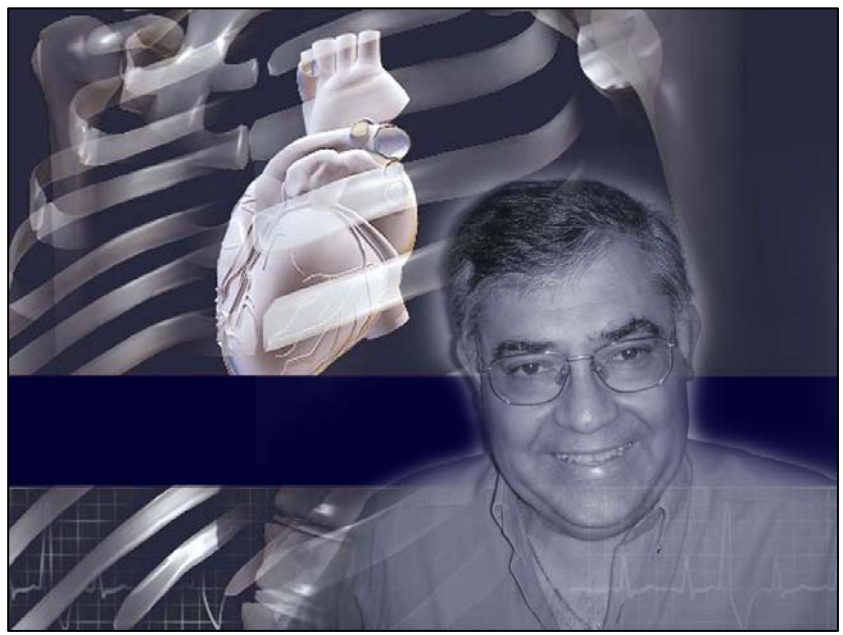
THE BRUGADA SYNDROME
ECG-VCG DIAGNOSIS



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DEFINITION

Brugada syndrome is a clinical-electrocardiographic arrhythmogenetic disease, sporadic (≈67%) or genetic (≈ 33%)[1] with autossomal dominant transmition mode characterized by ST-segment elevation in the right precordial leads (V_1-V_2) or anterior septal wall (V_1-V_3), eventually with presence of IRBBB or CRBBB frequently atypical and an increased risk of syncopes or nocturnal SCD (death occurs predominantly during sleep) in young adults, and occasionally in children and infants secondary to malignant episodes of fast polimorphic VT/VF in the absence of apparent structural heart disease.

The entity is also known as Sudden Unexpected Death Syndrome (SUDS).

1) Schulze-Bahr E Hum Mutat. 2003; 21:651-652.

THE BRUGADA "ENTITIES"

✓ **Genetic Familial cases (≈17%):** true Brugada disease. The disorder is caused by mutations in the SCN5A gene encoding Nav1.5 located on the short arm of the third chromosome. Autossomal dominant transmition mode. Mutations in SCN5A associated with the BrS phenotype. The loss of function of cardiac Na^+ channels is the basis of the BrS clinical phenotype.

✓ **Sporadic cases (≈63%):** Brugada syndrome.

✓ **Acquired forms or Brugada-like repolarization patterns:** those entities or clinical pharmacological conditions, where the Brugada phenotype or Brugada-type ECG may be found as a consequence of promoting increase in transient outward potassium current (I_{to}) function or decrease L-type calcium current on epicardium of RVOT.

BRUGADA-LIKE REPOLARIZATION PATTERNS OR ACQUIRED FORMS OF THE BRUGADA SYNDROME.

- **Acute pericarditis.**
- **Drug-induced:**
  - **Tricyclic antidepressant overdose.**
  - **Intracoronary injection of acetylcholine and/or ergonovine maleate**
  - **Ischemia-induced ST-segment elevation.**

THE MAIN CHARACTERISTICS

1) Is it a primary electrical disease or a cardiomyopathy?. Is it time to include ion channel diseases among cardiomyopathies?

2) Is it a functional electrical disorder or it has an organic substract?: The entitie has not *apparently* structural heart disease;

3) It's a distinctive subgroup of idiopathic ventricular fibrillation;

4) It's a channelopathy or ion channel diseases.

THE MAIN CHARACTERISTICS

5) Autosomic dominant transmition mode;

6) Abnormal electrophysiologic activity in RVOT epicardium;

7) ECG abnormalities constitute the *hallmark* of the entity;

8) Frequent inductibility of S-VT/VF in the PES;

9) The incidence of BrS is high in male vs. female 8:1 to 10:1;

10) It occurs with increased frequency in Asians.

CARDIOMYOPATHIES
NEW PROPOSAL OF CLASSIFICATION

1) **CYTOSKELETAL CARDIOMYOPATHY:** "force transmission" disease: DCM;

2) **SARCOMERIC CARDIOMYOPATHY:** HCM and RCM "force generation disease";

3) **CELL-CELL COMMUNICATION OR JUNCTION DISEASE CARDIOMYOPATHY:** (desmosomalopathy): ARVD;

4) **ION CHANNEL (CHANNELOPATHIES) CARDIOMYOPATHIES:** If we consider also cardiomyopathy as ion channel disease (LQTS, SQTS, BrS, and CPVT), because they are diseases of the myocardium associated with electrical dysfunction. Monogenic ion channel defect can progressively lead to myocardial structural anomalies.

Thiene G, et al. Cardiovasc Pathol. 2005;14:165-169.

IS IT A FUNCTIONAL ELECTRICAL DISORDER OR IT HAS AN ORGANIC SUBSTRACT?

Despite an apparently normal heart at noninvasive evaluation, endomyocardial biopsy and autopsy have revealed structural abnormalities: Fatty tissue deposition in the RVOT, the nodal cells in SA node reduced with fatty tissue and fibrosis[1], microaneurysms in RV and LV, cardiomyophatic changes and localized right ventricular myocarditis[2].

1) Morimoto S, et al. J Cardiovasc Electrophysiol. 2005;16: 345-347
2) Frustaci A, et al. Circulation. 2005 112: 3680-3687.

BRUGADA SYNDROME TYPES

1) Brugada Syndrome Type 1 (BrS1)
2) Brugada Syndrome Type 2 (BrS 2)

BrS Type 1

- **CHROMOSOME:** is located on the short arm of the third chromosome;
- **GENE MAP LOCUS:** *SCN5A mutations.* 3p21-23[1];
- **OMIM NUMBER SIGN:** OMIM 601144 and 600163.
- **Na+ CHANNEL:** The loss of function of cardiac Na+ channels is the basis of the BrS clinical phenotype.
- **ANKYRIN-G:** It is directly associated with ankyrin-G. Ankyrins are membrane adaptors molecules.
- **GENETIC HETEROGENEITY:** There is evidence of genetic heterogeneity.

1) Chen Q, et al. Nature 1998;392:293-296.

BRUGADA SYNDROME TYPES

BrS Type 2

BrS2 locus distinct from SCN5A on chromosome 3p22-25 is associated with progressive conduction disease, a low sensitivity to procainamide testing, and a relatively good prognosis in a single large pedigree[1].

1) Weiss R, Circulation 2002; 105:707-713.

DIAGNOSIS

1) INTERROGATORY:
a) Eventual positive history of SCD on first-degree relatives under 45 years old. Family history of SCD un young relatives.
b) Syncope;
c) Cardiac arrest from VF frequently during sleep (≈80%): Nocturnal events;
d) Palpitations in patient with supraventricular arrhythmias (≈30%);
e) Asymptomatic patient.

2) PHYSICAL EXAMINATION: frequently negative.

3) GENETIC RESEARCH: mutations on SCN5A gene which encodes the sodium channel on chromosome 3p21-23, in ≈15-20% of cases BrS1.

MAIN ECG FEATURES

RHYTHM

Sinus rhythm is the usual.

✓ **Supraventricular arrhythmias are observed in ≈ $^1/_3$ of cases since the arrhythmogenic substrate is not just limited by the ventricles.**

✓ **Atrial fibrillation is observed in 30% of the cases.**

HEART RATE

✓ **The function of both the SA and N-AV nodes are attenuated in patients with PES-induced VF[1]. Corrected SA node recovery time and Sino-atrial conduction time are frequently prolonged.**

✓ **There are references of association with Sick Sinus Syndrome. The number of nodal cells (or P cells) is reduced[2].**

1) Morita H,et al. Circ J. 2004; 68:473-476.

2) Morimoto S, et al. J Cardiovasc Electrophysiol. 2005;16:345-347

MAIN ECG FEATURES

P WAVE
There references about prolongation in P wave duration.

PR INTERVAL
Prolonged in ≈ 50% of cases.
> HV interval: intra-His or infra-His block. Eventually split-His.

QRS AXIS DEVIATION

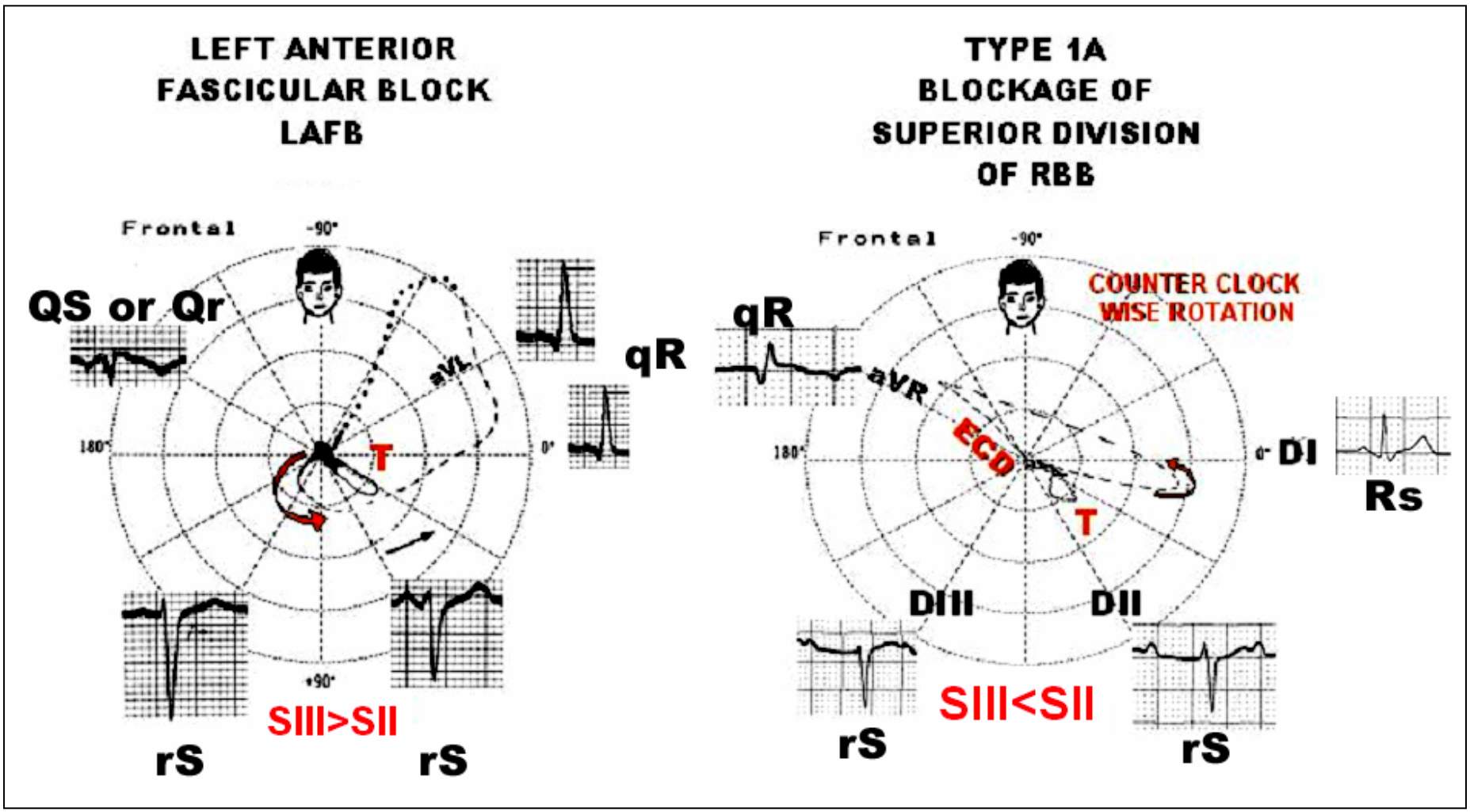
Extreme left QRS axis deviation on FP is present in ≈ 9.5% of cases.

