V_3) and/or high right precordial leads V_{1H}, V_{2H} and V_{3H}.

Proposal of classification of type 1 Brugada pattern

Right precordial leads

Subtype 1A

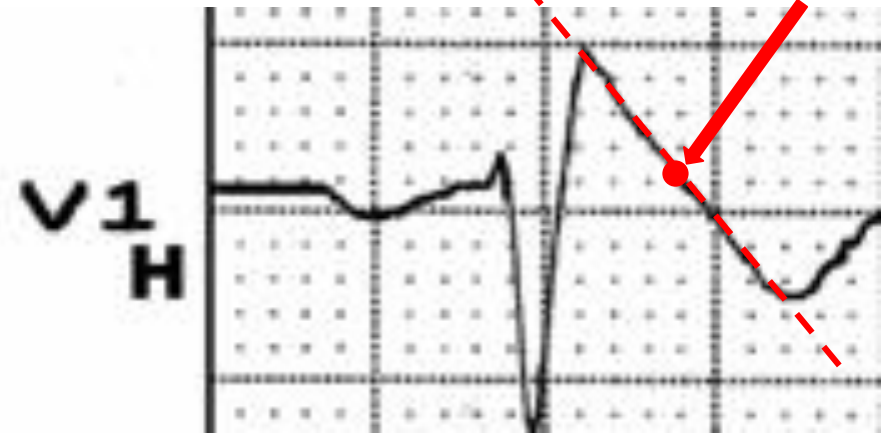
STSE convex upward



The dotted line is tangent line

Subtype 1B

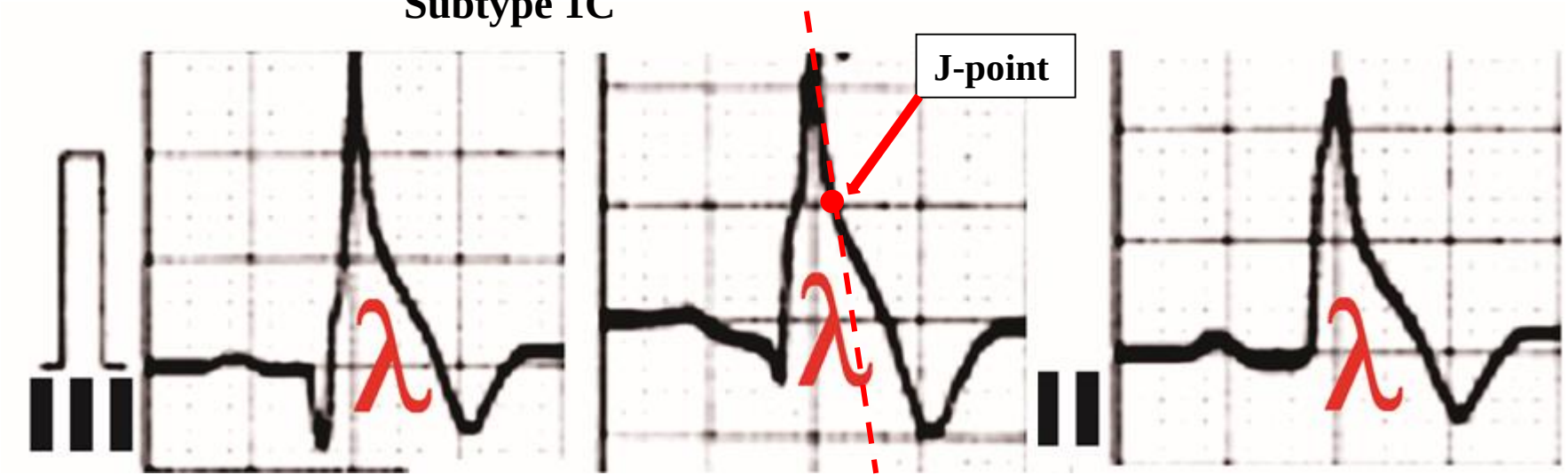
STSE rectilinear oblique descendent



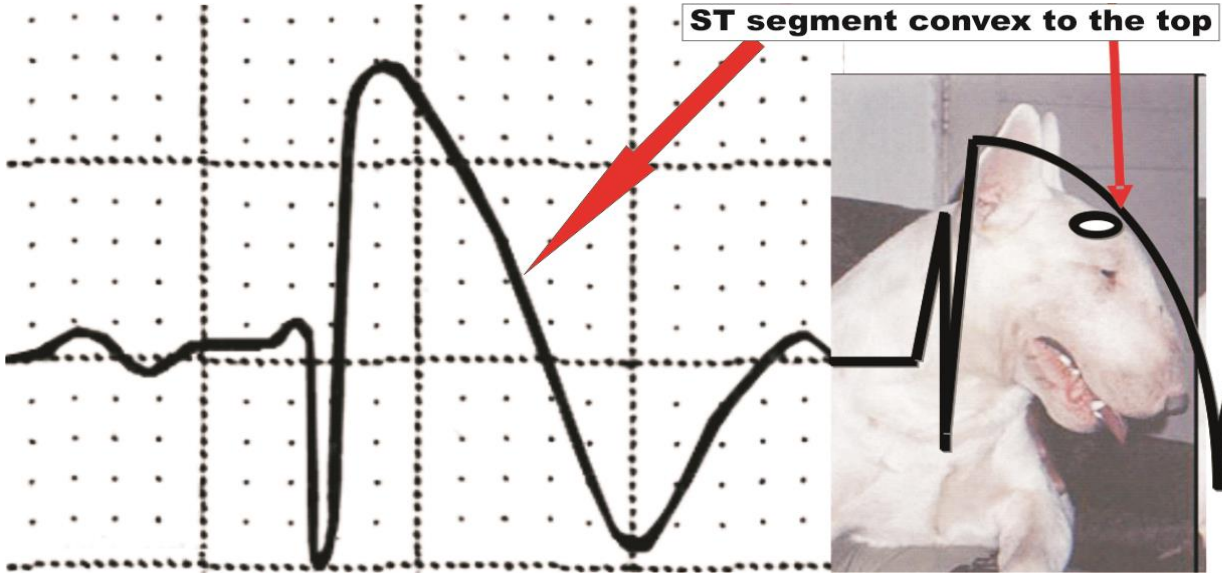
The dotted line is tangent line

Inferior leads

Subtype 1C

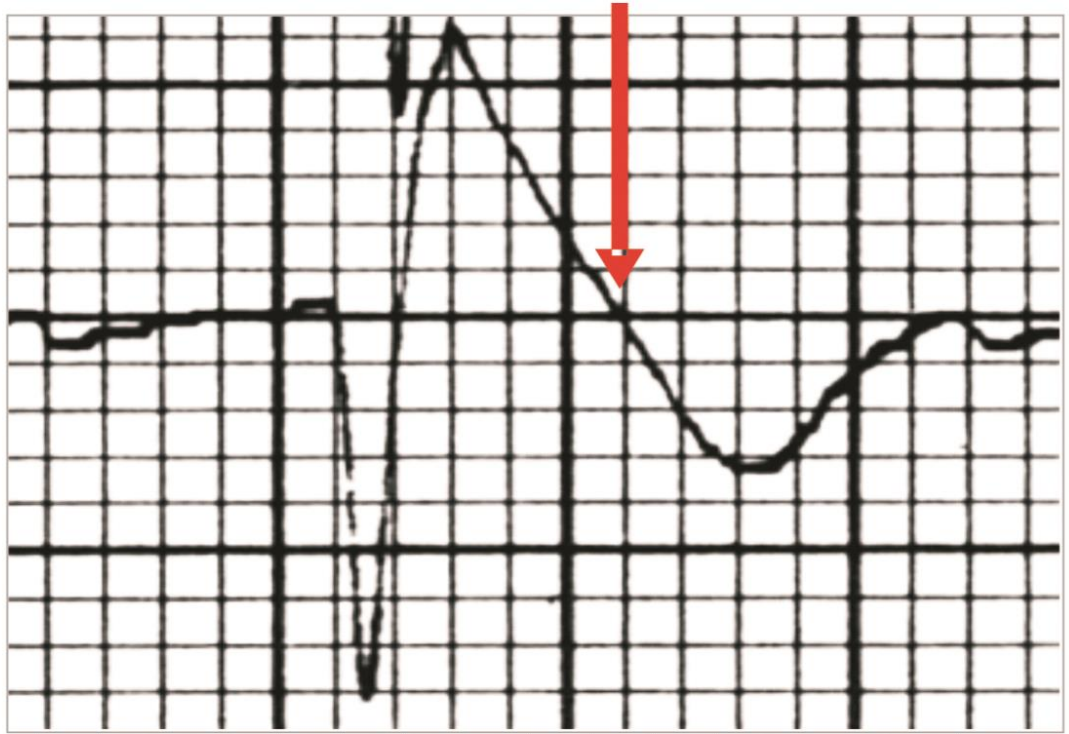


See next slide



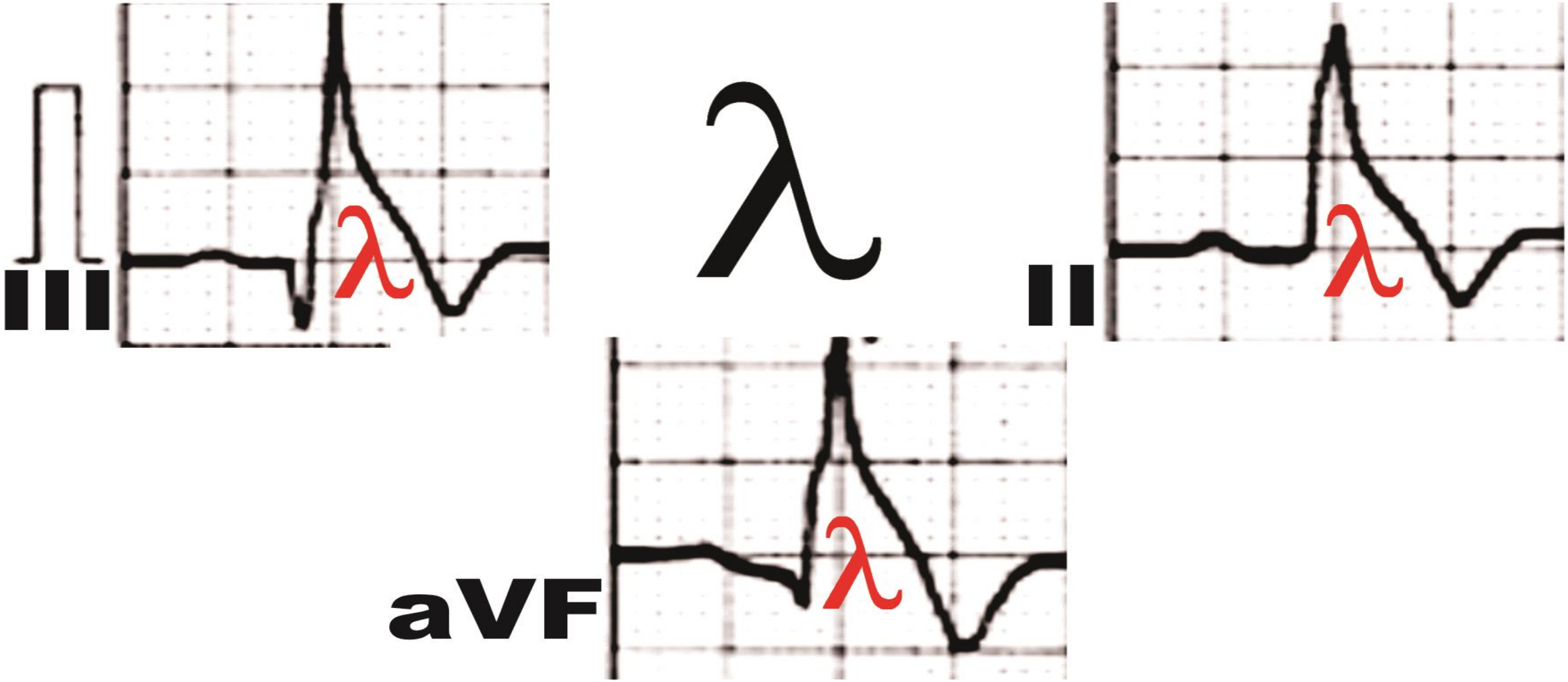
Subtype 1 or “English Bull Terrier shape”

ST segment
descending oblique rectilinear

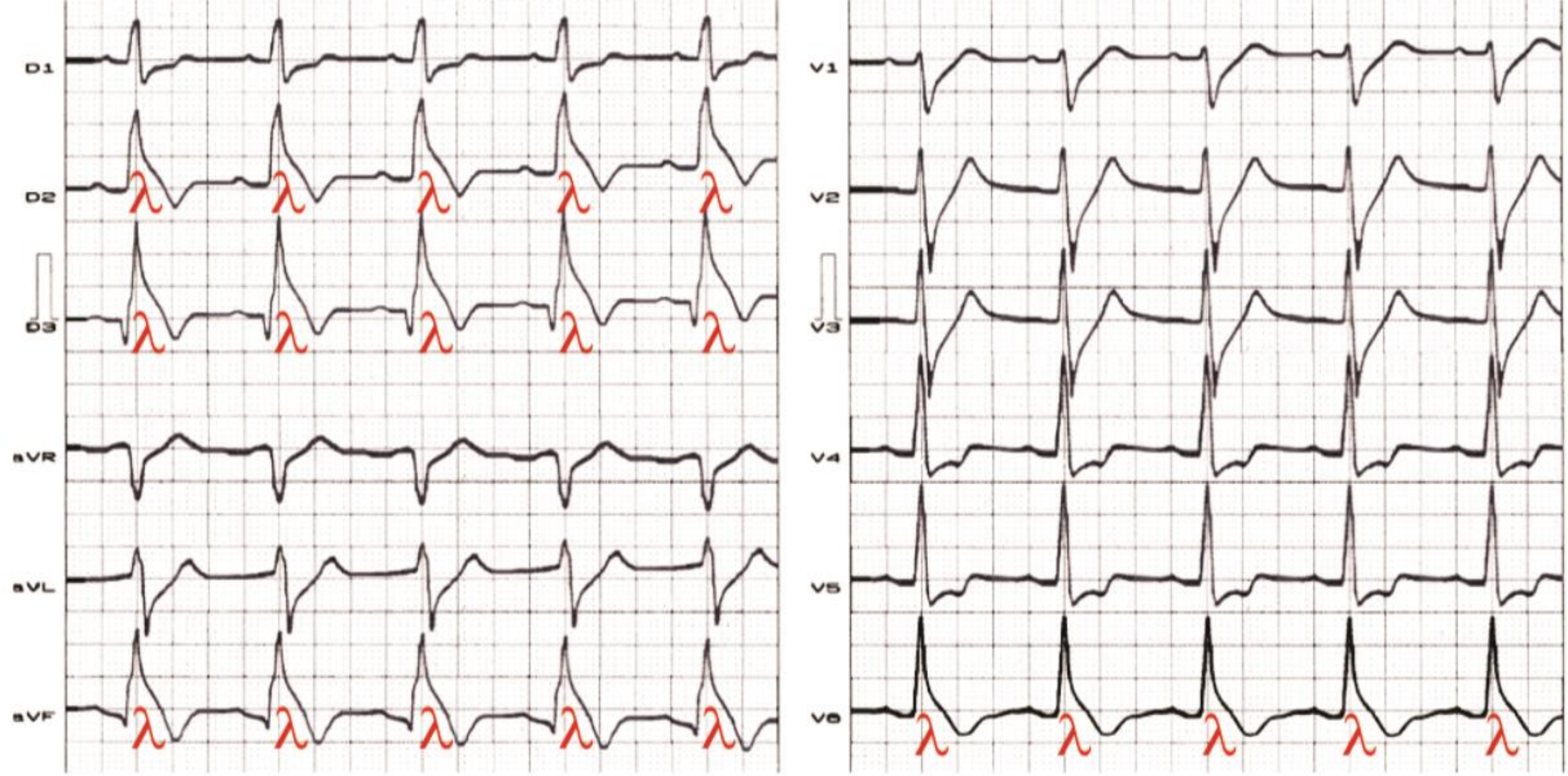


Subtype 2

Subtype 1C

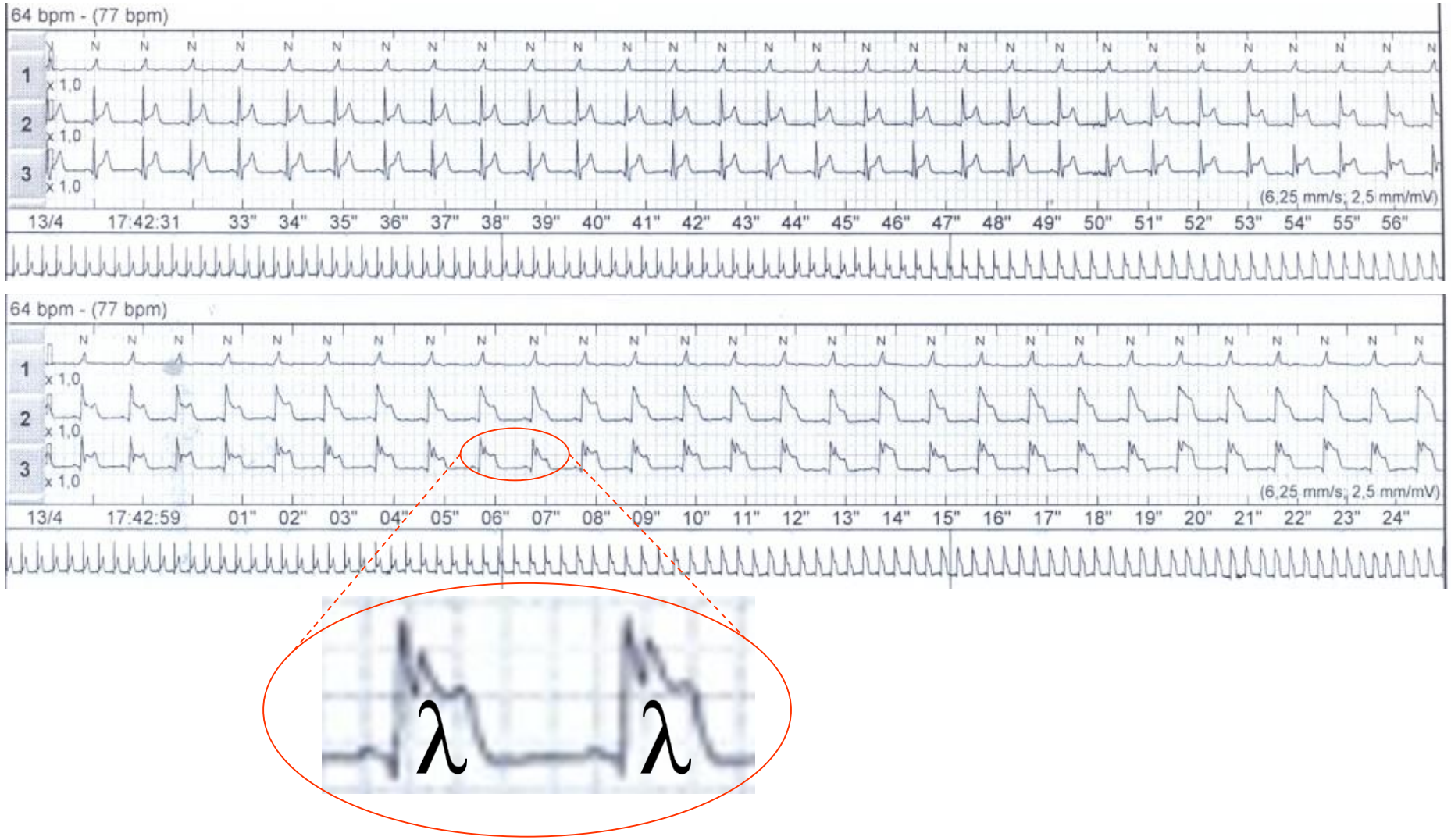


Subtype 1C: J point and ST segment elevation ≥2 mm in inferior, lateral, or inferolateral wall, with an aspect resembling the Greek letter lambda.(**Gussak 2004; Riera 2004**). This pattern is associated with high tendency to ventricular fibrillation, also in the site of acute coronary syndrome (**Kukla 2008**). We observe lambda wave pattern in the site of variant angina or prinzmetal angina. See next slide.



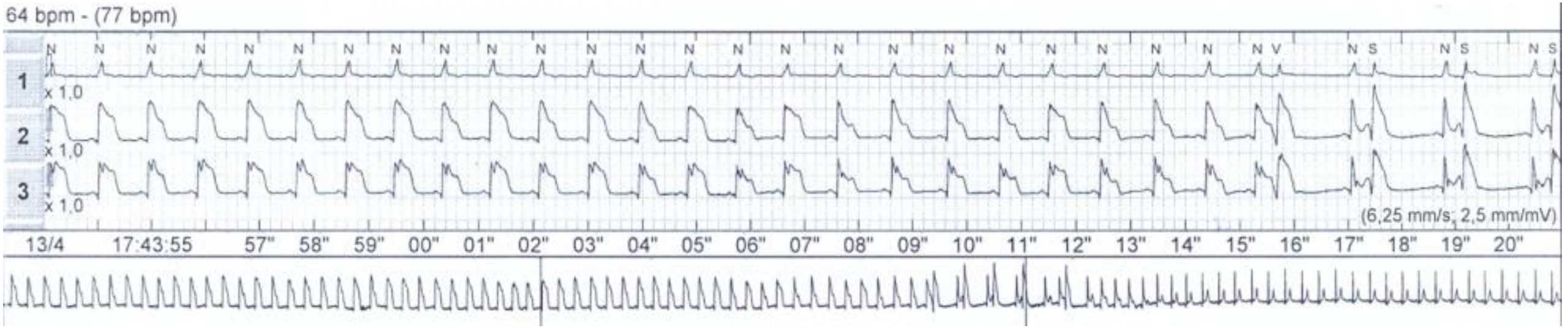
The ECG shows persistent ST segment elevation in the inferior and apical leads, associated to concomitant reciprocal or mirror image in the anterior wall that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia (**Riera 2004**).

Lambda wave registered in variant angina (Prinzmetal)

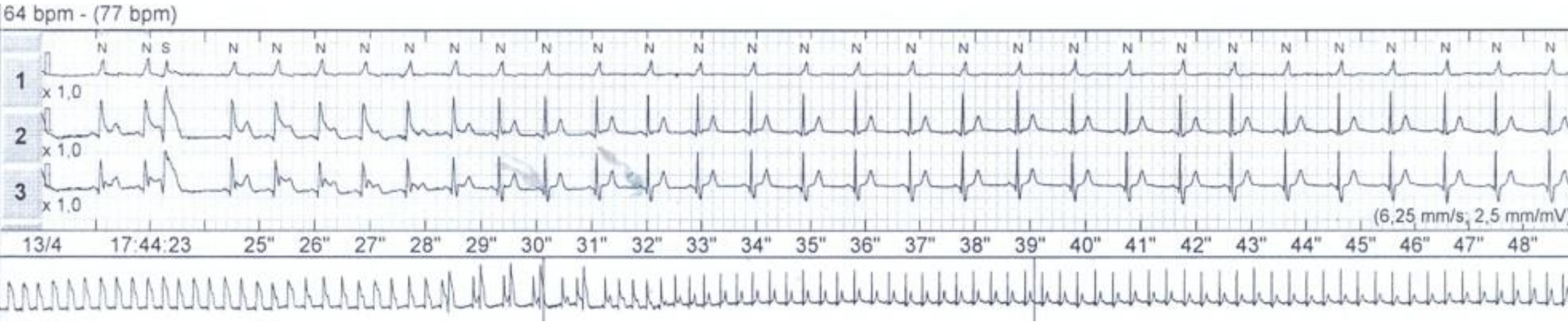


Man who had coronary revascularization a time ago.

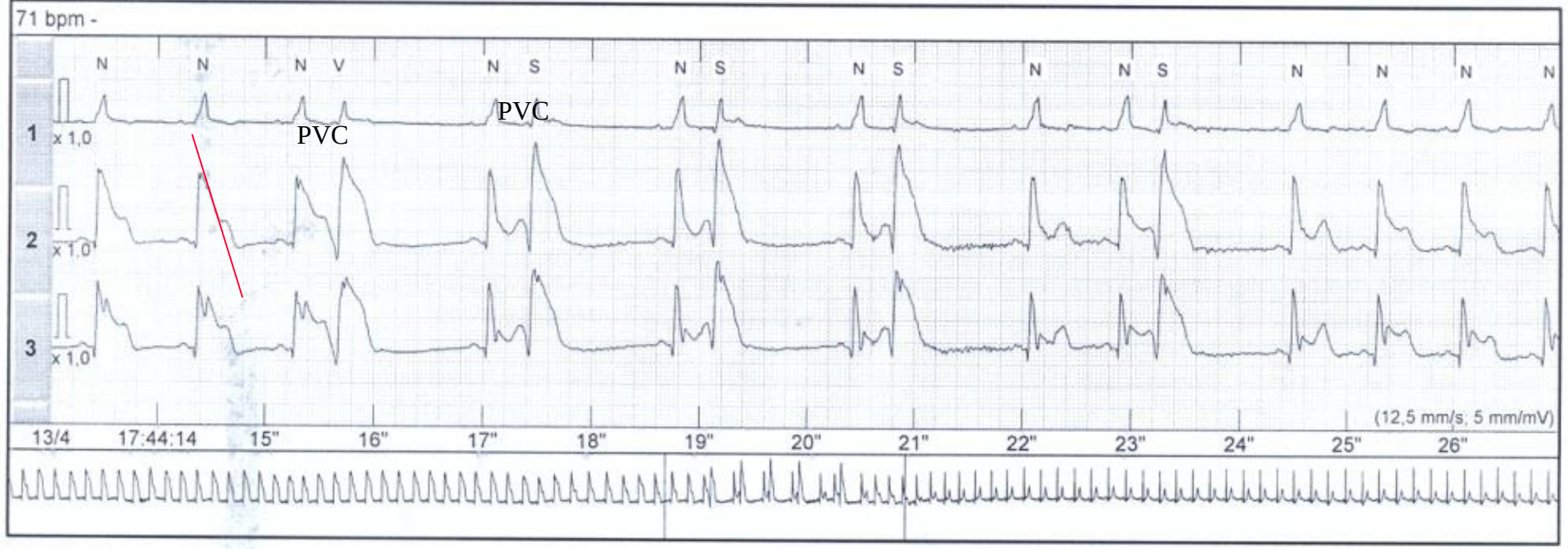
Continuous Holter monitoring during an episode of angina and concomitant ST segment elevation and ischemic giant J-wave "lambda-like type" associated with Premature Ventricular Contractions with Bigeminy sequence and very short coupling. The PVCs disappear immediately after cessation of vasospastic ischemia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



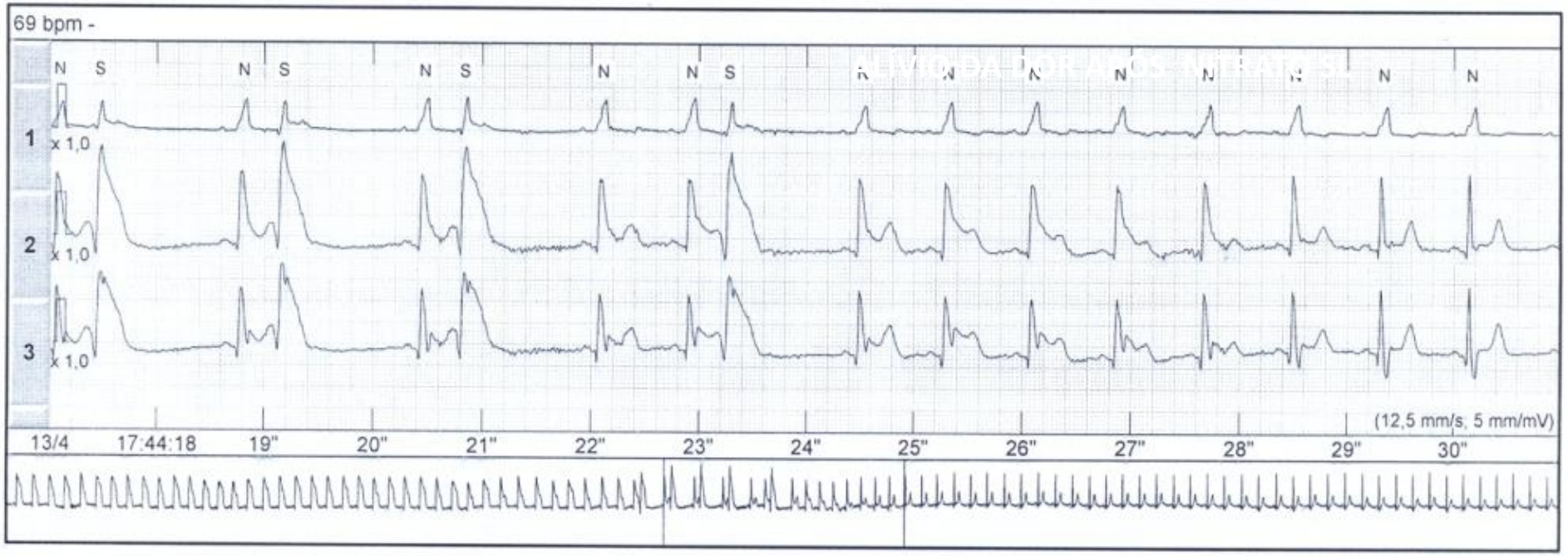
Holter monitoring shows STSE with lambda wave pattern during Prinzmetal angina. The last 4 group of beats are formed by sinus beat followed by premature ventricular contraction.

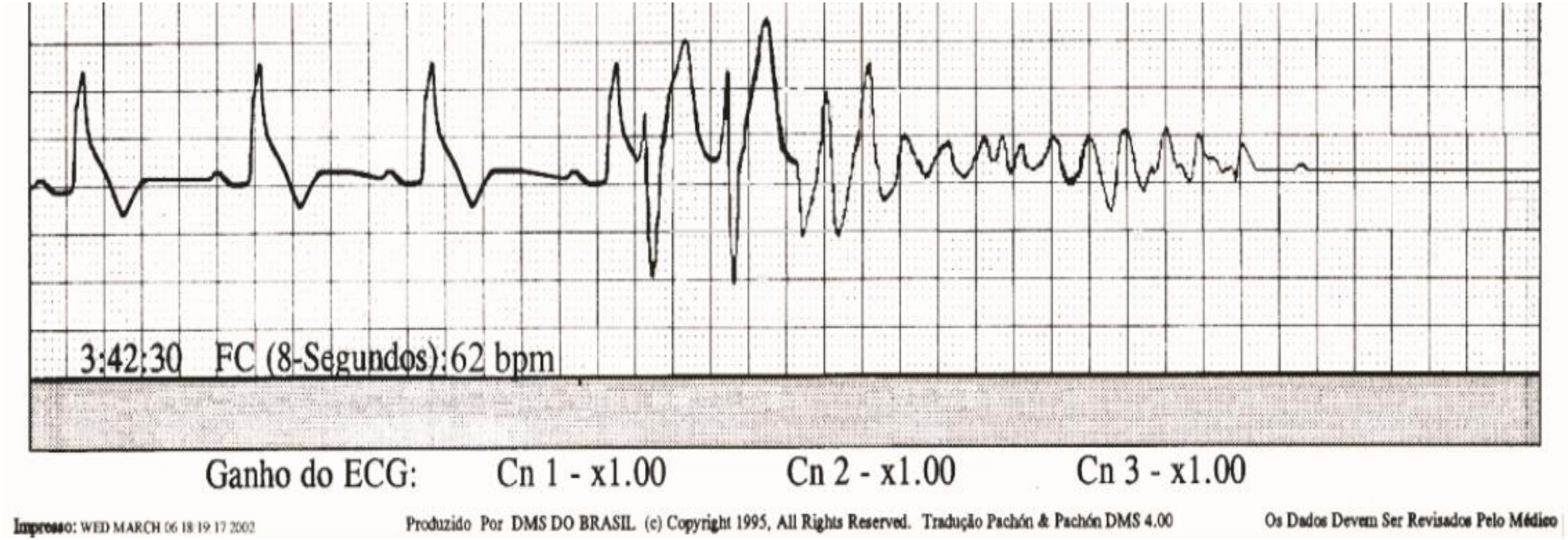


The first beat is sinus rhythm with minimal STSE. The second one has drastical augmentation of STSE followed by short coupled PVC. From third to eighth beat there are minimal STSE. The remaining trace has normal ST segment level.



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

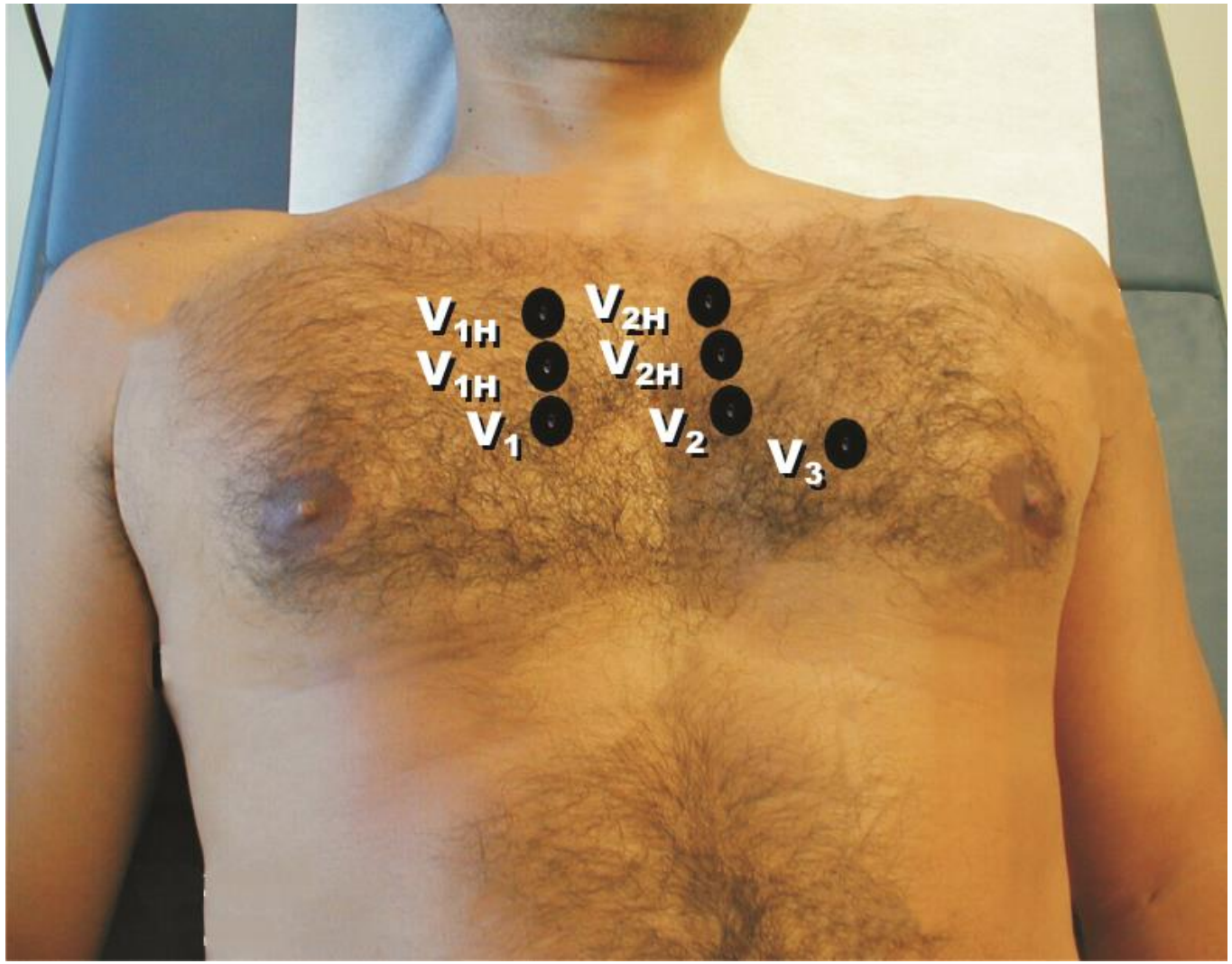




Holter monitoring recorded the final event by Holter, manifested by PVT episode with initial short-coupling ventricular premature contractions (R on T) that ended quickly in VF and asystole.

