English version

SIGNIFICANCE OF ELECTROCARDIOGRAM IN THE BRUGADA SYNDROME AND IN OTHER ARRHYTHMOGENIC ENTITIES. GUIDELINES FOR PREVENTION OF SUDDEN CARDIAC DEATH

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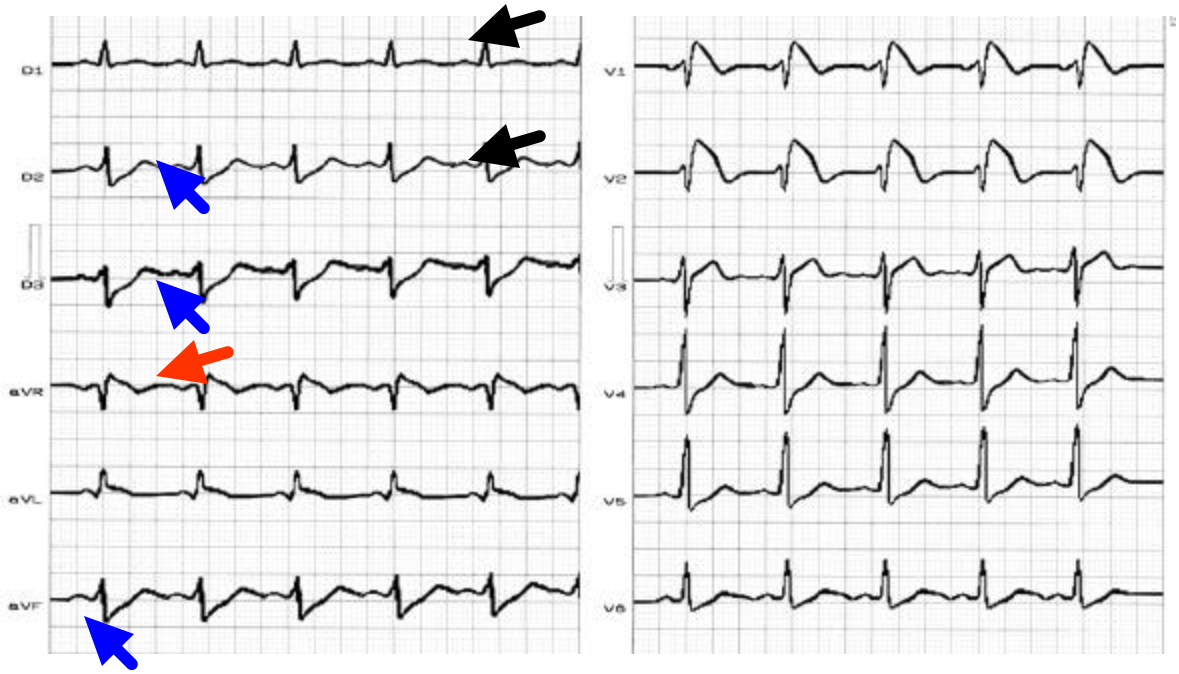
The Brugada Syndrome constitutes a subgroup within idiopathic ventricular fibrillation (IVF) representing a percentage of the total share to be established. The diagnostic criteria for these cases are not yet clearly defined **(1)**.

The entity is part of the so-called primary electric diseases, and it is mostly caused by abnormal electrophysiologic activity in the right ventricle epicardium **(2)**. It is characterized by an electrocardiographic pattern constituted by atypical right bundle branch block (RBBB), conduction disorder through this branch or incomplete right bundle branch block (IRBBB) associated to persistent and possibly transitory (or fluctuating) elevation of the J point or the ST segment that can vary substantially in time. The typical ST is convex toward the top ("coved type") observed in precordial leads: V_1 to V_2 or V_3, corresponding to the antero-septal territory **(3)**. This electrocardiographic association is a diagnostic key (IRBBB + elevated ST), which has been properly called "the Brugada sign" (idiopathic J wave), very seldom observed in the inferior wall. There is a great tendency to the appearance of very fast idiopathic polymorphic ventricular tachycardia (IPVT) and/or IVF with a high annual rate for sudden cardiac death (SCD) in cases of lack of intervention **(4)**.

TYPICAL ECG BRUGADA SYNDROME (FIGURE 01)



Elevation of J point and ST segment, convex toward the top, ST in right precordial leads from V_1 to V_2(black arows) : Brugada sign or idiopathic J wave.Unipolar aVR face the RV epicardium on the outflow tract show tenuous J point and ST segment elevation too (red arows). Inferior leads show mirror image (blue arows).