Possibe cause:

- **Left Anterior Fascicular Block (LAFB) or**
- **Block of Superior Division of Right Bundle-Branch (BSDRBB)[1].**

1) **Pérez Riera, AR et al. The Brugada Syndrome From Bench to Bedside, Chapter 7. Value of 12 lead electrocardiogram and derived methodologies in the diagnosis of Brugada disease".2005; pg; 87-110.**

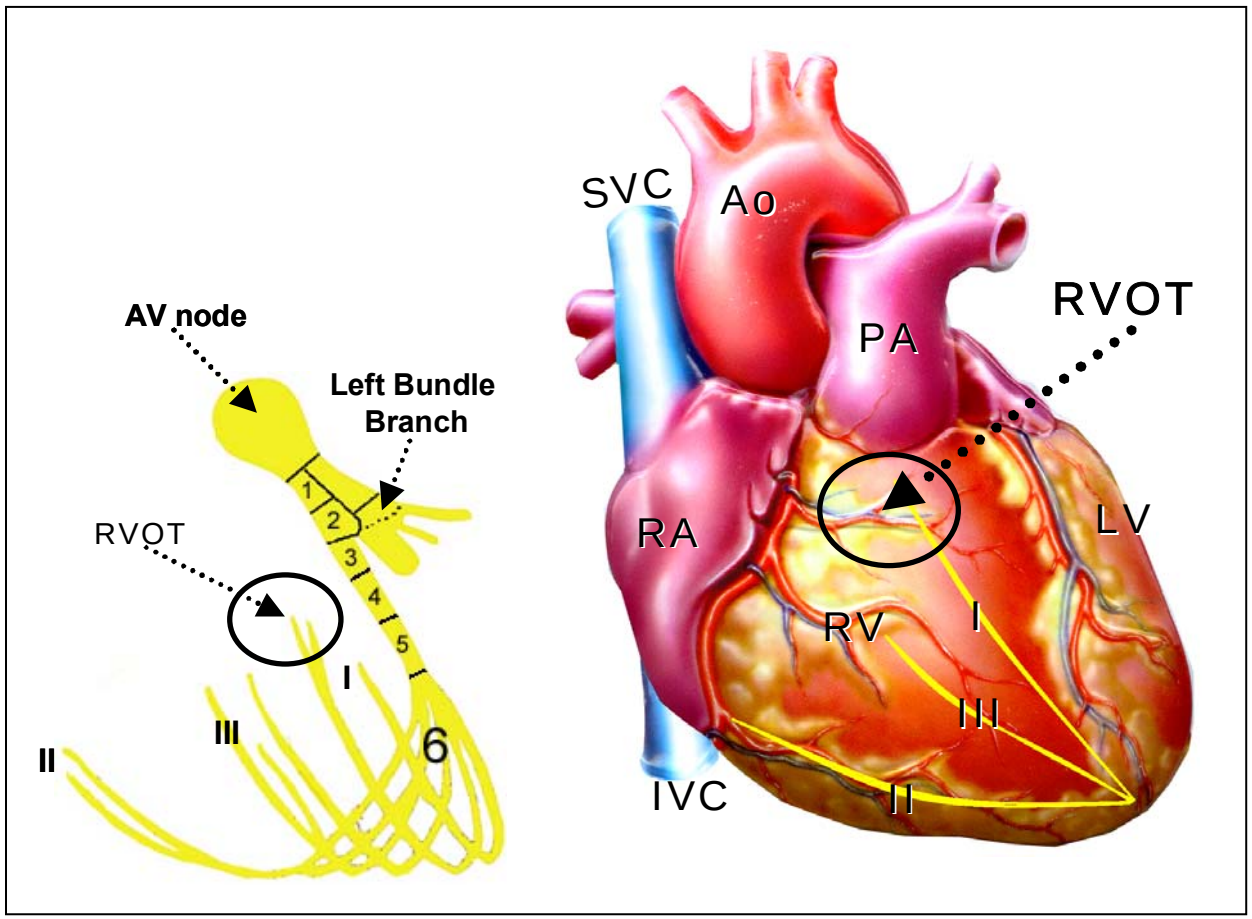
LEFT ANTERIOR FASCICULAR BLOCK OR BLOCK OF SUPERIOR DIVISION OF RIGHT BUNDLE-BRANCH



LEFT ANTERIOR FASCICULAR BLOCK OR BLOCK OF SUPERIOR DIVISION OF RIGHT BUNDLE-BRANCH

	LAFB	BSDRBB
INITIAL 10 to 20ms VECTOR:	Downward and to the right	Downward and to the left
DI – aVL MORPHOLOGY:	qR	Rs or R
SDII/DIII RELATION:	SDII < SDIII	SDII >SDIII
R WAVE OF aVR LEAD:	Maybe low or absent.	Prominent.
QRS FRONTAL LOOP ROTATION:	Counterclockwise.	Counterclockwise.
END CONDUCTION DELAY LOCATION:	On top left quadrant.	On top right quadrant

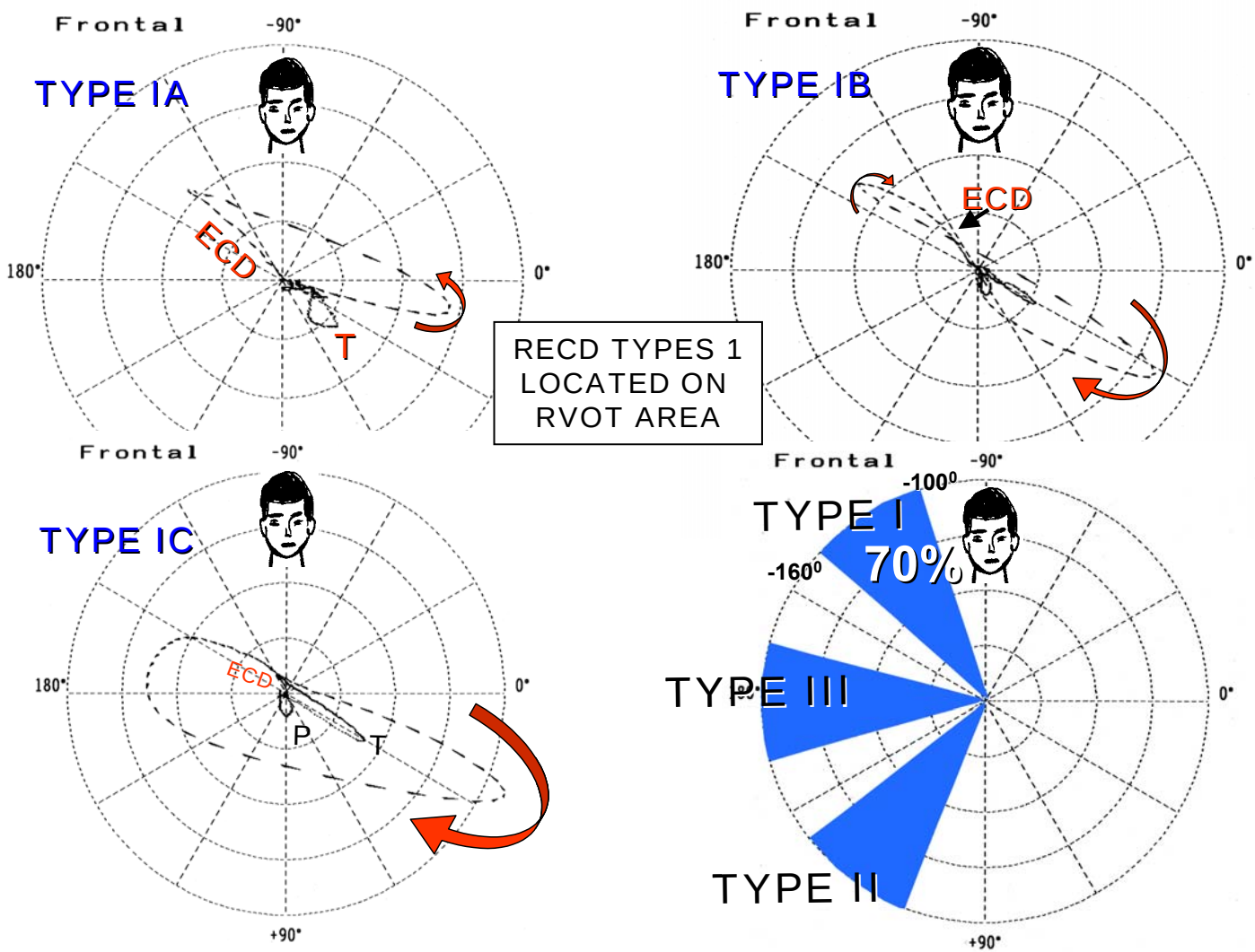
RECD PATTERN



We observed constant presence of RECD, located in the superior portion located in the RVOT: BLOCKAGE OF SUPERIOR DIVISION OF RIGHT BUNDLE-BRANCH.

1) **Pérez Riera, AR et al. The Brugada Syndrome From Bench to Bedside, Chapter 7. Value of 12 lead electrocardiogram and derived methodolgies in the diagnosis of Brugada disease". pg; 87-110,2005.**

THE VECTORCARDIOGRAPHIC VARIANTS OF SUPERIOR RIGHT END CONDUCTION DELAY(SRECD), TYPE 1 OR RIGHT ANTERO-SUPERIOR DIVISIONAL BLOCK (RASDB): TYPES IA, IB AND IC. FRONTAL PLANE



MAIN ECG FEATURES

QRS DURATION: 110ms ± 2ms: 90ms to 130ms[1].