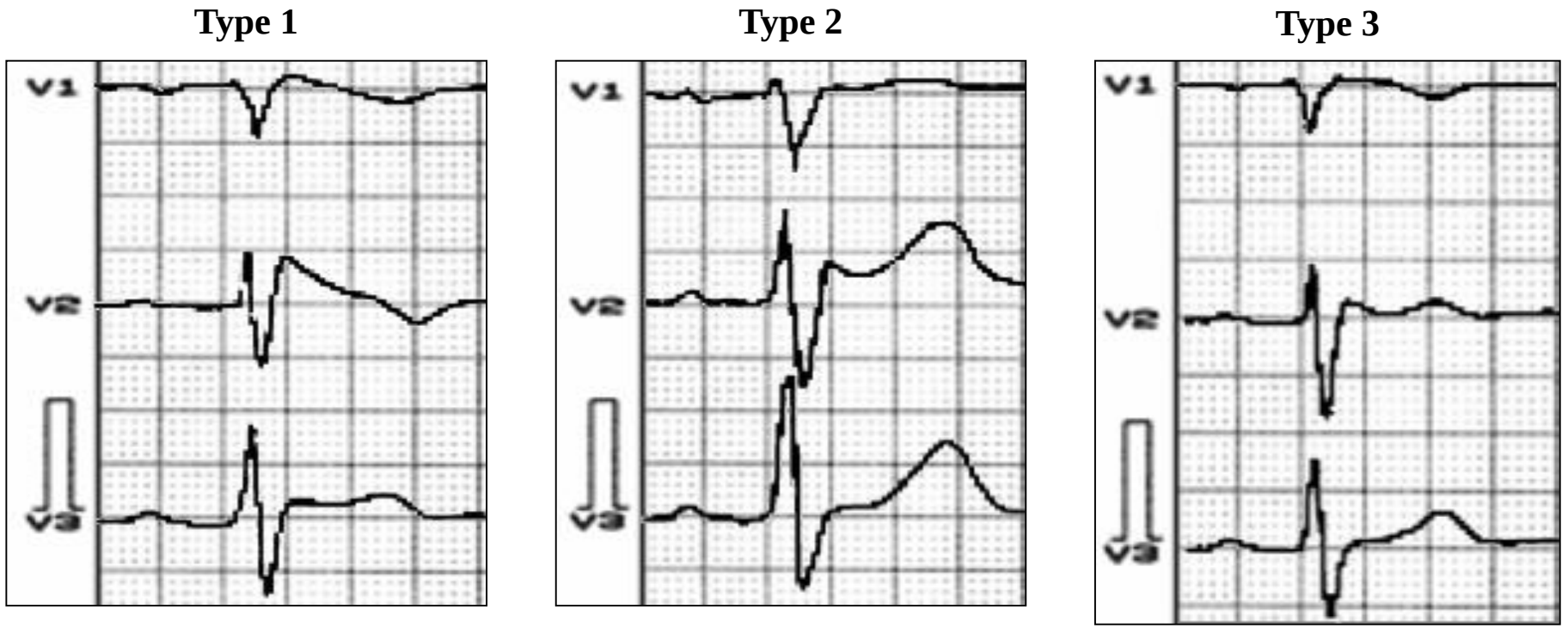
Pattern 1C of repolarization has been observed in acute myocardial infarction by Kukla et al (**Kukla 2007**). These authors raised the hypothesis that the "Lambda-like ST" could be a new marker of risk of acute infarction with ST segment elevation.

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 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).

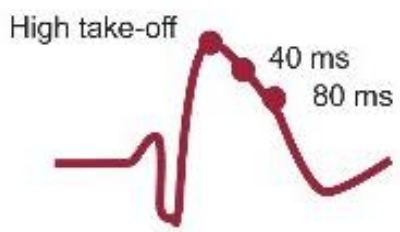
Type 2: J point and ST segment elevation ≥ 2mm (0.2mV) with saddleback appearance, and remains at least 1 mm above the isoelectric line, followed by positive or biphasic T wave.

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.

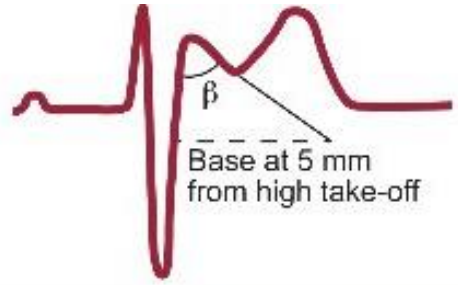
In the new ECG criteria, only 2 ECG patterns are considered: pattern 1 identical to classic type 1 of other consensus (coved pattern) and pattern 2 that joins patterns 2 and 3 of first consensus (saddle-back pattern). (**Bayés de Luna, 2012**)

Type 1 Brugada pattern in V1-V2



- At the end of the QRS, an ascending ST segment with a high take-off of ≥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).

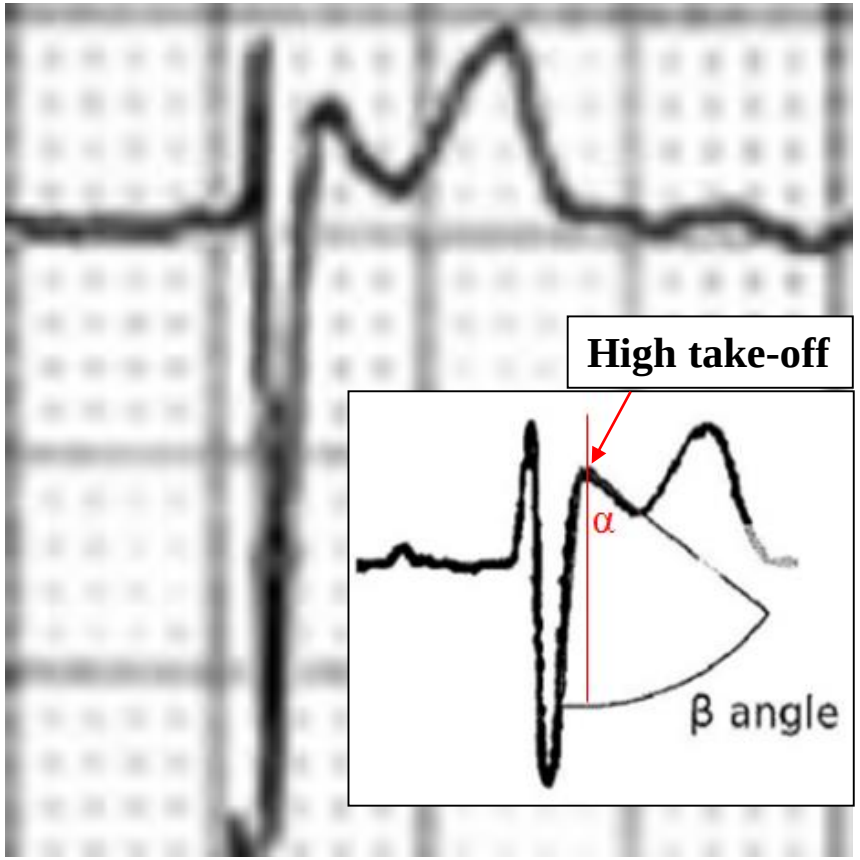
Type 2 Brugada pattern in V1-V2



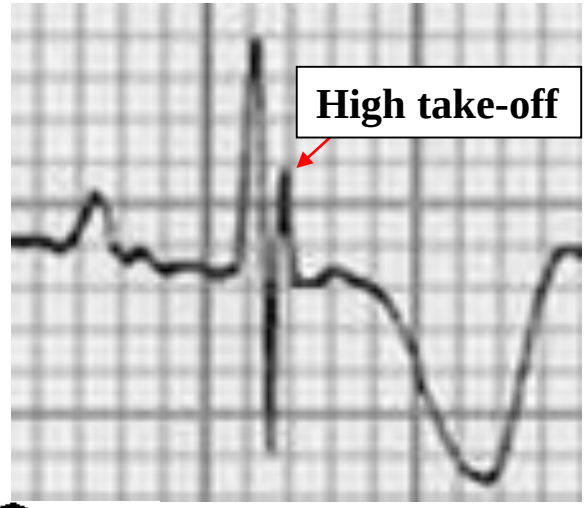
- High take-off that does not coincide with the J-point ≥ 2 mm.
- The descending arm of r' coincides with the beginning of ST segment.
- ST segment upslope is at least 0.5 mm.
- ST segment is followed by positive T wave in V2.
- The characteristics of the triangle formed by r' enables the different criteria 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.

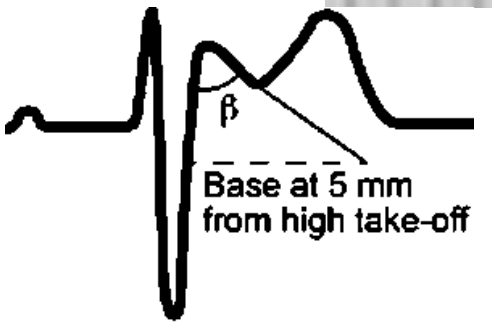
Type 2 Brugada pattern versus ordinary “innocent” incomplete RBBB

Type 2 Brugada pattern



Ordinary “innocent” incomplete RBBB



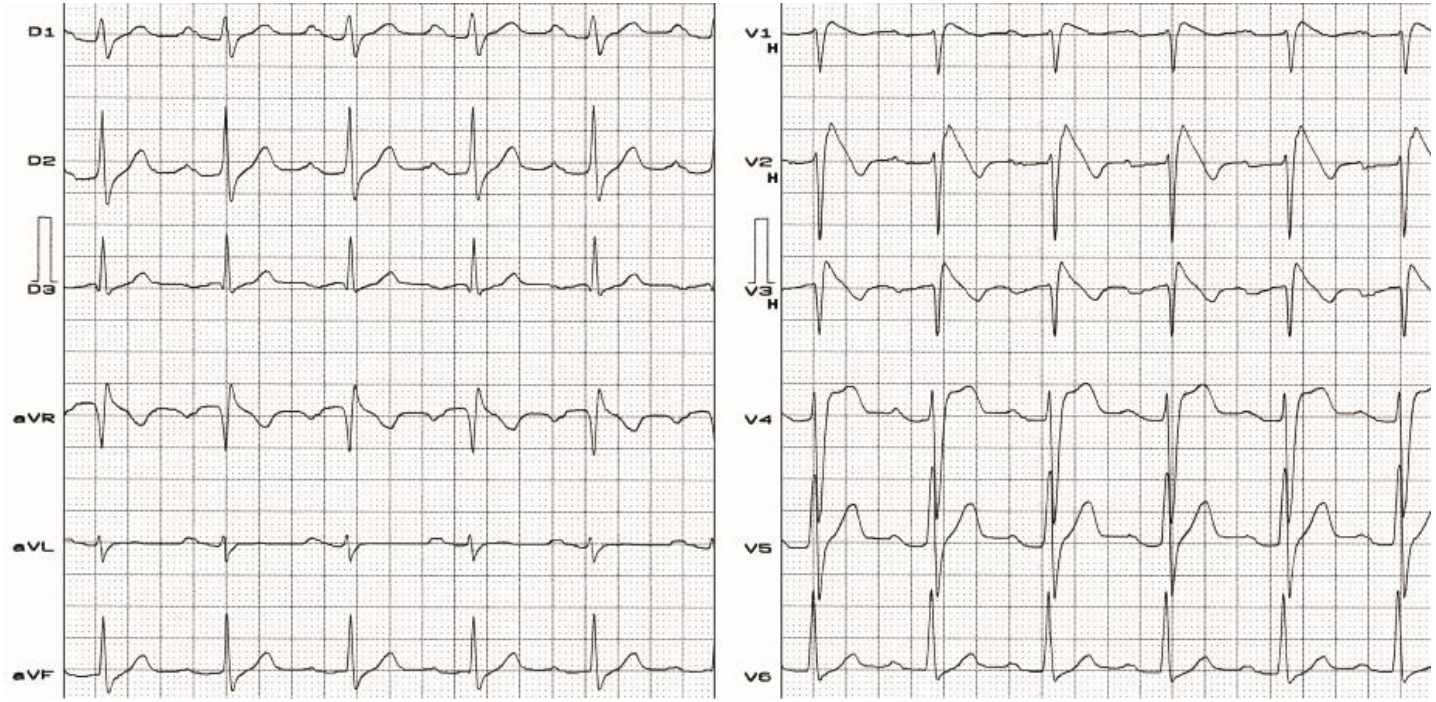


β angle (**Chevalier 2011; Ohkubo 2011**)	Cut-off > 58°	Acute
α angle	Mayor	Minor
T-wave	Positive or plane	Negative
Duration of triagle base from the high take-off	Cut-off ≥ 4 mm	Minimal
High take-off	Wide	Acute

ECG markers in identifying patients at risk in the Brugada syndrome

Spontaneous type 1 ECG pattern is an established risk marker for fatal arrhythmias whereas drug-induced type 1 ECG shows a relatively benign prognosis. Current guidelines recommend ICD implantation only in patients with spontaneous type 1 ECG pattern, and either history of aborted cardiac arrest or documented Sustained VT (class I), or syncope of arrhythmic origin (class IIa) because they are at high risk of recurrent arrhythmic events (up to 10% or more annually for those with aborted cardiac arrest).

Name: AS**; Age:** 35 yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 72kg; **Height** 1,71m.



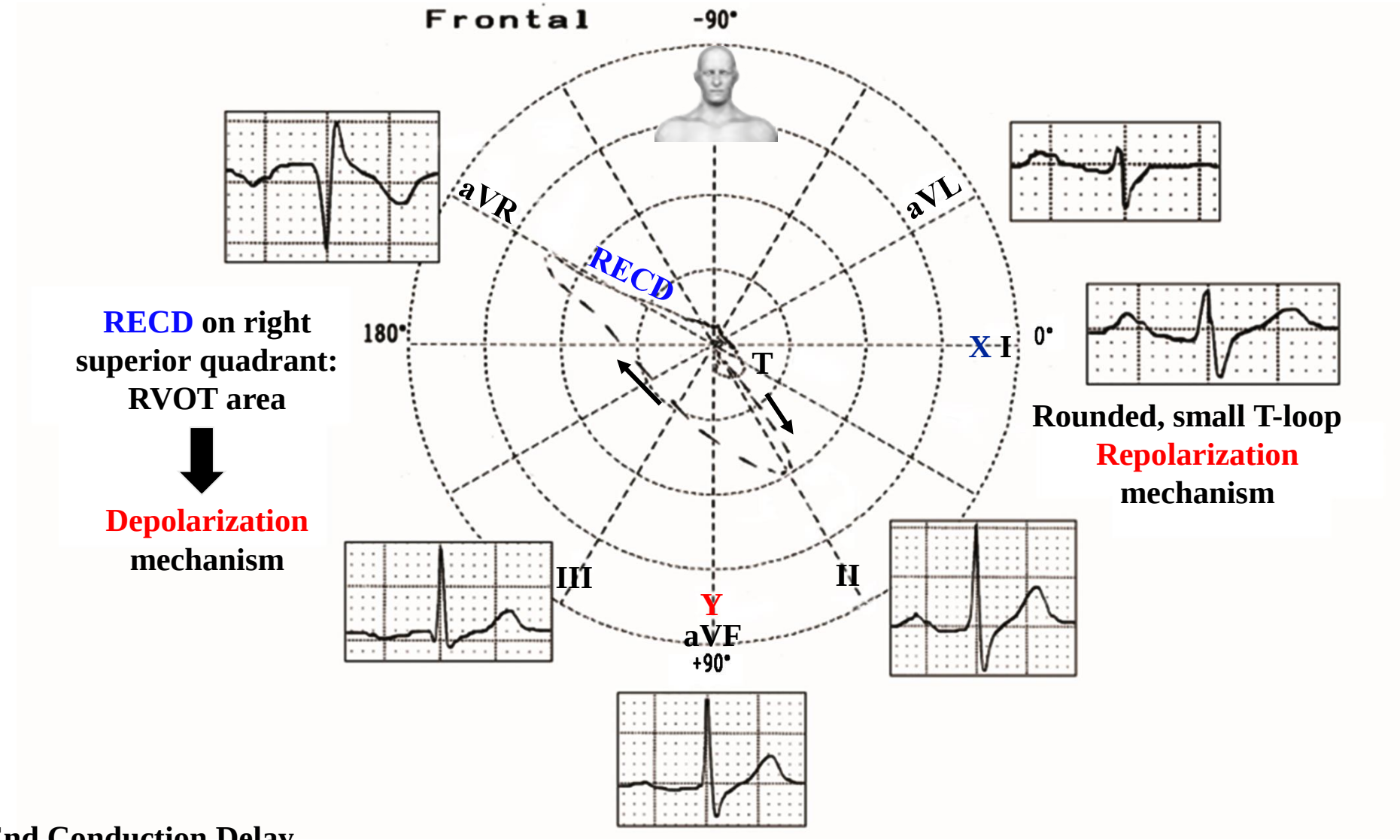
Clinical features: Aborted sudden death, positive familiar background of sudden death, family history of premature sudden death (<35years) in first-degree relatives. Genetic research performed: negative.

ECG diagnosis: HR: 82bpm, P axis: +33°, P duration 160ms(prolonged), PR Interval: 258ms(prolonged), QRS Axis: +84°, QRS Duration: 112ms (prolonged); final R wave of aVR =3mm(aVR sign), J point and ST segment elevation on right precordial leads followed by a negative T wave (type 1 Brugada ECG pattern).T Axis +50° on frontal plane and to back on HP. QT/QTc: 360/420ms.

Conclusion: Interatrial block, first-degree AV block, prolonged QRS duration, prominent final R wave in aVR: “aVR signal”; Brugada type 1 ECG pattern.

ECG/VCG correlation in the Frontal Plane

Name: AS **Age:** 35yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 72kg; **Height** 1,71m.



RECD on right superior quadrant: RVOT area

Depolarization mechanism

Rounded, small T-loop
Repolarization mechanism

RECD: Right End Conduction Delay

ECG/VCG correlation in the Horizontal Plane

Name: AS **Age:** 35yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 72kg; **Height** 1,71m.

RECD on right posterior quadrant

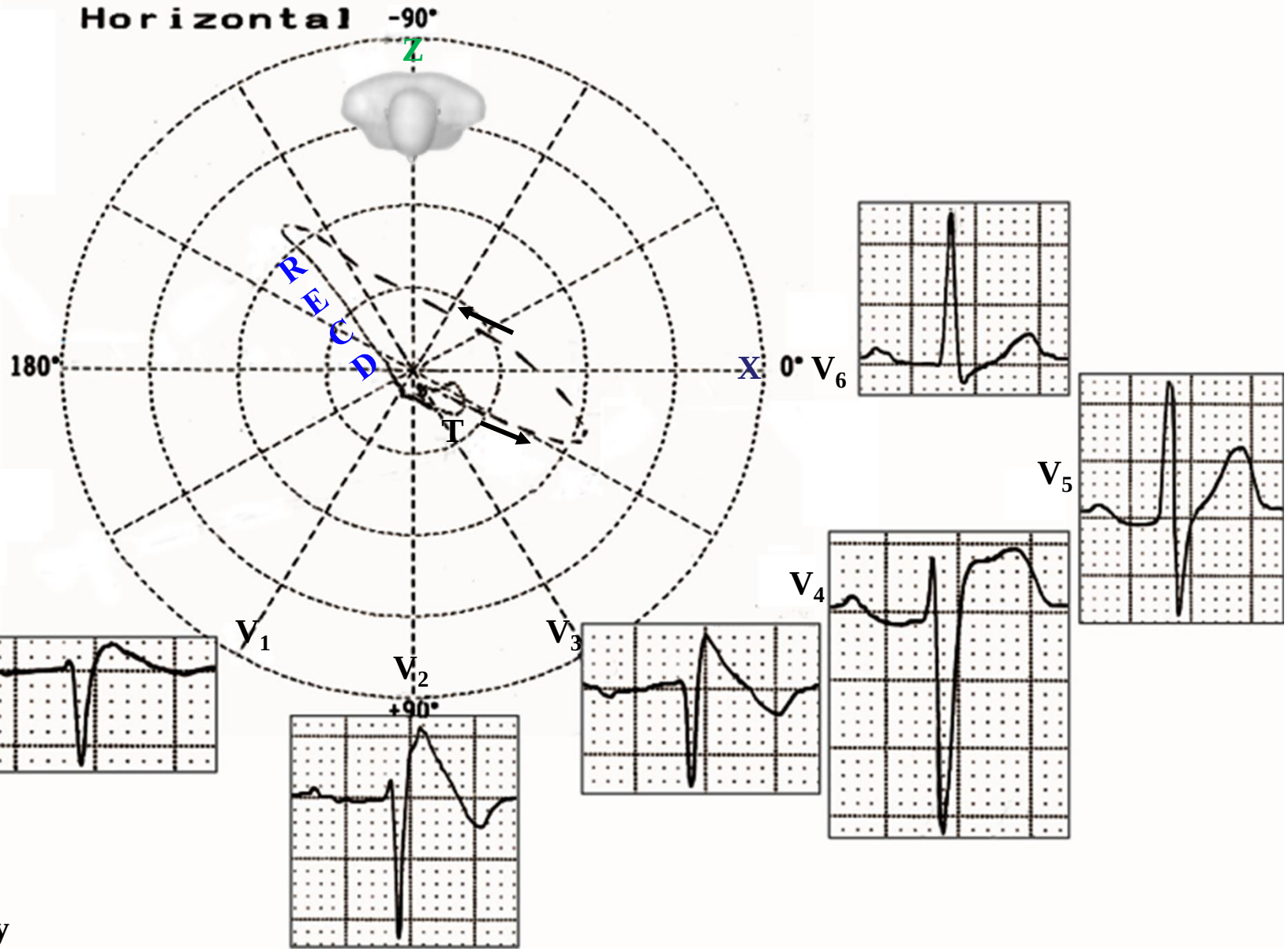
⬇

Depolarization mechanism

Rounded, small T-loop

⬇

Repolarization mechanism



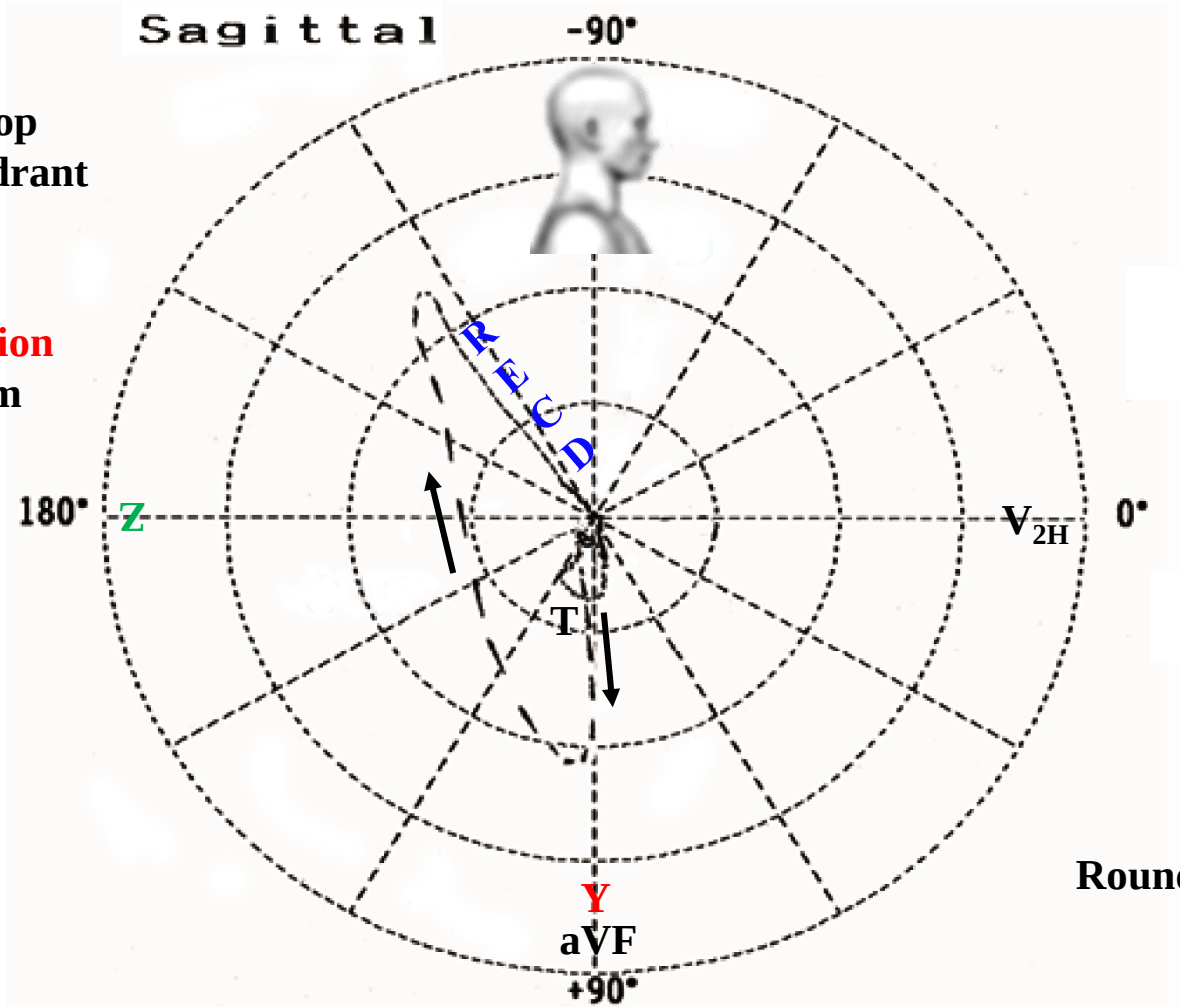
RECD: Right End Conduction Delay

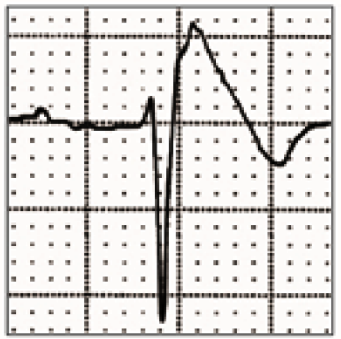
ECG/VCG correlation in the Right Sagittal Plane

Name: AS **Age:** 35yo; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 72kg; **Height** 1,71m.

RECD on top posterior quadrant

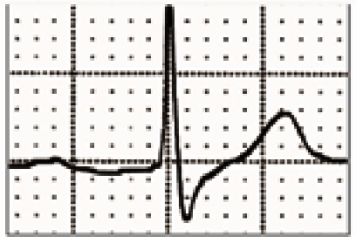
Depolarization mechanism





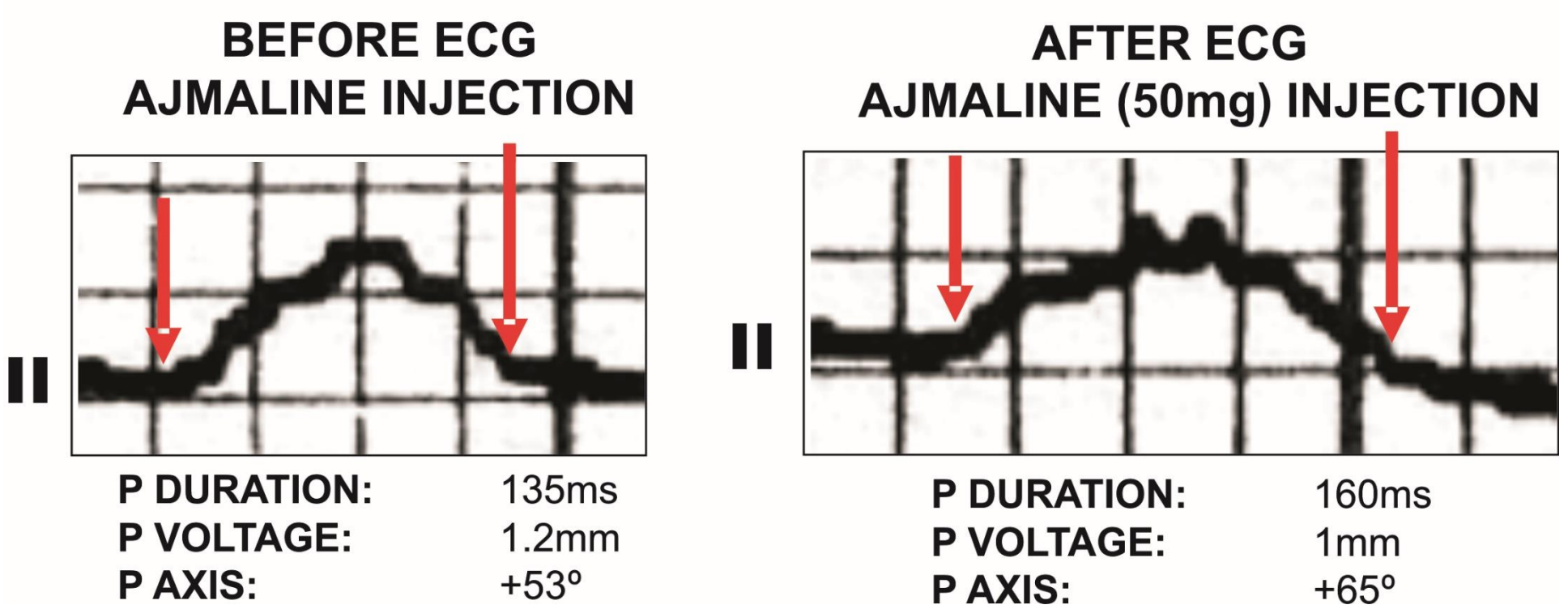
Rounded, small T-loop

Repolarization mechanism



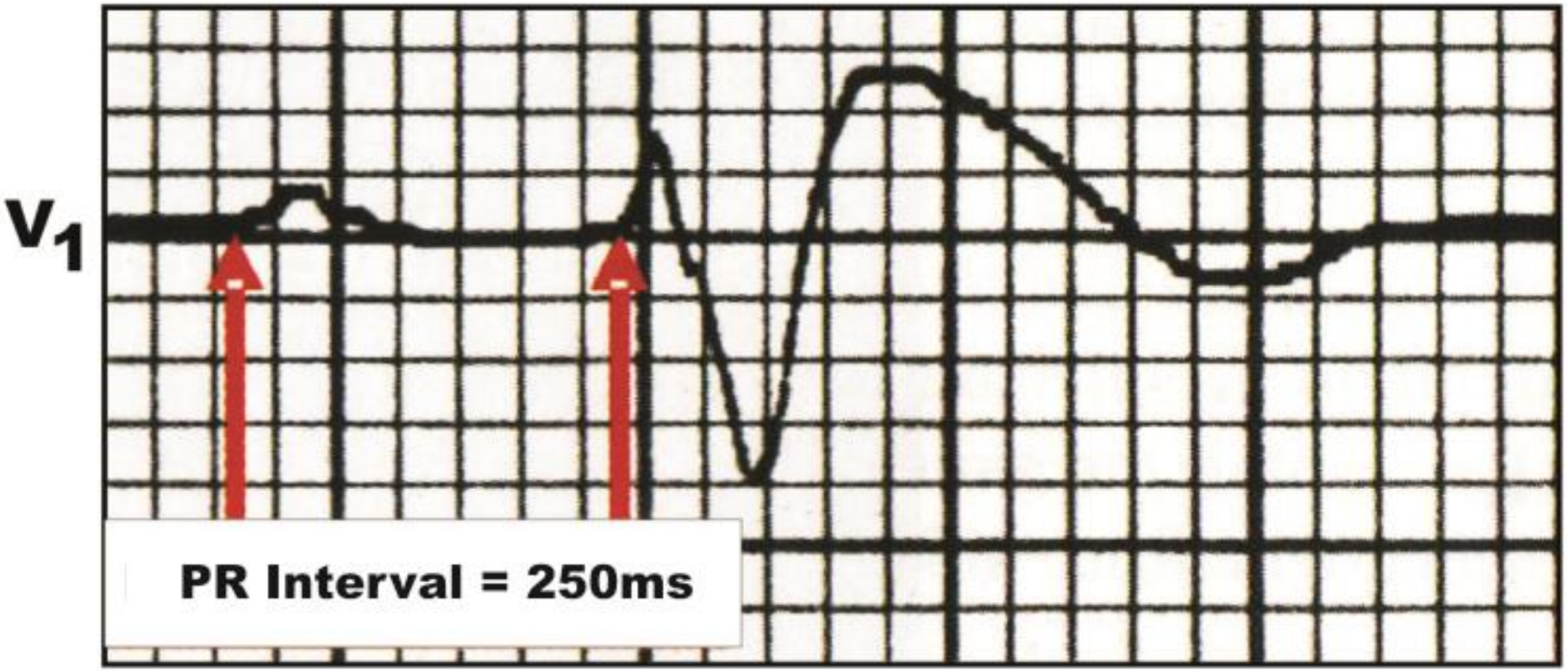
RECD: Right End Conduction Delay

2. Augmented P-wave duration in lead II, P-wave dispersion (**Letsas 2009**).



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)

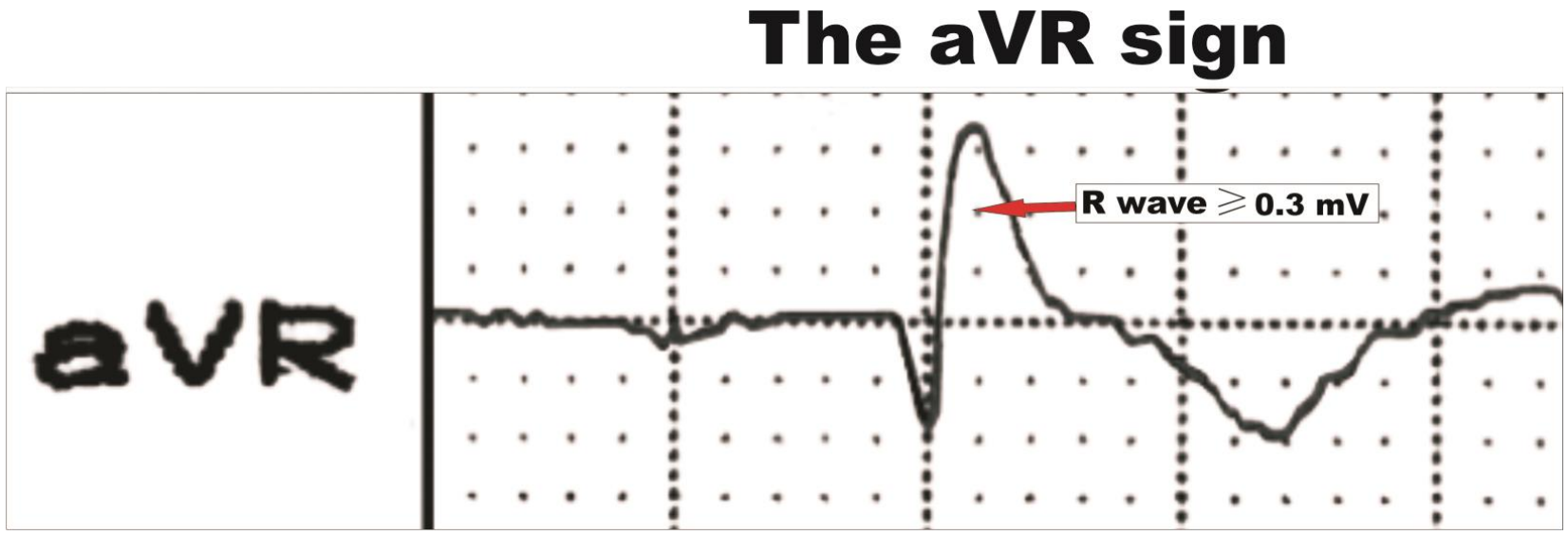
3. PR prolongation consequence of HV split or HV prolongation (**Miyamoto 2011**).



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).