Among the total VF, 80 to 90% present structural heart disease, and 10-20% do not have a demonstrable heart disease. These people are frequently young, and in some cases SCD is the first and only episode. The possible causes are: IVF, family-inherited long QT syndromes, and Brugada syndrome **(5)**. The existing electric instability does not have a demonstrable underlying organic substrate, atherosclerotic or vasospastic coronary heart disease (which can coexist with vasospastic angina or Prinzmetal variant), electrolytic disorder, cardiomyopathy or any other. The clinical presentation includes cardiac arrest secondary to IPVT/IVF with a very fast frequency that happens predominantly during night sleep or rest (in 85% of cases), yet, in 15% of the patients it is observed during physical activity **(6)**. This night predominance of events suggests that increase of vagal activity and decrease of sympathetic tone occurring during the night can have a significant role in arrhythmogenesis **(7)**.

The association of atypical RBBB, persistent or fluctuating elevation of the J point and the ST segment convex toward the top ("coved type") or the saddle type in precordial leads V_1 to V_2 or V_3 with normal QTc in yellow race male patients, frequently from some Asian countries (mostly Thailand, The Philippines and Japan) or Caucasians who survived SCD, characterize the clinic syndrome electrocardiographically.

The prevalence, incidence and prognosis of ECG of the Brugada kind was analyzed in the whole of the/general population in Japan, based on a study of four decades. Thus, from a universe of 4788 individuals, 32 ECG of the Brugada kind were detected; the prevalence and incidence being 146.2 in 100,000 people and 14.2 per 100,000 individuals/year, respectively. This incidence was nine times higher in men than in women; the intermittence of ECG of the Brugada type was found in 26% of cases of those who underwent sudden cardiac death, and the Cox survival analysis showed that unexpected mortality was significantly higher in subjects with ECG of the Brugada type than in control subjects **(8)**.

The entity causes from 4 to 10 SCD per 1000 inhabitants/year in Thailand and Laos. In these countries, the disease represents the most frequent cause for death between young male adults **(9)**.

From about 12000 non-selected and non-cardiac patients from just one University Hospital, collected prospectively for a period of two years, there were 52 cases with the typical electrocardiographic pattern, i.e., with Brugada sign **(10)**.

The ECG is a simple, non-expensive means, very useful to identify cases with underlying risk. A recent publication points that electrocardiographic patterns suggesting the entity are associated to high risk of SCD **(11)**.

The electrocardiographic manifestations can show transitory normalization in many patients, and they can eventually be unmasked by some IA class anti-arrhythmic fast sodium channel blockers (ajmaline and procainamide) and IC class anti-arrhythmic blockers, such as flecainide **(12)**.

In five children of the same family, who unexplainably died because of heart arrest, Brugada syndrome was suspected, considering the typical manifestations of ECG in one of them. The genetic mutation in the sodium channel was confirmed, which points out that death can happen early in this entity **(13)**.

It has been proposed that the mutation in the sodium channel could be responsible for certain cases of sudden cardiac death syndrome in children or SIDS –Sudden Infant Death Syndrome- **(14)**.

SCDs constitute 19% of SCD among children from 1 to 13 years, and a 30% of SCD occuring from 14 to 21 years. Incidence of SCD shows two peaks, one from 45 to 75 years, which develops from coronary heart disease, and another from birth to 6 months of age, caused by SIDS. Recent discoveries hint primary electric diseases as the Brugada Syndrome and long QT as responsible for SCD in infants and children **(15)**.

The entity, of family occurrence in 25% of cases **(16)**, is due to dominant autosomal transmission, and has been mapped in chromosome 3, in the alpha subunit of the SCN5A gene, where mutations in the fast channel of sodium have been observed, which ultimately cause its spontaneous malfunctioning, plus an increase in worsening of the function depending on the effect of blocking drugs, such as anti-arrhythmic agents of the IA class, ajmaline and procainamide, and those of the IC class, flecainide. A decrease in the function of the fast channel of (I_{Na}), which determines a higher increase in the depth of phase 1 mediated by the I_{to} channel in the cells of the epicardium, but not in the RV endocardium, causes a pattern that resembles the early repolarization in right precordial leads.

The channels affected in the Brugada syndrome are primarily the fast sodium channel, and secondarily, the I_{to} channel, of potassium initial outflow ("transient outward current"), or channel sensitive to 4 aminopyridine ("4 aminopyridine sensitive outward current"), and the slow calcium channel of phase 2 or L-type (slow or long-lasting) $I_{Ca\text{-}L\ type}$ $I_{Ca^{++}\text{-}L}$ **(17).**

We use the term "Brugada pattern" in those cases in which we only find electrocardiographic manifestations in asymptomatic patients, without positive family history, and without the tendency to develop fast onsets of PVT/VF with syncope or SCD.

A benign clinical evolution is possible within asymptomatic patients with the ECG "Brugada pattern", without family history of SCD, as proved by Takenaka et al. in 11 patients followed by a mean time of 43 months **(18)**. Within the universe of 11 patients, in 8 of them had EPS carried out; 7 of which were not inducible. On the contrary, there is a recent publication about an asymptomatic patient without family history of SCD, who had only the ECG "Brugada pattern", and who had a cardioverter defibrillator implanted due to the inducibility shown in the PVE. During follow-up, the machine was activated three times, thus confirming retrospectively the accuracy of the adopted management **(19)**.