There is a manuscript showing that BrS may present prolongation in QT interval duration from V_1 to V_3 and consequently prolongation of the QTc interval in the right precordial leads[2]. Localized prolongation of QRSd interval in V_1-V_3 / QRSd interval in V_4-V_6 > than 1.2 has been found in 97% of cases of ARVC/D. It is an evidence of right ventricular parietal block [3].

1) **Bianco M, et al. Eur Heart J 2001; 22:504-510.**
2) **Pitzalis MV, J Am Col Cardiol. 2003; 42:1632-1637.**
3) **Marcus FI. J Electrocardiol. 2000; 33:1-10.**

IRBBB OR CRBBB?

The diagnosis of RBBB cannot be performed completely accurately in the absence of broad terminal S wave on left leads DI, aVL, V5 and V6. This element, essential for an accurate diagnosis of RBBB in some cases of BrS could not be present. The phenomenon originated confusing terms as "pseudo RBBB," "RBBB-like," or atypical RBBB.

CONCLUSION: Sometimes RBBB is absent in BrS.

IRBBB OR CRBBB?

- ✓ **Frequently absence of triphasic pattern in right precordial leads : rSr', rsr', rsR', rSR' or "M" complex type;**

- ✓ **Sometimes there is no negative final broad S wave on left leads: DI, aVL and V_6;**

- ✓ **Sometimes there is no final R wave on unipolar aVR limb lead;**

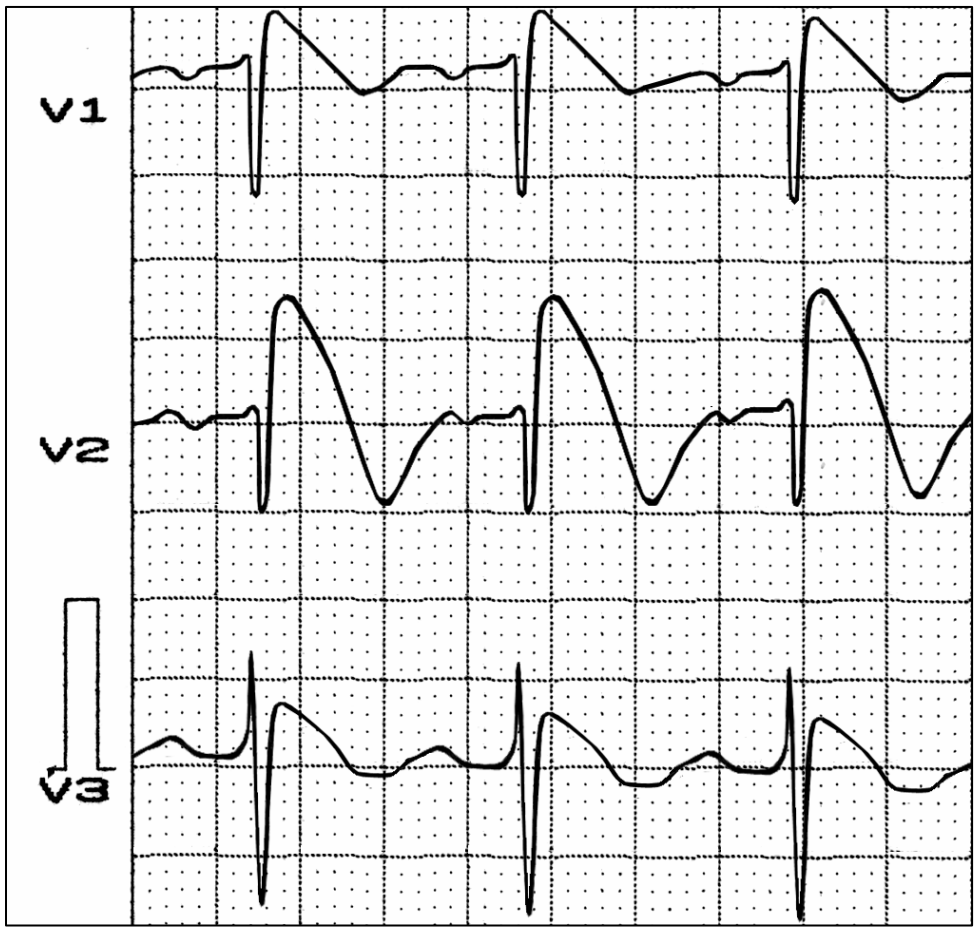
- ✓ **Sometimes the QRS duration is normal.**

REPOLARIZATION DISORDERS

The first European consensus about the syndrome classified the repolarization disorders occurred in the right precordial leads (V_1 and V_2) or in the anteroseptal wall (V_1 to V_3) in three types:

Wilde AA, et al. Eur Heart J 2002; 23:1648-1654.

MAIN ECG FEATURES

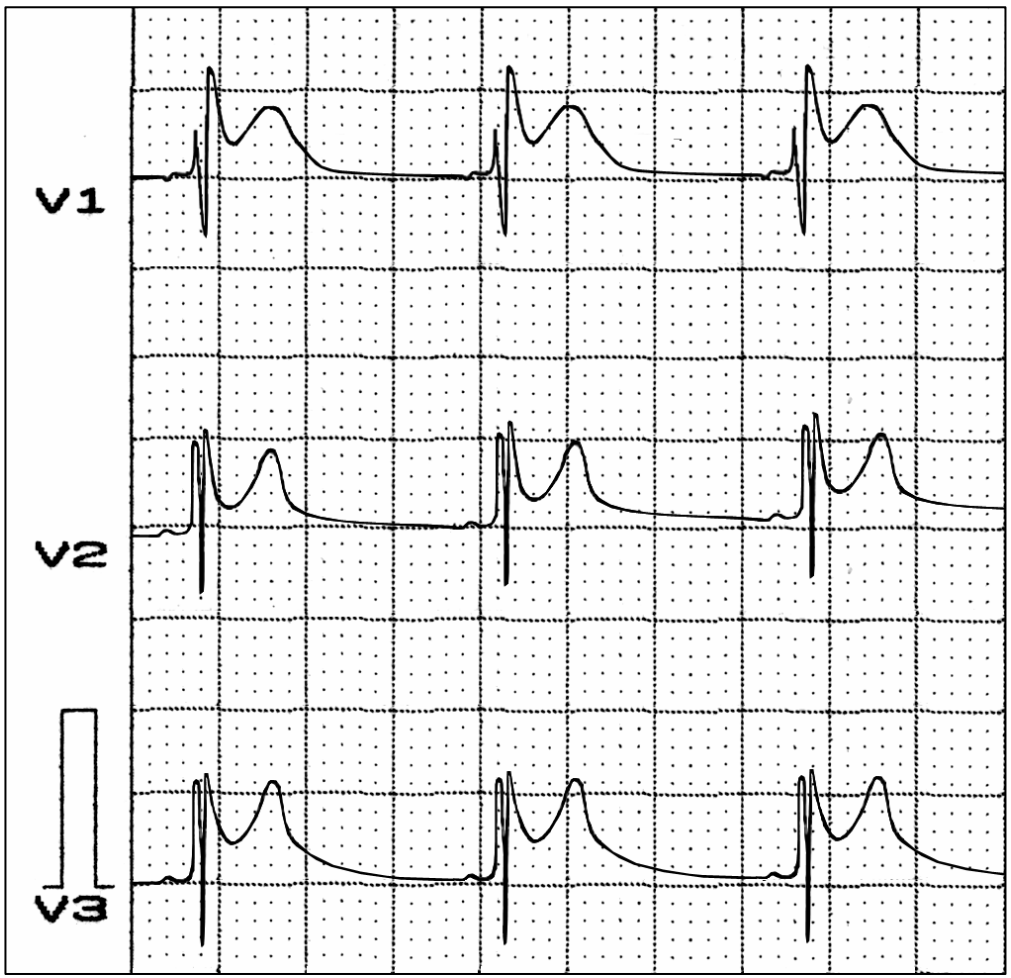


Type 1: ST-segment elevation is triangular or coved to the top ("coved type") ≥ 2mm (0.2mV), in at least 2 precordial leads and followed by negative T wave (Brugada phenotype). Only the type 1 is considered diagnostic. It is electrocardiographic hallmark of BrS.

In the case of a Type 1 ECG, there are not indication for pharmacological challenge with sodium channel blockers.

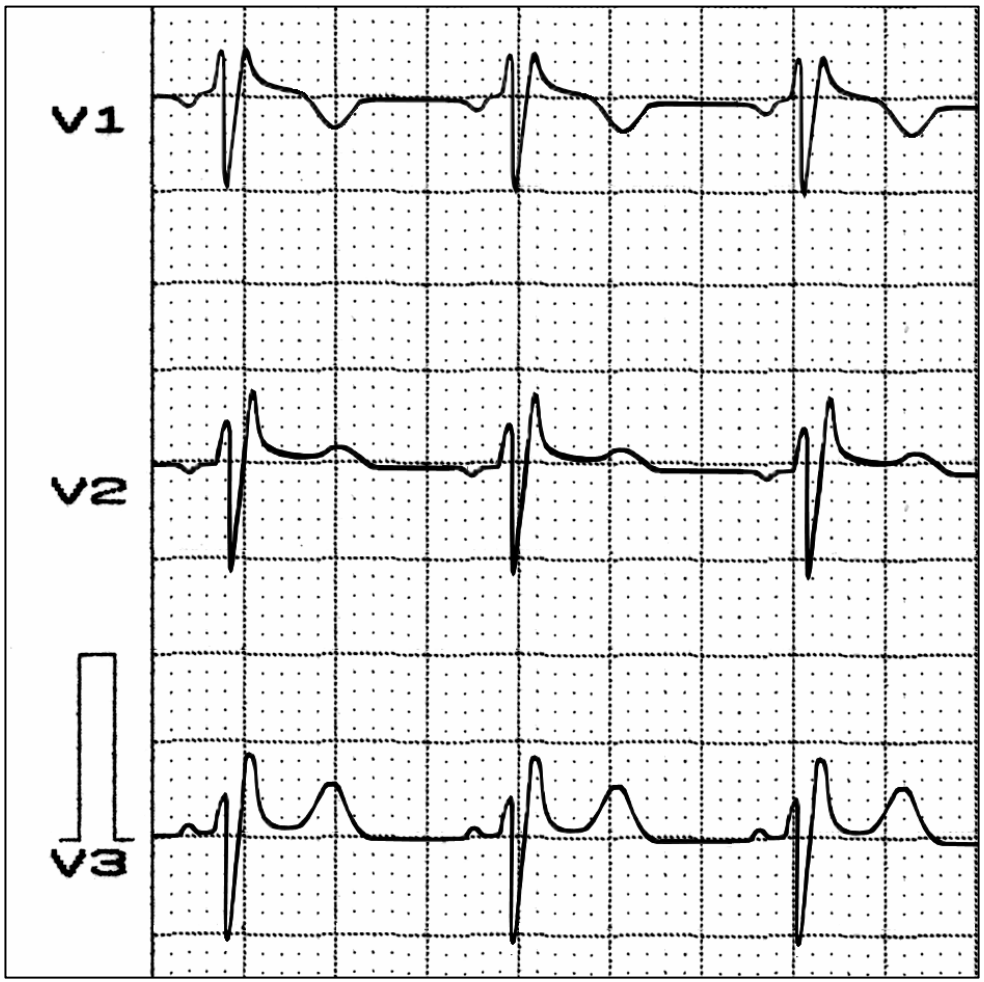
Brugada R, et al. J Electrocardiol. 2006;39:115-118

MAIN ECG FEATURES



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. The saddleback-type ST-segment elevation cannot be a sensitive finding for the Brugada syndrome.