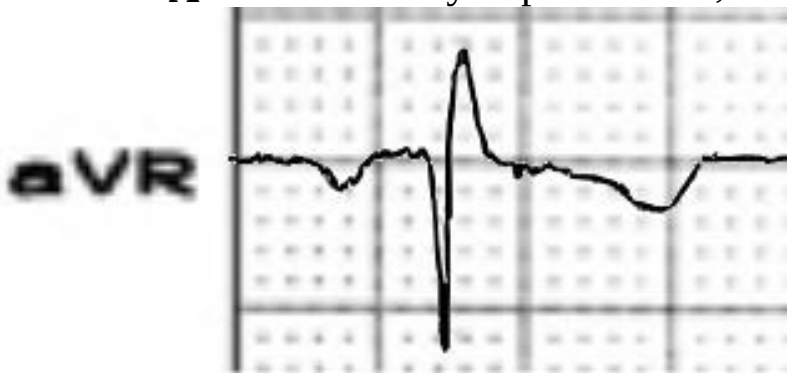
In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes 100 ms (**Yokokawa 2007**). This prolongation of the PR interval is observed predominantly in cases where the SCN5A gene mutation can be proven (carriers). The presence of a prolonged HV interval is possible in His bundle electrogram (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**).

4. 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.

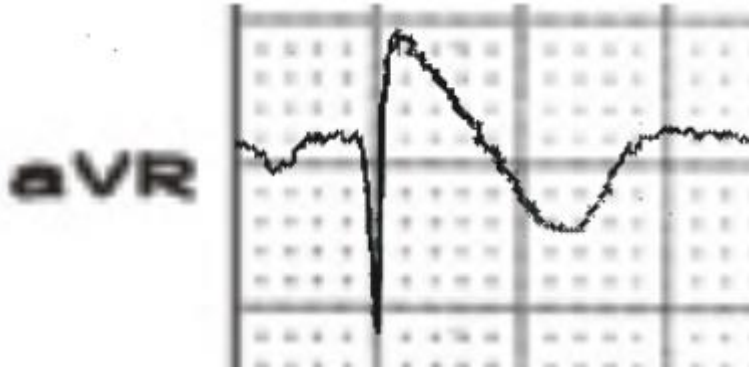


aVR sign : final R wave of aVR lead >3mm

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



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

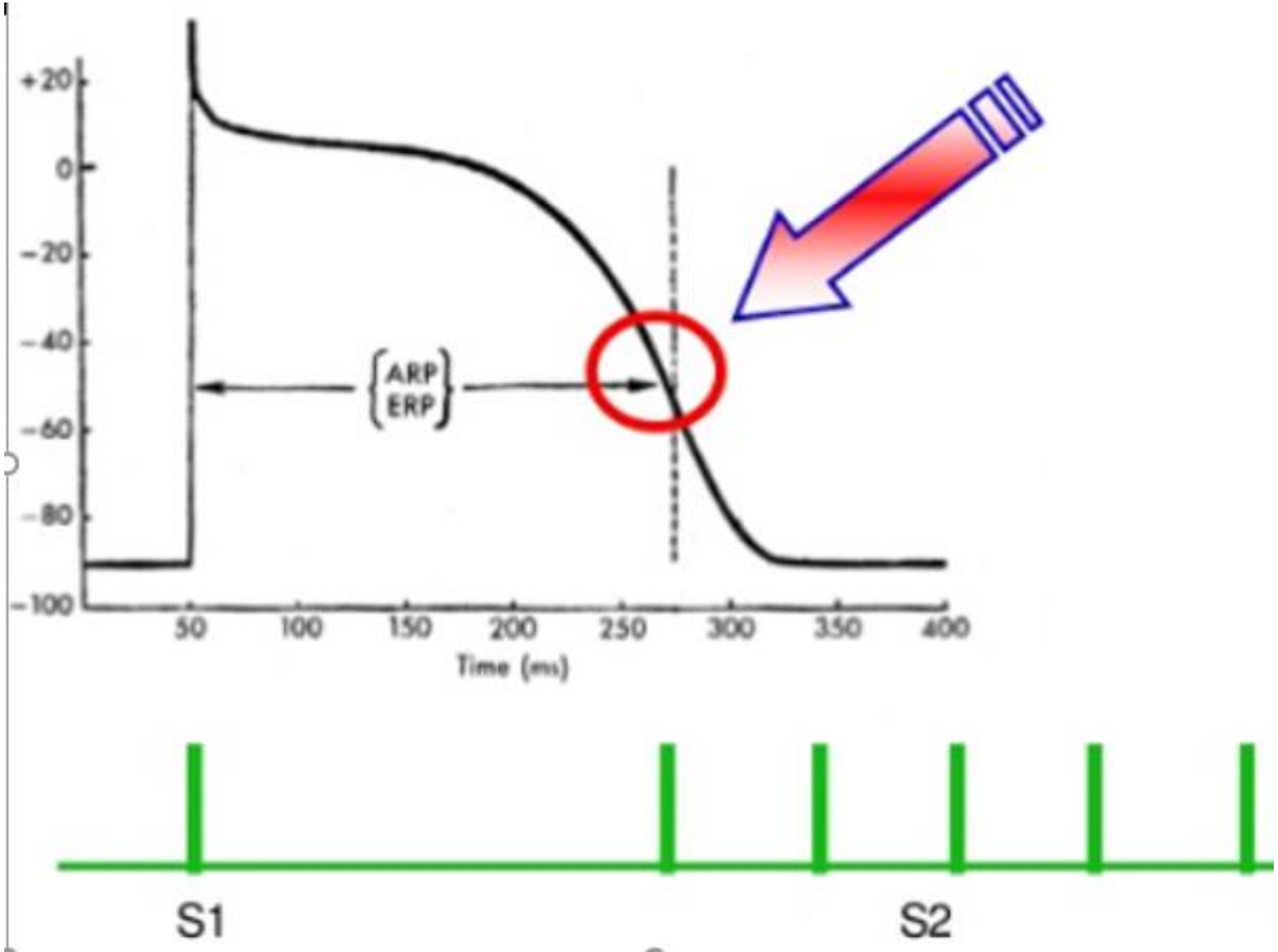


Terminal broad R-wave of the QRS complex in lead aVR(1)

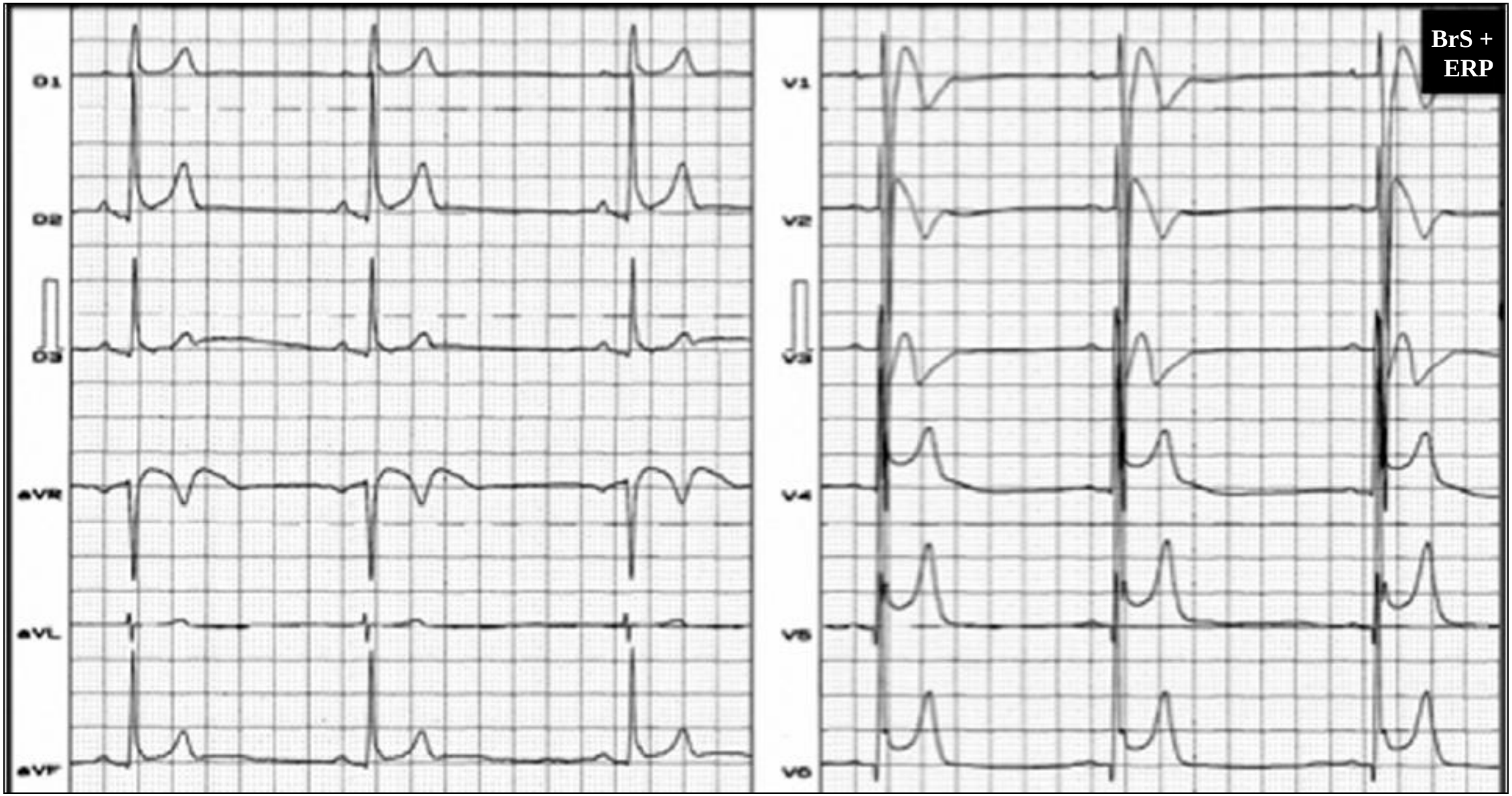
The aVR sign: Presence of prominent final R wave on aVR lead R wave ≥ 3 mm or R/q ≥ 0.75 in lead aVR (aVR sign). Slow conduction at the RVOT may contribute to the induction of VF by PVS (**Babai Bigi 2007**).

5. The presence of a spontaneous type I ECG, history of syncope, ventricular effective or absolute refractory period (ERP) < 200 ms, and fQRS seem useful to identify candidates for prophylactic ICD (**Priori 2012**). Effective or absolute refractory period, (phase 2) ERP is the longest amount of time when cells cannot be depolarized again. The longest input that fails to conduct, Normal values for: Atria 200-270ms; Ventricles 200-270 ms; and AV node 280-450ms.

Effective or absolute refractory period



6. Inferolateral early repolarization (**Kamakura 2009; Sarkozy 2009**). The prevalence of ER in inferolateral leads was high and an especially persistent form of ER is associated with a worse outcome in BrS patients with documented VF (**McIntyre 2012; Kawata 2013**).

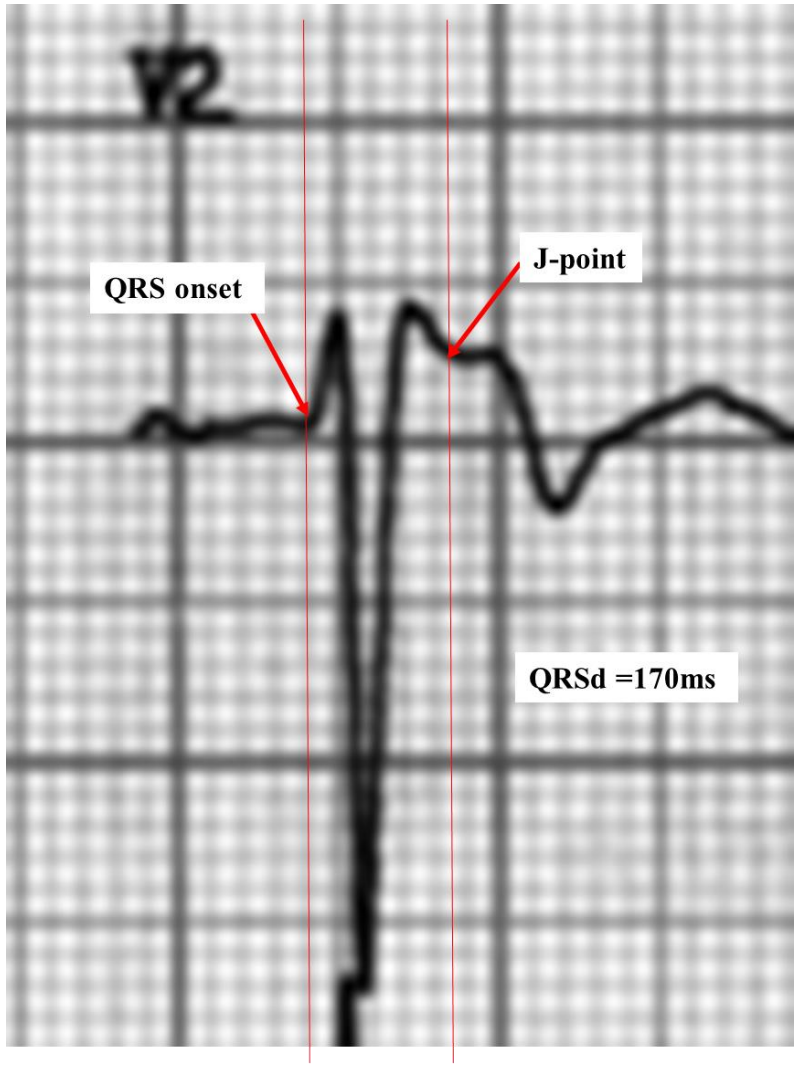


Coexistence ECG that shows concomitant early repolarization pattern in inferior lateral leads associated with type 1 Brugada pattern in young soccer player Caucasian man.

Similarities between early repolarization pattern and Brugada syndrome

1. Both are much more frequent in the male gender
2. Both are predominantly observed in young adults
3. Both do not present apparent structural heart disease
4. Both frequently present conduction disorder patterns in the right His system
5. 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**).
6. Both may display saddleback pattern quite frequently
7. 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)**
8. 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 199)**
9. Both may have modification in the *I*to and $I_{Ca}{}^{++}{}_{-L}$ channels by electrophysiologic substrate, which explains the J point and STSE causing intensification of the notch in phase 1 and decrease in phase 2 duration in the ventricular epicardium thickness **(Antzelevitch 2000)**
10. 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).

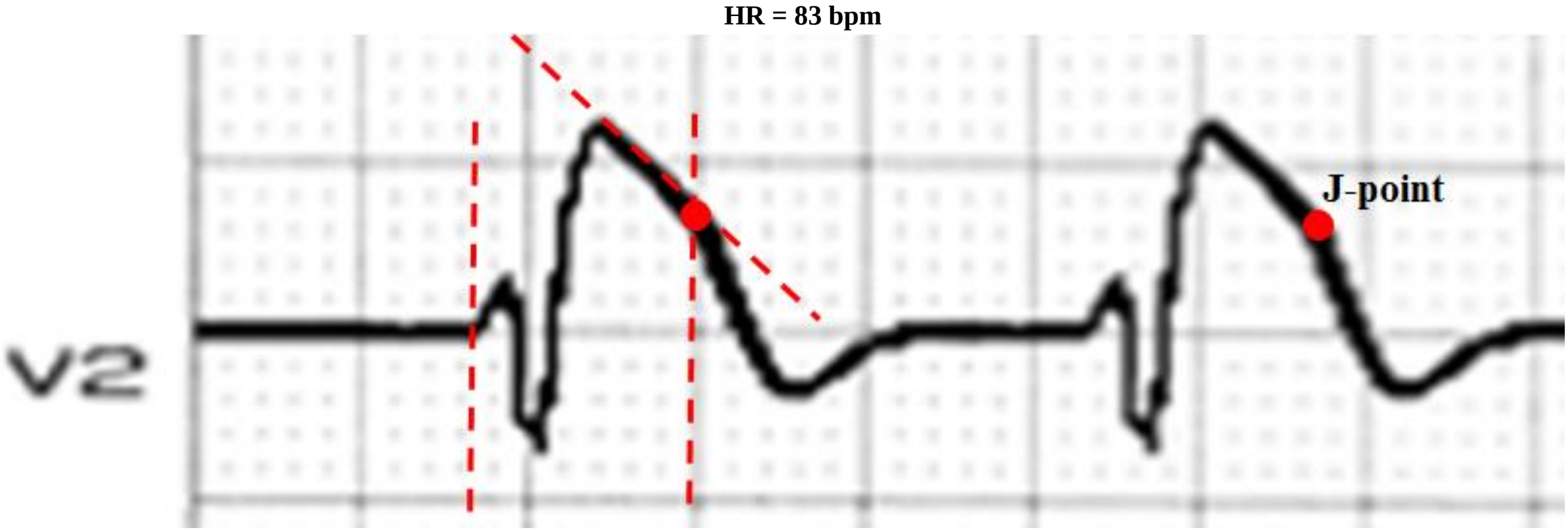
7. Prolonged QRS duration measured from lead II or lead V2 ≥ 120ms (**Junttila 2008**).



The QRS interval measured from QRS onset to the J point in leads II and V2. The only significant difference between the symptomatic and asymptomatic patients is the QRS duration measured from lead V2. The mean QRS interval is 129.0 ± 23.9 ms in symptomatic patients versus 108.3 ± 15.9 ms in asymptomatic patients (**Ohkubo 2011**).

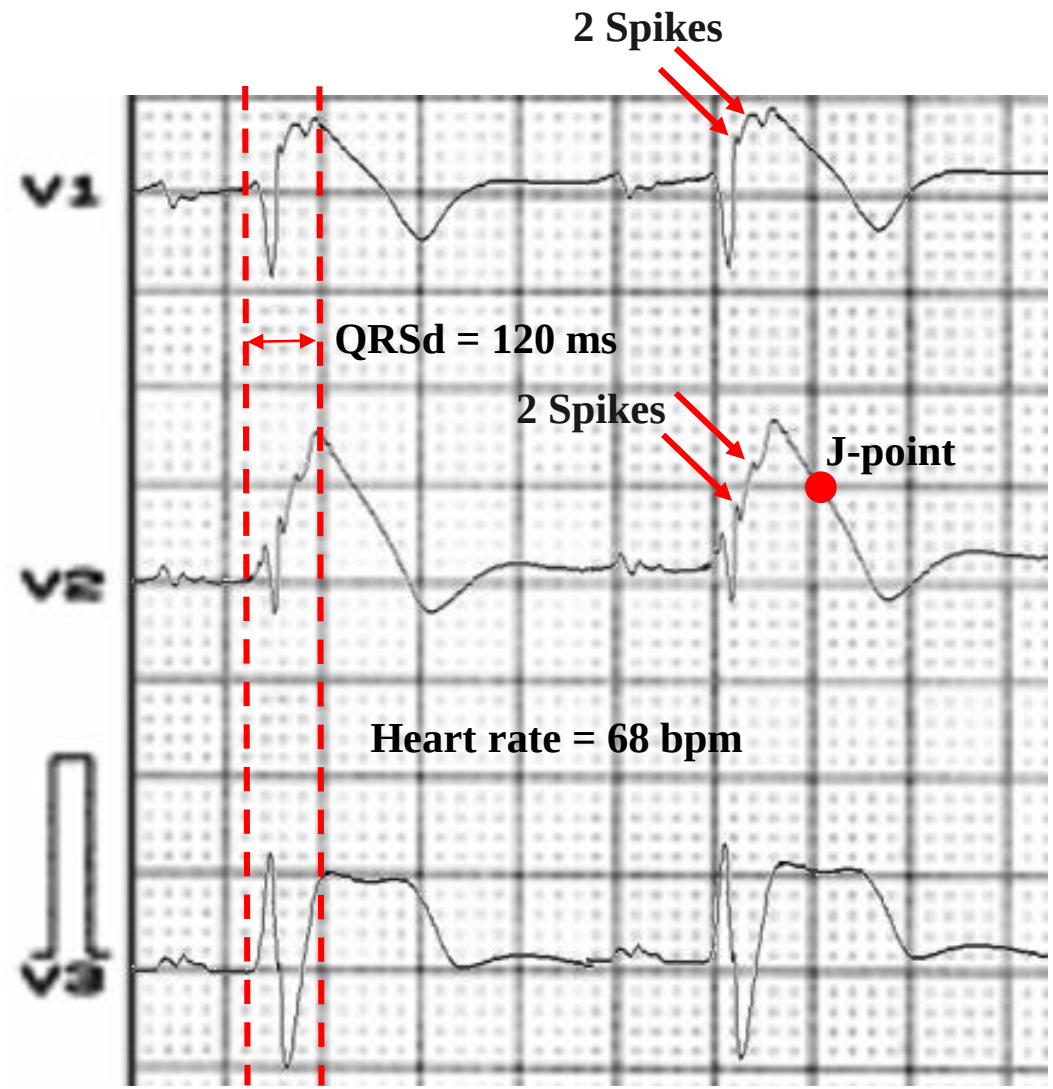
Prolonged QRS duration, measured in V2 and II from standard 12-lead ECG, is associated with symptoms and could serve as a simple noninvasive risk marker of vulnerability to life-threatening ventricular arrhythmias in BrS (**Junttila 2008**).

Prolonged QRS duration measured from lead II or lead V2 ≥ 120ms



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

8. QRS fragmentation (fQRS):

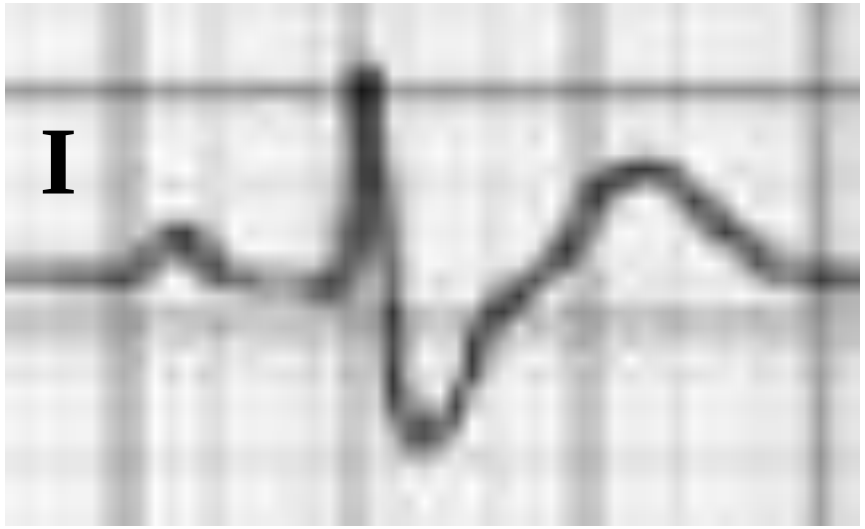


Dotted lines show onset and termination of the QRS complex

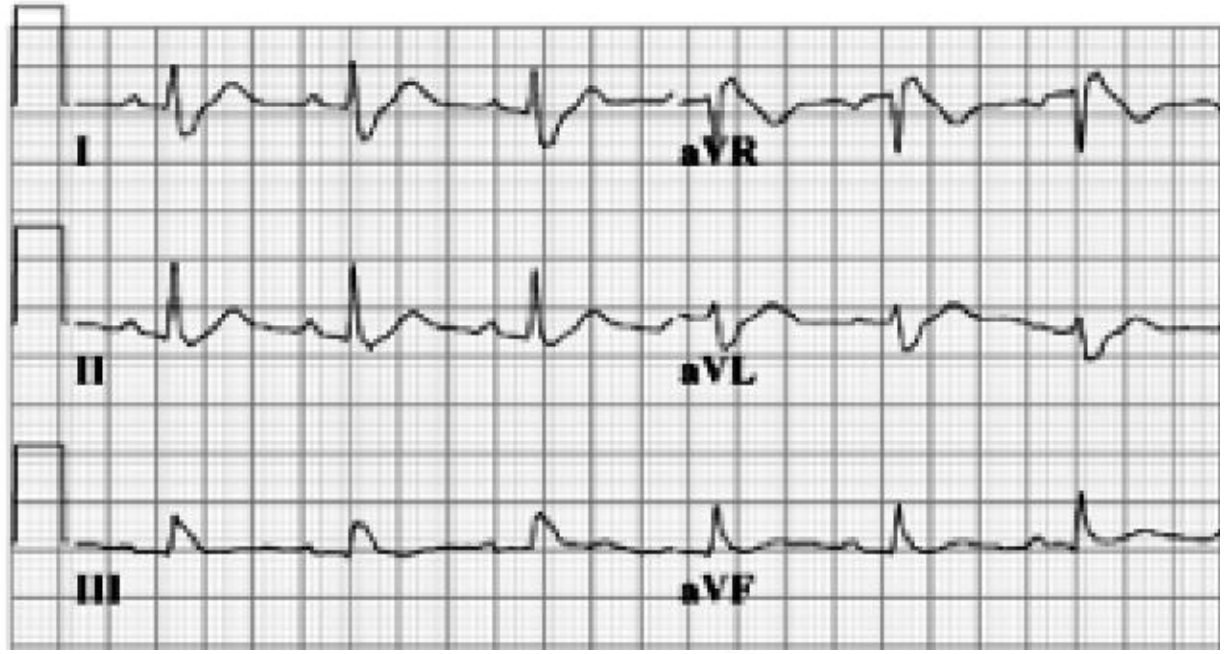
Two spikes are observed at the upstroke of the S wave in leads V_1 and V_2.

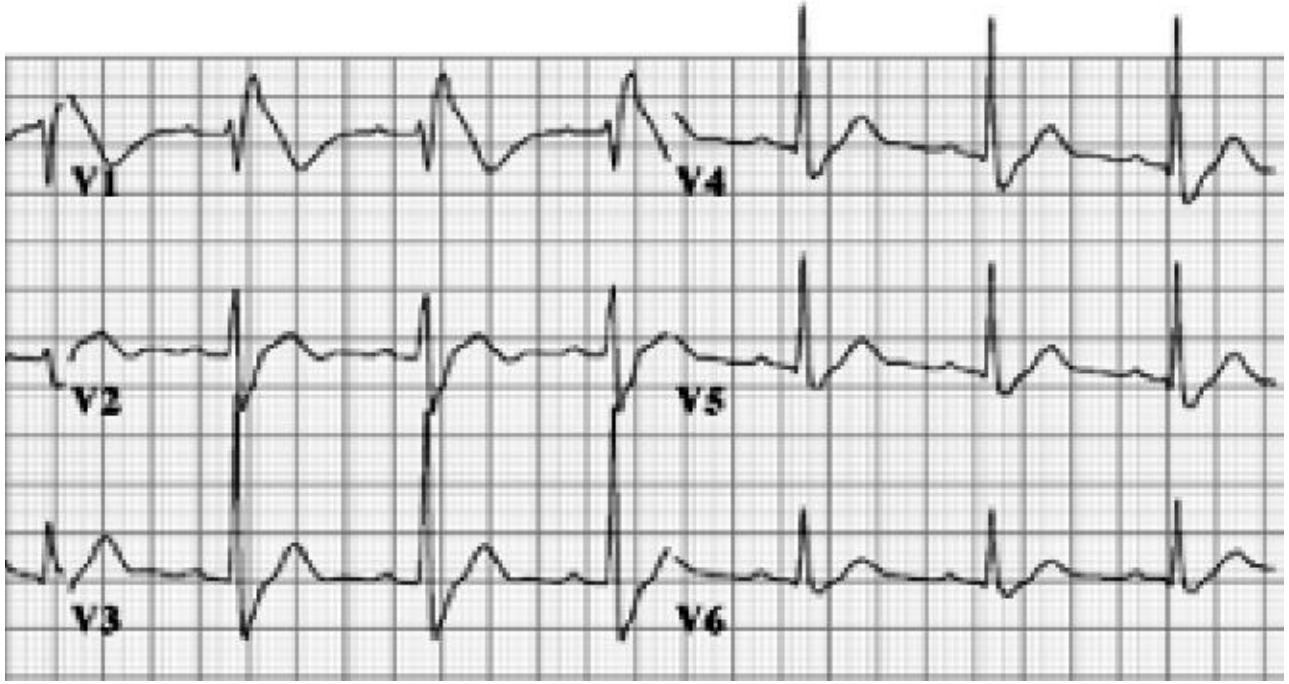
Fragmented wide QRS complex in a 35-year-old Asian male patient with BrS. f-QRS appears to be a marker for the substrate for spontaneous VF in BrS and predicts patients at high risk of syncope. It is a conduction abnormality within the QRS complex (**Morita 2008**).

9. A powerful marker for VF/SCD Is a significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I in patients with BrS and no history of cardiac arrest at presentation (**Calò 2016**).

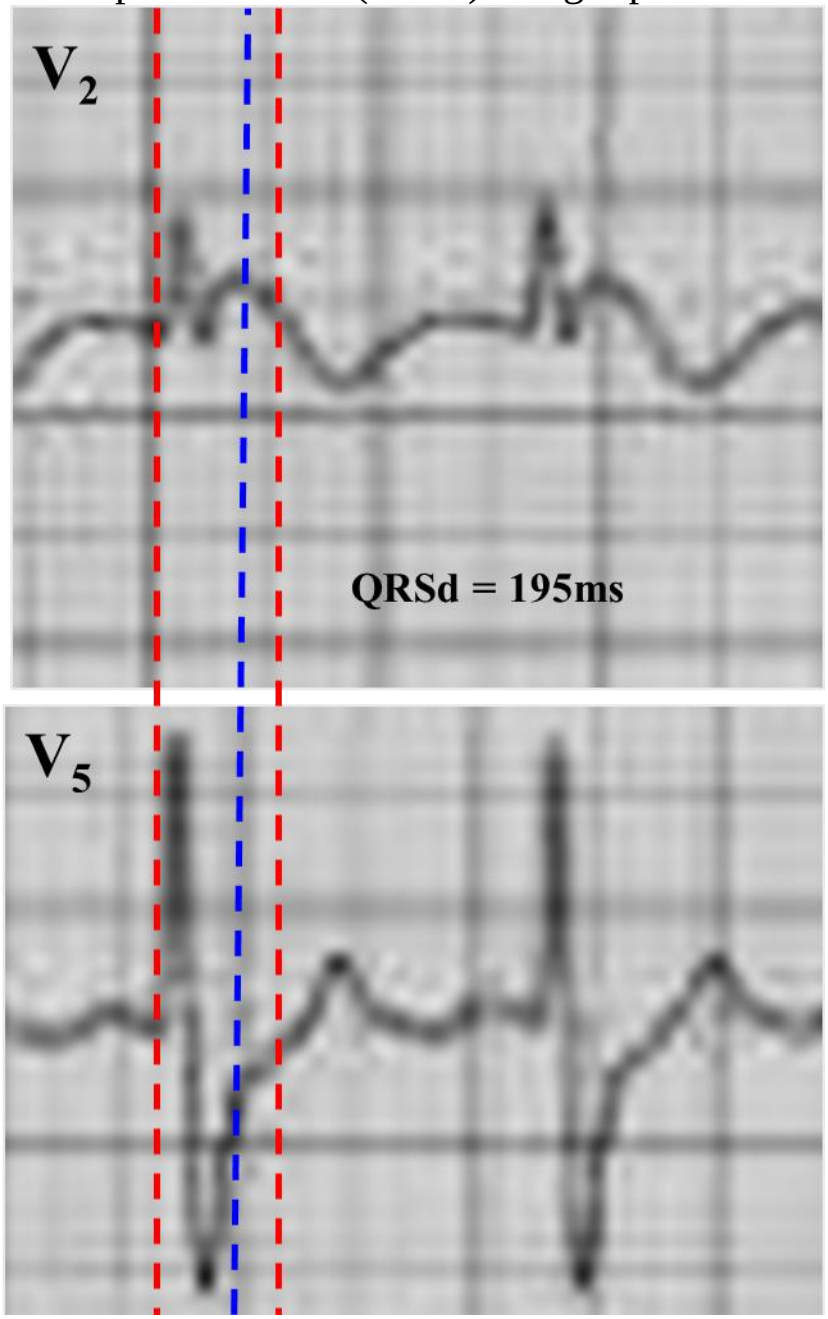


S-wave (≥0.1 mV and/or ≥40 ms)

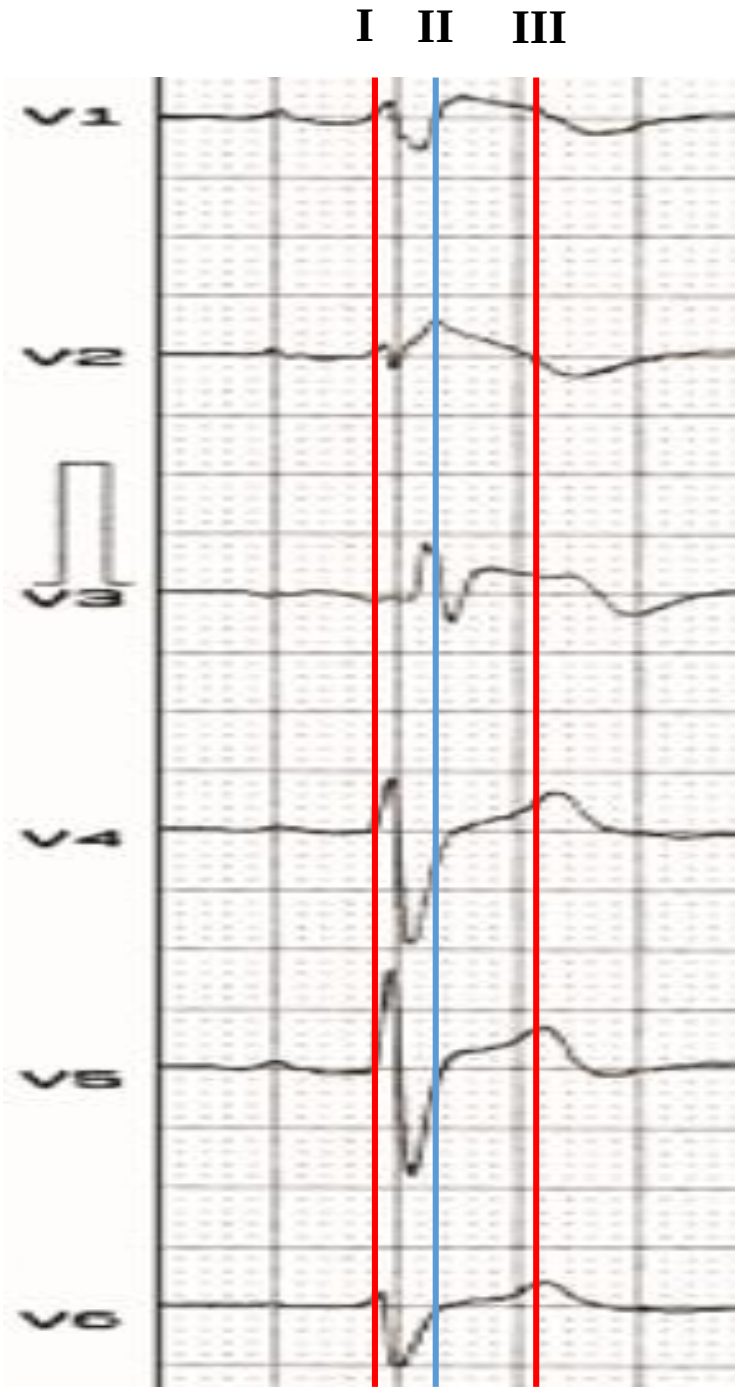




10. QTc interval more than 460 ms in lead V2 (**Take 2011**) and QT-interval prolongation in . right precordial leads (**Pitzalis 2003**). Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block.



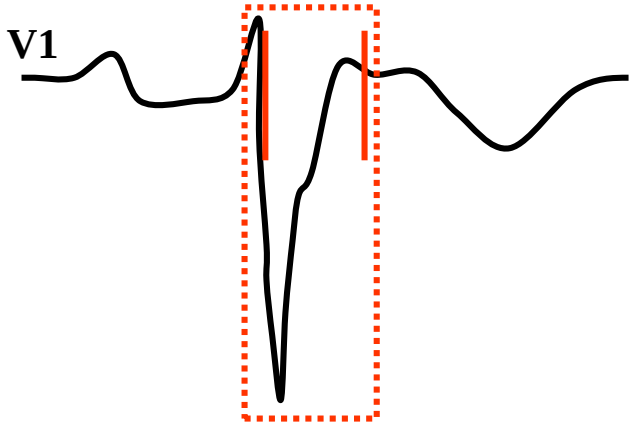
Pitzalis et al (**Pitzalis 2003**) identified selective prolongation of QT interval duration in the right precordial leads (V_1 to V_3) in comparison to the left ones (V4 to V6). As the QT interval is made up by ventricular depolarization (QRS) plus ventricular repolarization (ST/T) we think that this 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).