The rate of recurrence of VT/VF in the Brugada syndrome is very high, having been estimated in a 40% in a three-year follow-up. Asymptomatic individuals with a typical electrocardiographic pattern, have also a high risk of developing the first event. Every doctor should then recognize without hesitation the characteristic ECG pattern of the Brugada kind.

In patients with suggestive ECG, a careful study should be performed, with more sophisticated means, with the intention of ruling out an organic heart disease, an arrhythmogenic right ventricle dysplasia (ARVD) in its initial or minor form ("concealed form"), since this entity can present a similar **(20)** or even indistinguishable **(21-22)** electrocardiographic pattern. Other, more sophisticated methods to be used to differentiate both entities are:

1) Uni and bidimensional echocardiogram with Doppler and even transesophageal;
2) Ultra-fast Computerized Tomography ("Electron Beam Computed Tomography" - EBCT)
3) Helicoidal nuclear magnetic resonance, cine magnetic resonance imaging, Cine MRI, or with pulsated NMR with zero field (spin echo) ("ECG-Gated Spin-Echo Imaging");
4) Cardiac catheterization with right and left ventriculography and coronariography, if necessary with ergonovine test to rule out vasospastic angina.
5) Endomiocardial biopsy.

Note:
The ECG of long duration (Holter), or even better, the 15-day looper, could have a better theoretical chance of detecting tachyarrhythmic events, besides recording the possible increase of elevation of the J point and of the ST segment during sleep (night vagal worsening).
The ergometer test, in turn, can reveal the improvement of repolarization during effort, as a consequence of increase of adrenergic tone. This is because the I_{to} channel of the phase 1 is less prominent during the high frequencies that lead to a decrease of elevation of ST segment, which probably diminishes the incidence of ventricular arrhythmias **(23)**. Changes in the width of elevation of the J point and of the ST segment, dependent on the heart rate, can help as an important indicator in the detection of patients with high risk of SCD.
The High Resolution ECG does not allow a differentiation between the Brugada Syndrome and the ARVD since there are very frequent records of late potentials in both of them.

Characteristics of the Electrocardiogram

1) Rhythm:
The rule is a sinus rhythm, however, atrial arrhythmias are found in a 10 to 25% of the cases since the arrhythmogenic substrate is not just limited to the ventricles. In the original discovery by the Brugada brothers **(24)**, temporary atrial fibrillation (AF) was mentioned, by authors from Brazil **(25)** and from Japan **(26)**. The latter mention that the paroxysmal form of AF is observed in a 30% of cases.
A recent publication by Eckardt L, et al **(27)**, indicates a frequency for supraventricular arrhythmias of 29%.
These authors described episodes of AV supraventricular tachycardia with reentry.

2) Heart rate:
Without special characteristics in this item.

3) PR interval:
The PR interval of the surface electrocardiogram, with a border maximum normal value in adults of 200msec. for frequencies from 70bpm and 90bpm, corresponds to the addition of the P-A (30 to 50msec); A-H (60 to 125msec) and H-V (35 to 55msec) intervals of the Hissian electrogram.
In the Brugada Syndrome the PR Interval of ECG and HV of the electrogram are prolonged in approximately a 50% of cases, being able to reach figures of 100msec **(28)**. It is possible to find a prolonged HV interval in the electrogram due to the existence of the intra or infrahissian block, while the ECG PR interval still remains in normal values (less than 200msec). The phenomenon is explained because the depolarization of the His bundle (H deflection) is short and only represents a 10% of the whole duration of the PR interval (15 to 20 or 30msec). In these cases –called concealed AV blocks of the first degree- the electrogram can show “split His.”
FIGURE 02.