MAIN ECG FEATURES



Type 3: J point and ST segment elevation < 1mm and with variable shape: whether coved type or saddleback appearance.

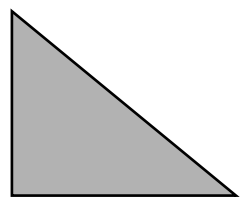
In Type 3, the terminal section of the ST segment never exceeds 1 mm above the isoelectric line.

Type 2 and Type 3 are classified as suspicious pattern but not diagnostic for the disease.

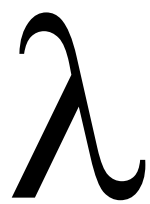
PROPOSAL OF CLASSIFICATION OF TYPE 1 BRUGADA ECG PATTERN

TYPE 1A: COVED SHAPE OR “BULL TERRIER” WAVE

TYPE 1B: TRIANGULAR SHAPE



TYPE 1C: “LAMBDA” (λ) OR GUSSAK WAVE

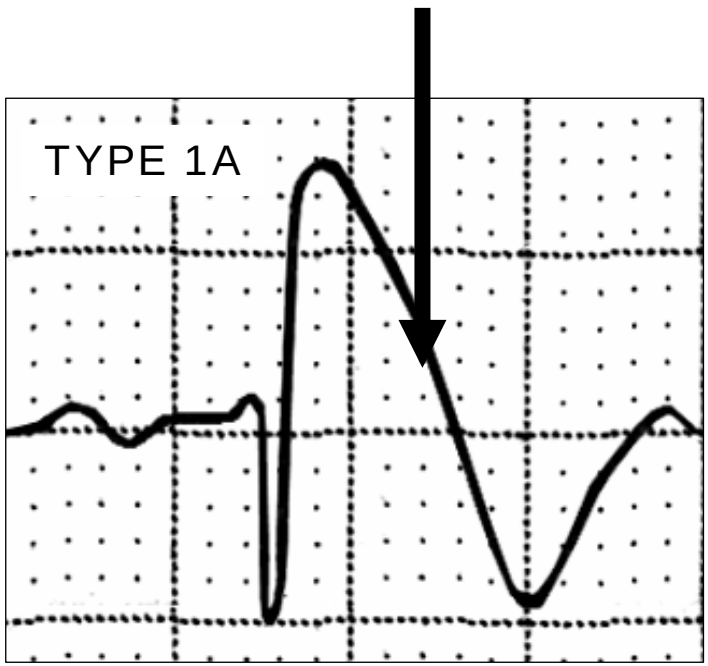


GREEK SMALL LETTER LAMBDA

PROPOSAL OF CLASSIFICATION OF TYPE 1 BRUGADA ECG PATTERN

TYPE 1A

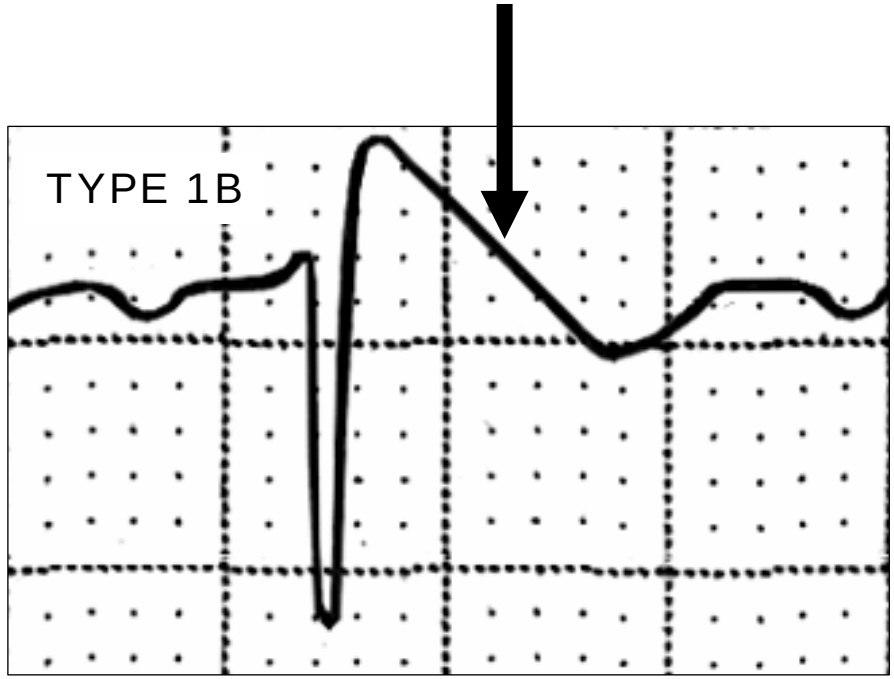
COVED TYPE
(CONVEX TO THE TOP)