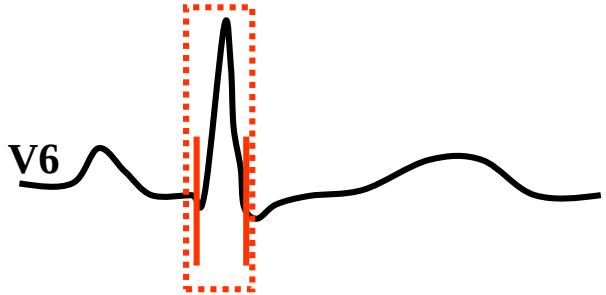
Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block I: Onset of the QRS complex
II: Termination of the QRS complex from V4-V6
III: Termination of the QRS complex from V1-V3

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)**

QRSD: >110 ms

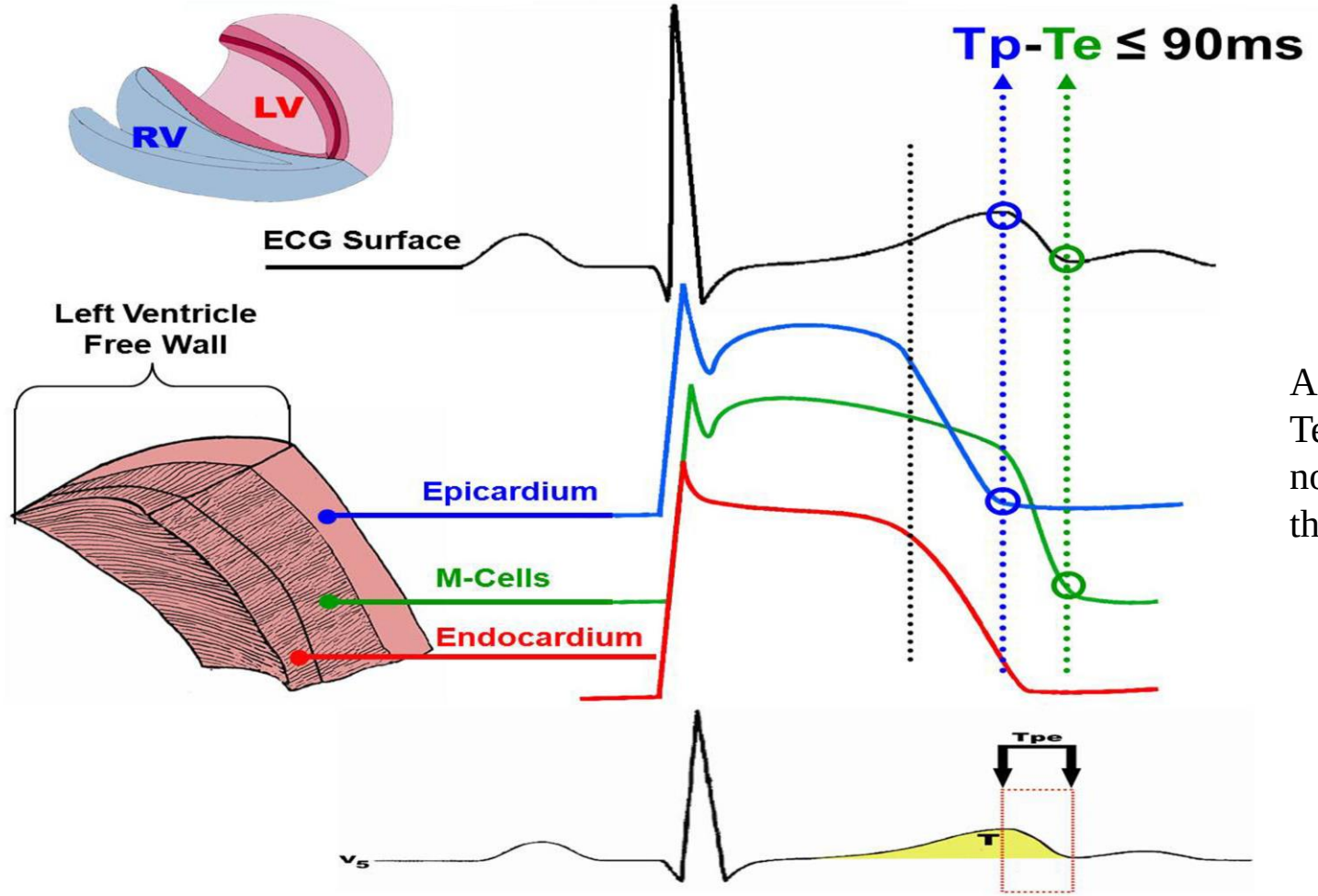


QRSD: 90 ms



50 mm/s 20 mm/mV

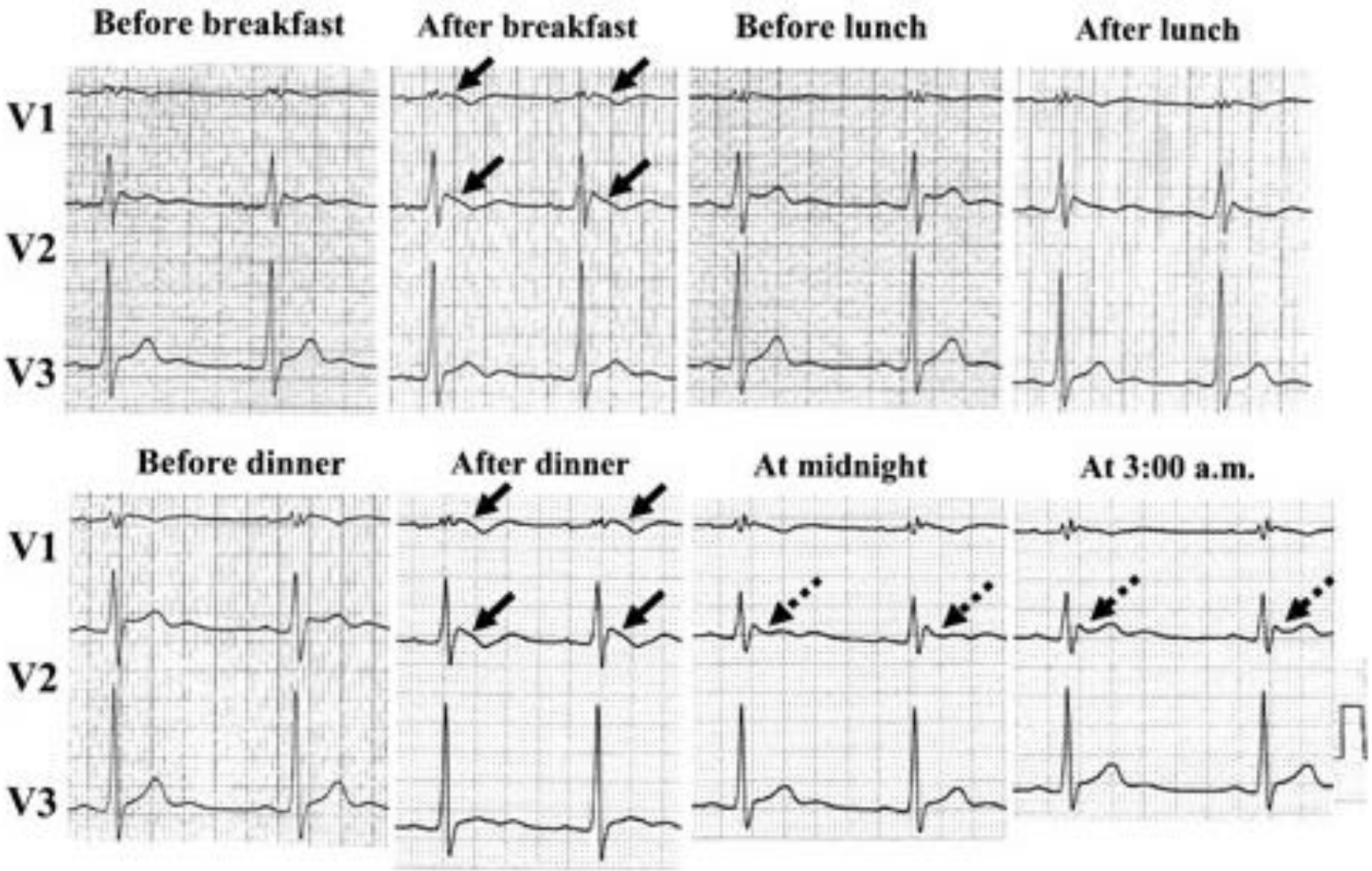
11. T peak − Tend prolongation and T peak − Tend dispersion (**Castro Hevia 2006; Sangawa 2009**): The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patients carriers 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.



Assessment of the Tpeak-Tend interval and Tpeak-Tend/QT ratio in lead V1 is potentially useful as a non-invasive risk marker for BrS patients with life-threatening arrhythmias (**Zumhagen 2016**).

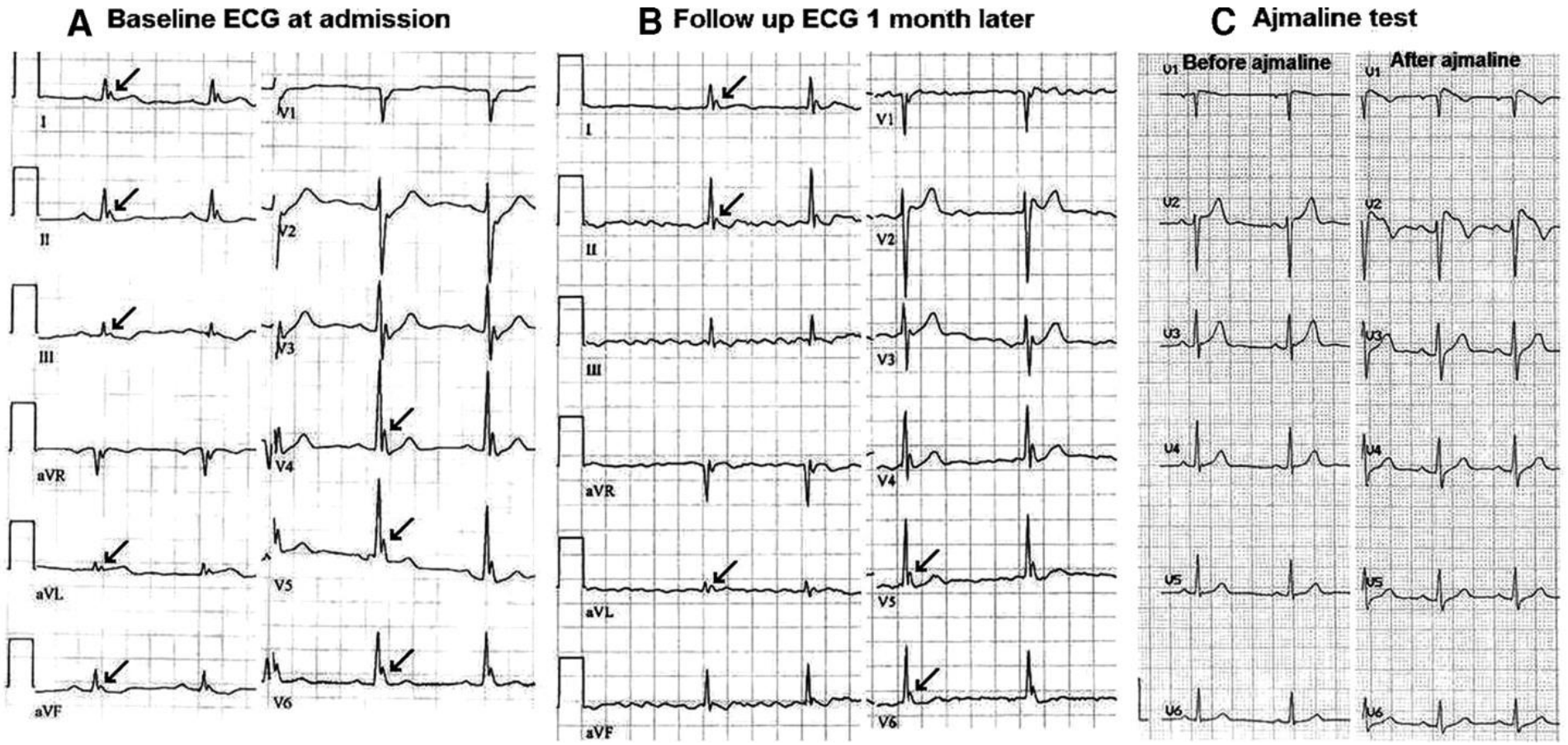
Representation of the Tpeak/Tend interval (Tpe).This is the interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias.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

12. Dynamic alterations in the amplitude of the ST elevation (**Take 2011**). Variations of ST elevation are frequently associated with meals. Aggravation of ST elevation is most prominent in the evening to night after dinner rather than the period between midnight and early morning. This information may help to predict event times at high risk for life-threatening arrhythmias in BrS.



A typical case presentation showing morphological variations of ST segment associated with taking meals. Saddle-back-type ST segment before each meal changed to coved type after breakfast, lunch, and dinner. ST segment morphology returned to saddle-back-type at midnight and at 3:00 a.m. from coved type. Please note that the changes are most markedly present in lead V2 (**Nishizaki 2008**).

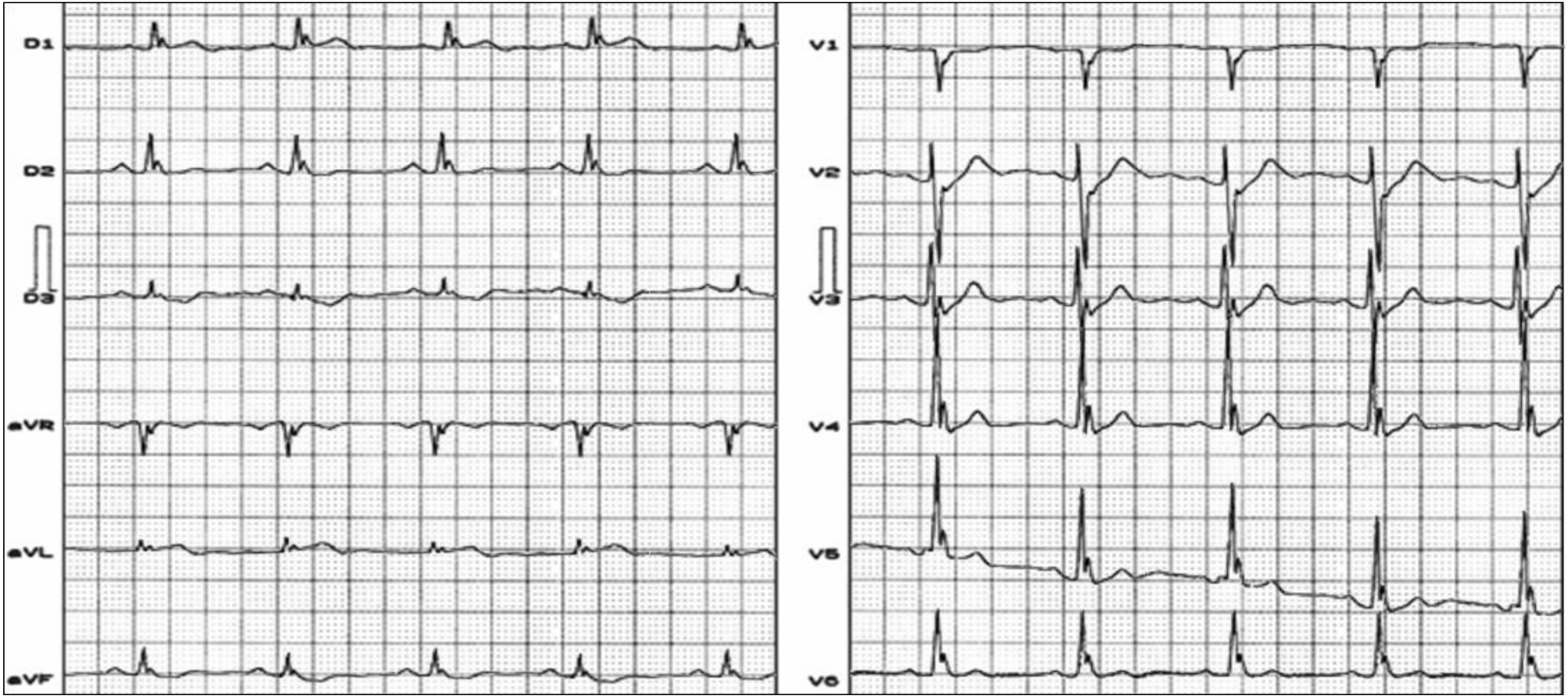
13. Loss of rate-dependent QT dynamics (**Sangawa 2009**).
14. The presence of horizontal (as opposed to rapidly ascending) ST segment after the J point (**Takagi 2013**).
15. Augmentation of the ST segment elevation during the early recovery phase of exercise test (**Makimoto 2010**).
16. Deep negative T wave in lead V1 (**Miyamoto 2011**).
17. The presence of atrial arrhythmias (**Bordachar 2004**) and atrial fibrillation (**Kusano 2008**).



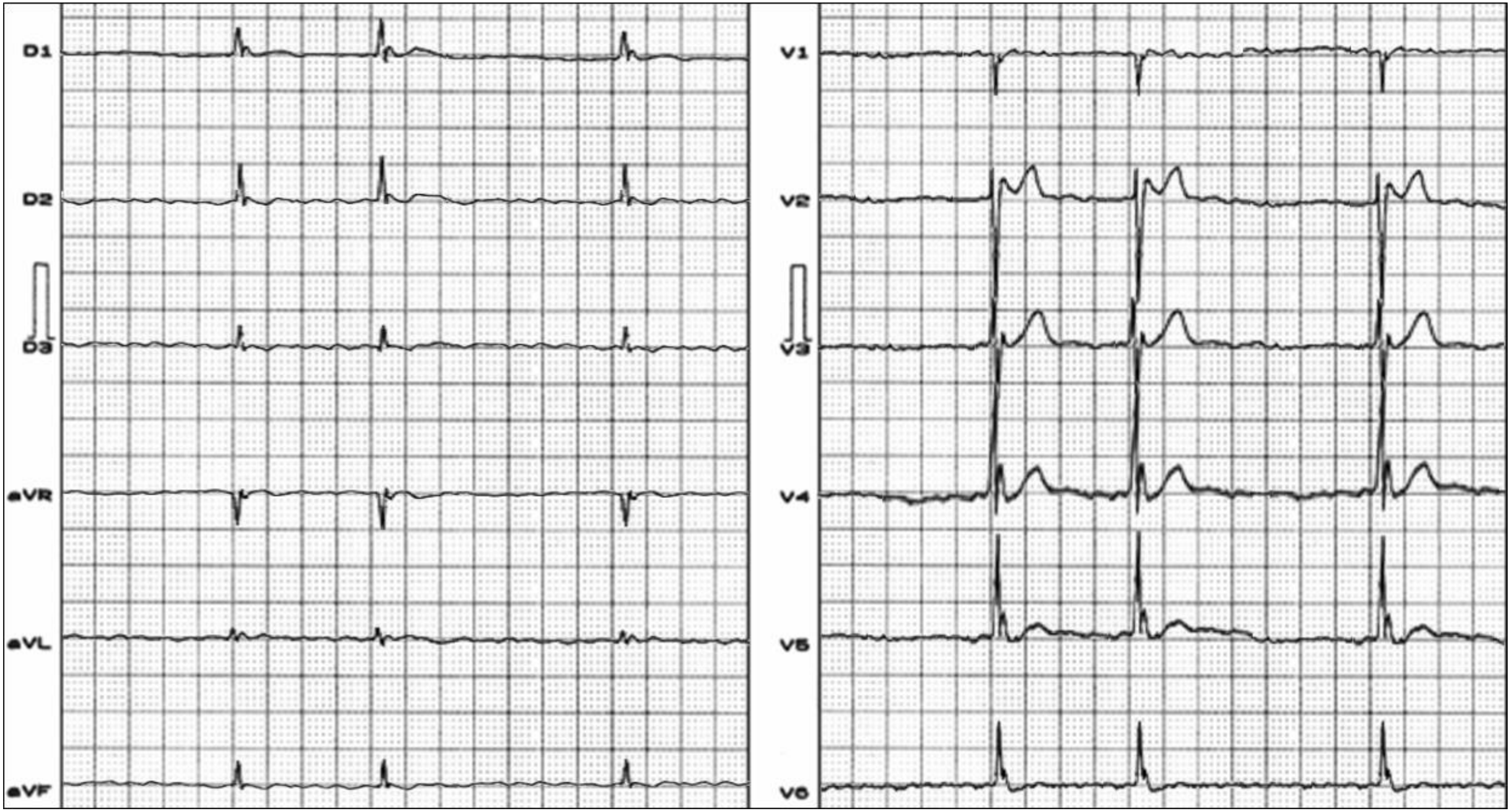
Example of a spontaneous notched J wave in both the inferior and lateral leads. A, The ECG of a 53-year-old Asian male proband after admission with aborted SD shows notched J wave both in the inferior and lateral and even in the precordial leads V3 to V6 (arrows). B, A follow-up ECG shows in the inferior leads less pronounced J wave (arrows) in the presence of AF and type II saddle back BrP in the right precordial lead V2. C, The administration of 0.5 mg/kg ajmaline provoked the diagnostic type I ECG pattern in the right precordial leads V1 and V2.

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 BrS.

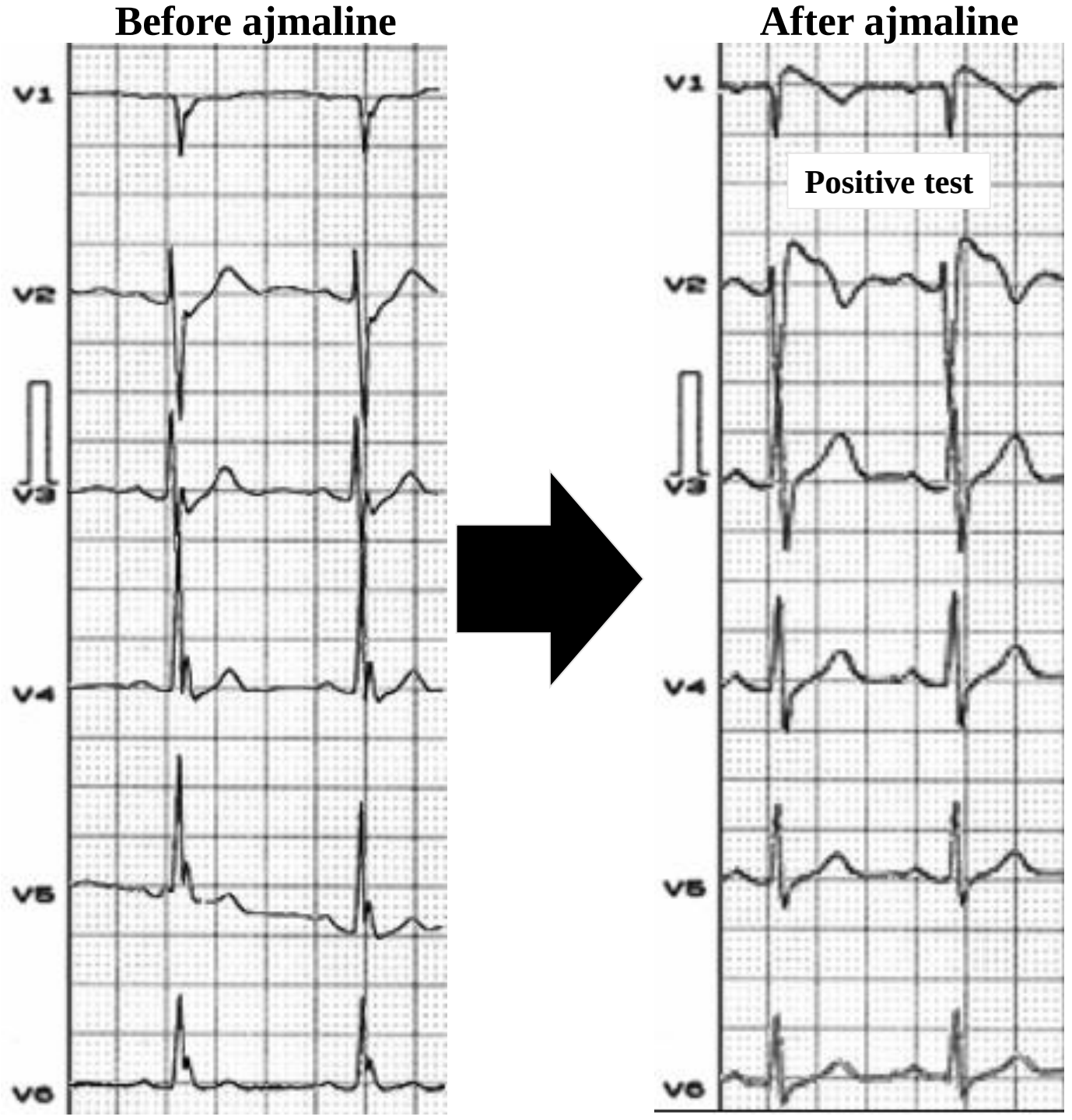
Sinus rhythm J-wave in anterolateral and inferior leads without ST segment elevation



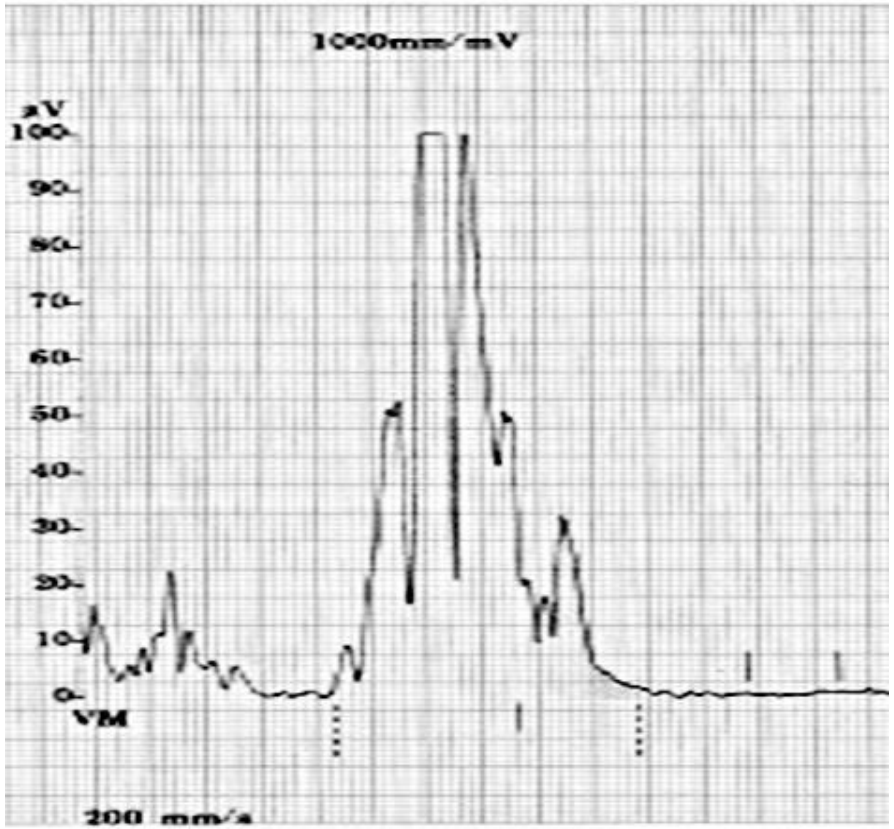
The same patient during AF J-wave in anterolateral leads without ST segment elevation and type 2 Brugada pattern in V2

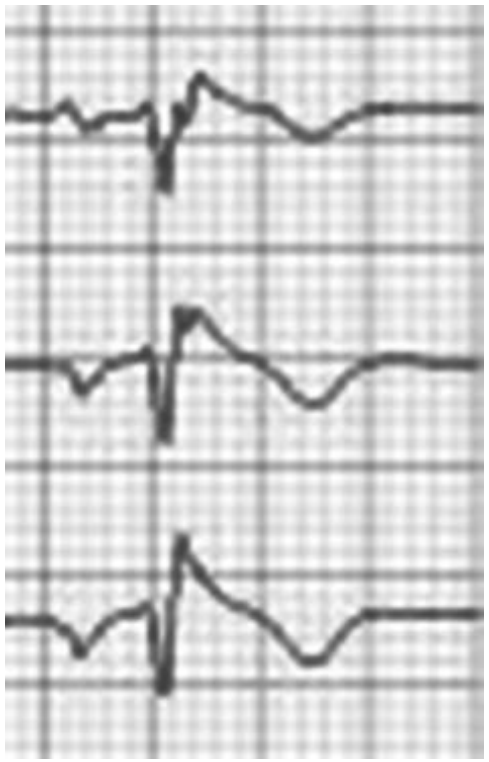


We performed intravenous ajmaline test. See next slide.


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

1. Combination of depolarization and repolarization abnormalities: A history of VF and syncope episodes, paroxysmal AF, spontaneous type 1 pattern, markers of depolarization abnormalities (QRS duration ≥120 ms in V2 and II, f-QRS) and repolarization abnormalities (inferolateral early repolarization pattern and QT interval prolongation) are associated with later cardiac events. On multivariable analysis, a history of VF and syncope episodes, inferolateral ER pattern, and f-QRS are independent predictors of documented VF and SCD (**Tokioka 2014**).
2. The presence of Late potentials (LPs) (**Huang 2009; Ikeda 2011**). 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 bundle branch block, 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.





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).

In BrS recognized risk factors include symptoms, male sex, and spontaneous type 1 ECG pattern, but the role of PES as prognosis value remains controversial and seems to depend on the phenotypic expression of the channelopathy. Different groups have published contradictory data. Risk stratification in BrS is important to guide ICD implantation and prevent SCDs. Long-term follow-up is needed to clarify this issue. Inducibility of ventricular arrhythmias at PES ranges between 50% and 80% of patients with BrS. However, the variety of PES protocols and the lack of data relative to a control group or to ventricular arrhythmia reproducibility contribute to a still undefined interpretation of PES outcome in BrS. PES inducibility is deeply influenced by the protocol used. PES outcome is reproducible at a mid-term follow-up mainly if a categorical endpoint (inducible vs noninducible) is used. The need to assess the predictive value of specific PES protocols in targeted studies is widely emerging (**Gasparini 20002**). Patient are considered inducible if a sustained ventricular arrhythmia (VF, polymorphic VT, or monomorphic VT (SMVT) lasting >30 seconds or requiring emergency intervention) is induced (**Brugada 2003**). The recommended protocol is a single site of stimulation on right ventricular apex, 3 basic pacing cycles (600, 500, and 430 ms), and introduction of 1, 2, and 3 VPBs down to a minimum of 200 ms. The stimulation current is 4 mA and 2.0 ms width, without repetition of extra stimulation. Its low reproducibility is explained by the highly variable protocols used in various centers (**Priori 2012; Probst 2010; Brugada 2003**). Current international guidelines recommend EPS with class IIB1 (**Priori 2012**), however, Sieira et al (**Sieira 2015**) in a study with 20-year follow-up showed that EPS is a good predictor of outcomes in BrS individuals, but not absolute. It might be of special value to guide further management when performed in asymptomatic individuals. The overall accuracy of the test makes it a suitable screening tool to reassure noninducible asymptomatic individuals. VAs inducibility with single or double extra-stimuli in patients with type 1 BrS ECG is a negative prognostic indicator, compared to the protocol with triple extra-stimuli. The number of extrastimuli that induced VA served as a prognostic indicator for patients with type Brp. Single extrastimulus or double extrastimuli are adequate for PES of patients with BrS (**Makimoto 2012**). Are factors that affect VAs inducibility at EPS the presence of symptoms, male sex, a conduction delay with prolonged HV interval, and first-degree AV block, supporting the hypothesis of the conduction/depolarization anomaly. Inducible VF in a BrS patient with pre-existing RBBB, is a negative prognostic factors. The conduction disturbances are associated with repolarization dispersion in BrS and may worsen the prognosis. The controversial role of EPS in risk-stratification could depend on the dynamic phenotypic channelopathy expression. International guidelines recommend provocative drug tests with IV administration of Na^+-channel blockers in class IC1, because of their diagnostic key role when BrS is suspected. They can unmask BrS pattern by unbalancing the transmembrane ion fluxes equilibrium in favor of the repolarizing I_{to} current, resulting in J-wave and ST-segment elevation in the right precordial leads. Since a negative EPS could be interpreted as a low-risk non-type 1 BrS, or depend on the dynamic nature of the ECG modifications and on its unclear reproducibility, when type 1 BrS is suspected drug challenge is mandatory. In this case, VAs induction by PES occurred after maximizing type 1 BrP during ajmaline administration, and did not occur otherwise. PES induced VF only when type 1 BrP.

Mechanisms underlying the electrocardiographic and arrhythmic manifestations of Brugada syndrome

There are four hypothesis:

1) **Depolarization mechanism:** Conduction delay or conduction slowing in atria and ventricles mainly in RVOT, first degree AV block, HV prolongation, split His, fragmented QRS, late potentials, which reflect delayed and discontinuous ventricular depolarization structural changes involved, albeit relatively mild changes which may not become evident with echocardiography and magnetic resonance imaging). In an explanted heart and in right ventricular biopsies it was found that structural abnormalities (fibrosis, myocarditis, apoptosis) were present. Transmural dispersion of repolarization would require complete uncoupling of endocardium and epicardium (**Morita 2008**), which is not physiological possible in the human heart. Coronel et al (**Coronel 2005**) studied a BrS patient without clinically detected cardiac structural abnormalities underwent cardiac transplantation for intolerable numbers of ICD discharges. The patient's explanted heart was studied electrophysiologically and histopathologically. Whole-cell currents were measured in HEK293 cells expressing wild-type or mutated sodium channels from the patient. The RVOT endocardium showed activation slowing and was the origin of VF without a transmural repolarization gradient. Conduction restitution was abnormal in the RVOT but normal in the LV. Right ventricular hypertrophy and fibrosis with epicardial fatty infiltration were present. HEK293 cells expressing a G1935S mutation in the gene encoding the cardiac Na^+ channel exhibited enhanced slow inactivation compared with wild-type channels. Computer simulations demonstrated that conduction slowing in the RVOT might have been the cause of the ECG changes. Recently, catheter ablation therapy in BrS revealed that the RVOT epicardium has abnormal potentials associated with myocardial fibrosis and conduction delay.30 In the conduction abnormality theory, the reentrant circuit that maintains rapid polymorphic ventricular arrhythmias can also be in a small area within the RVOT (**Krummen 2014; Pandit2013**).

2) **Repolarization mechanism**: Action potentials (Aps) recorded from epicardial and M cells, unlike those recorded from endocardium, display a spike-and-dome morphology, the result of a prominent transient outward current-mediated phase 1. M cells are distinguished from endocardial and epicardial cells by the ability of their AP to prolong disproportionately in response to a slowing of rate and/or to agents with class III actions. This intrinsic electrical heterogeneity contributes to the inscription of the ECG as well as to the development of a variety of cardiac arrhythmias. The transmural dispersion of repolarization is in large part responsible for the inscription of the J wave and T wave of the ECG. **Experimental demonstration**: It is well established that mutations leading to a decrease in inward currents (I_{Na} or I_{CaL}) or increase in outward currents (I_{to} and $I_{K\text{-}ATP}$) are capable of causing BrS in humans (**Delpón 2008; London2007; Antzelevitch 2007**). Milrinone and cilostazol, oral phosphodiesterase (PDE) type III inhibitorsincrease L-type calcium channel current ($I_{Ca}{}^{+2}$) and modestly increase heart rate by elevating the level of intracellular cyclic adenosine monophosphate. Milrinone as a more potent alternative to cilostazol for reversing the

repolarization defects responsible for the ECG and arrhythmic manifestations of BrS. Both drugs normalize ST-segment elevation and suppress arrhythmogenesis in experimental models of BrS (**Szél 2013**). Phase 2 reentry is a possible mechanism of BrS. A canine model of BrS shows that the dynamic action potential heterogeneity at the RVOT generates a voltage gradient within the epicardium at phase 2 of the AP and promotes functional reentry (phase 2 reentry).8–10 Phase 2 reentry occurs in tissues with an area of 1–2cm^2 and reentrant VT within such a small area can be a focal activation pattern in the BSM recordings (**Morita 2008; Yang 1999; Morita 2007**).