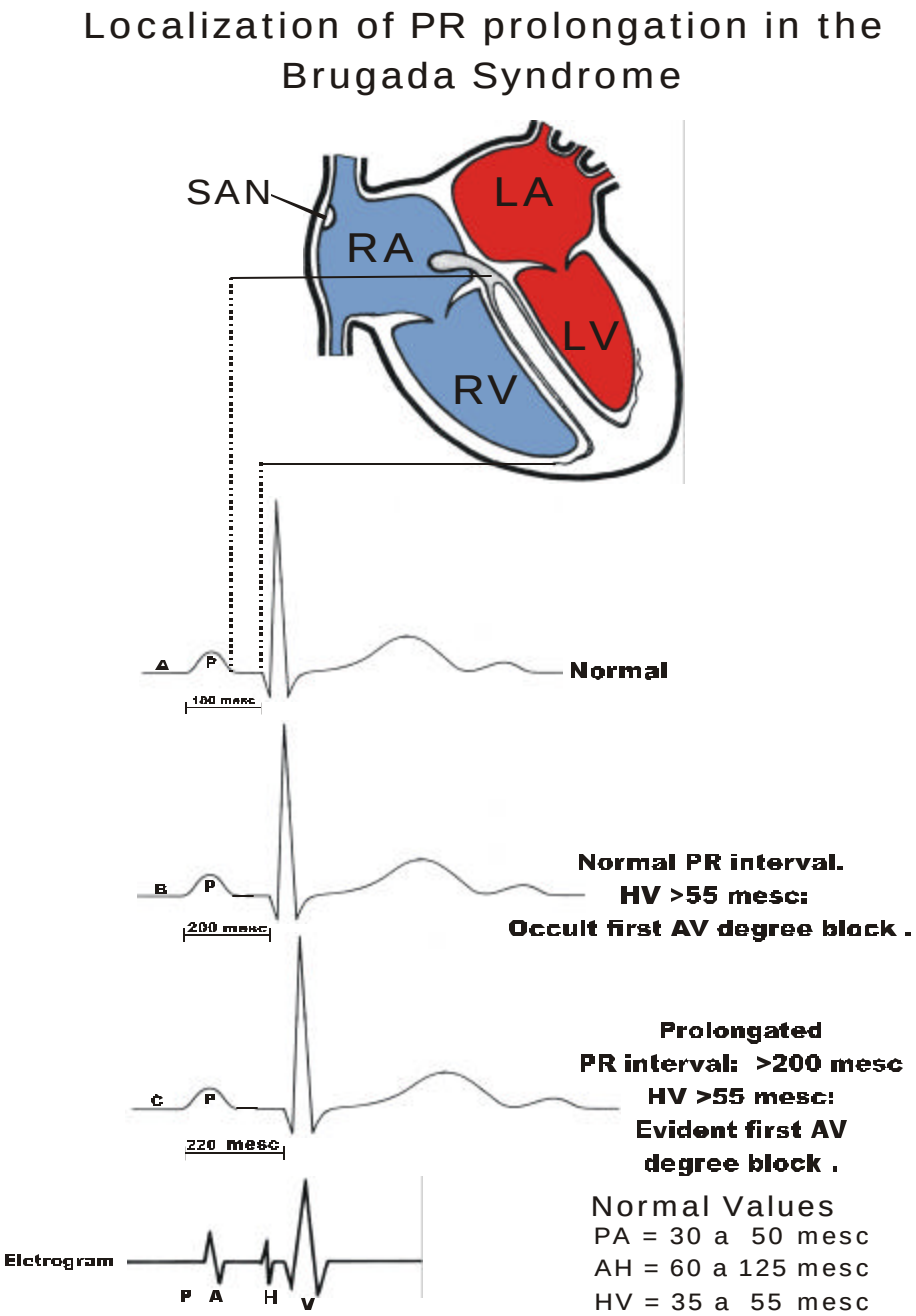


FIGURE 02.

The SCN5A gene codifying the alpha subunit of the sodium channel, can lead to another phenotype that causes progressive fibrotic dromotropic disorder of the His-Purkinje system, without the ECG pattern of the Brugada kind: the Lenègre disease **(29)**. Until a short while ago, this entity was classified within the primary electrophysiologic abnormalities of the intraventricular conduction system with potential to cause SCD together with fibrosis and calcification of the "cardiac skeleton," known as the Lev disease **(30)**.

Progressive cardiac conduction defect (PCCD), also called Lenegre-Lev disease is one of the most common cardiac conduction disturbances. It is characterized by progressive alteration of cardiac conduction through the His-Purkinje system with right or left bundle branch block and widening of QRS complexes, leading to complete atrioventricular block and causing syncope and sudden death. It represents the major cause of pacemaker implantation in the world (0.15 implantations per 1,000 inhabitants per year in developed countries). Of unknown origin, PCCD is considered a primary degenerative disease or an exaggerated aging process with sclerosis affecting only the conduction tissue. Familial cases with right bundle branch block have been

reported. One locus, designated HB1, maps to 19q13.3. Lev's and Lenegre's disease are pathologic diagnoses; both involve idiopathic fibrosis of the conducting system. Since they are pathologic diagnoses, I do not know if they can be distinguished clinically, although Lenegre's disease is said to affect younger patients. Lev's and Lenegre's disease can be due to fibrosis of the conduction system in individuals less than 40 years of age (Lenegre's disease) while in older individuals it is known as Lev's disease.