V_1 to V_2 or V_3

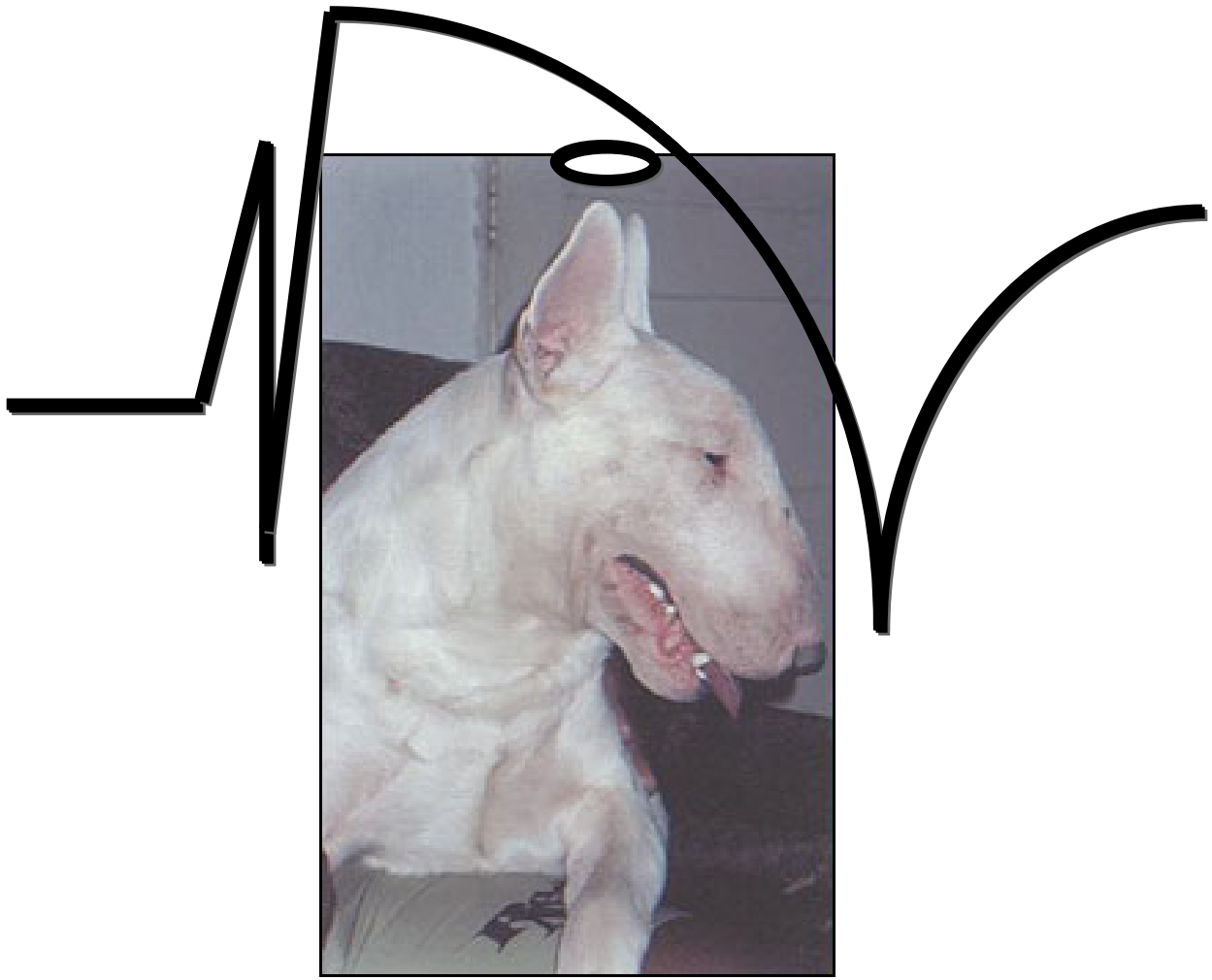
TYPE 1B

TRIANGULAR SHAPE

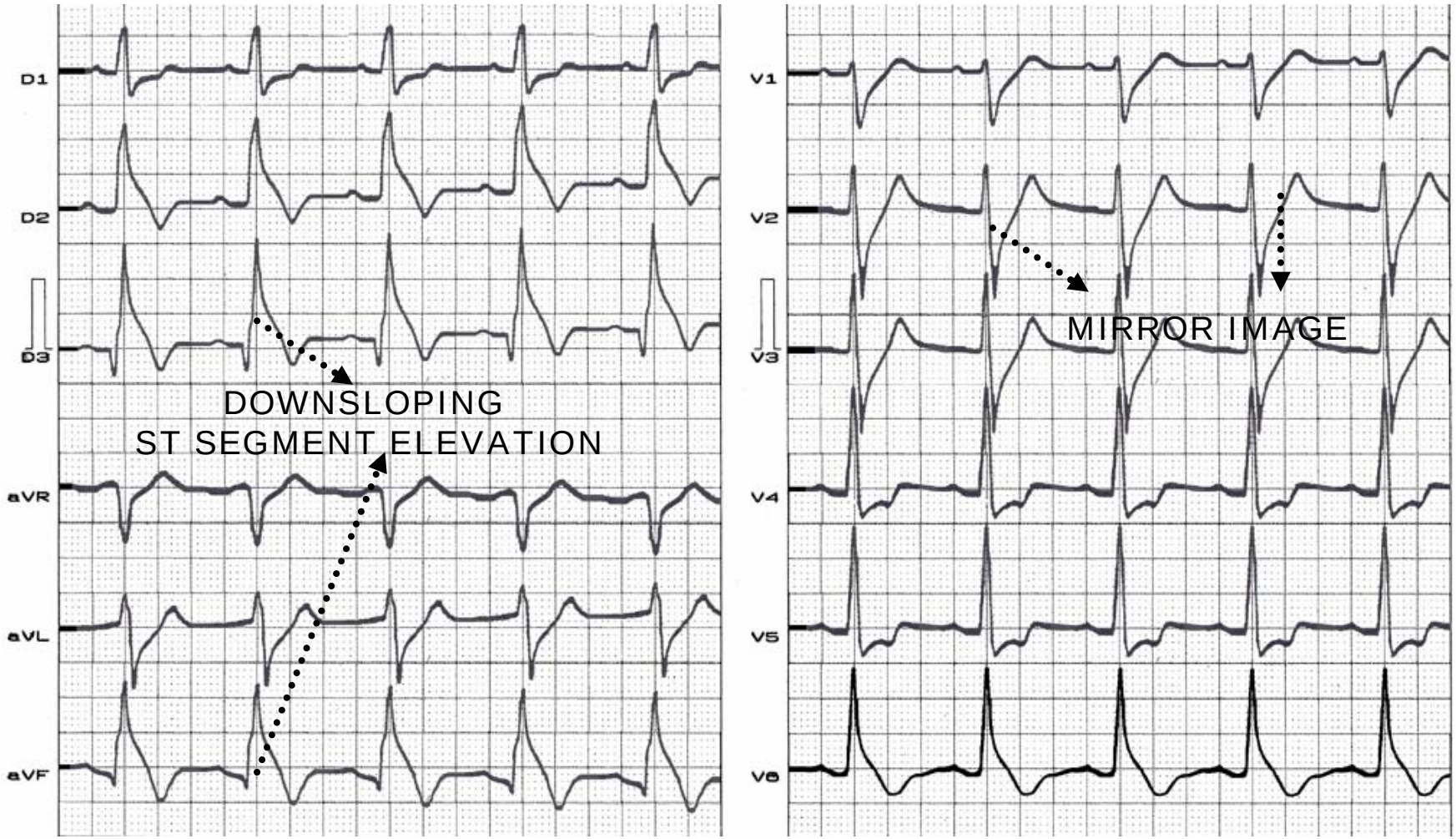


V_1 to V_2 or V_3

“BULL TERRIER” OR TYPE 1A BRUGADA PATTERN

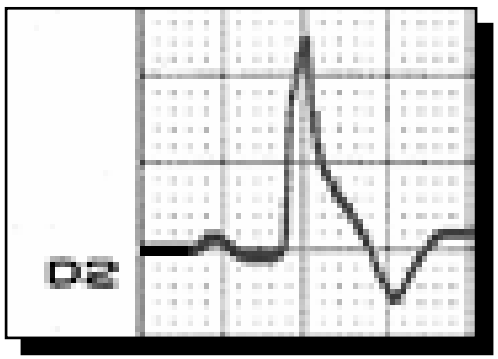


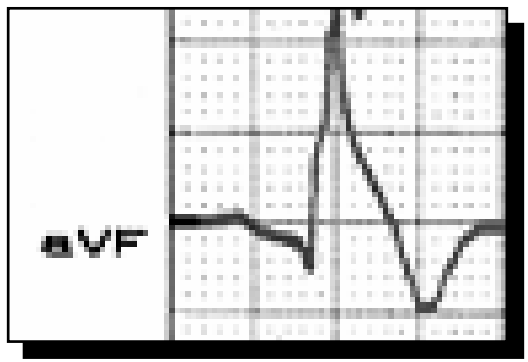
PROPOSAL OF CLASSIFICATION OF TYPE 1C BRUGADA ECG PATTERN

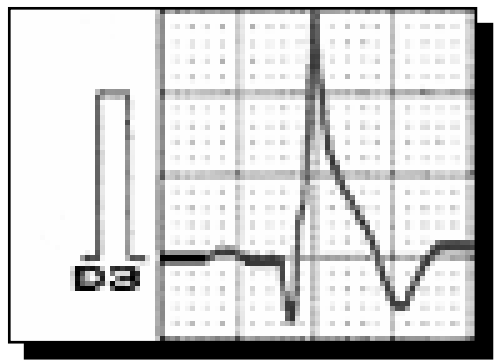


Riera AR, et al. J Electrocardiol 2004; 37:101-104.

TYPE 1C WAS DENOMINATED “LAMBDA” WAVE BY GUSSAK I ET AL







λ

Type 1C: ST-segment elevation is triangular or coved to the top (“coved type”) ≥ 2mm (0.2mV), and followed by negative T wave located in inferior leads.

Gussak I, et al. J Electrocardiol 2004;37:105-107.

THE BRUGADA ECG IS OFTEN CONCEALED, BUT CAN BE UNMASKED OR MODULATED BY A NUMBER OF DRUGS AND PATHOPHYSIOLOGICAL STATES INCLUDING:

Class 1A antiarrhythmic drugs: Ajmaline, procainamide	**Worsening Repolarization**
Class 1A antiarrhythmic drugs: Quinidine	Improve Repolarization
Class 1C antiarrhythmic drugs: Flecainide, propafenone	**Worsening Repolarization**
Class II antiarrhythmic agents: beta-adrenoceptor blockers: propranolol intoxication	Worsening Repolarization
Class III antiarrhythmic agents: Amiodarone	**Worsening Repolarization?**
Potassium opener channels: Pilsicainide	Worsening Repolarization.
Adrenergic agents: Isoproterenol dobutamine, catecholamine, hyper sympathetic nervous activity	**Improve Repolarization**
Increase in parasympathetic tone: cholinergic agents, acetylcholine, vagal nerve manipulation during deep neck dissection, bradycardia dependent changes	Worsening Repolarization.

THE BRUGADA ECG IS OFTEN CONCEALED, BUT CAN BE UNMASKED OR MODULATED BY A NUMBER OF DRUGS AND PATHOPHYSIOLOGICAL STATES INCLUDING:

Antidepressant: tricycles overdose and others psychotropic drugs: lithium.	**Worsening Repolarization**
Antihistaminic agents: dimehydrinate (First generation antihistaminic)	Worsening Repolarization
Diphenhydramine overdose	**Worsening Repolarization**
Hormones: Insulin	Worsening Repolarization
Cocaine	**Worsening Repolarization**
Antimalarials	Worsening Repolarization
Cilostazol	**Improve Repolarization**
Prajmalium bitrartrate	Worsening Repolarization

THE BRUGADA ECG IS OFTEN CONCEALED, BUT CAN BE UNMASKED OR MODULATED BY A NUMBER OF DRUGS AND PATHOPHYSIOLOGICAL STATES INCLUDING:

I_{to} Channels blockers: Quinidine	**Worsening Repolarization**
Anesthetics: bupivacaine	Worsening Repolarization
Dimethyl lithospermate: It is an extract of Danshen, a traditional Chinese herbal remedy	**Worsening Repolarization**
Fever	Worsening Repolarization
Hypokalemia	**Worsening Repolarization**
Hyperkalemia	Worsening Repolarization

CASE 1

Mr. PAU

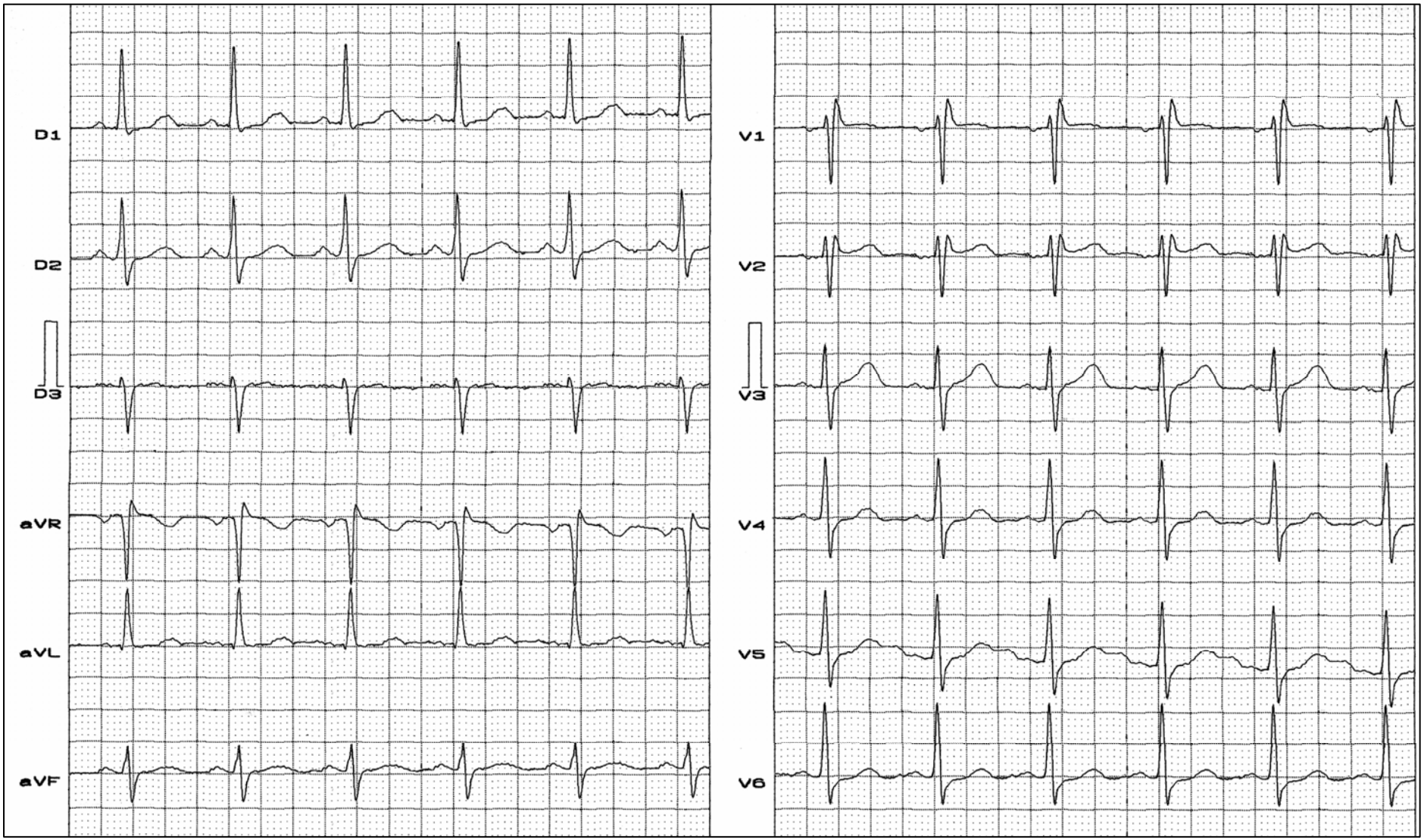
1) Symptomatic: one episode of recuperated SCD at rest.