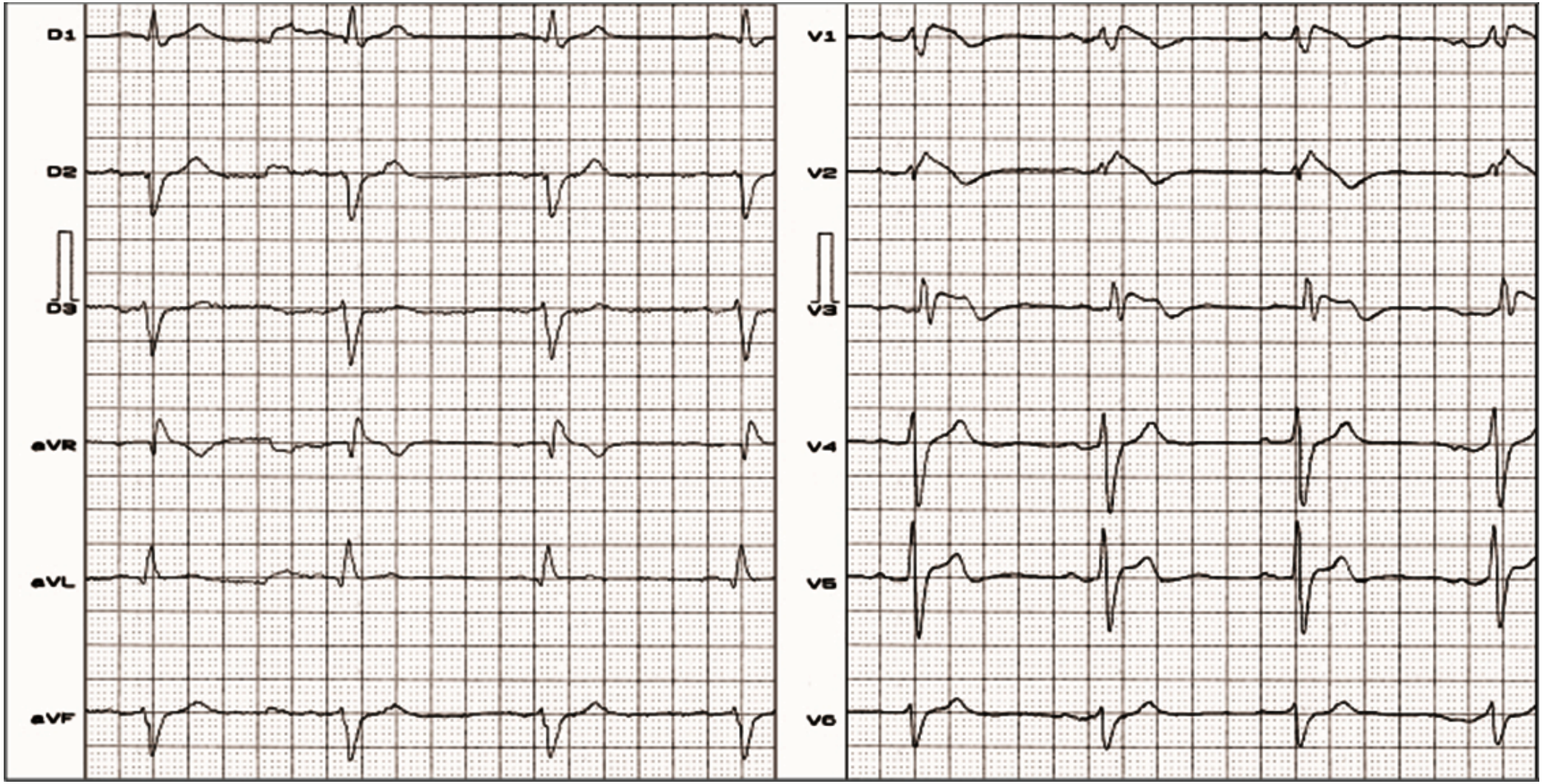
Basic and clinical evidence indicates that J waves are repolarization rather than depolarization/conduction abnormalities. J waves as repolarization components are commonly seen in young males without structural heart disease. However, depolarization/conduction abnormalities are commonly found in aged individuals with obvious structural heart diseases.

J waves display a characteristic pause-dependent accentuation.(**Aizawa 2012; Mizimaki 2004**) In addition, isoproterenol diminishes J waves and can prevent VF in subjects with J wave syndromes, which does not favor J wave syndromes as depolarization/conduction disorders. This is because that depolarization/conduction defects should become more prominent with tachycardia in the presence of isoproterenol and improve during bradycardia. The magnitude of J waves decreases during tachycardia because the I_{to}-mediated AP notch decreases from inadequate time for the I_{to} to full recover. More solid evidence in support of J wave syndromes as repolarization abnormalities is the inhibitory effect of quinidine on both I_{Na} and I_{to}. Quinidine diminishes J wave amplitude and the concealed phase 2 reentry by inhibiting I_{to} and suppressing so-called “late ventricular potentials” and VF in BrS and other J wave syndromes (**Yan 1999; Szél 2014**).

4. **Eclectic theory**: We demonstrate using ECG/VCG that in the BrS both mechanism depolarization and repolarization are operative. The following case of our series demonstrate both mechanism Right End Conduction Delay on RVOT area and primary T wave: velocity of inscription of afferent and efferent limbs of the T loop (circular, small, of symmetrical limbs) and with a 1:1 length/width ratio (**Pérez-Riera 2008**).

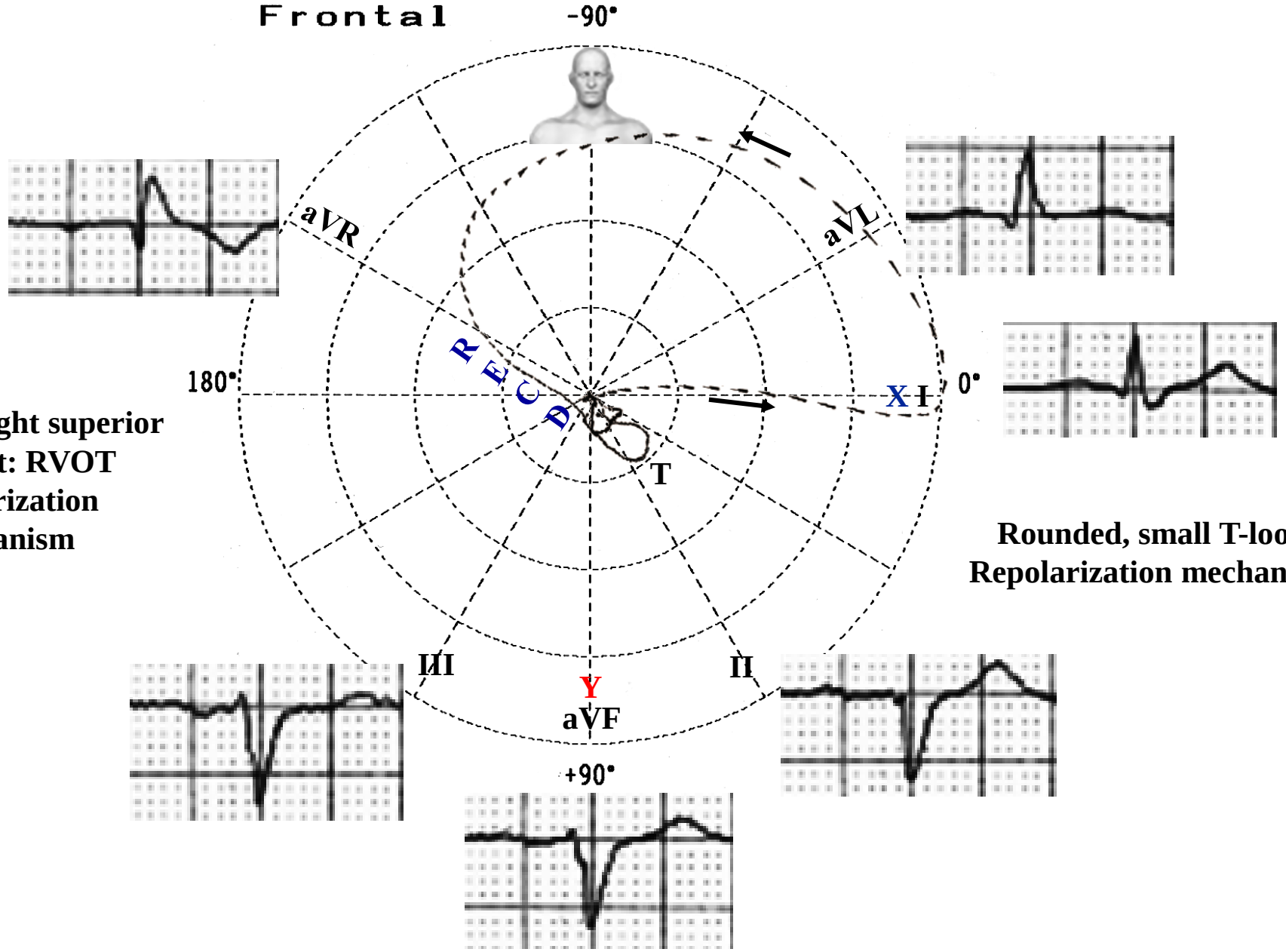
Clinical features: Syncope. Positive familiar background of sudden death in young (≤35yo) first-degree relative. Genetic research performed: negative.

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



ECG diagnosis: Sinus bradycardia (heart rate under 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 or RECD Type IA?

ECG/VCG correlation in the Frontal Plane

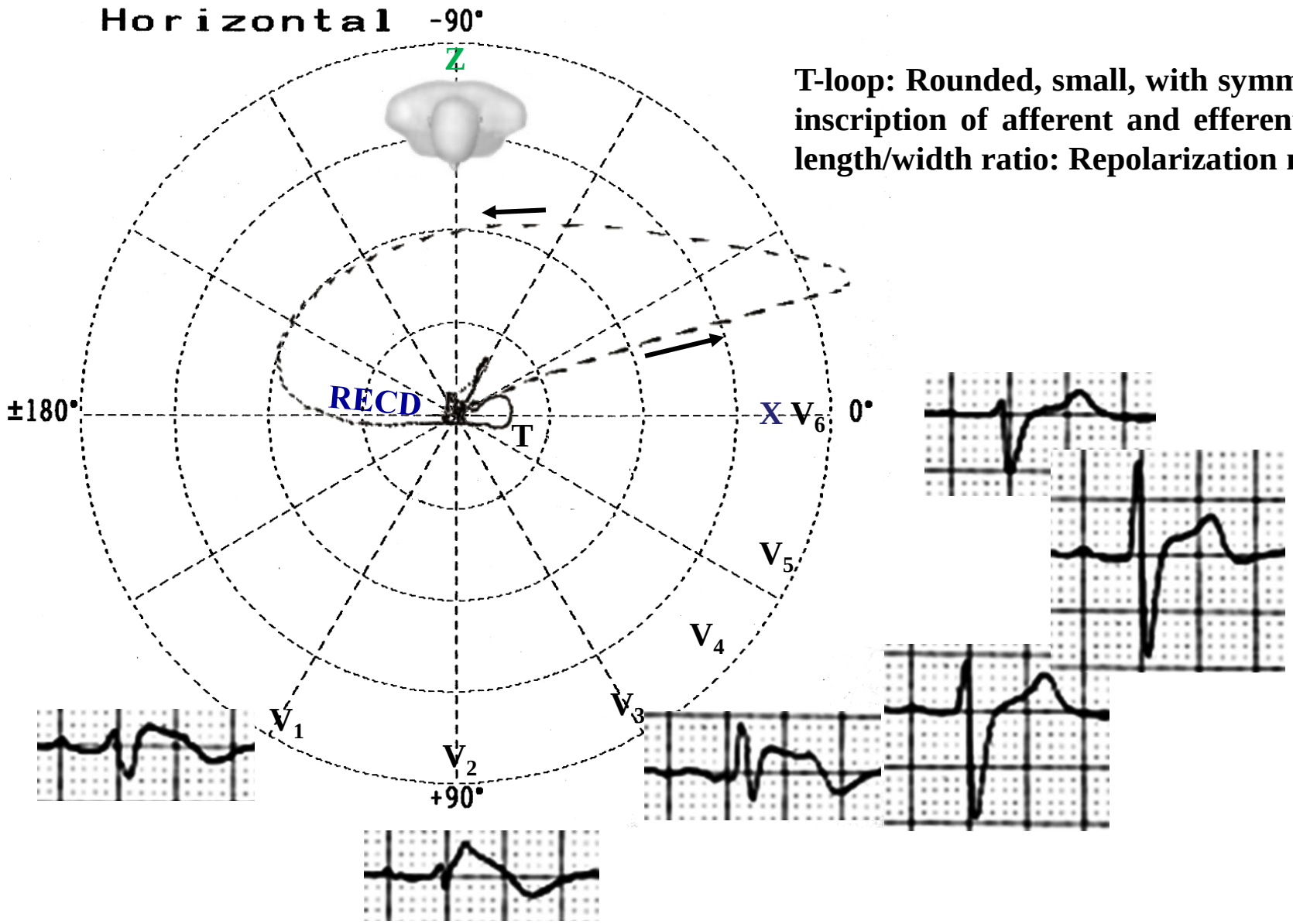


RECD on right superior quadrant: RVOT Depolarization mechanism

Rounded, small T-loop Repolarization mechanism

Initial 20 ms QRS forces directed to left, SII>SIII, extreme left axis deviation, CCW, **RECD** located near -150° : prominent final R wave in aVR.

ECG/VCG correlation in the Horizontal Plane

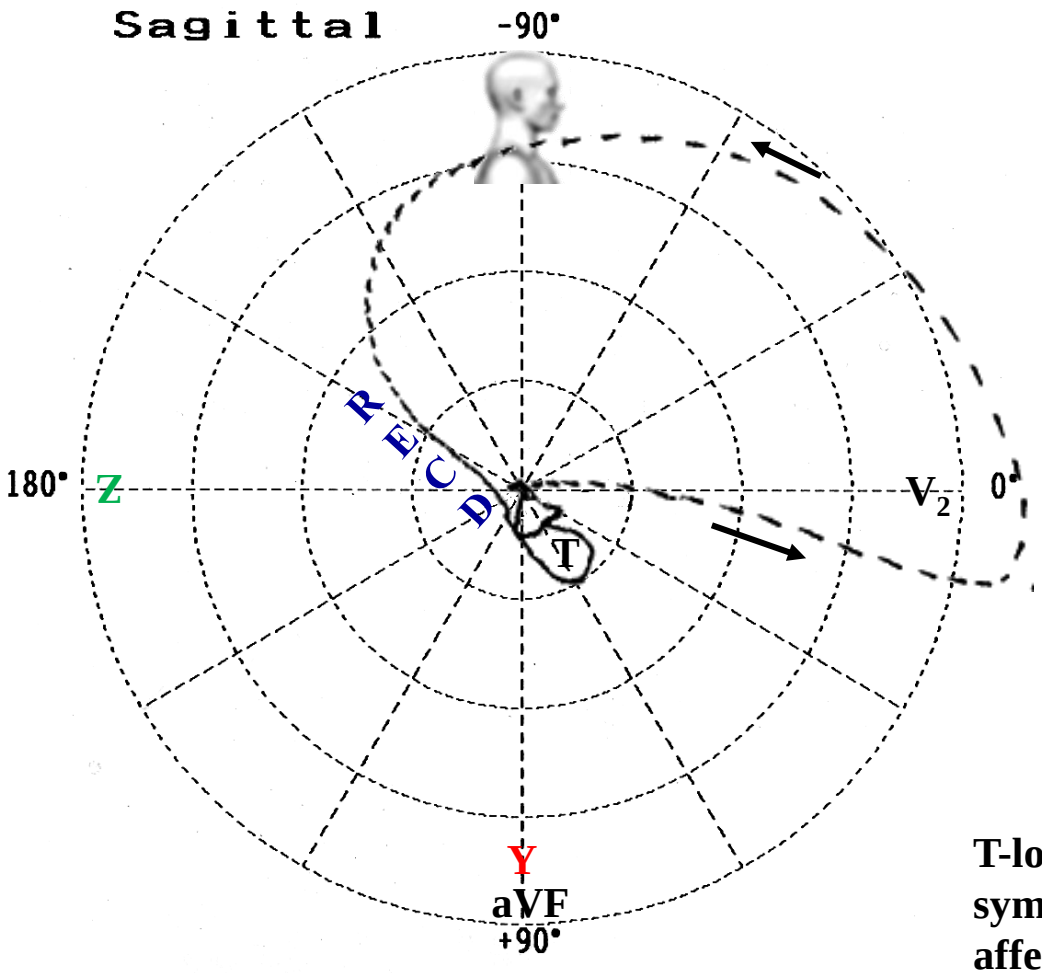


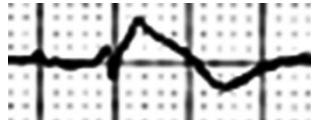
T-loop: Rounded, small, with symmetrical velocity of inscription of afferent and efferent limbs and a 1:1 length/width ratio: Repolarization mechanism.

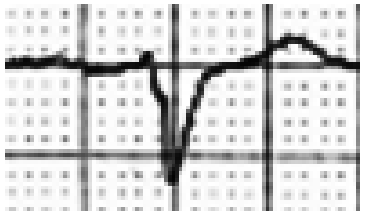
Type 1 BrP, initial forces directed to left and backward, **RECD** on orthogonal X lead (±180°), rS/RS in left leads with S > R, primary T-loop.

ECG/VCG correlation in the Right Sagittal Plane

RECD on upper posterior quadrant: Depolarization mechanism

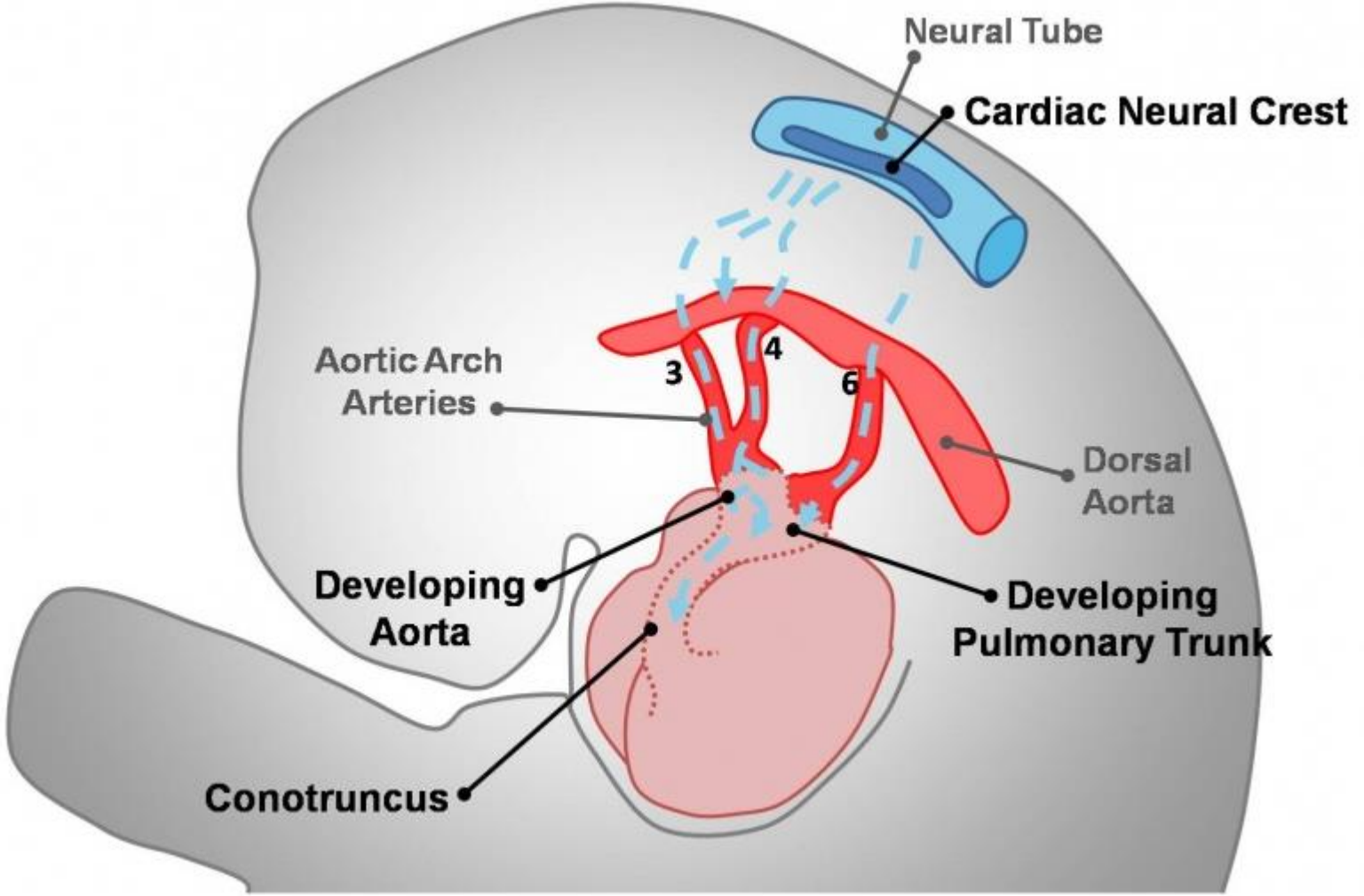






T-loop: Rounded, small, with symmetrical velocity of inscription of afferent and efferent limbs and a 1:1 length/width ratio: Repolarization mechanism.

4. **Abnormal expression of cardiac neural crest cells in heart development** (**Elizari 2007**) in fact this theory is also eclectic because it admits both mechanisms: depolarization and repolarization. The cardiac neural crest cells are a subpopulation of cranial neural crest discovered nearly 33 years ago by ablation of premigratory neural crest. The cardiac neural crest(CNC) cells are necessary for normal cardiovascular development.



Cardiac neural crest (CNC) cells migrate from the neural tube to the circumpharyngeal ridge (i.e.,circumpharyngeal crest), caudal pharyngeal arches (third, fourth, and sixth), and outflow tract (OFT) just before asymmetrical remodeling of the aortic arch arteries. Some of the CNC cells migrate in and envelop the nascent aortic arch arteries, while others continue to migrate and eventually colonize to later form the aorticopulmonary septum.

Elizari et al has been proposed regarding the etiopathogenesis of the BrS linked to the abnormal expression of the cardiac neural crest (CNC) on myocardial development of the RVOT. Of the four cardiac chambers, the RV is anatomically, phylogenetically, and developmentally the most complex. Additionally, clinically, it is the most critical chamber because the most complex congenital cardiac anomalies involve the RV, as do the congenital arrhytmogenic syndromes. RVOT formation, which comprises the free wall and the aortopulmonary septum, requires participation of an extracardiac cell source, the CNC. The contribution of the CNC cells to cardiac development was first recognized by Kirby (**Kirby 1983**). In experimental studies, showed the relationship between outflow tract malformations and the disturbed CNC. Kirby´s manuscript showed that ablation of specific points of the premigratory CNC in chicken embryons caused a wide spectrum of outflow tract and great arteries malformations. In mutant and transgenic mice have refined this theory, indicating that "the outflow tract septation is a very vulnerable process" and that "the abnormalities that can be evoked include the myocardium (**Gittenber-de Groot 2000**; Moreover, the neural crest cell death program plays an active role in stimulating outflow tract myocardialization (**Poelmann 1999; van den Hoff MJ, 1999**). A population of CNC cells migrates toward the arterial pole of the embryonic heart, and the aortic arch. On the other hand, a second route of migratory CNC cells uses the venous pole as entrance to the heart. These neural crest cells reach the area of the future location of the AV node, His bundle, and beginning of the bundle branches. They are distinguished around the mitral and tricuspid orifices and the pulmonary veins (**Gittenber-de Groot 2000**; **Poelmann 1999**). Neural crest cells also contribute to the development of part of the atrial tissues that play an important role in closing the primary atrial septal foramen and septation of the AV canal. Likewise, they are involved in morphogenesis of the pulmonary veins. Thus, eventual abnormalities in this developmental process may be correlated with the fact that a proportion of patients with BrS exhibit paroxysmal AF and other supraventricular arrhythmias (**Antzelevitch 2005**). Consequently, it is reasonable to postulate that the arrhytmogenic substratum in BrS should not be restricted to the ventricular level and may well also account for the occurrence of supraventricular arrhythmias. Among other molecules, the connexins (Cxs), particularly Cx 43, are known to be strongly involved in neural crest cell migration and are expressed in adult working myocardium. Cx 43 function may be of critical importance in downstream events involving migration of neural crest cells and that heart defects, when present, involve the RV (**Ewart 1997**). Slower or faster migration of neural crest in vitro and in situ was directly correlated with overexpression or underexpression of Cx43 (**Waldo 1999**). Quantification by immunofluorescence has demonstrated significantly lower expression of Cx 43 in subepicardial compared with deeper layers, thus creating and contributing to transmural heterogeneity (**Poelzing 2004**). It has also been postulated that mistiming of CNC migration or malfunction of the crest cells as a consequence of altered gap junctional communications may have profound effects on tissue remodeling depending on CNC cells (**Söhl. 2004**). Cx43 contribute to the propagation proprieties of the cardiac impulse. Interestingly, transmural distribution of Cx43 is heterogeneous, being twice as abundant in midmyocardium

and endocardium compared with epicardium (**Yamada 2004**). Lesser expression of Cx43 and, hence, gap junctional impairments in the epicardium may contribute to heterogeneous electrophysiologic properties throughout the ventricular wall favoring both transmural repolarization heterogeneity and slower dromotropic velocity in the epicardium. The effect of such heterogeneity would influence both repolarization and depolarization proprieties (**Smits 2002**). Abnormal myocardialization dependent on CNC expression in the RVOT might also explain repolarization heterogeneities underlying the phenotype of BrS. Inhomogeneous transmural and regional Cx43 distribution in the RVOT may lead to conduction slowing and late activation of the RVOT in BrS. The wide spectrum in the severity or magnitude of ECG and clinical manifestations of BrS must correlate with the existence of a wide spectrum in the severity of underlying cellular abnormalities in the RVOT. Similarly, the well-known dynamic changes of the Brugada phenotype should be interpreted as the consequence of the interaction between the magnitude of the pathophysiologic compromise of the substrate and the strength of the triggers. A pre-ECG alteration very close to threshold may readily shift from unapparent to manifest or vice versa. The fact that Na^+ channel blockers exacerbate repolarization changes and depress conduction, increasing QRS duration to a grater extent in patients with BrS than in controls, suggests the presence of a Na^+ channel and/or a gap junctional disorder, In an area with scarce, poor devoid of, Purkinje fibers as it happens in the RVOT, a reduced Na^+ current under the effect of a Na^+ -channel blocking drug and a poorer distribution of gap junctions in the RVOT may lead to slow conduction contributing to the ECG/VCG and electrophysiologic manifestations of BrS.

The exact manner in which abnormal expression of the CNC affect ionic current and/or gap junctions should be explored.

It can be hypothesized that repolarization gradients causing ST-SE occur not only between the epicardium and endocardium but also between the RVOT ad normal surrounding myocardium. The unequal distribution of repolarizing forces between the epicardium and subendocardial layers due to stronger I_{to} expression in epicardium than in endocardium might also apply between the RVOT and surrounding normal myocardium.

Probable relationship between abnormal expression of neural crest cell migration and “idiopathic” arrhythmias

As already mentioned, during development of the heart, neural crest cells play a fundamental role in normal cardiac morphogenesis using two main routes: the arterial pole and the venous pole using the pharyngeal arches and the dorsal mesocardium, respectively. Neural crest cells using the arterial pole are involved on development of the outflow tracts and the aortopulmonary septum, part of the interatrial septum, the semilunar aortic and pulmonary valves, and the initial segments of the great vessels.

The vast majority of RVOT VTs and PVCs (both septal and free wall) arise from myocardium within the first 1 to 2 cm beneath the pulmonary valve. The occurrence of any form of ventricular arrhythmia arising form the RVOT brings to mind its probable relationship with the same or an analogous substrate of BrS and a similar and peculiar embryogenesis and development of this cardiac area.

Cine magnetic resonance imaging and right ventriculagraphy, disclosed a substantial incidence of segment contraction abnormalities and local thinning of the RVOT in patients with arrhythmias originating from the RVOT as in BrS (**Antzelevitch 2005; Morita 2003; Papayassiliu 2004**). Notably, a significant number of patients with the typical picture of BrS show the same configuration of RVOT PVCs and RVOT tachycardias. The same etiopathogenic mechanism may also be postulated in other idiopathic arrhythmias arising in semilunar aortic and pulmonary valves and around the mitral ring considering that theses areas are related to a similar embryogenesis.

Phase 2 reentry is a possible mechanism of BrS. A canine model of BrS shows that the dynamic action potential heterogeneity at the RVOT generates a voltage gradient within the epicardium at phase 2 of the action potential and promotes functional reentry (phase 2 reentry). Phase 2 reentry occurs in tissues with an area of 1–2cm^2 and reentrant VT within such a small area can be a focal activation pattern in the BSM recordings.

Brugada Syndrome (BrS) Expert Consensus Recommendations on Brugada Syndrome Diagnosis (Priori 2013)

1. BrS is diagnosed in patients with ST-segment elevation with type 1 pattern≥ 2mm lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS is diagnosed in patients with type 2 or type 3 STSE ≥ 1 lead among the right precordial leads V1,V2, positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induce a type 1 ECG pattern.

Expert Consensus Recommendations on Brugada Syndrome Therapeutic Interventions

Class I
1. The following lifestyle changes are recommended in all patients with diagnosis of BrS:
   a) Avoidance of drugs that may induce or aggravate STSE in right precordial leads: visit www.Brugadadrugs.org
   b) Avoidance of excessive alcohol intake.
   c) Immediate treatment of fever with antipyretic drugs.
2. ICD implantation is recommended in patients with a diagnosis of BrS who:
   a) Are survivors of a cardiac arrest and/or b) have documented spontaneous sustained VT with or without syncope.

Class IIa
3. ICD implantation can be useful in patients with a spontaneous diagnostic type 1 ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
4. Quinidine can be useful in patients with diagnoses of BrS or history of arrhythmic storms defined as more than two episodes of VT/VF in 24hours.
5. Quinidine can be useful in patients with diagnoses of BrS:
   a) Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or b) Have a history of documented supraventricular arrhythmias that require treatment.
6. Isoproterenol infusion can be useful in suppressing arrthmic storms in BrS patients.

Class IIb
7. ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during PES (inducible patients).
8. Quinidine may be considered in patients with a diagnosis of BrS and history of arrhythmic storm or repeated appropriate ICD shocks.
9. Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

Class III
10. ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and on the basis of family history of SCD alone.

My own approach to asymptomatic Brugada syndrome*

Spontaneous type I

Yes → **Quinidine**

If quinidine not tolerated:
Risk factors + → cilostazol ?
Risk factors - → hope for the best

No EPS

No → **No therapy**

Repeat ECG and Holter
NO ajmaline test

*** Class 1-D indication (based on non-expert opinion)**

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. The rapid Na^+ channel block accounts of its greater effect on depressing V_{max} at faster rates. In the Brugada disease it is used by its property to block the Ito channel and thus restorer electrical homogeneity across ventricular myocardial wall and in abolishing arrhythmias by phase 2 reentry. Quinidine, by virtue of its actions to block I(to), has been proposed as adjunctive therapy, with an implantable cardioverter defibrillator as backup. Additionally the drug has a benefic vagolytic effects occur through muscarinic (M_2) receptor block.

Channels and receptors block by Quinidine

Fast Na+ current; Ito1 channel or transient outward current; Inward rectifier IK1, delayed rectifier: IKS, IKR and IKUR, I KATP or adenosine triphosphate ATP sensitive potassium channel, IK-Ach, lpha 1 and alpha 2 adrenergic receptors: can cause orthostatic hypotension and reflex sinus tachycardia; M2 muscarinic receptor.

Pharmacokinetics

Bioavailability: 70% to 85%; Protein binding: 70% to 95% with alpha 1 Glicoprotein; Time to Peak Concentration: 1h to 4h; Elimination T1/2: 6h o 8h; Therapeutic Range 2 to 5 micrograms/ml; Elimination Route: hepatic through the cytochrome P450 system.

Effects on ECG and Electrophysiological intervals

SCL: > or 0; PR interval: 0; QRS interval > +; QT/QTc interval: > ++; JT interval: > ++; AH interval: <+; HV interval: >+; Atrium Effective Refractory Period: >+; Atrioventricular Node Effective Refractory Period: >+; His-Purkinje system Effective Refractory Period: > +; Ventricle Effective Refractory Period: >+; Accessory Pathway Effective Refractory Period >+.

In 1987, Imaizumi et al (**Imaizumi 1987**) showed that quinidine induced inhibition of transient potassium outward current, potassium initial outflow ("transient outward current"), or "4-aminopyridine sensitive outward current" in cardiac muscle**.**

Yatani et al **(Yatani 1993.)** cloned cardiac K^+ channel transient outward type by quinidine**.**

Research from the Masonic Medical Research Laboratory has suggested a new pharmacological approach to therapy using "transient outward current" blockers. This pharmacologic alternative may be critically important in many parts of the world where ICDs are not affordable (**Antzelevitch2000.).** Additionally, this is particularly important because Brugada patients are at risk of SCD since the age of 6-month-old (**Suzuki 2000.**), and ICD implant is not feasible in very young children (**Gaita 2004.**). Belhanssen et al **(Belhassen 1999)** performed EP studies in 34 consecutive patients who had IVF with (n = 5) or without (n = 29) the BrS. All patients with inducible SPVT/VF underwent repeated EP evaluation after oral administration of quinidine. Patients rendered noninducible received this therapy on a long-term basis. SPVT/VF were induced in 27 (79.4%) patients at baseline studies. Quinidine effectively prevented induction of SPVT/VF in 26 (96%) patients. Of the 23 patients

treated with these medications, no patient died or had a SVT during a mean follow-up period of 9.1 +/- 5.6 years (7 to 20 years in 15 patients). Two deaths occurred in patients without inducible SPVT/VF at baseline studies who had been treated empirically. Its results suggest that EP-guided therapy with quinidine is a reasonable, safe, and effective approach for the long-term management of it patients.

Chen et al (**Chen 2008**) observed a decrease or disappearance of ST elevation in right precordial leads with administration of quinidine by decreasing in the initial outflow of potassium through the Ito channel. The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalize the elevation of the ST segment in BrS (**Alling 2001**). Additionally, it could improve repolarization due to its vagolytic effect (M_2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone. At a dose of 1000mg (**Mok 2004**) to 1500mg/day oral (300mg every 6 hours) quinidine bisulphate can be successful for suppress the electrical storm. The drug also normalize the ST-segment elevation in right precordial leads, suppress all ambient unifocal PVCs and induction of VF on PES. Hydroquinidine therapy prevented VT/VF inducibility in 76% of asymptomatic patients with BrS inducible arrhythmia, as well as VT/VF recurrence in all BrS patients with multiple ICD shocks. These preliminary data suggest that preventive treatment with it drug may be an alternative strategy to ICD placement in asymptomatic patients with BrS and inducible arrhythmia **(Hermida 2004).**

Management of patients with BrS is still far from being well defined. Interestingly in some reports, hydroquinidine has been found to reduce the incidence of ventricular arrhythmia in the follow-up as well as the rate of ventricular arrhythmia induction in the EP lab. Yet, prophylactic ICD implantation remains the treatment of choice in symptomatic and inducible patients. **(Anselme 2005).** After arrhythmic storm quinidine could be effective to stop these new omiosus events (**Marquez 2005**).

Schweizer et al (**Schweizer 2010**) presented a case with successful acute and long-term management of electrical storm in BrS using orciprenaline and quinidina.

Mehrotra et al (**Mehrotra 2011**) related a case of a 10-year-old girl developed life-threatening recurrent PVT following surgical closure of a secundum atrial septal defect successful post hoc analysis of a Holter recording suggested BrS. After managing the acute phase, a dual chamber defibrillator was implanted. One week later she experienced VF electrical storm (ES), needing 96 appropriate shocks within a few hours. Quinidine, by virtue of its I_{to} blocking property, is the only drug reported to be useful in managing VF-ES in BrS. Non availability of quinidine led us to try its diastereomer, intravenous quinine, which succeeded in controlling the VT. ES in the setting of ion channelopathy can be difficult to manage, and sometimes requires innovative therapies.