The PCCD many cause left bundle branch block or right bundle branch block associate with and Left Antero-Superior Divisional Block,(LASDB) Left posterior -inferior divisional block (LPIDB) , and antero-medial division of the left bundle branch of His antero-medial divisional block (AMDB)

The left bundle is a large robust structure on the left side of the septum that divides into and anterior, middle and posterior fascicles. Conduction can be blocked or slowed by ischemia or infarction, often associated with left ventricular hypertrophy and/or dilation, aortic ou mitral valve disease, Progressive cardiac conduction defect (PCCD) and others micellaneuos causes as shown in the following list 1 below:

List 1

Possible etiologies for advanced left bundle branch block

Relationship of the causes quoted in literature:

1- Systemic arterial hypertension (SAH): main isolated or associated cause.
2- Coronary insufficiency (CI): controversial: 20 to 70% of cases.
3- Association of SAH and CI: 70% of cases.
4- Cardiomyopathies.
5- Post-surgery in myotomy/miectomy (septectomy) in hypertrophic cardiomyopathy.
6- Aortic-valve disease
7- Mitral valve disease
8- Sclerosis of the left side of the cardiac skeleton: Lev disease
9- Progressive “idiopathic” sclerosis of the His-Purkinje conduction system: Lenègre disease
10- Miscellaneous causes secondary to:
- congenital heart diseases
- cardioplegia with blood or crystalloid
- use of taxol, anti-neoplasmic cytotoxic agent
- primary amyloidosis
- sarcoidosis
- hyperkalemia
- without apparent cause

In these Lenègre patients, the survival depends more on the extension of the lesion, and a pacemaker may eventually be needed in symptomatic cases to avoid SCD by progression of complete LBBB.

A recent publication **(31)** tells about the discovery of two new heterozygotic allelic mutations in the Brugada syndrome, located in the alpha subunit of the sodium channel in the SCN5A gene, which is clinically translated into AV block. These two mutations are the result of the substitution of the serine amino acid by glycine (G298S) in the dominion of the I S5-S6 loop, and of asparagine for aspartic acid within the S3 of the IV dominion (D1595N). Both mutations cause:

1) obstruction for fast inactivation

2) reduction of density in sodium channels

3) increased slow component of inactivation

This combination of facts slows down the conduction and leads to AV block.

4) AQRS:

Possible deviation of **ÂQRS** to the left. This deviation has been estimated in a 9.5% of the total cases of ECG with Brugada pattern in a prospective study of three years of follow-up between a population of workers of the Tokyo area **(32)**.

5) Morphology and duration of QRS:

The atypical pattern of right bundle branch block or disorder of conduction through the branch, is characteristic. This abnormality, translated as the absence of S wave with initial delay, or long in the left leads: V_5 and V_6, and normal duration of QRS, produced the denominations "pseudo RBBB" and "RBBB-like" **(33)**. The diagnosis for RBBB should not be done in absence of S with initial delay and prolongation of QRS duration. The mean duration of QRS in the Brugada syndrome is 110msec +- 2 msec. The absence of these two essential elements for diagnosis of RBBB, suggests that in some cases the RBBB could not be true. We believe that in these atypical cases, the vectocardiogram could easily clarify this doubt. The presence of a real RBBB could be a factor interfering with the results of the high resolution ECG, since taking into account the usual criteria, the record of posterior potentials cannot be applied in the presence of branch block. However, a recent study points out that high resolution ECG is an extremely accurate method as a non-invasive marker for fatal ventricular arrhythmias in the syndrome. The high resolution ECG is the only non-invasive marker for SCD with significance.

6) J point and ST/T:

It has been established that ventricular repolarization alterations are responsible for arrhythmias. Incomplete block of right bundle branch has been observed associated to the elevation of the J point and the ST segment usually convex towards the top ("coved type") in the septal or antero-septal wall leads V_1 and V_2 or V_3 (Brugada sign), and seldom in the inferior wall. Which would be the degree of elevation of ST necessary to consider it present? This fact is not yet conventionally established; nevertheless, many authors consider elevations of the ST segment > or = 0.1mV = 1mm in the V_1 and V_2 or V_3 leads as enough to consider the Brugada sign present **(34)**. A more restrictive criterion can be used, considering the Brugada sign present only when the elevation of the ST segment was > or = 0.2mV in the V_1 and V_2 or V_3 leads. These facts should be defined with the aim of establishing permanent criteria.