2) Positive family background: history of SCD in a young first-degree relative (< 45 years old);

3) Genetic research performed: negative;

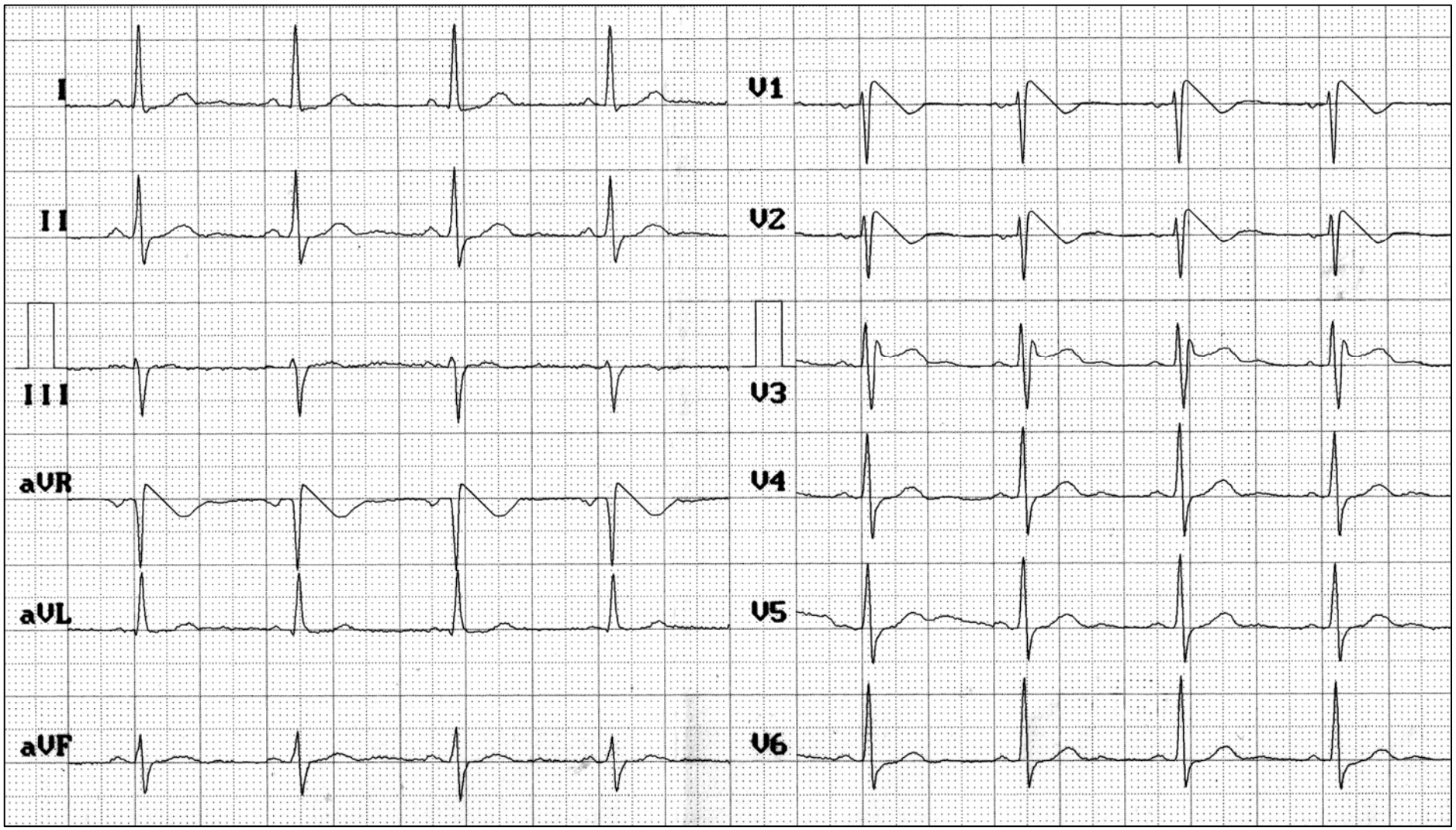
4) The patient refusal the indication of ICD implantation, we started treatment with quinidine orally, in a dose of 1600 mg/day (400 mg each 6 hours).

Name: PAU; Date: 03/25/2005; Age: 31 y; Sex: M;
Race: Y Weight: 75 Kg; Height: 1.81 m; Biotype: normoline



ECG diagnosis: sinus rhythm, HR: 85bpm, QRSd: 105ms, triphasic QRS pattern in V1-V2 leads, IRBBB, Brugada Type 3 pattern of repolarization.

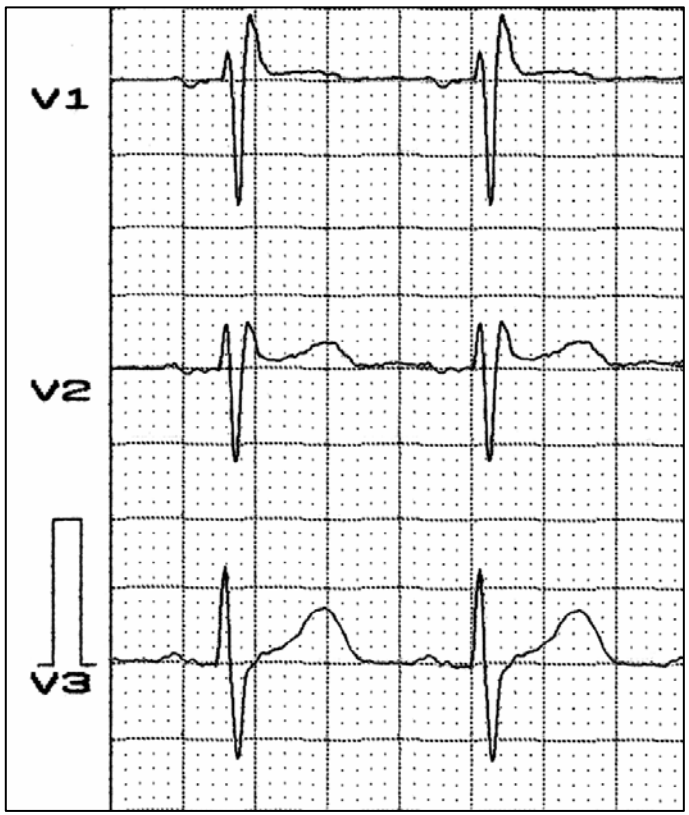
Name: PAU; Date: 06/07/2005; Age: 31 y; Sex: M;
Race: Y Weight: 75 Kg; Height: 1.81 m; Biotype: normoline



ECG diagnosis: sinus rhythm, HR: 61bpm, QRSd: 120ms, Brugada Type 1 pattern, wide coved last R wave in aVR lead.

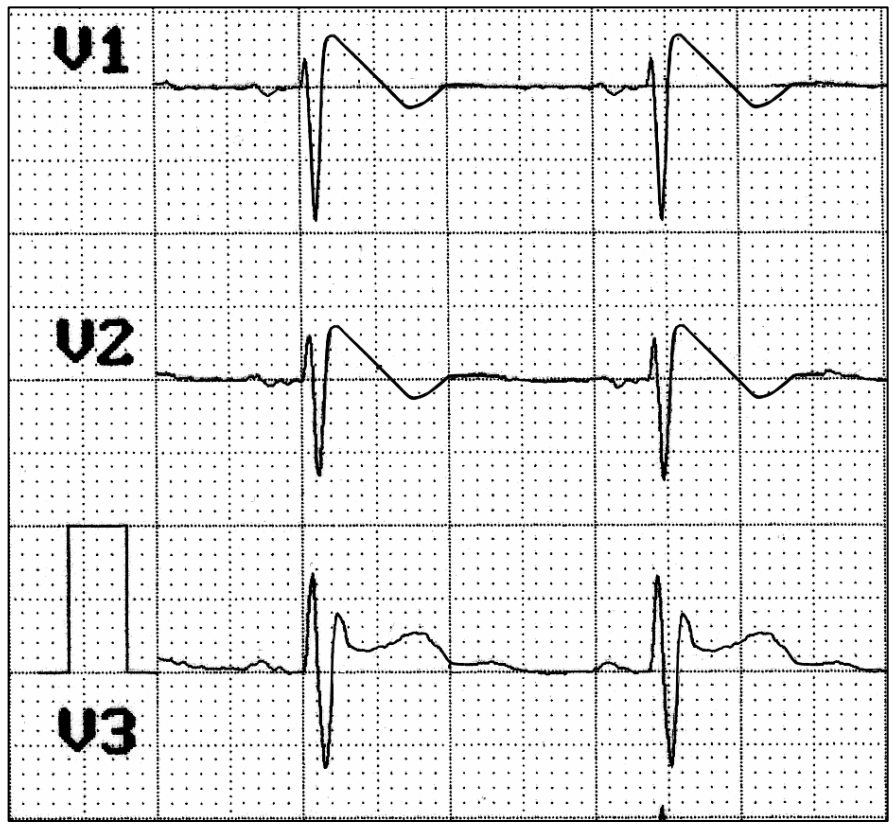
DEMOSTRATION OF DINAMIC REPOLARIZATION CHANGES

Name: PAU;
Date: 03/25/2005;



TYPE 3 BRUGADA PATTERN

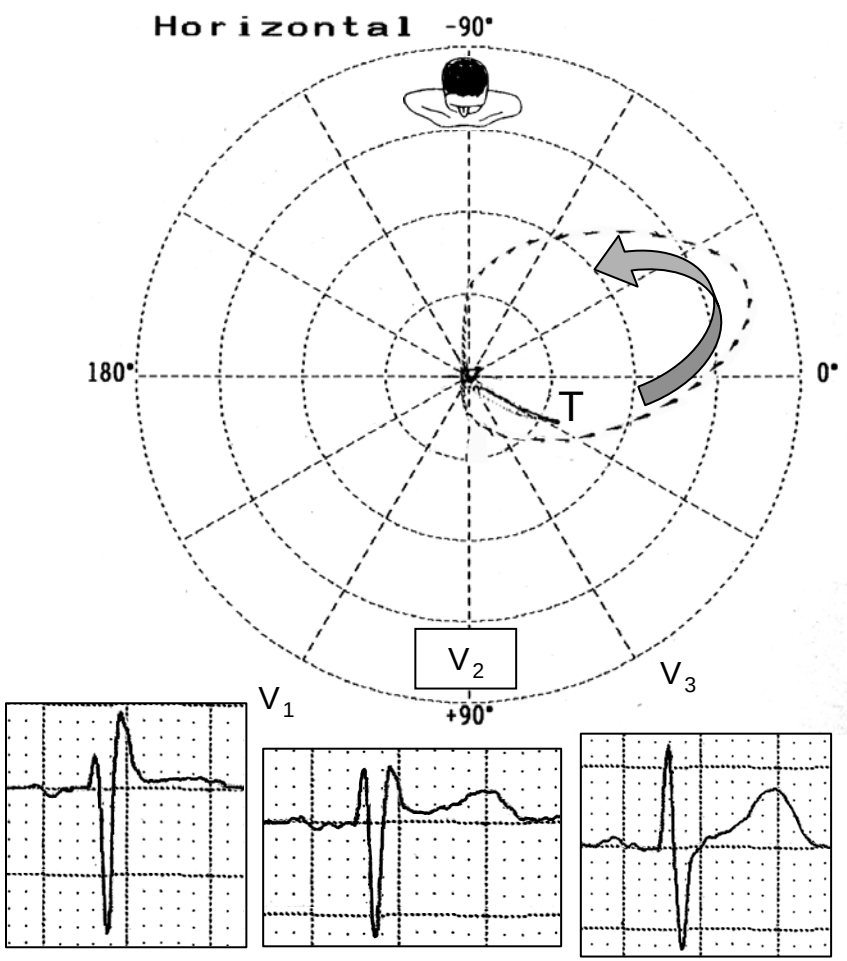
Name: PAU;
Date: 06/07/2006;