Bouzeman et al (**Bouzeman 2014)** evaluated the long-term efficacy and safety of an electrophysiologically guided therapy, based on a strategy of treatment using hydroquinidine (HQ) among asymptomatic BrS patients with inducible VF. In two French reference centers, consecutive asymptomatic type 1 BrS patients with inducible VF were treated with HQ (600 mg/day, targeting a therapeutic range between 3 and 6 µmol/L) and enrolled in a specific follow-up (mean 6.6 ± 3 years), including a second PVS under HQ. An ICD was eventually implanted in patients inducible under HQ, or during follow-up in case of HQ intolerance, as well as occurrence of arrhythmic events. From a total of 397 BrS patients, 44 were enrolled (47 ± 10 years, 95% male). Of these, 34 (77%) were no more inducible (Group PVS-), and were maintained under HQ alone during a mean follow-up of 6.2 ± 3 years. In this group, an ICD was eventually implanted in 4 patients (12%), with occurrence of appropriate ICD therapies in one. Among the 10 other patients (22%), who remained inducible and received ICD (Group PVS+), none of them received appropriate therapy during a mean follow-up of 7.7 ± 2 years. The overall annual rate of arrhythmic events was 1.04%, without any significant difference according to the result of PVS under HQ. One-third of patients experienced device-related complications. This long-term follow-up results emphasize that the rate of arrhythmic events among asymptomatic BrS patients with inducible VF remains low over time. This results also suggest that residual inducibility under HQ is of limited value to predict events during follow-up. Recently, Anguera et al (**Anguera 2016**) verifed shock reduction with long-term quinidine in patients with brugada syndrome and malignant ventricular arrhythmia episodes. Belhassen et al (**Belhassen 2015**) studied with an aggressive protocol of PVS 96 patients with BrS. 10 were cardiac arrest survivors, 27 had presented with syncope, and 59 were asymptomatic. VF was induced in 66 patients, including 100%, 74%, and 61% of patients with cardiac arrest, syncope, and no symptoms, respectively. All but 6 of the 66 patients with inducible VF underwent EPS testing on quinidine (n=54), disopyramide (n=2), or both (n=4). 54 (90%) patients were electrophysiological responders to >1 AAD with similar efficacy rates (≈90%) in all patients groups. Patients with no inducible VF at baseline were left on no therapy. After a mean follow-up of 113.3±71.5 months, 92 patients were alive, whereas 4 died from noncardiac causes. No arrhythmic event occurred during class 1A AAD therapy in any of EPS drug responders and in patients with no baseline inducible VF . Arrhythmic events occurred in only 2 cardiac arrest survivors treated with ICD alone but did not recur on quinidine. All cases of recurrent syncope (n=12) were attributed to a vasovagal (n=10) or nonarrhythmic mechanism (n=2). Class 1A AAD therapy resulted in 38% incidence of side effects that resolved after drug discontinuation. The authors concluded that electrophysiologically guided class 1A AAD treatment has a place in therapeutic armamentarium for all types of patients with BrS.

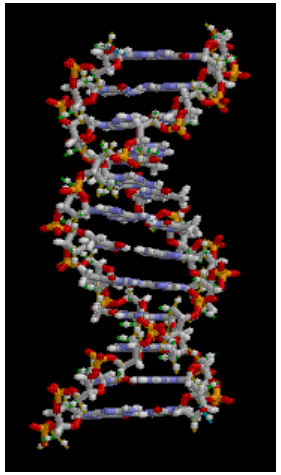
Phenocopies

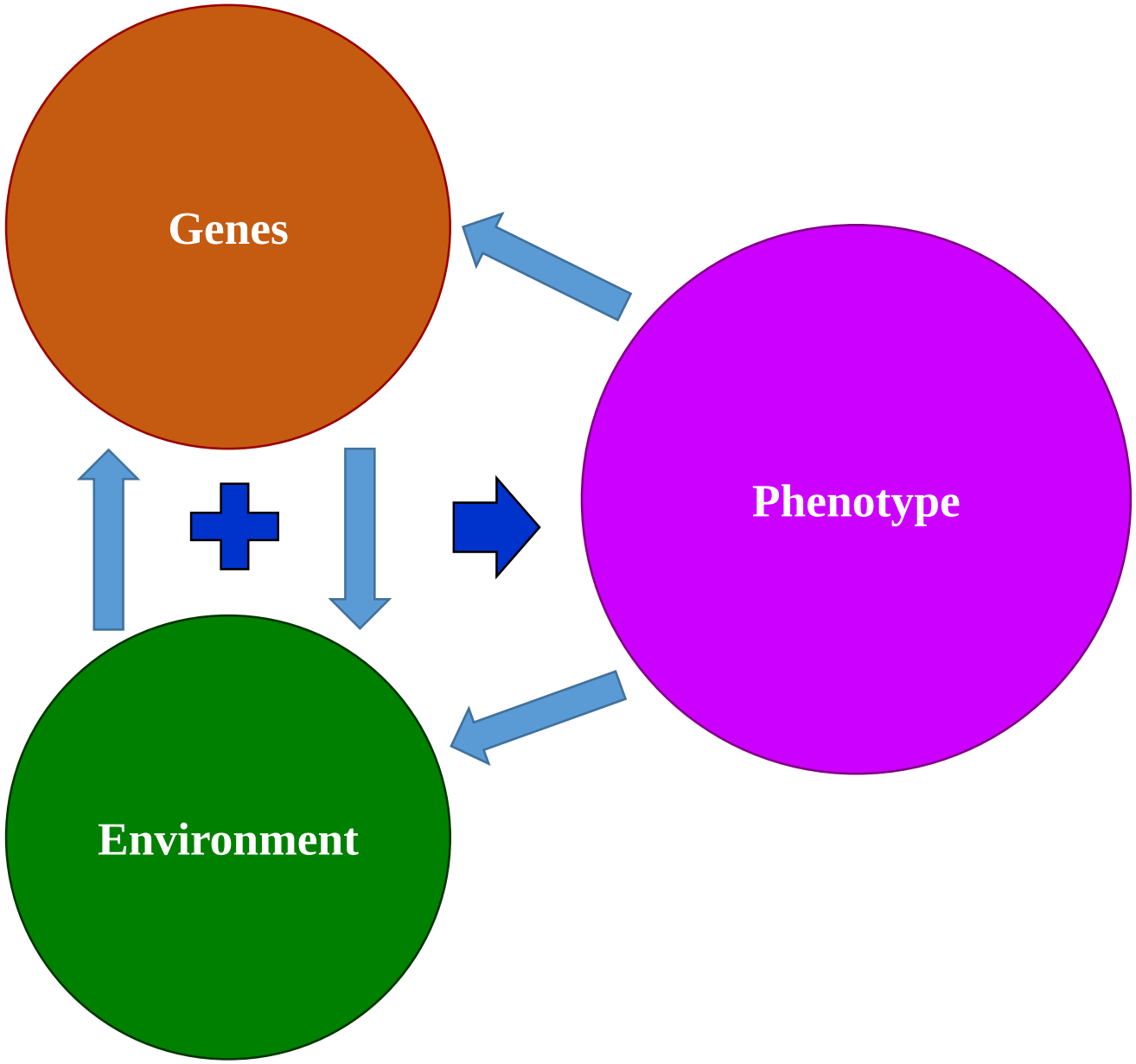
“ An environmental condition that imitates or copies one produced by a gene”

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 BrS. 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 BrS. Therefore a provocative test with a sodium channel blocking agent such as ajmaline, flecainide, or procainamide will not reproduce the ECG pattern (**Baranchuk 2012**). What is the definition of a phenocopy? A phenocopy is an environmental condition that imitates (copies) the phenotype produced by a gene. Brugada phenocopy describes conditions that present with a Brugada ECG pattern (BrP) but without true congenital Brugada syndrome (BrS). BrS is a genetically determined familial disease with autosomal dominant transmission and variable penetrance, conferring a predisposition to sudden cardiac death due to polymorphic ventricular tachycardia/ventricular fibrillation (PVT/VF). The pathogenesis of VF in these patients is most likely a combination of both genetically determined repolarization abnormalities and conduction delay in the right ventricular outflow tract (RVOT) epicardium. Additionally, phenotype is the appearance of an organism or part of them (i.e. electrocardiogram pattern) resulting from the interaction of the genotype and the environment.

The interaction of genes and environment in the determination of phenotype





The term phenocopy was coined by Richard Benedict Goldschmidt at the beginning of the past century (**Goldschmidt 1935; 1946**). He was a visionary Jewish-German-born American unorthodox geneticist. He did not believe that Charles Darwin's idea of slow and gradual changes could account for the origin of species.

Clinical situations that result in a Brugada electrocardiographic pattern are numerous (BrP). This fact made me think that the term created by Goldschmidt was appropriate to describe these cases that mimic the typical phenotype pattern of inherited BrS. I believed that it should replace the common term "Brugada-like pattern" used for the first time by Tarim et al in 1999 (**Tarim 1999**). This confusing term is unfortunately most frequently used to describe such cases to date. Additionally, we should not confuse Brugada phenocopy with **acquired** Brugada syndrome. Wataru Shimizu coined the latter term in 2005 (**Shimizu 2005**). Patients with BrS or suspected mutation carriers can have normal ECG recordings at times. In these cases, a diagnostic challenge with a sodium channel blocker such as ajmaline, flecainide, or pilsicainide may induce type 1 ECG BrP and support the diagnosis. However, many pharmacological agents that are not related to class I anti-arrhythmic agents have been reported to induce Type 1 BrP including tricyclic antidepressants, fluoxetine, lithium, trifluoperazine, antihistamines, cocaine, and others. As published reports of drug-induced BrP have become increasingly prevalent, there is growing interest in the mechanisms responsible for this ECG pattern and its clinical significance. It is possible that drug-induced BrS may be due to an individual susceptibility that favors drug-induced ECG abnormalities, possibly as a result of an increase in latent ion channel dysfunction similar to that in drug induced LQTS. However, further evidence is needed to confirm this hypothesis. Channelopathies are diseases caused by dysfunctional ion channels, due to either genetic or acquired pathological factors. Inherited cardiac arrhythmic syndromes are among the most studied human disorders involving ion channels. Acquired LQTS are believed to have a genetic predisposition or subclinical form (frustrated form) of congenital LQTS. This has been supported by findings of congenital LQTS mutations in patients with the acquired form. A subclinical form of BrS may similarly predispose an individual to the development of acquired forms of BrS. The genetic background in patients with this acquired form of BrS is unclear. However, mutations in SCN5A or other candidate genes will likely be identified in the future, as was found in LQTS. Theoretically, an acquired intervention that causes a sufficient imbalance of inward and outward currents in the RVOT may induce a BrP in an individual, although the likelihood of arrhythmias is unclear. Whether this requires an underlying genetic predisposition, or represents latent BrS has not been established. Experimental studies have suggested that an intrinsically prominent transient outward current-mediated action potential (AP) notch and subsequent loss of the AP dome in the epicardium, but not in the endocardium, of the RVOT give rise to a transmural voltage gradient, resulting in ST-segment elevation and phase 2 reentry-induced VF. Therefore, any intervention that increases Ito (e.g., transient outward current, adenosine triphosphate-sensitive potassium current, delayed modifier potassium current) or decreases inward currents (e.g., L-type calcium current, fast sodium current) at the end of phase 1 of the AP can accentuate or unmask ST-segment elevation, similar to that found in BrS, thus producing acquired forms of BrS.

Brugada Phenocopies are clinical situations that have an identical ECG pattern to true congenital BrS, but are elicited by various underlying conditions. The Type 1 BrP is diagnostic for BrS in the presence or absence of a sodium channel blocker and in the absence of apparent structural heart disease (structurally normal heart.). BrS is not caused by an identifiable underlying condition, such as coronary artery disease, electrolytic disturbance, effect of certain drugs, or compression of the RVOT. Additionally, diagnosis of BrS requires the presence of at least one of the following elements (**Antzelevitch 2005**): Documented VF; very fast polymorphic VT; when visible, with very short initial coupling of the first PVC; family history of sudden cardiac death in relatively young first-degree relatives (younger than 45 years old); types 1 or 2 Brugada ECG patterns in first-degree relatives
Inducibility of VT/VF with programmed electrical pacing; yncope and nocturnal agonal breathing

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**).

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**):

I. Metabolic conditions
II. Mechanical compression
III. Ischemia
IV. Myocardial and pericardial disease
V. ECG modulation
VI. 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 (**Alvarez 2011; Ruta 2012**) 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**); acute anterior myocardial Infarction (**Ferrando-Castagnetto 2016**); percutaneous coronary intervention of the right coronary artery (**Peters 2016**); ablation of ventricular tachycardia (**Gottschalk 2016**); takotsubo cardiomyopathy.(**Kirbas 2016**); coronary anomalies (**Dendramis 2015**); exercise-induced (**Enriquez 2016**); acute pulmonary embolism (**Zhan 2014**); intracranial hemorrhage (**Labadet 2014**); hyperkalemia (**Recasens 2013**); hypokalemia (**Genaro 2014**); adrenal crisis (**Dogan 2013**); concurrent hypokalemia and hyponatremia (**Mok 2008: Hunuk 2016**); acute myocarditis due to hyperesinophillic syndrome (**Nayyar 2009**); rhabdomyoma of the interventricular septum (**Nguyen 2011**) 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**); concomitant ethanol and heroin overdose (**Rambod 2015**). 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.

Solved once again after IV.

Diagnosis of Brugada Phenocopy

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

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

II. The patient has an underlying condition that is identifiable

III. The ECG pattern resolves upon resolution of the underlying condition

IV. There is a low clinical pretest probability of true Brugada syndrome determined by a lack of symptoms, medical history, and family history

V. The results of provocative testing with a sodium channel blocker such as ajmaline, flecainide, or procainamide are negative

VI. Provocative testing is not mandatory if surgical RVOT manipulation has occurred within the last 96 hours).(**Rambod 2014**)

VII. 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 BrS.

VIII. Correction of the hypokalemia.

Fallot´s pentalogy: another Brugada syndrome phenocopy

Clinical-ECGs/ vectorcardiograms (VCG) data:

Child who is a carrier Fallot´s pentalogy (The four characteristics of Fallot's tetralogy syndrome, plus a patent foramen ovale or atrial septal defect.) in whom in the immediate post-operative stage after total repair surgery had as approach the right ventricle outflow tract (RVOT), site corresponding to the electrophysiologically affected area in Brugada syndrome.

Pre-operative ECG shows the classical features of Fallot´s tetralogy. (ECG number 1 before surgery).

Immediate Post-operative ECG showed the Brugada Type 1 ECG phenocopy pattern, Brugada-like ECG type 1 pattern, Brugada type 1 ECG phenotype, acquired Brugada syndrome or Brugada ECG signal.

Late pos-operative ECG/VCG preformed four months after surgery showed only Complete Right Bundle Branch Block (CRBBB), anterior subepicardial ischemia (T wave profoundly negative, wide base, symmetrical limbs and acute nadir: subepicardial ischemia. Named T wave in “seagull wings”.

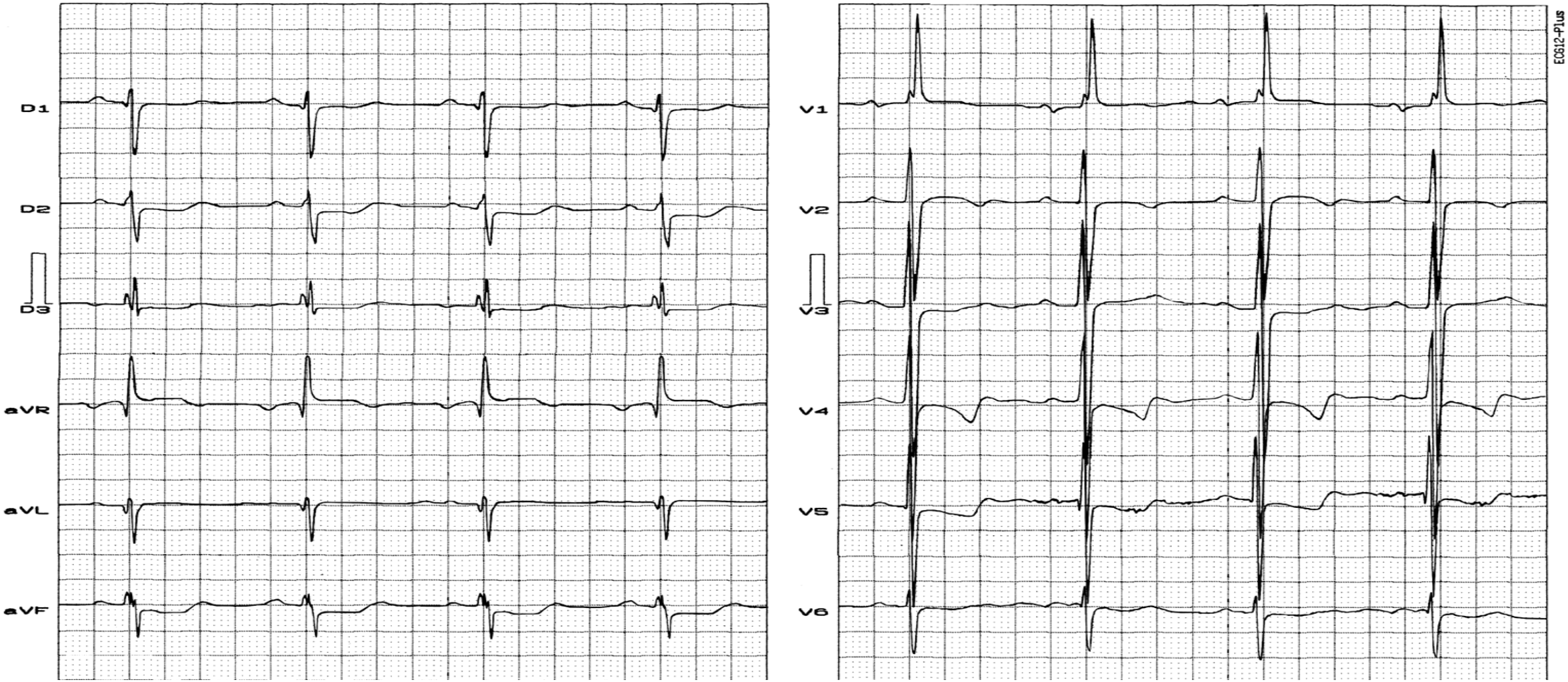
Prolonged QTc interval for heart rate: 506ms.

The VCG in horizontal plane shows Grishman type or Kennedy type 1 (afferent limb behind X orthogonal line) CRBBB pattern, with typical terminal finger-like appendage in “glove finger” with delay (tears or comets very close one to another in both afferent and efferent limbs) located in the right anterior quadrant.

Finally, T loop of VCG directed to back with symmetrical afferent and efferent limbs: anterior sub-epicardial ischemia.

ECG number 1 before surgery

Name: RCPL; **Age**: 7 years; **Gender**: female; **Ethnic group:** mixed; **Weight**: 23.800 Kg; **Height**: 1.21 m; **Date**: 08/18/03; **Time**: 14:30; **Medication used**: none stated.



ECG diagnosis: Rhythm: sinus; HR: 75 bpm; P wave: P axis: + 38° in the FP, and to the front in the HP; P duration: 80 ms; P voltage: 1 mm; P shape: rounded; **PR interval duration:** 167 ms; **QRS:** QRS axis: - 191° : extreme deviation in the right superior quadrant; QRS duration: 79 ms (normal). In V_1 lead, wide monophasic R wave with notch at the bottom of the ascending ramp and brisk transition from V_1 to V_2:

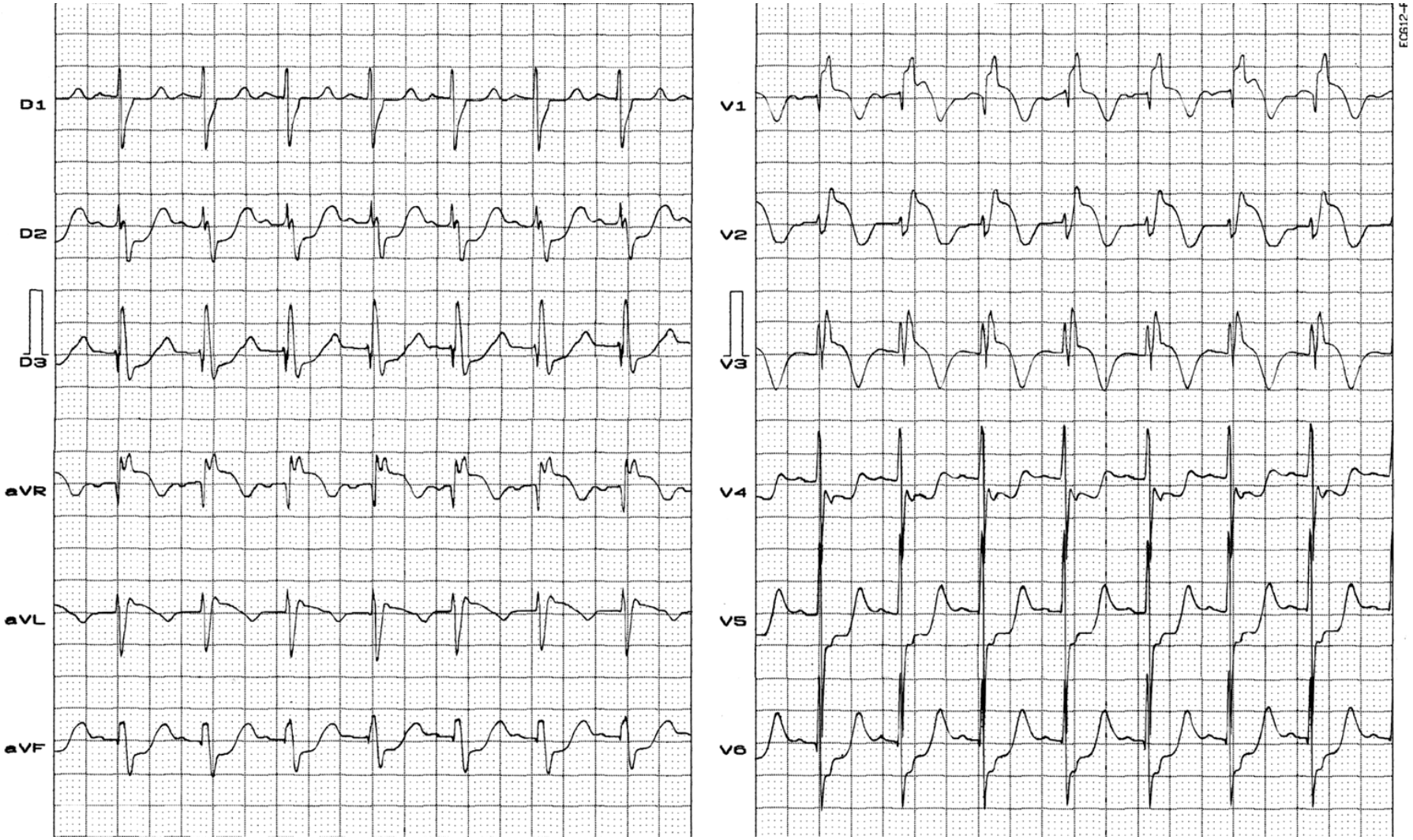
QRS complexes predominantly positive in V_1 to complexes of the rS type in V_2. The sign is considered characteristic of Fallot's tetralogy (present in approximately 48% of the cases in this entity). The predominant hypertrophy of the lateral-posterior-basal section of the right ventricle and the crista supraventricularis is responsible for the sudden change in polarity from V_1 to V_2. In children between 3 to 8 years old a progressive increase of voltage of R in V_1 through V_5 should be observed, as well as a concomitant decrease of S until V_6; "adult progression" of the R/S ratio in the precordial leads. This fact is absent in this ECG. QRS complexes in left precordial leads V_5-V_6: predominantly negative QRS complexes. In 75% of the cases of Fallot's tetralogy is observed an rS or RS pattern in these leads. The R voltage in V5 is = 8.5 mm. In children between 3 and 8 years old, the mean voltage of the R wave in V_5 is 21 mm. In V_6 the voltage of the R wave is 2.5 mm. In normal children in this age group, the R wave voltage is 14 mm.

ST/T: T axis in - 227º in the FP and backwards in the HP (negative T wave in V_2);

QT interval: 380 ms; QTc: 424 ms (normal).

ECG number 2: Immediate Post-operative ECG

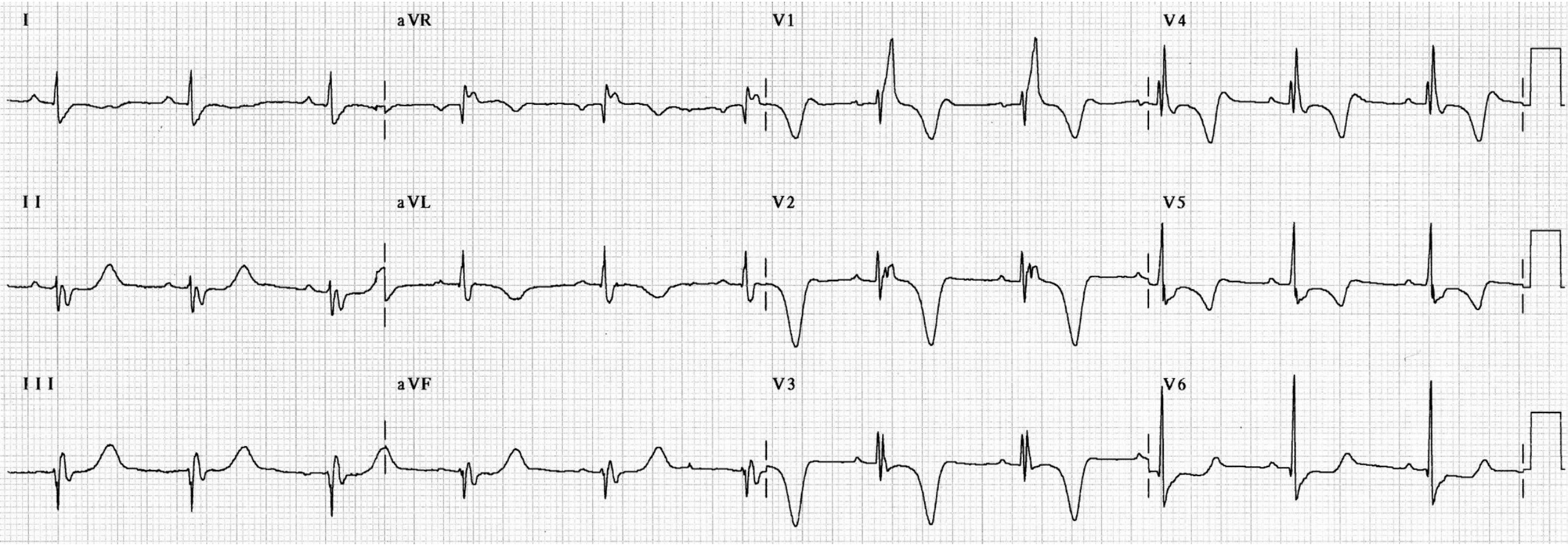
Name: RCPL; Age: 7 years; Gender: female; Ethnic group: mixed; Weight: 23.800Kg; Height: 1.21m;



Brugada Type 1 ECG phenocopy, Brugada-like ECG type 1 pattern, Brugada type 1 ECG phenotype, acquired Brugada syndrome or Brugada ECG signal.

ECG number 3: Late pos-operative ECG four months after surgery

Name: RCPL **Age:** 7 years; **Sex:** female **Ethnic group:** mixed **Weight:** 26.000Kg; Height: 1.23m **Date:** 12/12/03
Medication used: none stated.

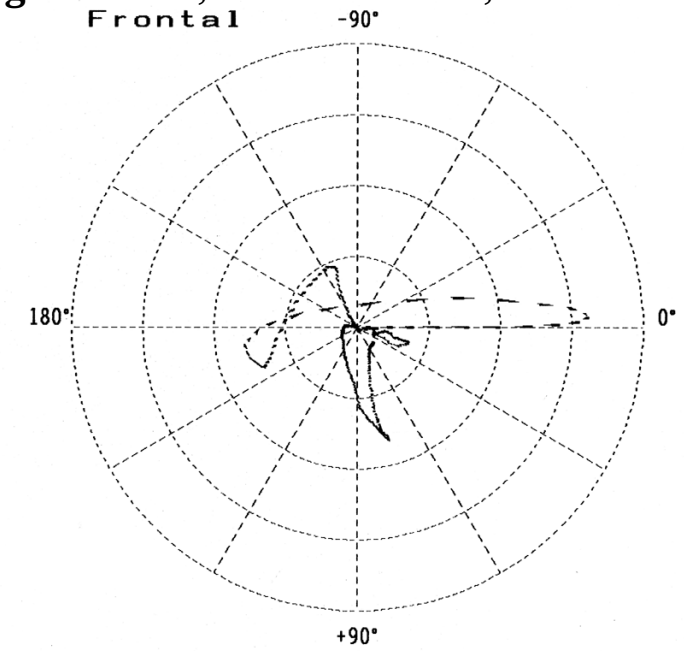


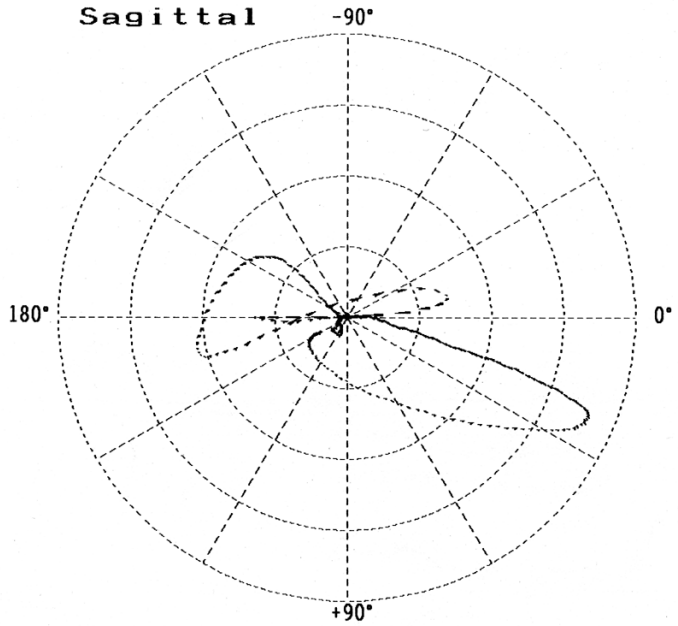
Clinical diagnosis: Late Pos operative total correction of Fallot Pentalogy.
Electrocardiographic diagnosis Rhythm: sinus; **HR:** 65bpm; **P wave:** SAP + 26° and to ahead; Duration: 60ms; Voltage: 0.7mV; Aspect: rounded; **PR:** 166ms; **QRS:** SAQRS: - 225°; Duration of QRS: 133ms (CRBBB). **ST/T:** + 109°; **QT:** 487ms. **QTc:** 506ms (prolonged).
Conclusion: 1) Complete RBBB: duration of QRS < 120ms (133ms); rsR in V1 and V2, rsR' V3; RSR's'. In aVR lead prominent and broad final R wave and S wave in I, aVL, V_5-V_6; 2) Extreme deviation of SAQRS in the right superior quadrant (between + 45° and +- 180° (-225°); 4) Anterior Ischemia .T wave with symmetrical branches, profoundly negative and broad base. 5) QTc: prolonged for heart rate: 506ms.

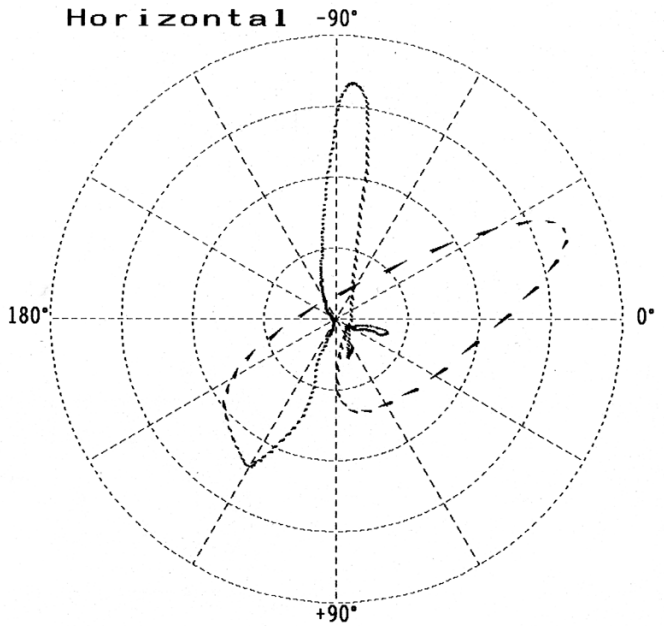
Late pos-operative vectorcardiogram four months after surgery

Name: RCPL; **Age:** 7 y/o; **Sex:** F; **Race:** mixed; **Weight:** 26.000Kg; **Height:** 1.23m; **Date:** 12/12/03; **Medication in use:** none stated.