The Brugada syndrome is one of the causes for elevation of the ST segment. The others mentioned in literature are:

1) Early repolarization syndrome: it is considered to be present when at least two adjacent precordial leads show elevation of the ST segment, with values equal or higher than 1mm. The syndrome is characterized by a diffuse elevation of the ST segment of upper concavity, ending in a positive T wave of V2 to V4 or V5 **(35)**. The phenomenon constitutes a normal variant, it is almost a rule in athletes (present in 89% of the cases in this universe). However, it is found in a 36% of sedentary men. The mean duration of QRS in the Brugada syndrome is 110msec +- 2msec, it is higher than in individuals with early repolarization syndrome, who present a mean duration of QRS of 90msec +- 10msec (up to 100msec). Just an 8% of tracings of athletes with early repolarization are similar to the Brugada syndrome. These are not accompanied by positive family history for syncope or SCD. In short, there are significant differences between the ECG for the Brugada syndrome and that of early repolarization regarding duration of QRS, and the characteristics and location of the elevation of the J point and the ST segment **(36)**. In the Brugada syndrome many changes in the morphology of ST are described **(37)**.
2) Young pattern;
3) asthenic habits;
4) technical problem of inertia with the recording machine;
5) Arrhythmogenic right ventricle dysplasia (ARVD);
6) Acute phase of myocardial infarction;
7) Prinzmetal vasospastic variant angina: the electrocardiographic manifestation of the Brugada syndrome could be similar to those found during variant angina and could represent a stable model in some forms of lesion and ischemia **(38)**. In both entities elevation of the ST segment is observed, although due to different causes, since in variant angina it is caused by transitory vasospasm of subepicardial vessels; in the Brugada syndrome an increase in heterogeneity of ventricular wall thickness is observed due to genetic determinants, especially in the RV epicardium. There are references in literature to coexistence of both entities in the same patient. In these, coronariography did not reveal organic stenosis. The

patients presented elevation of ST coinciding with episodes of angina pain or after the intracoronary injection of acetylcholine that lead to an intense vasospasm. The basal ECG out of the pain crisis was the typical Brugada pattern with RBBB and elevation of ST segment in the right precordial leads with worsening of repolarization with anti-arrhythmic agents class I and inducibility in the electrophysiologic study. The authors conclude that the susceptibility to develop VF could be modulated by an interaction of coronary vasospasm with the Brugada syndrome and vice versa, which constitutes a significant fact to determine the coexistence of the two entities in such patients **(39)**.

We summarize the main differential features of these two entities in the table 1 (Table 1):

Table 1

Differential diagnostic between Brugada syndrome and Pinzmetal angina

	Brugada Syndrome	**Prinzmetal Variant Angina**
Precordial pain:	No.	Yes.
Tendency to VT/VF	High.	High.
Structural heart disease	Absent.	Could exist.
Response to nitrates and nitroglycerin	Null.	Improvement or suppression of clinical/electrocardiographic manifestations.
Permanence of elevation of ST segment	Persistent (or fluctuating) and without pain.	Very brief, transitory and accompanied by pain.
Cause	Genetic alteration of sodium channel	Possible alteration in production of nitric oxide in vascular wall.
Presence of image in mirror or reciprocal in ECG	Absent.	Present.
Topography of ST elevation	Right precordial leads of V_1 to V_3. It could rarely be observed in inferior wall and triggered or increased by anti-arrhythmic agents of the IC **(40)** and IA classes.	Variable. It could alternate between precordial leads and inferior ones. It could be triggered by hyperventilation.
Dromotropic disorders	AV block of the first degree by extension of H-V in 50% of cases.	It could happen in a transitory way until a high degree of AV block during the episode, and it is associated to a higher risk of arrhythmia and SCD.
Inversion of persistent T	Negative T wave in precordial leads of V_1 to V_3 is not observed in the Brugada syndrome.	Inverted and deep T waves from V1 to V4, associated to anterior hypokinetics suggesting myocardial "stunning", which indicates a critical lesion of the anterior descending artery: "LAD-T wave pattern".
Transitory Q wave	No.	It could happen.
Effort test	It could normalize the elevation during effort.	Variable response.
Myocardial scintigraphy	Normal.	Transmural transitory