TYPE 1 BRUGADA PATTERN

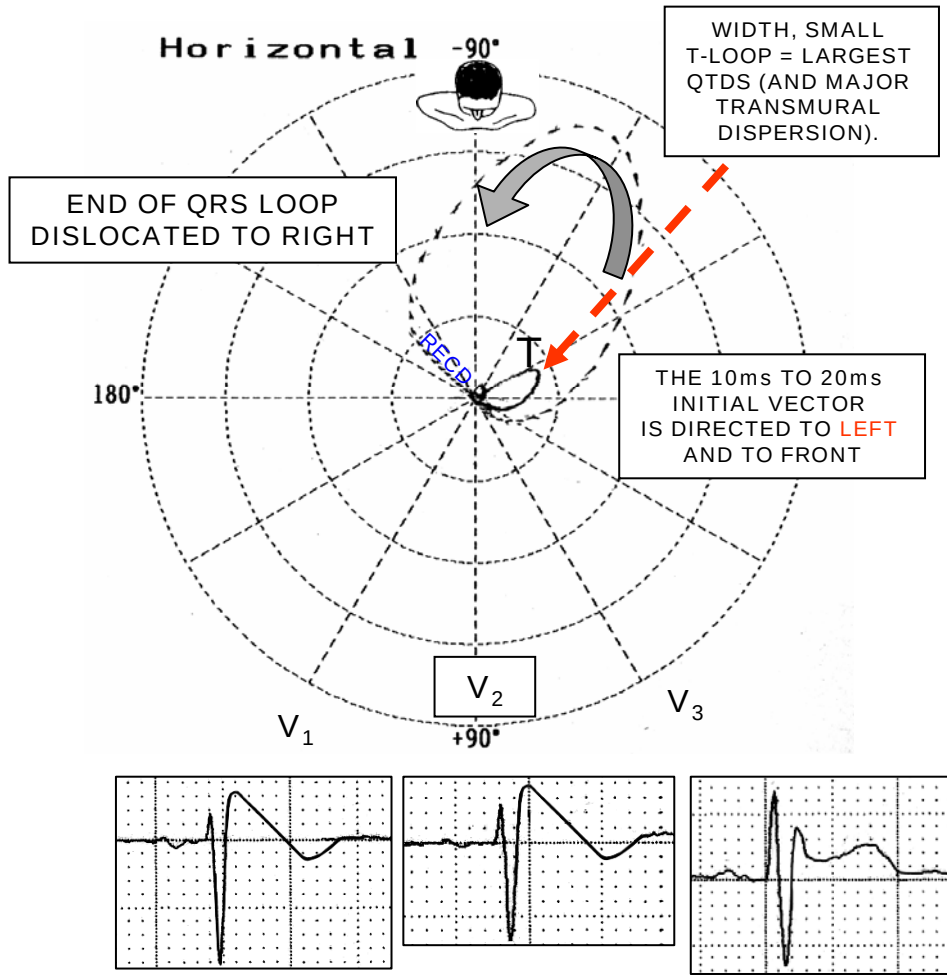
ECG/VCG CORRELATION HORIZONTAL PLANE

Name: PAU;
Date: 03/25/2005;



TYPE 3 BRUGADA PATTERN

Name: PAU;
Date: 06/07/2006;



TYPE 1 BRUGADA PATTERN

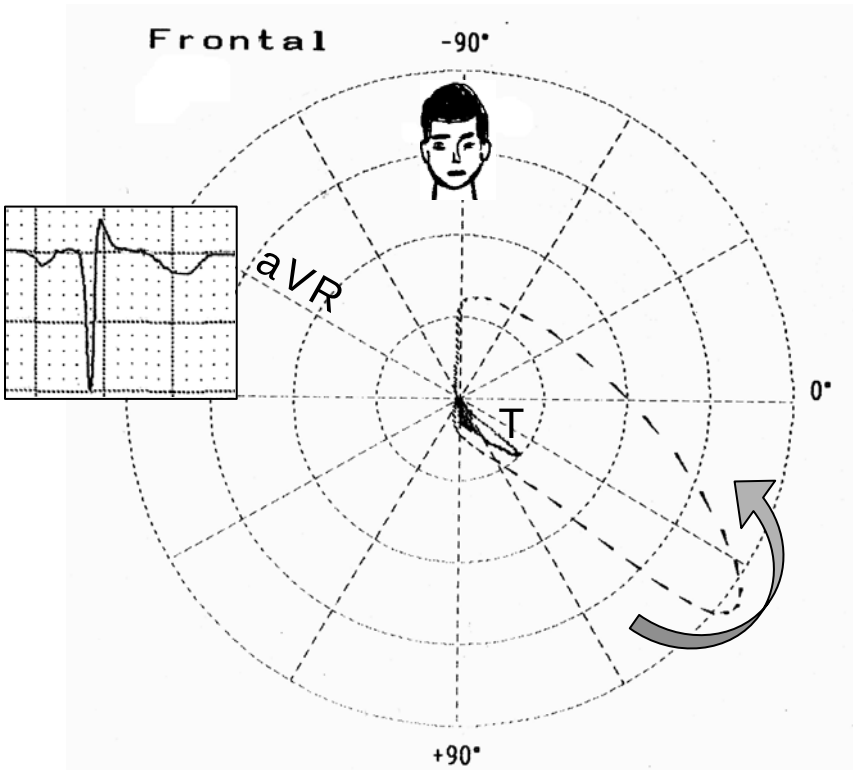
THE T-LOOP SHAPE OR T-LOOP MORPHOLOGY

- **The normal T-loop is usually elongated or elliptical and sometimes almost linear in configuration.**
- **The T-loop became more *circular and bulgy during coronary occlusion* [1].**
- **QT dispersion is as an attribute of T-loop morphology [2].**
- **T-loop morphology appear to be strong, independent risk indicators of cardiac events in the elderly. Subjects with an abnormal T-loop morphology had increased risks for fatal cardiac events and nonfatal cardiac events [3].**
- **In BrS Type 1 pattern we observed T-loop morphology on HP: circular, bulge, small. We think that this is e signal of transmural dispersion on ventricular wall.**

1) Nowinsky K, et al. J Intern Med. 2000; 248:126-136.
2) Kors JA, et al. Circulation; 1999; 99: 1458-1463.
3) Kors JA, et al J Electrocardiol.1998; 31: 54-59.

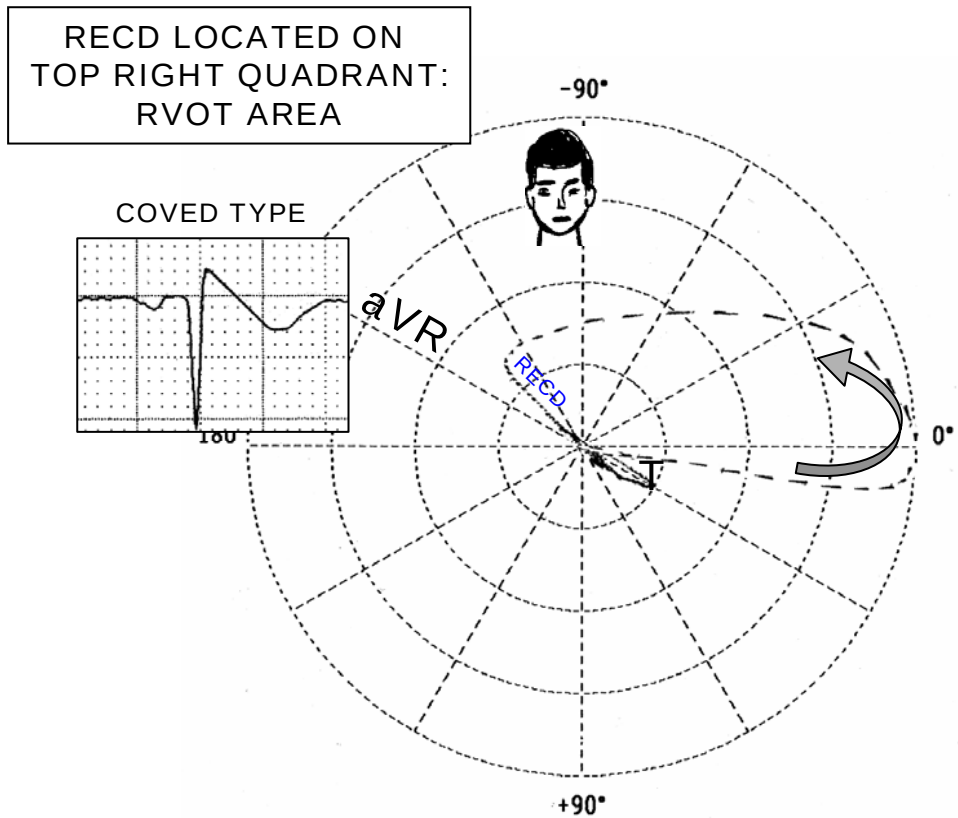
ECG/VCG CORRELATION FRONTAL PLANE

Name: PAU;
Date: 03/25/2005;



Name: PAU;
Date: 06/07/2006;

RECD LOCATED ON
TOP RIGHT QUADRANT:
RVOT AREA



ECG WITH MODIFIED PROTOCOL HIGH RIGHT PRECORDIAL LEADS

Several manuscripts carried out conclude that 12-lead ECG sensitivity increases by applying accessory leads located in the high right precordial area (V1H – V2H), over the 3rd or 2nd intercostal space, just to the right (V1H) or left (V2H) of the sternum. In certain cases, Brugada sign that was not observed using only the 12 conventional leads, is now visualized. The procedure is founded on the fact that modified precordial leads on right precordial leads (V1H - V2H) or on anteroseptal wall (V1H to V3H) at higher intercostal space positions are located exactly opposite to the RVOT.

1) Teijeiro R, et al. J Cardiovasc Pharmacol Ther. 2006;11:153-5.