Sensi.	4
Timer	2 msec
Loop	All Loop
Sagittal	Left
Z Axis	Back
Filter	Hum
	Muscle
	Drift

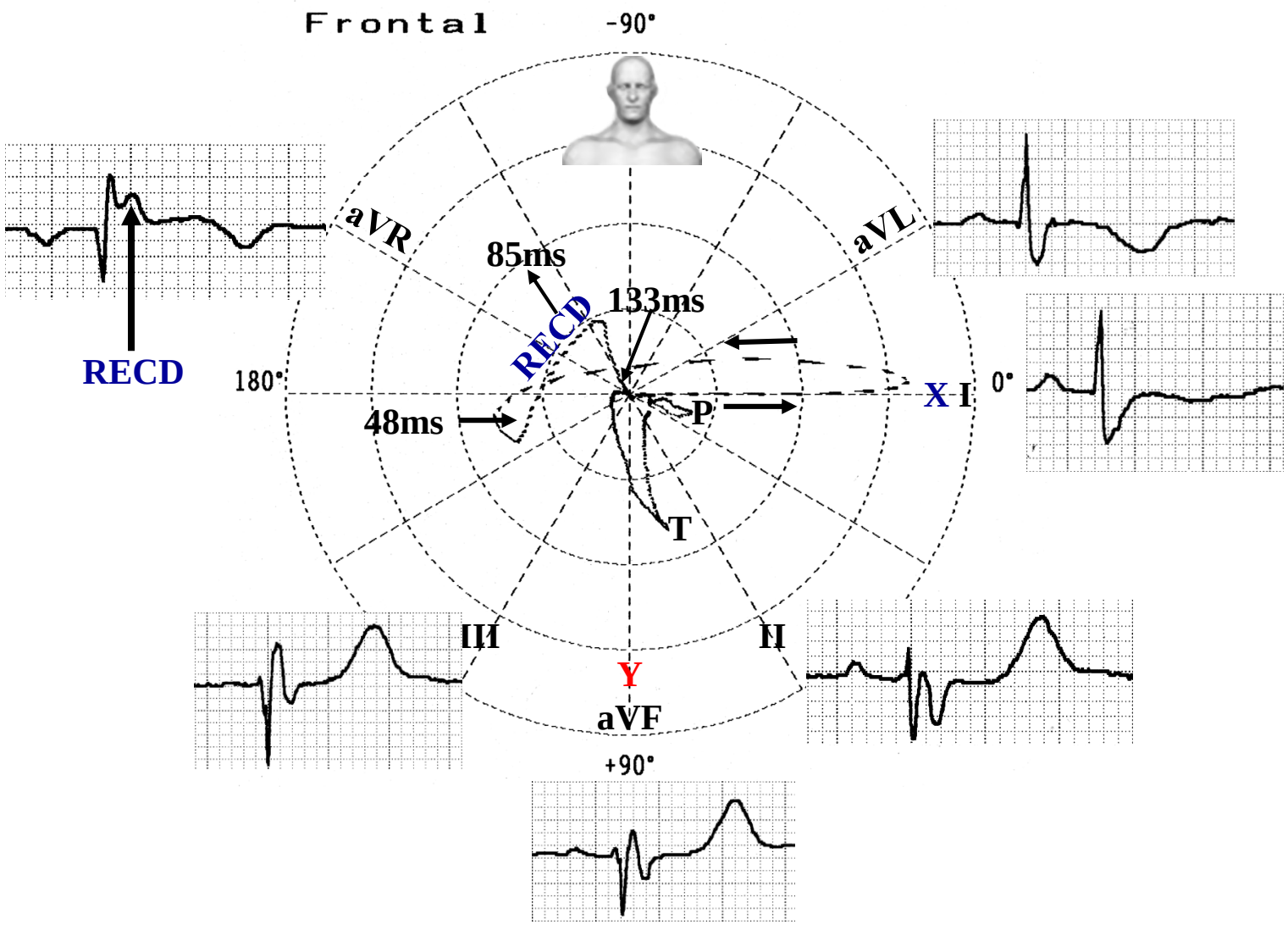






Late pos-operative ECG/VCG correlation four months after surgery

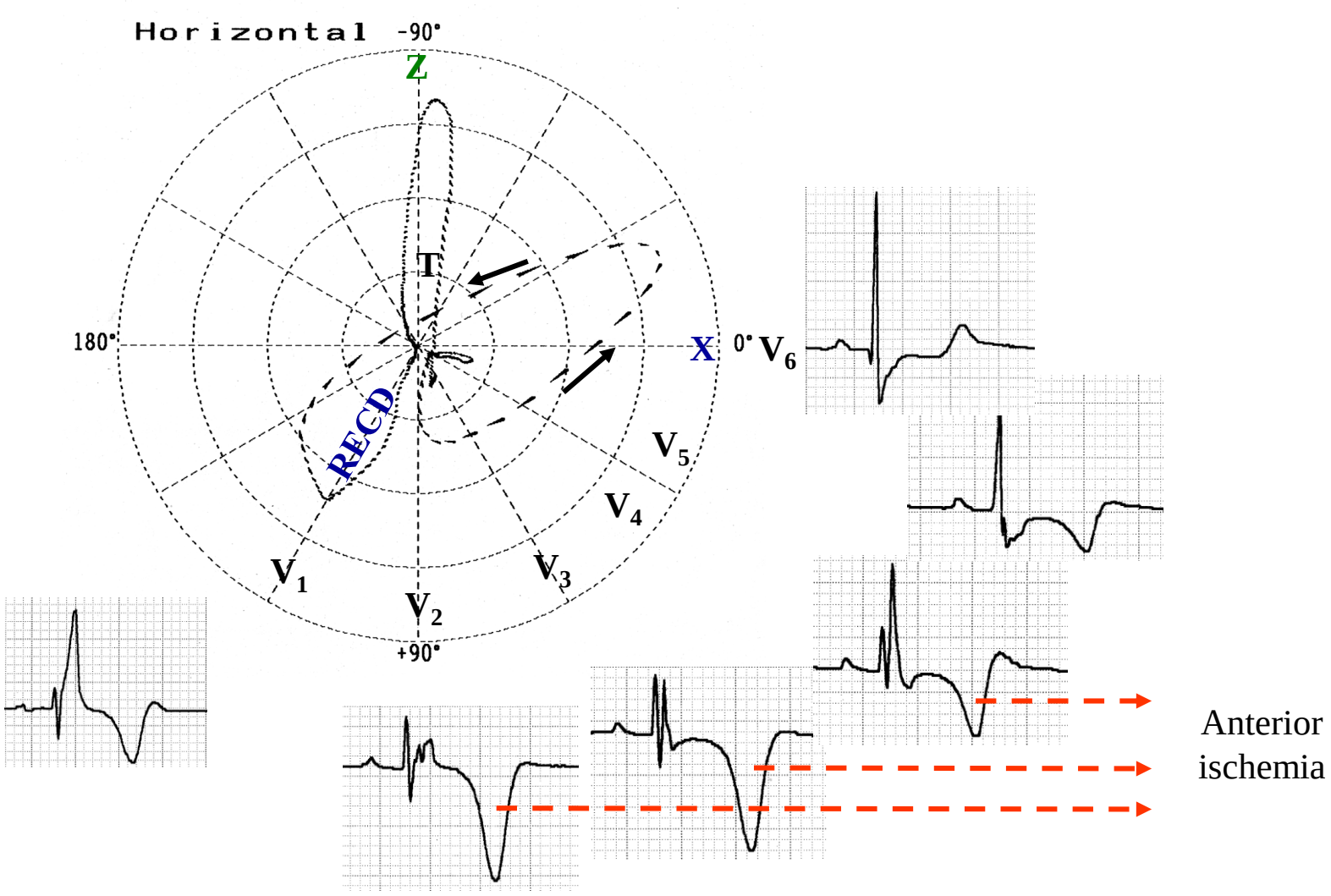
Name: RCPL; **Age:** 7 y/o; **Gender:** F; **Ethnic group:** mixed; **Weight:** 26 Kg; **Height:** 1.23m; **Date:** 12/12/03; **Medication used:** none stated.



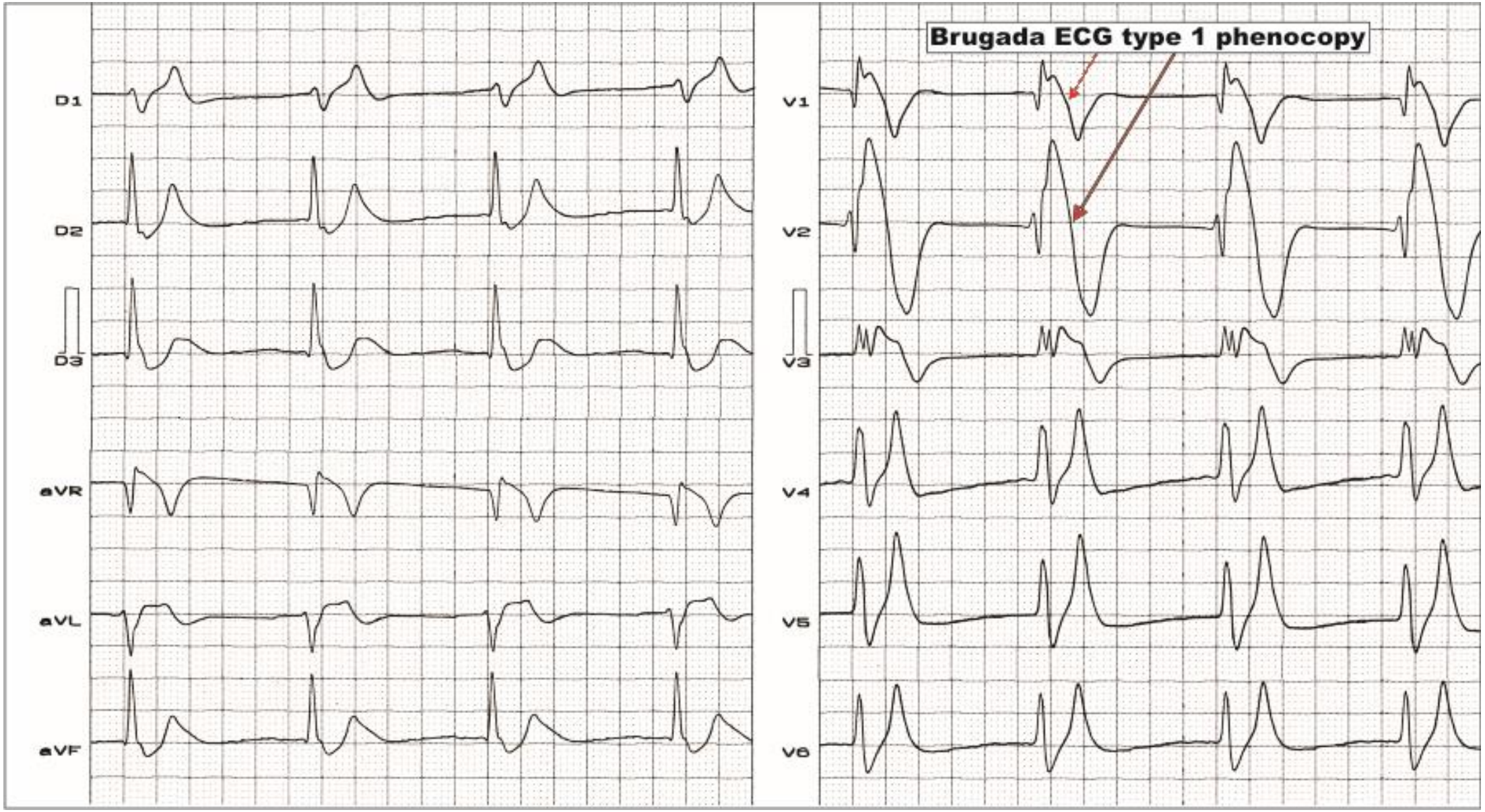
Diagnosis: CRBBB QRSD: 133 ms (>120ms). **RECD (85ms)** located on RVOT area.

Late pos-operative ECG/VCG correlation four months after surgery

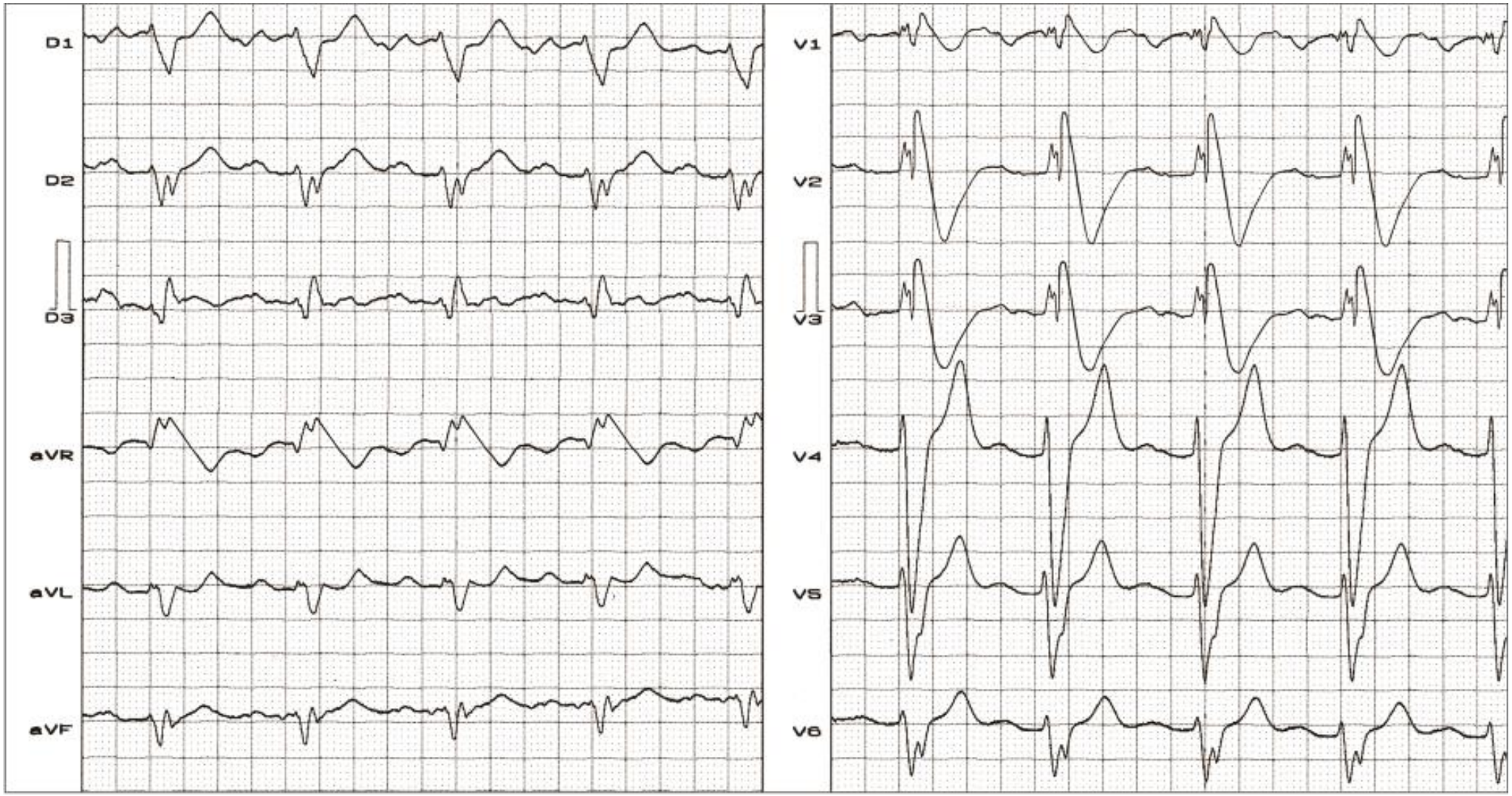
Name: RCPL; **Age:** 7 y/o; **Gender:** F; **Ethnic group:** mixed; **Weight:** 26 Kg; **Height:** 1.23m; **Date:** 12/12/03; **Medication used:** none stated.



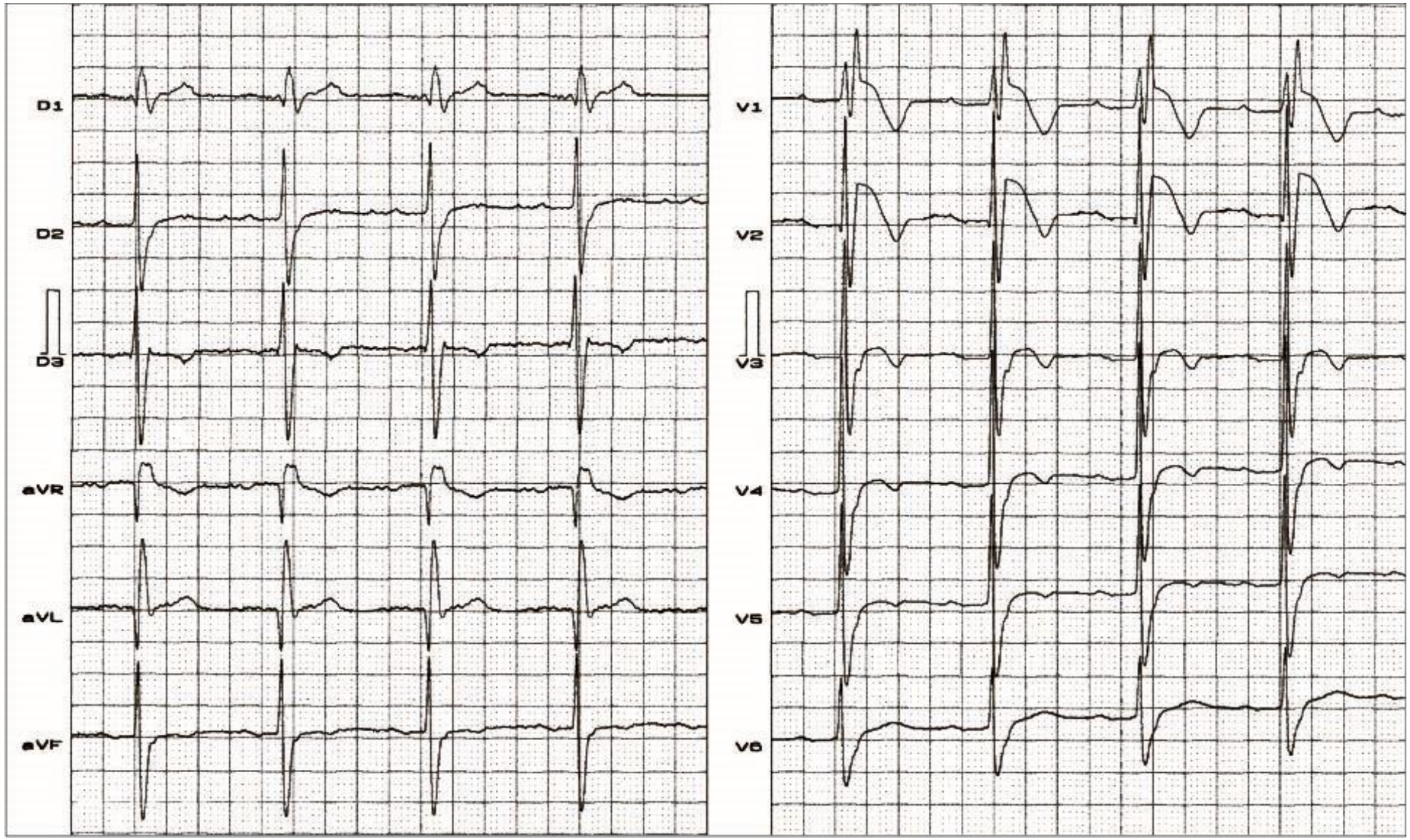
Diagnosis: CRBBB Grishman Type or Kennedy Type 1 (afferent limp behind **X** orthogonal leads). **RECD:** terminal finger like appendage in "glove finger" with delay located in the right anterior (tears very close together). Anterior ischemia: T wave with symmetrical branches, profoundly negative and broad base. T loop directed to back with symmetrical afferent and efferent limbs: Anterior ischemia.



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.

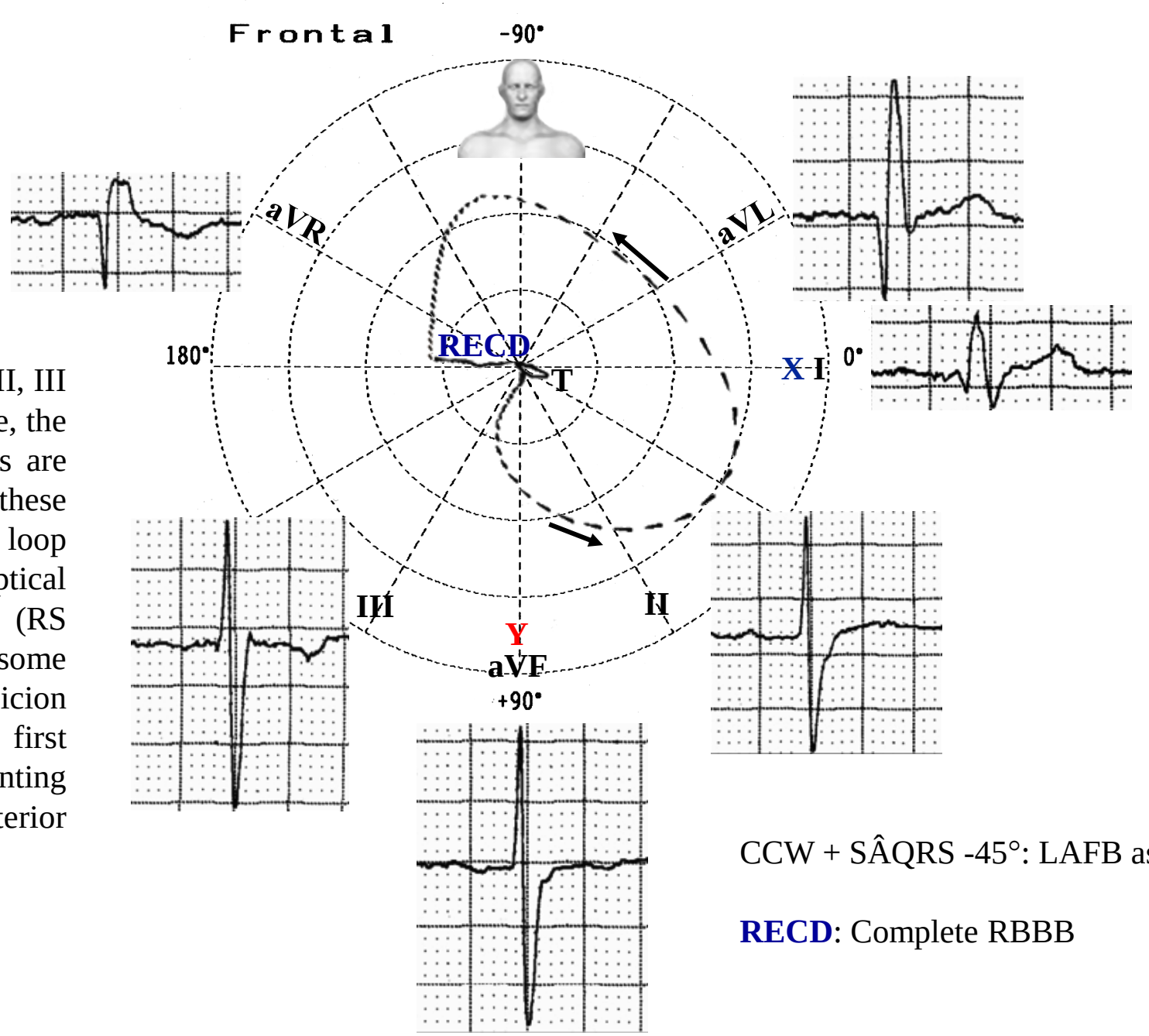


Clinical diagnosis: myotonic muscular dystrophy (Steinert's disease) / type 2 diabetes mellitus / high blood pressure. Brugada syndrome? Brugada phenocopy?

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



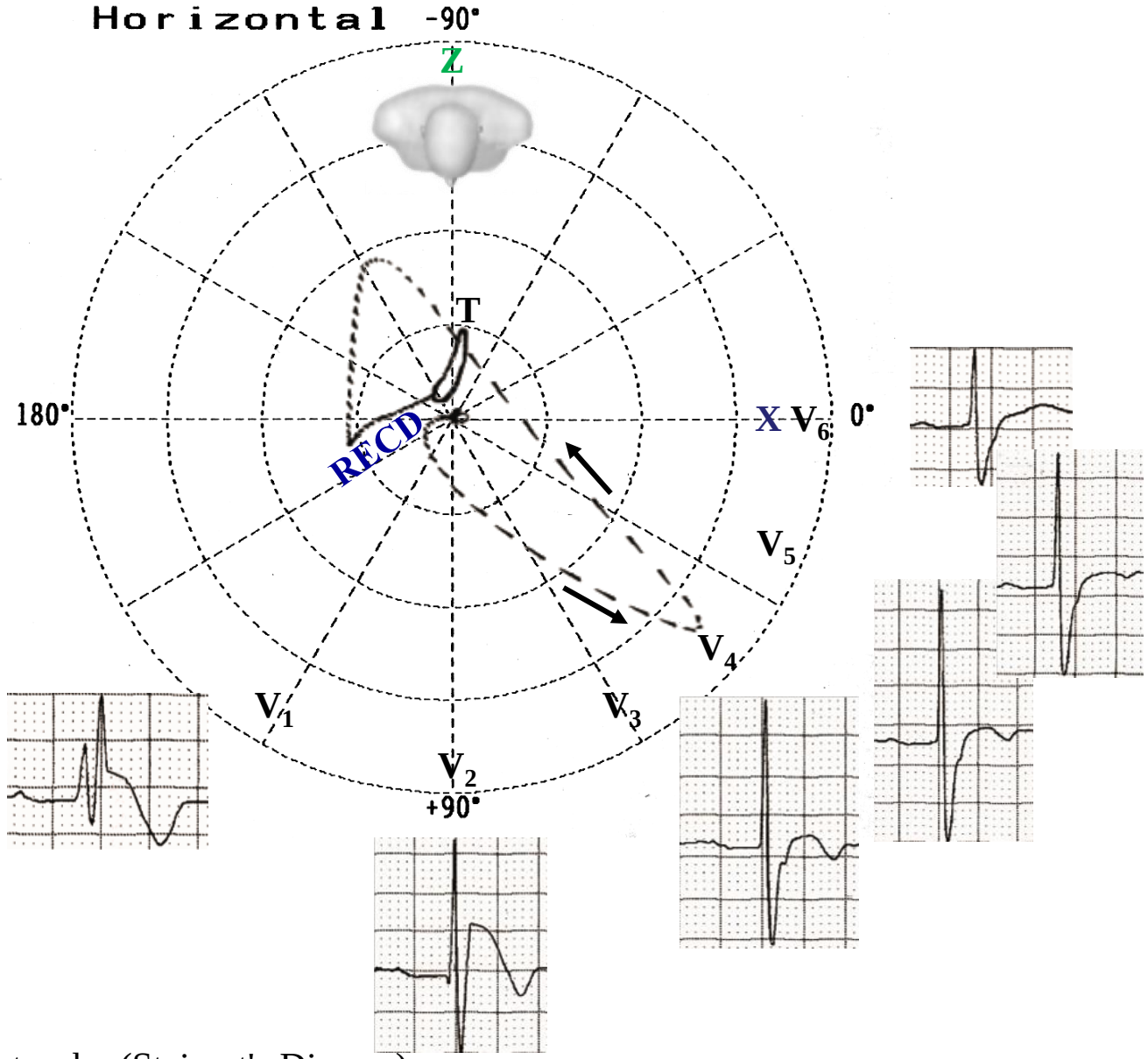
In classical LAFB, the inferior leads II, III and aVF, show rS pattern. In this case, the voltage of R waves in inferior leads are greater, originating RS pattern in these leads. Additionally, QRS loop morphology is rounded and not elliptical as in typical LPFB. Both facts (RS pattern and rounded shape) 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.

CCW: counterclockwise

CCW + SÂQRS -45°: LAFB associated with LPFB

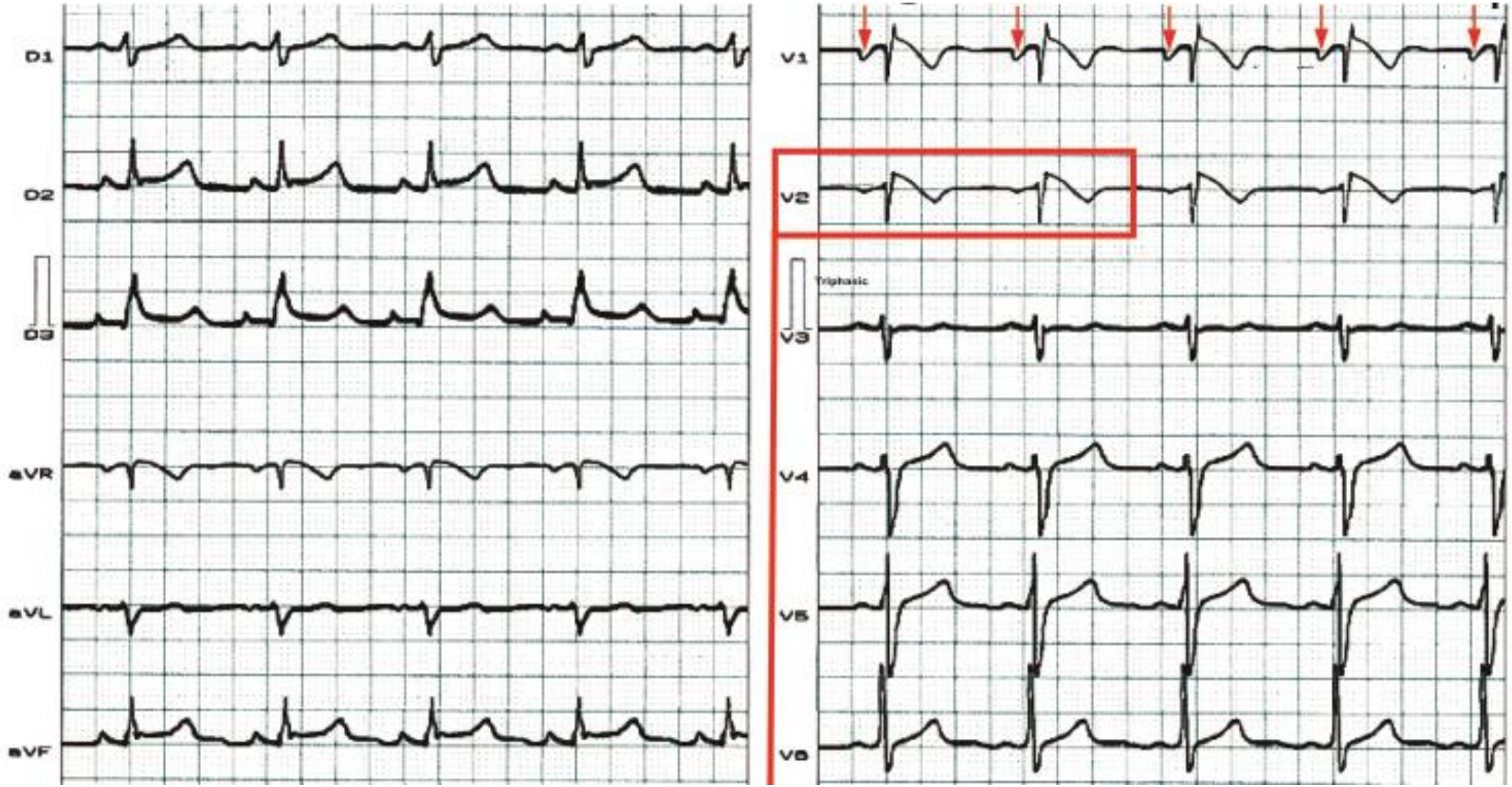
RECD: Complete RBBB

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: BrP phenocopy

ECG of a 18yo male patient with pectus excavatum and Brugada type 1 ECG pattern: Brugada phenocopy



ECG diagnosis: Spontaneous type 1 BrP. Negative P wave in V1 (red arrows), characteristic of pectus excavatum (**Martins de Oliveira 1958**). Brugada phenocopy.

Second admission: Two weeks after ICD implantation

History of pleuritic pain and 2 syncopal episodes.

The patient did not tolerate the supine decubitus as chest pain worsened. Pain is relieved by sitting up and leaning forward.

On physical examination drew attention by the presence of jugular venous distention, muffled heart sounds, pericardial friction (a flickering sound resembling the purr of a cat) and hypotension.

It was discarded arrhythmic event since the analysis of the device did not reveal any event.

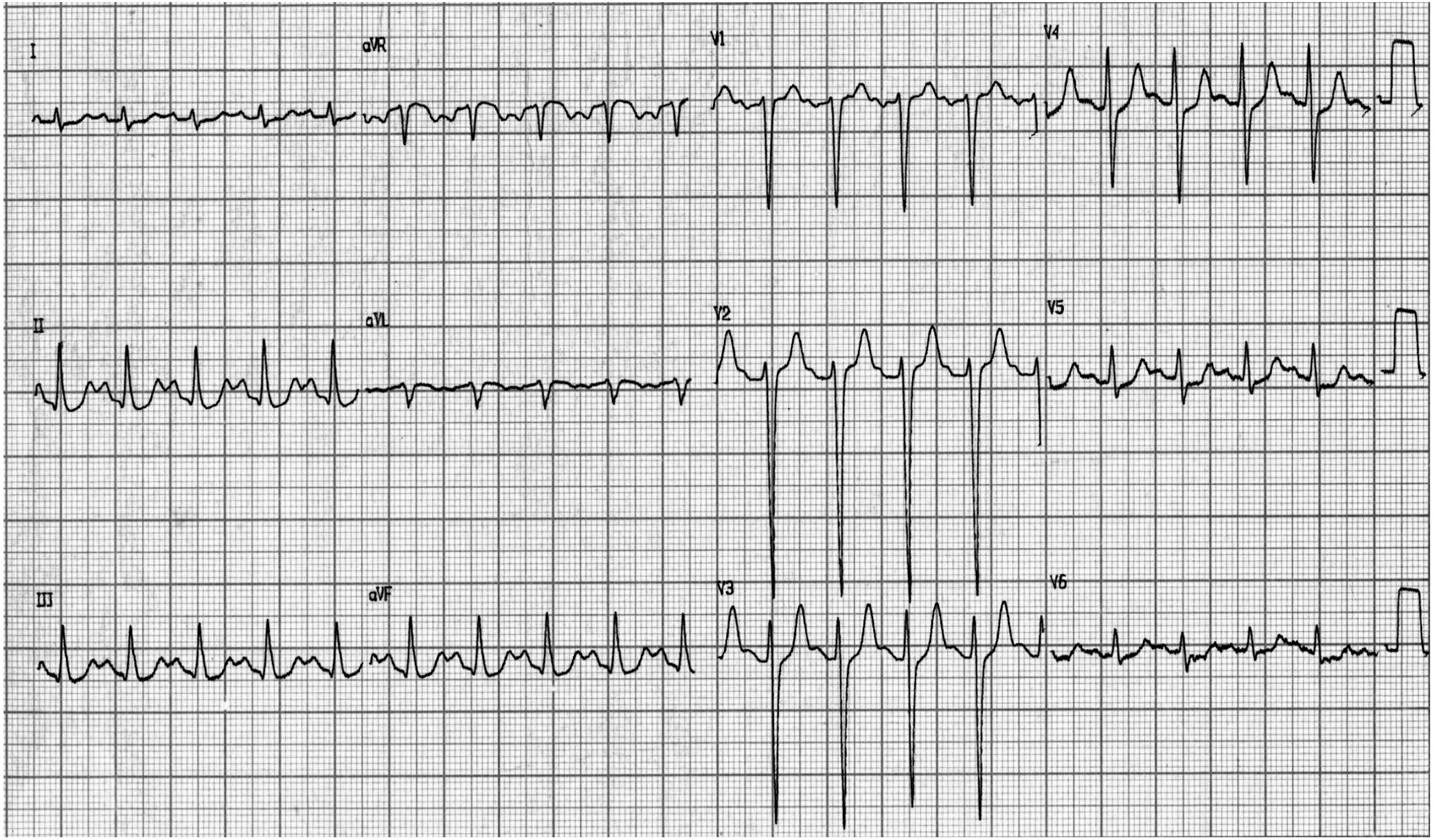
Echocardiogram that revealed pericardial effusion with signs of diastolic restriction.

He underwent thoracotomy with bloody fluid. No liquid drainage had myocardial signs of perforation caused by the electrodes.

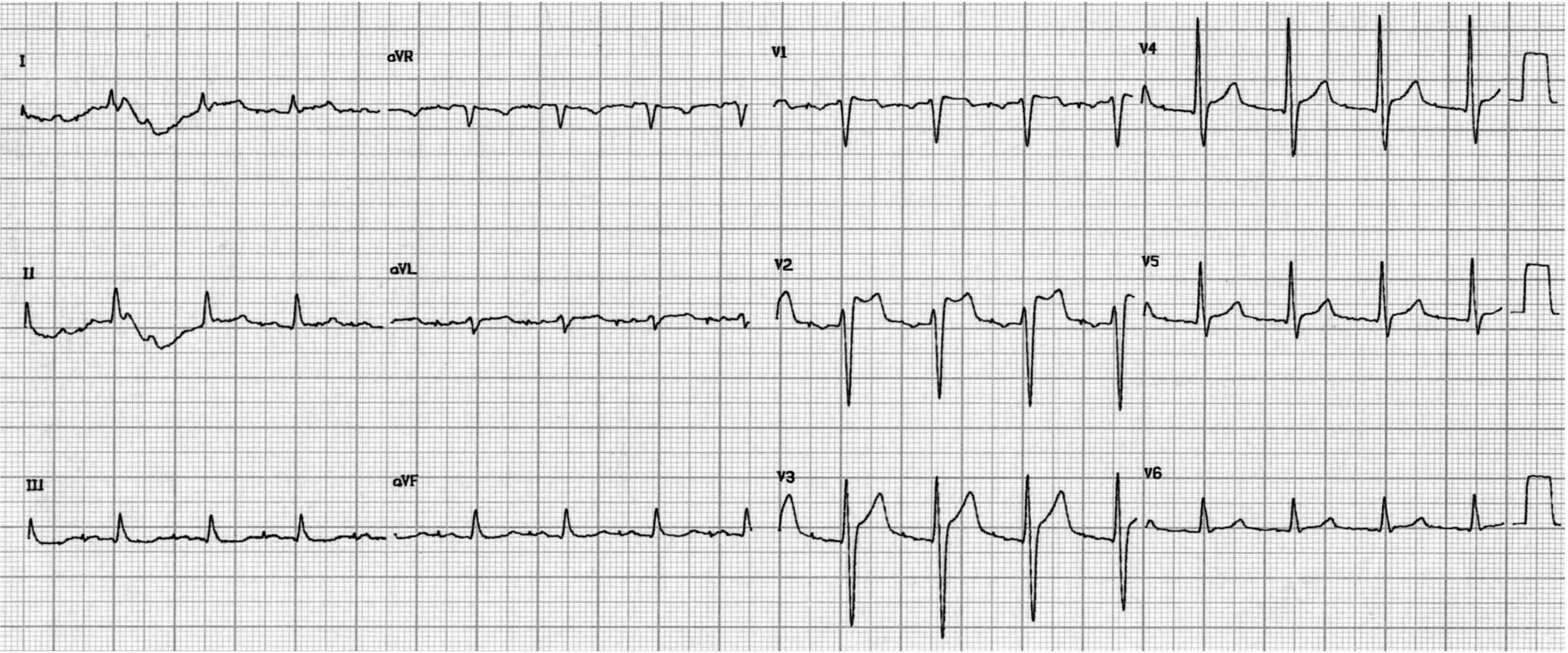
After the procedure there was stabilization of the frame.