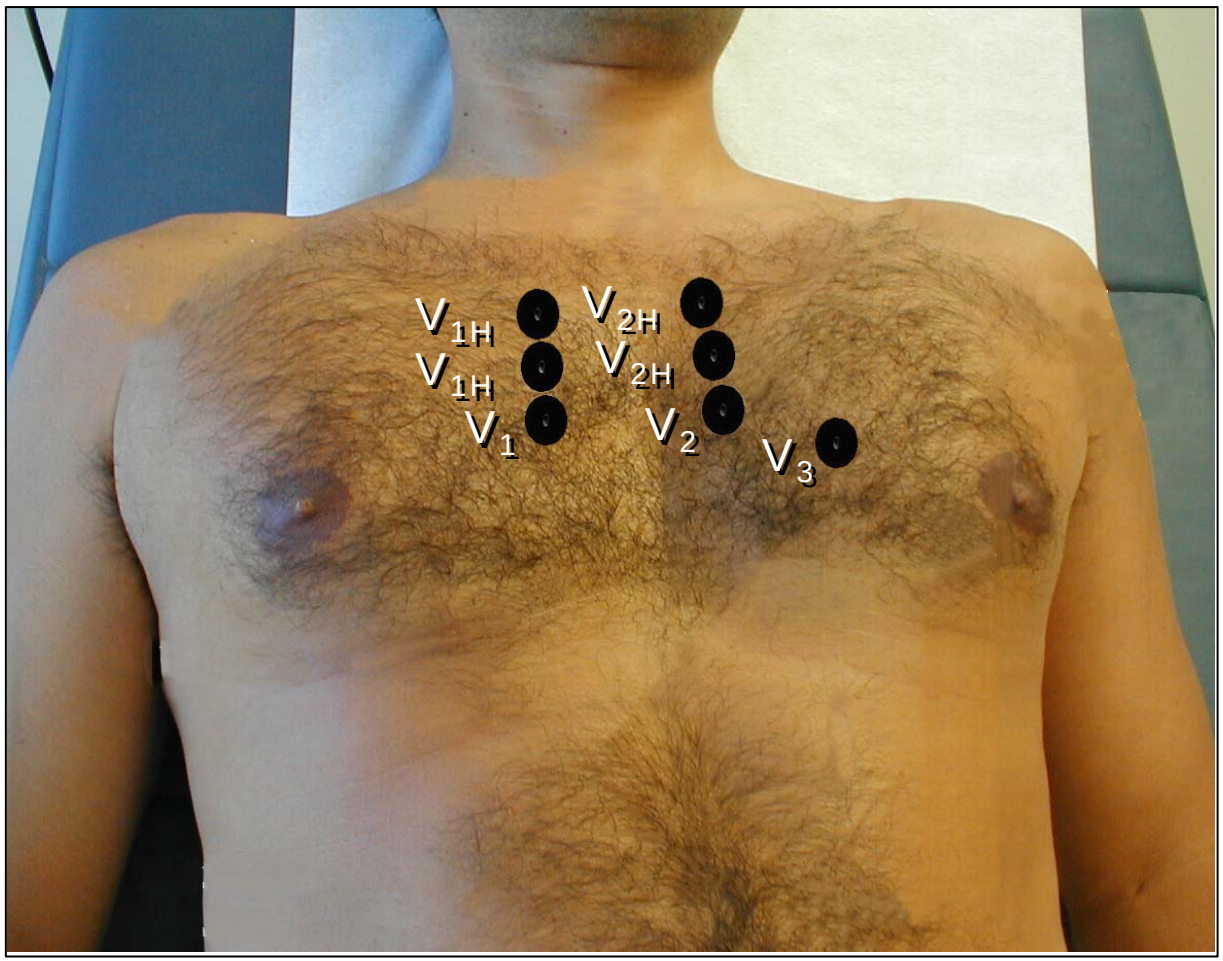
ECG WITH MODIFIED PROTOCOL HIGH RIGHT PRECORDIAL LEADS

During the ajmaline test the ECG leads V3 and V5 are sacrificed and replaced with leads placed over the third intercostal space, cranial from V1 (V1-IC3) and V2 (V2-IC3).

V3=V1-IC3: V3 located over the third intercostal space, cranial from V1

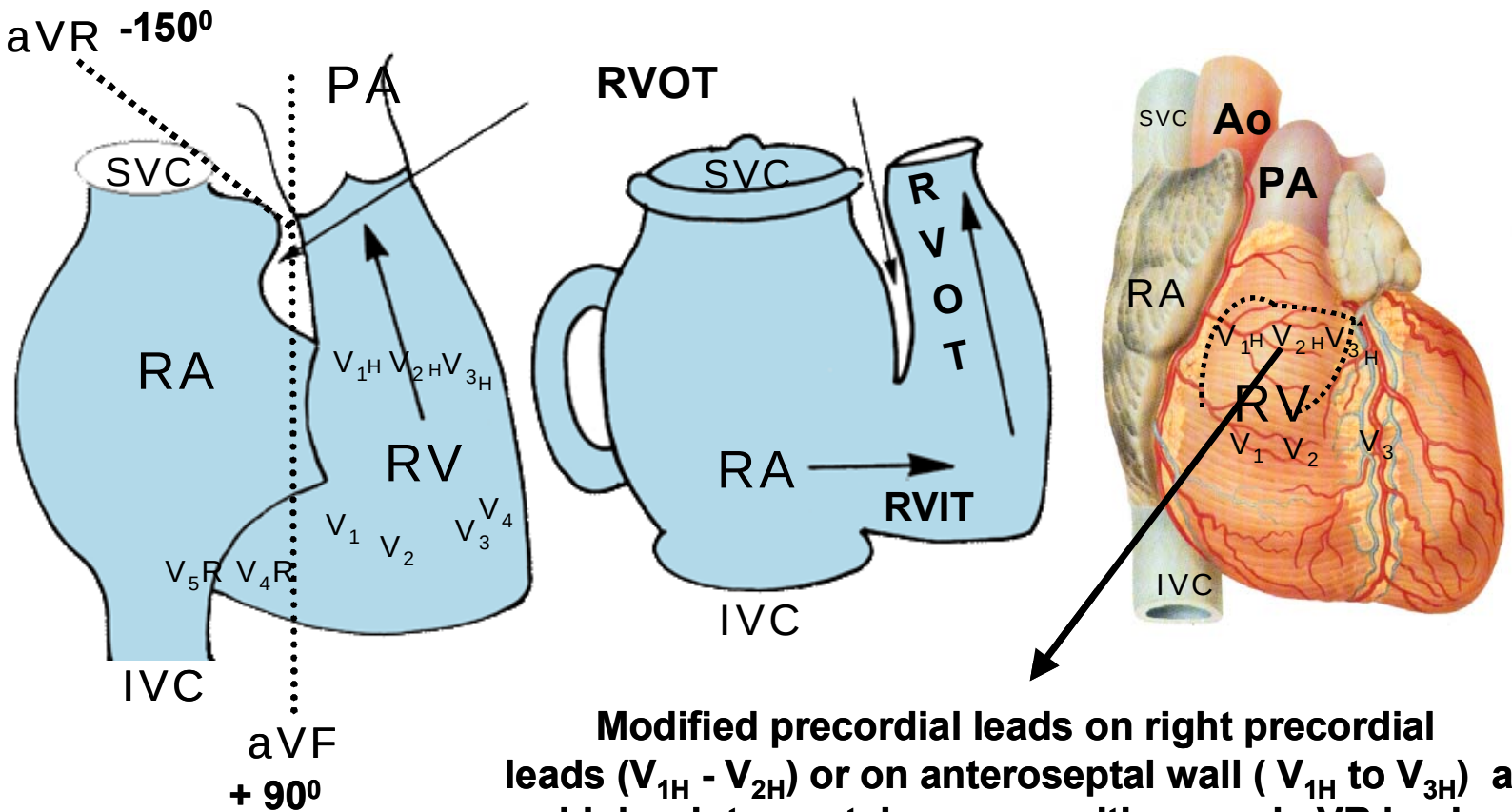
V5=V2: V2 located over the third intercostal space, cranial from V2 (V2-IC3).

ECG WITH MODIFIED PROTOCOL HIGH RIGHT PRECORDIAL LEADS



V1H – over the 3rd or 2nd intercostal space, just to the right of the sternum.
V2H – over the 3rd or 2nd intercostal space, just to the left of the sternum.

REGIONS OF RV AND CORRESPONDING LEADS



Modified precordial leads on right precordial leads (V_{1H} - V_{2H}) or on anteroseptal wall (V_{1H} to V_{3H}) at higher intercostal space positions and aVR lead.

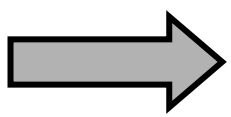
RIGHT VENTRICLE REGIONS AND THEIR CORRESPONDING LEADS

The right ventricle has five regions that are better detected by the following leads:

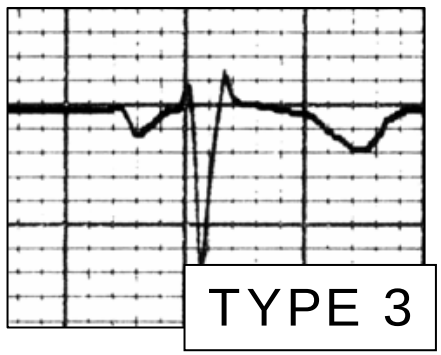
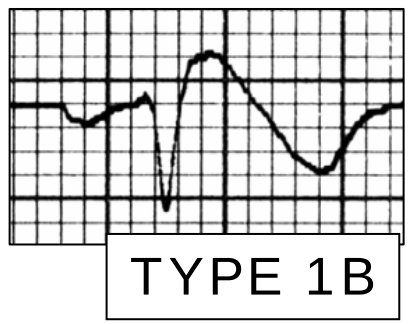
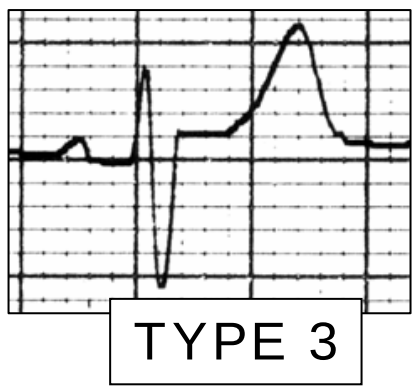
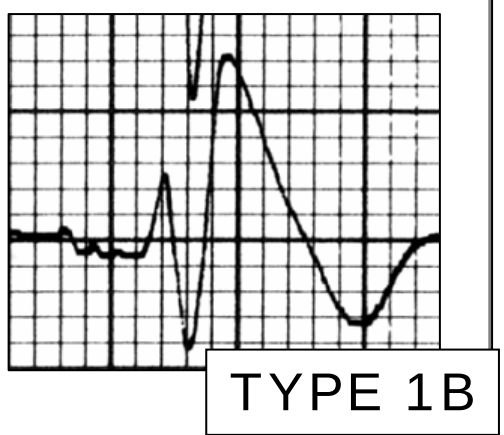
1) V2 and V3.: trabecular area;
2) V3 – V4: Low right paraseptal area;

3) V1 to V4.: Free wall;

4) aVF, V4R and V5R: Right Ventricle Inflow Tract (RVIT);

5) aVR, V1H, V2H, V3H :  **RVOT: the area affected in the Brugada syndrome.**

ECG ANALYSIS
BEFORE / AFTER AJMALINE INJECTION – 70mg

	BEFORE	AFTER
V1 **V3=V1**		
V2 **V5=V2**		

CONCLUSION: Conversion to Brugada type 1 pattern: positive test.