He was discharged after three weeks.

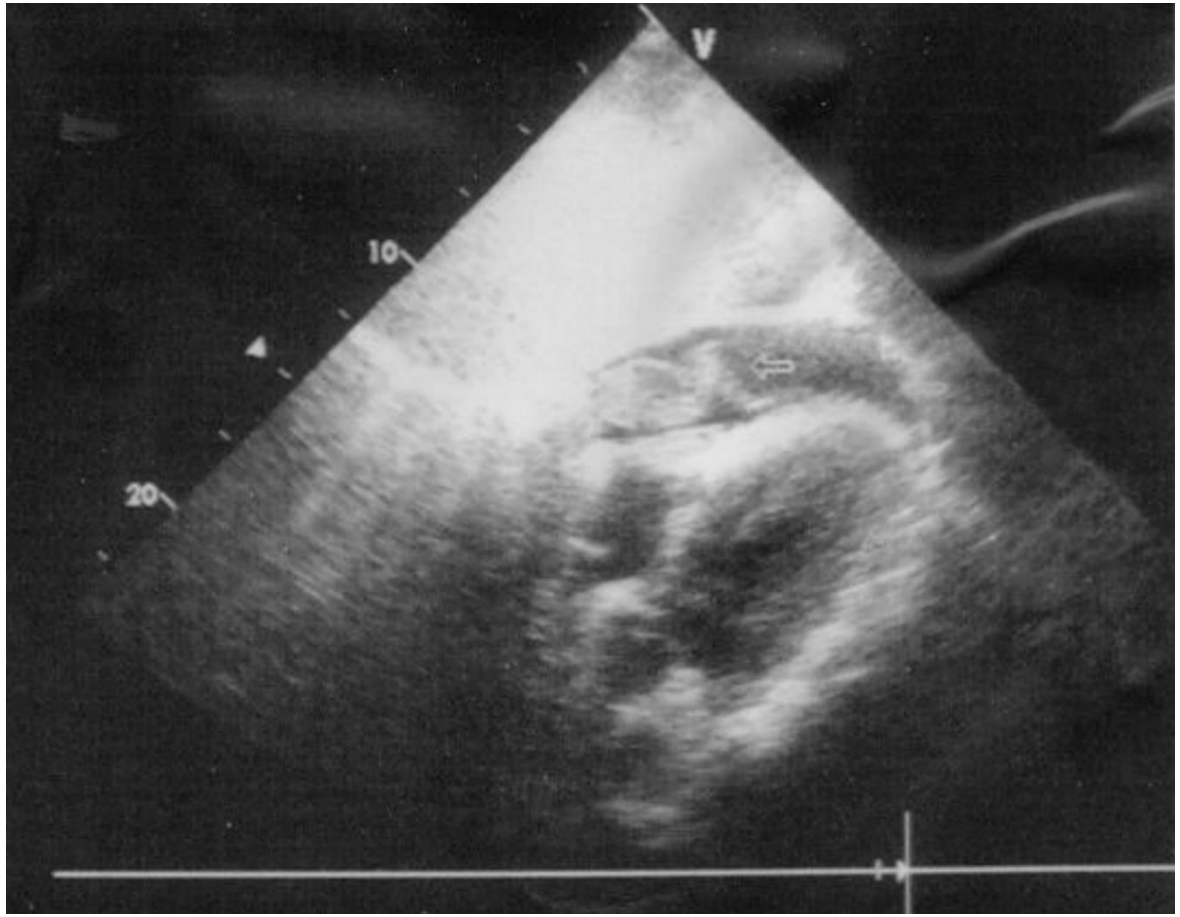
Second admission (ECG1) performed two weeks after ICD implant (October 2008)

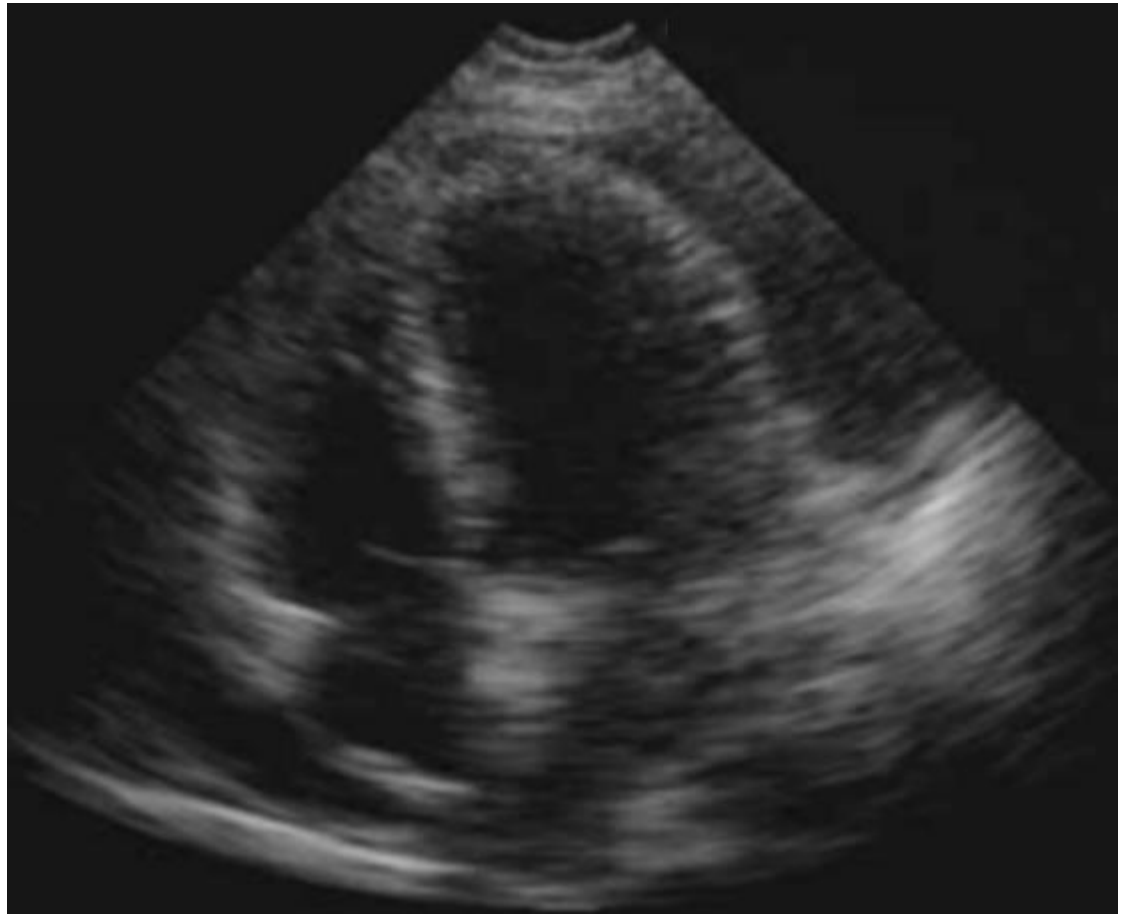


ECG2 of the second admission (October 2008)



Typical first phase of acute phase of pericarditis ST segment elevation (<5mm) of superior concavity. It is observed only two hours before chest pain and it lasts for several days. ST segment changes are extensive and not too intense, normally noticeable in several leads simultaneously, excluding V_1. In this case from V2 to V5. Occasionally reciprocal alterations are observed in aVR.





Pericardial effusion visualized in the apical four chamber view

Echo/Doppler studies have revealed the limitations of the physical examination in many cardiac conditions, particularly in the early stages. It is now common experience that a limited Echo/ Doppler examination is able to provide more diagnostic accuracy, together with quantitative information, than the physical examination including inspection, palpation and auscultation **(Poopp 1998)**.

Third admission (October 2011)

Admitted at the ER with complaint of typical prolonged (> 30 minutes) constrictive retrosternal chest pain.

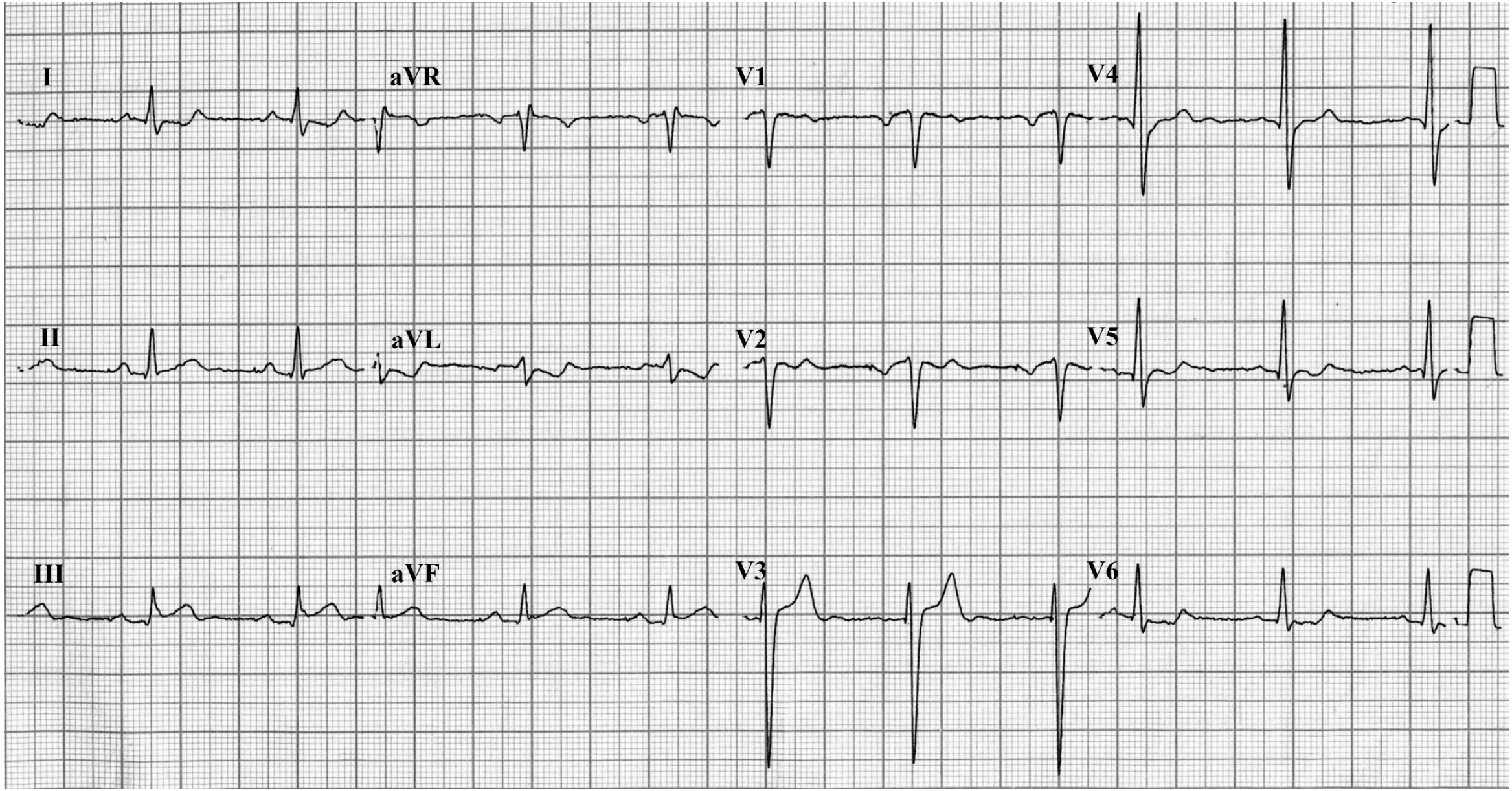
It was administered aspirin + clopidogrel.

ECG presented in the next slide.

He was referred to the hemodynamics laboratory which revealed acute occlusion of the right coronary artery. He has successfully been submitted to Percutaneous Coronary Intervention (PCI) (showed in the second ECG).

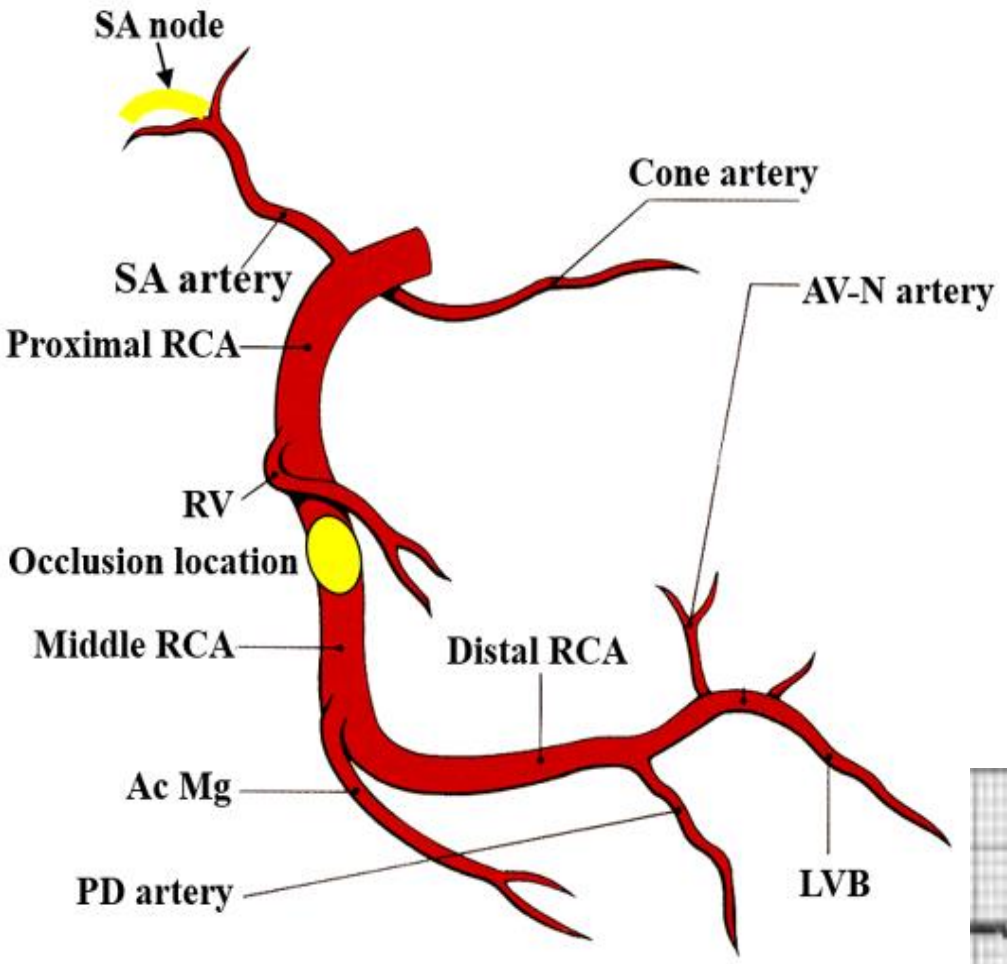
He was discharged after 1 week.

ECG1 of the third admission performed during prolonged (> 30 minutes) constrictive precordial pain in October 2011

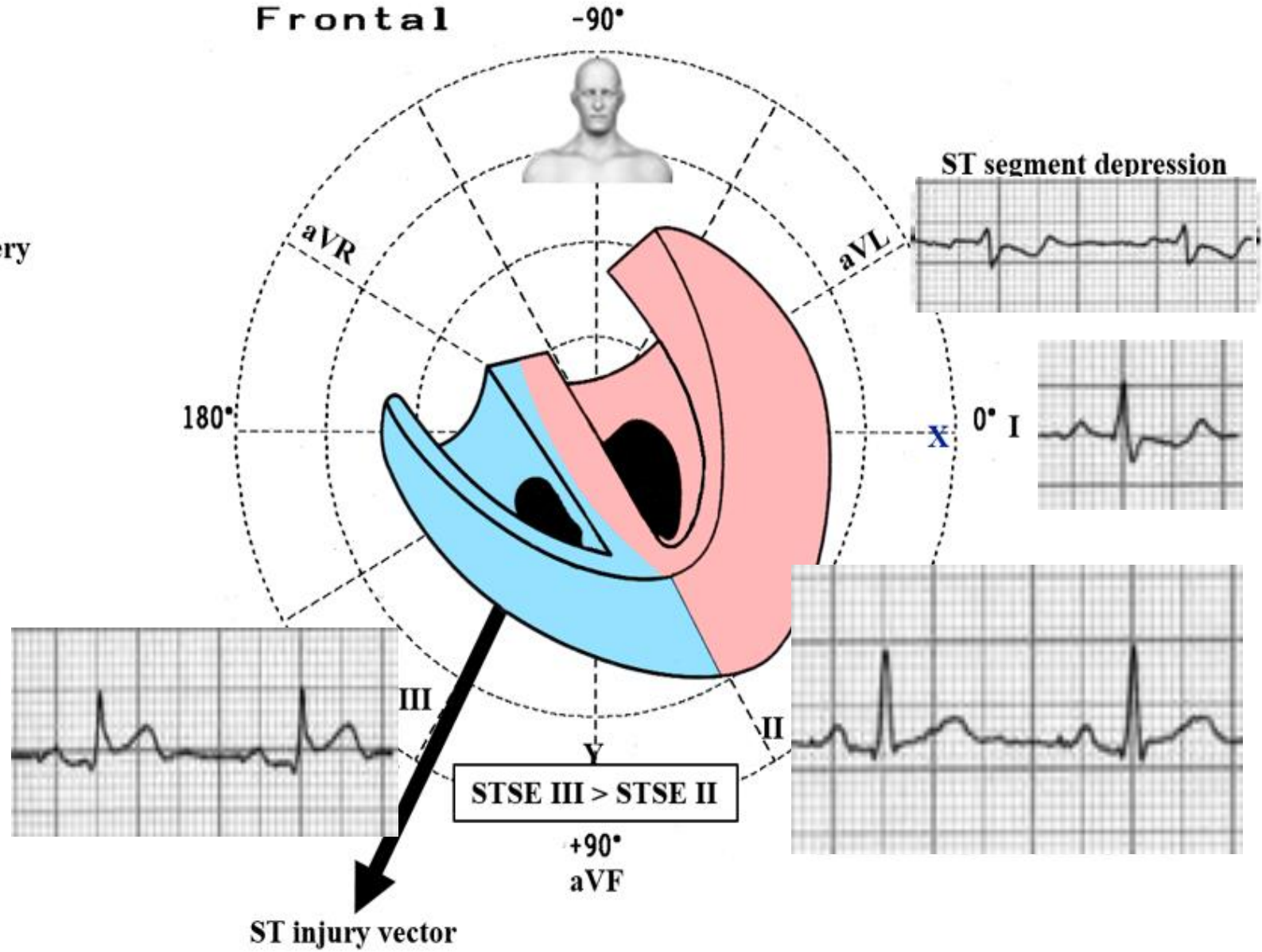


ST segment elevation in the inferior wall with reciprocal image or mirror in I and aVL (STS depression) + atrial pacing 1: 1 (small spikes)

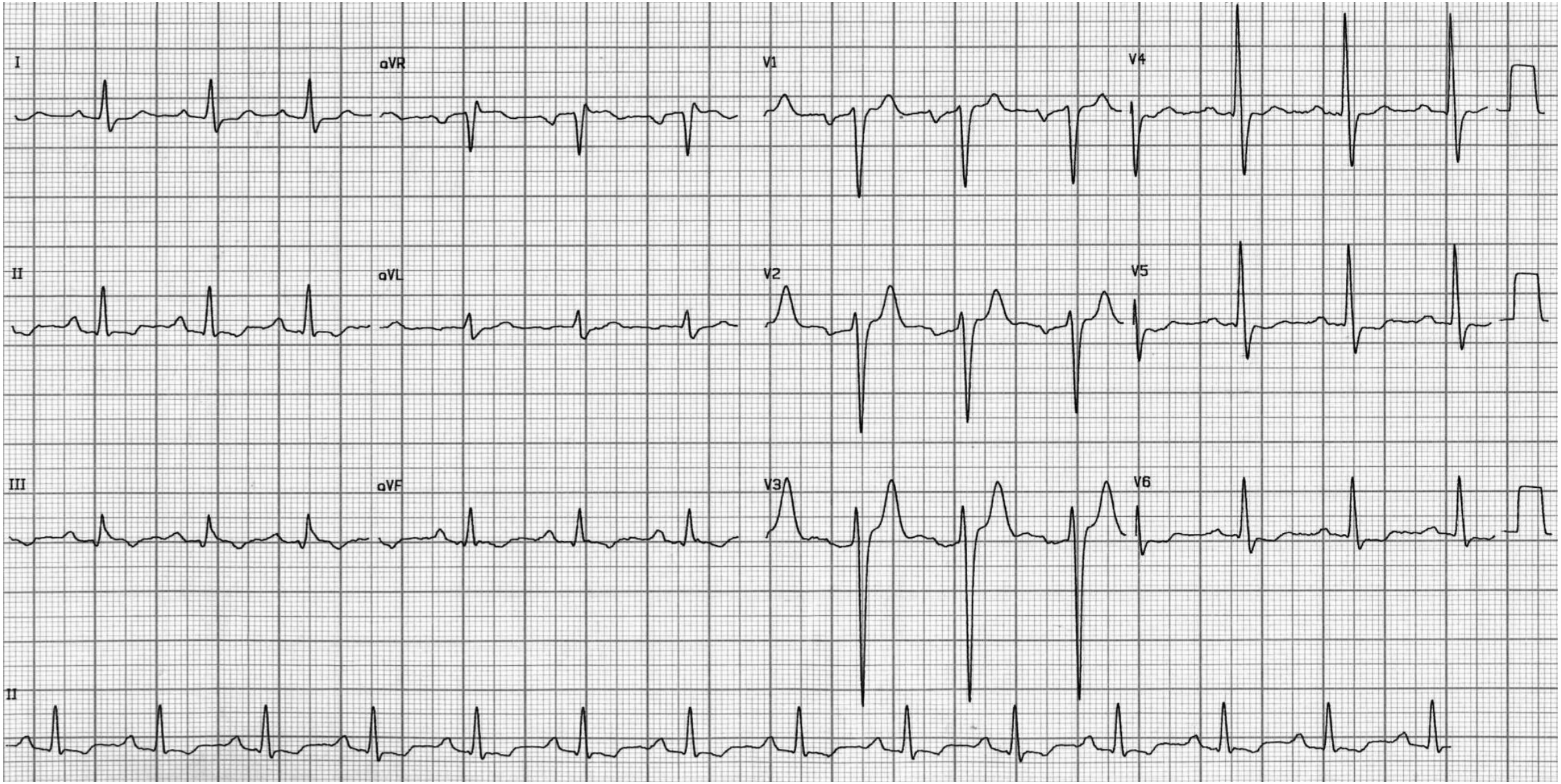
Acute Inferior MY by obstruction of RCA at the middle third: The ST injury vector pointed to III



SA node: Sinoatrial node; **RCA:** Right Coronary Artery; **Ac Mg:** Acute Marginal; RV: Right Ventricle artery; **PDA**: Posterior Descending Artery; **AV-N:** Atrioventricular Node artery; **LVB:** Left Ventricular Branch

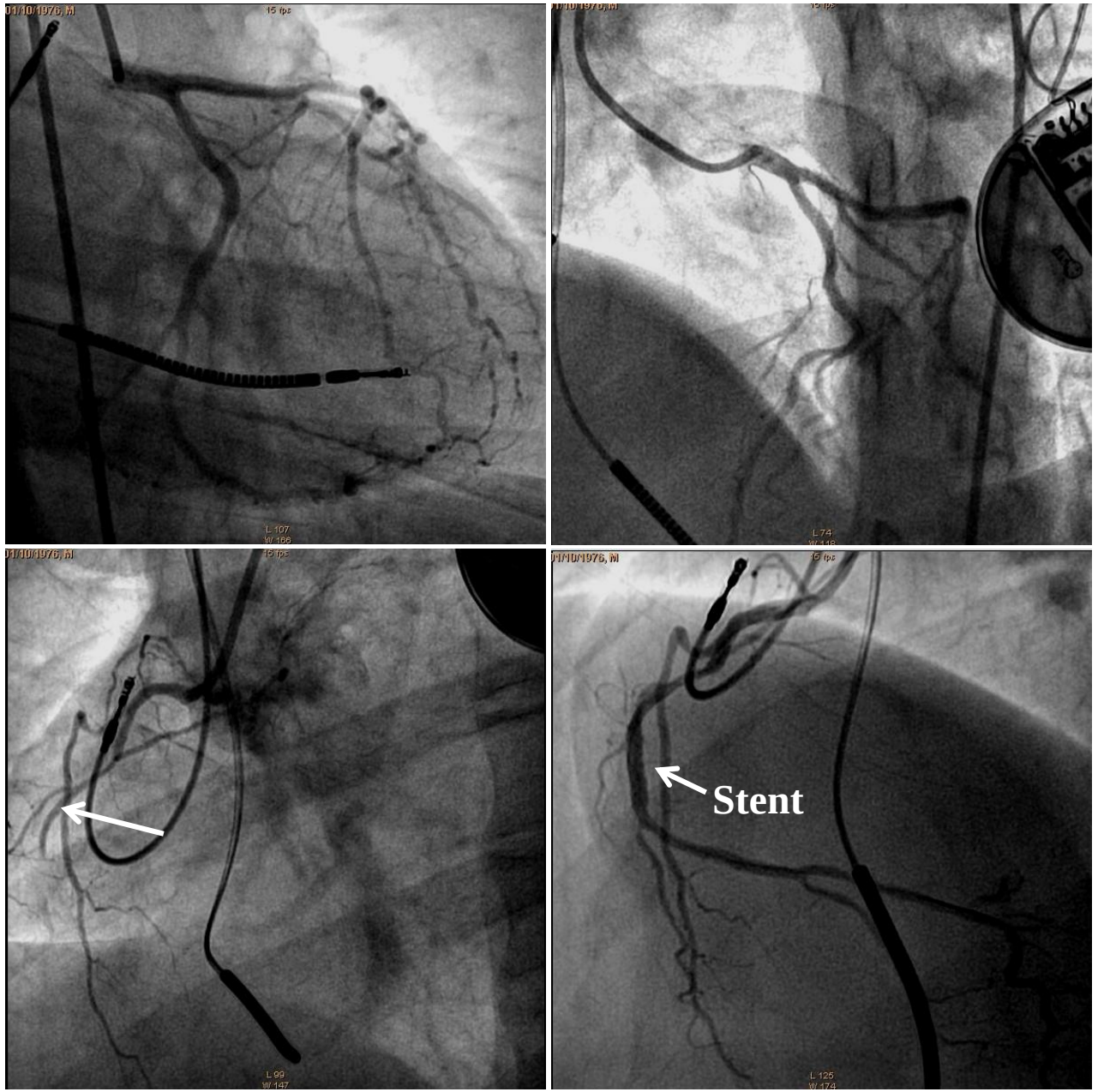


ECG2 of the third admission performed after PCI

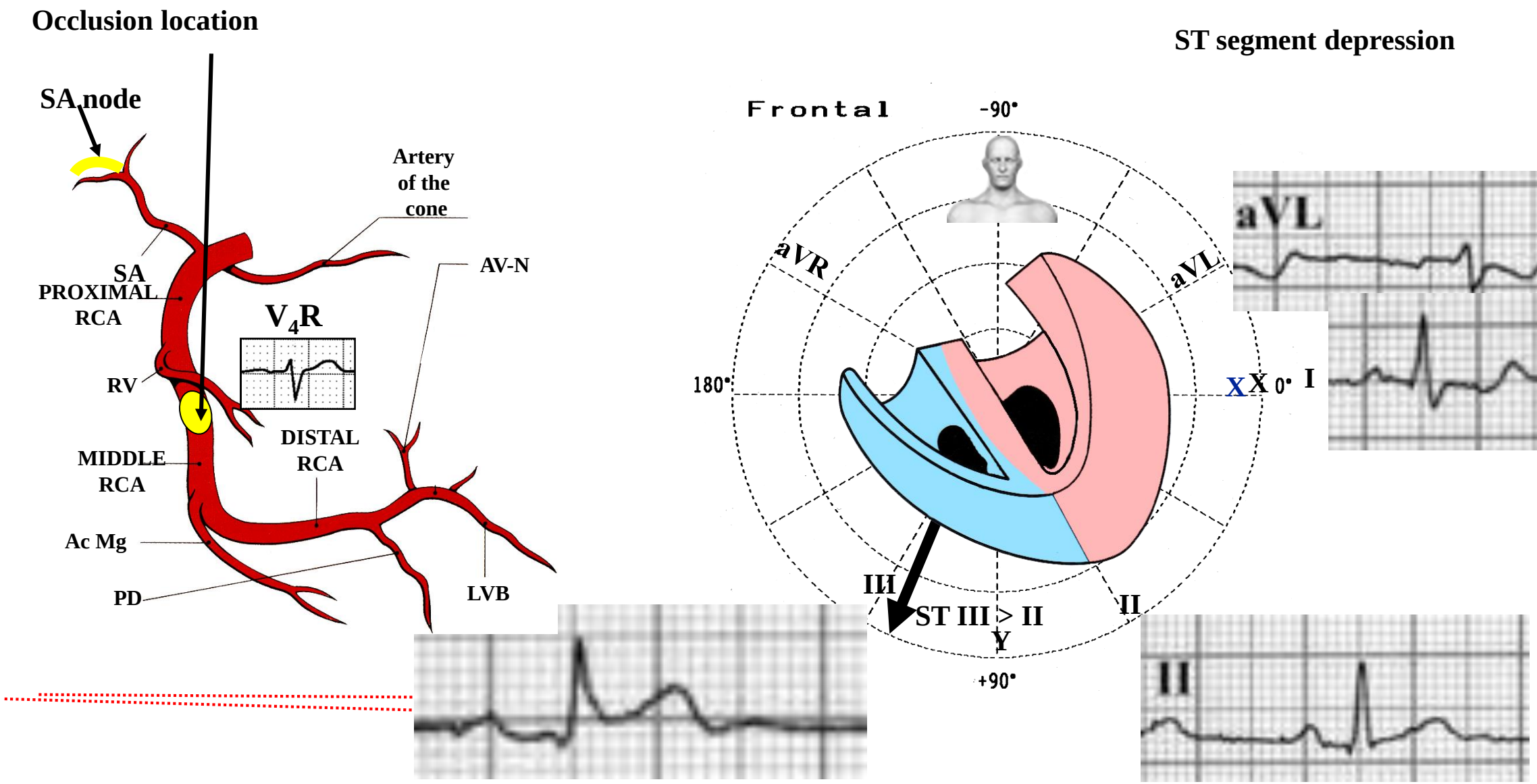


ECG shows early T wave inversion in inferior wall, suggesting successfully reperfused acute myocardial infarction. A deep inverted T wave in the acute phase of MI indicates an abundantly stunned myocardium (**Nakajima 1996**).

Coronariography showing acute obstruction of RCA after successfully stent placement



ST segment elevation in inferior leads. STSE III> II because the ST vector is pointed to III Concomitantly, ST segment depression in aVL and I



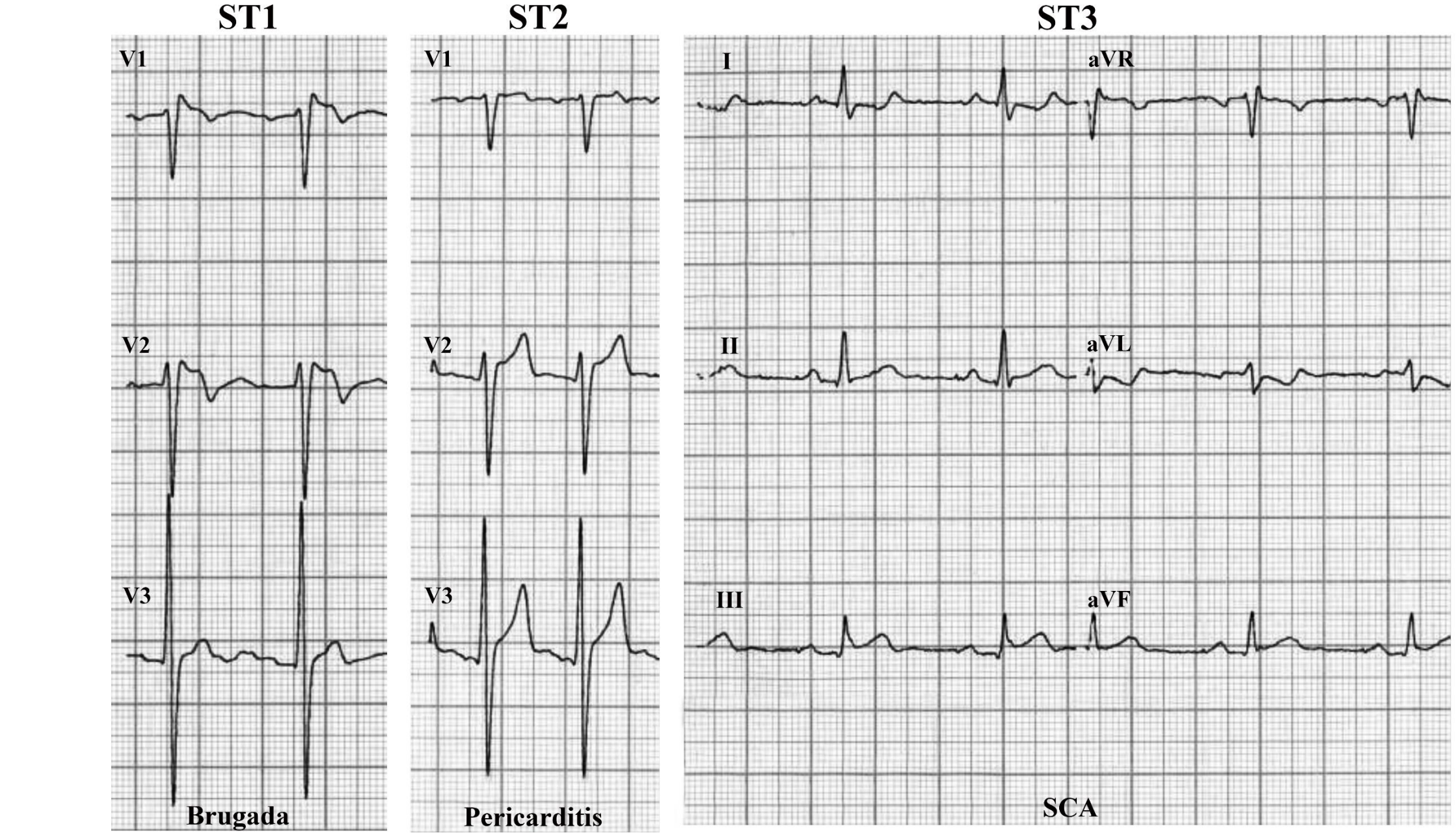
Differential diagnosis of acute pericarditis in early phase with early repolarization

	ERS	Acute pericarditis in early phase
Response to strain	Frequent return of ST to baseline. T wave may normalize	ST segment elevation is not modified
Hyperventilation	T polarity may be modified	T polarity is not modified
Presentation	Stable	Transitory
HR	Frequent bradycardia	Frequent tachycardia
Clinics	Asymptomatic	Marked alteration
Age range	20 to 40 years old	≥40
ST-segment–to–T-wave ratio	< 0.25 or more in V_6	≥ 0.25 or more in V_6

Differential diagnosis between acute pericarditis and coronary artery disease

	Coronary Artery Disease	Acute Pericarditis
Number of involved leads	Lesser (Segmental)	More (diffuse) extensive
Intensity of the phenomena	High	Low
Reciprocal effect	Present	Absent
ST segment shape	Usually convex, bowing upwardusually eventual reciprocal changes	Concave upward ST segments
Prolongation of the QRS and shortening of QT	Frequent in patients with acute STEMI	No

Comparative ECGs of the three admissions: ECG type 1 Brugada pattern, stage 1 of acute pericarditis and



Stage 1 ECG changes in a patient with acute pericarditis.

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