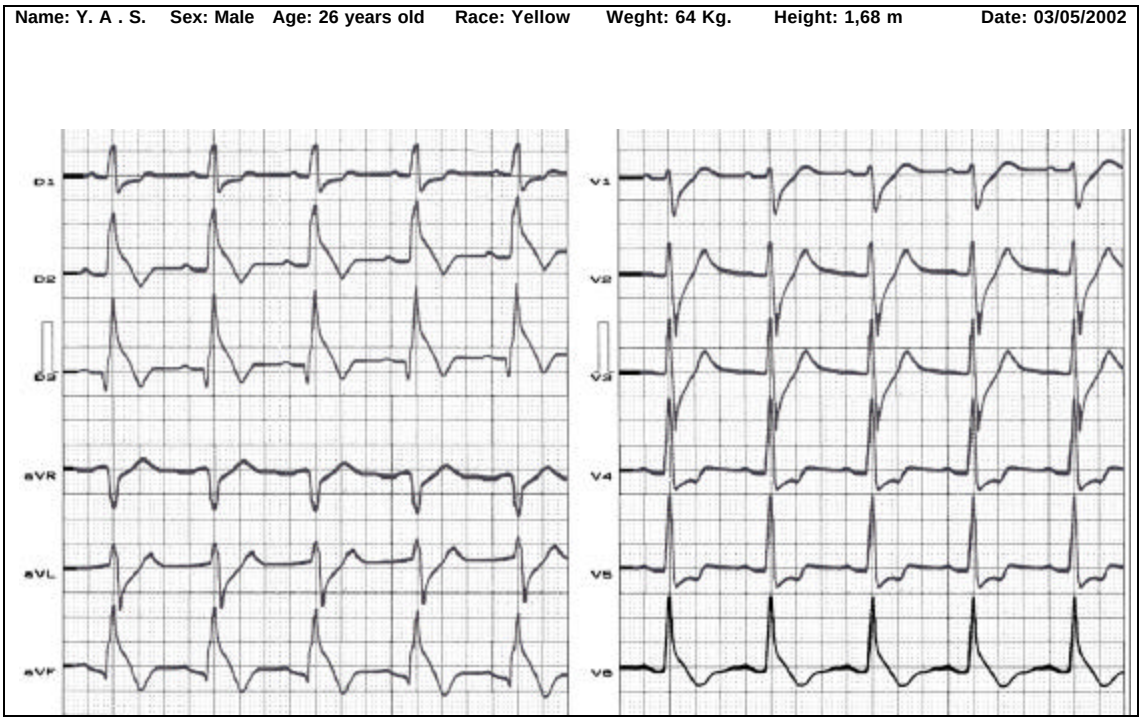
with thallium 201		hypo-uptake
Response to test of malate of endovenous ergonovine in doses of 0.05 to 0.40mg: (stimulant of alpha adrenergic and serotoninergic receptor)	There could be mild diffuse reduction of caliber without spasm when doses = or > than 0.40mg are used.	Intense coronary spasm accompanied by pain and ST elevation. Possible cardiac block, asystole and VT.
Response to hyperventilation.	It does not modify.	Severe spasm and reproduction of clinical-electrocardiographic manifestations.
Response to intracoronary acetylcholine, each dose given in a time above 1 minute in doses of 10, 25, 50 and 100 micrograms, separated by 5-minute intervals.	It could worsen the ST elevation with paradoxical dilatation of coronary vessels.	Severe spasm and reproduction of clinical-electrocardiographic manifestations.
Response to magnesium sulfate	Not mentioned.	Suppresses attacks induced by hyperventilation and exercise.
Treatment	Automatic implantable cardioverter defibrillator in association with amiodarone, a drug that contributes to diminish the number of shocks. Isoproterenol indicated in electric storm associated to general anesthesia and cardiopulmonary “bypass” or amiodarone.	Calcium antagonists, such as nifedipine, diltiazem, verapamil and felodipine associated to nitrates. Benefit with prazosin is mentioned.

8) Ventricular aneurysm;
9) Acute pericarditis;
10) Tumor invasion of the left ventricle. There are references in literature to Brugada pattern by mediastinum tumor **(41)**;
11) Left bundle branch block;
12) Left ventricular overload;
13) Acute cor pulmonale:
14) Myocardial lesion;
15) Ventricular trauma;
16) Hypothermia (J wave, of Osborn, late delta (δ), “camel-hump sign”, deflection similar to a hump (“hump-like deflection”) or potential of lesion);
17) Hypocalcemia;
18) Post-cardioversion;
19) Brain hemorrhage;
20) Hypopotassemia;
21) Anti-arrhythmic agents of IA and IC classes;
22) Psychotropic agents: transitory elevation of ST in right precordial leads originating the so-called “Brugada-like” pattern, with three-cycle antidepressants both in therapeutic doses **(42)** and excessive ones **(43)**.

23) Cocaine abuse. Recently, a case of a patient was narrated, making massive use of the drug, and in which a dysrrhythmic episode with long QRS aborted heart arrest and transitory Brugada pattern were observed. **(44)**.

There are references in literature to patients with elevation of the J point and ST segment in inferior leads in absence of hypothermia, ischemia or electrolytic disorders, which we call "atypical Brugada pattern" **(45)**.

FIGURE 03



Idiopathic J waves (Osborn) is present in inferior leads
Mirrow image seeing in anterior wall

Changes can be observed in the degree of elevation of the J point and of the ST segment triggered by factors called triggers. These are:

1) Fever: the Na^+ channel and other channels modify their functional state depending on temperature in the sense that they modify their permeability according to the former. Thus, an increase of 10ºC rises the voltage or width 1.3 to 1.6 times, and increases three times the time of opening and the number of times that the channel is opened. In the Brugada syndrome, the fever is associated to a higher possibility of tachyarrhythmic events, what suggests that the increase in temperature affects the Na^+ channel conductance **(46-47)**;
2) Anti-malaric agents;
3) Antidepressants: particularly excessive doses of three-cycle ones **(48)**;
4) Anti-arrhythmic agents class IA (ajmaline and procainamide) and IC (flecainide, propafenone and pilsicainide) and recently prajmalium bitartrate **(49)**. Flecainide (IC class) **(50)** and disopiramide (IA class) stress the ST elevation and extend the duration of QRS both in the Brugada syndrome and in normal people; however, in a much more intense way in the patients who are carriers of the syndrome. The effect is much higher with flecainide than with disopiramide, and extrasystoles only occur with flecainide in the Brugada syndrome **(51)**. Drugs that block the fast sodium channel are used to unmask the concealed forms of the syndrome **(52-53)**. These drugs identify the patients with risk of SCD that present ST segment elevation and RBBB without structural heart disease **(54)**. This drug is used to assess the inducibility during programmed stimulation both in apparent forms and in the concealed ones of Brugada syndrome. Since ajmaline is not available in USA, procainamide and flecainide are the

drugs of choice with this aim in this country. A better understanding of electrocardiographic abnormalities secondary to genetic mutations, could increase the ability of doctors to detect this entity.

5) Hyperglycemia.
6) Bradycardia.
7) Alcohol consumption.

On the contrary,in some patients with Brugada syndrome catecholamines decrease the elevation of ST**(55)**. Thus, adrenergic agents such as **dobutamine, isoprenaline** and **isoproterenol** improve ventricular repolarization, and decrease elevation of the J point and ST segment, and they can even normalize it in the Brugada syndrome, so that even the last drug is used in treating the so-called "electric storm" or ES **(56)**. This event, of ominous meaning, consists in the incessant appearing of recurring episodes and multiple VF or VT: 20 or more per day or 4 or more per hour, eventually observed in the Brugada syndrome. The ingestion of isoproterenol associated to general anesthesia and cardiopulmonary "bypass" is effective in diminishing the ST elevation in right precordial leads and in removing ES crisis of VF **(57)**. There are references about the efficacy of endovenous amiodarone in this kind of event **(58)**.

Dobutamine has been used as a pharmacological test in the identification of patients with risk, asymptomatic carriers, relatives of individuals with Brugada syndrome. The test, called "Ajmaline and Dobutamine Test" consists of the ingestion of ajmaline, and later if the patient develops the typical electrocardiographic pattern, he/she ingests dobutamine. If after this the electrocardiographic alterations disappear, he/she is considered positive, thus providing us with a basis for indicating electrophysiologic study **(59)**.

In the Brugada syndrome, normalization of elevation of ST segment is frequent during the ergometer test, a sure indication that is caused by the adrenergic release induced by effort. In other words, the syndrome is masked during exercise and it becomes apparent in the post-effort phase **(60)**. The I_o channel during high cardiac frequencies becomes less prominent, which explains the decrease in ST segment elevation and incidence of ventricular arrhythmias in higher frequencies. This fact is a basis for indicating overdrive pacing in prevention of ventricular fibrillation in the Brugada syndrome **(61)**.

Table 2, below, relates the factors that modify ventricular repolarization in the Brugada syndrome.

Table 2

Factors that modified the repolarization in the Brugada syndrome

	Increase elevation of the J point and ST segment: "triggers" of PVT/VF through reentry in phase 2	**Decrease elevation of the J point and the ST segment. Improve repolarization**
Adrenergic agents/catecholamines/beta-antagonists (62). Increase the entry of calcium in phase 2		**+**
Isoproterenol		**+**
Dobutamine		**+**
During physical exercise		**+**
Cocaine abuse	**+**	
Vagotony/Acetylcholine Muscarinic stimulus **(63).**	**+**	
Vagal maneuvering	**+**	
Fever	**+**	
Anti-malaric agents	**+**	
Hyperglycemia	**+**	

Three-cycle antidepressants:	**+**	
4 aminopyridine (4-AP) blocker of the I_{to} channel or transient outward current. **(64-65).**		**+** inhibits the I_{to} channel, and thus it decreases heterogeneity in thickness of ventricular wall.
Quinidine: blocker of the I_{to} channel **(66-67).**		**+** The drug reduces the magnitude of the I_{to} channel – mediator of phase 1 and consequently normalizes the elevation of the ST segment in the Brugada syndrome. Additionally, due to its vagolytic effect (M2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone could improve repolarization.
Disopiramide inhibits the I_{to} channel	**?? controversial.**	**?? controversial.**
Anti-arrhythmic agents class IA **1) ajmaline** ampoules of 50mg EV in 5'. The dose is **1mg/Kg** administered in 5' followed by continuing ingestion of 0.25mg/Kg in 15'. **2) Procainamide** Doses up to 10mg/Kg in 10'. 0,5mg/kg/min or total of 450mg	**+**	
Anti-arrhythmic agents class I C **1) Flecainide** in doses of **2mg/kg** in 10 minutes of ingestion **2) Propafenone** **3) Pilsicainide** **(68).**	**+**	
Prajmalium bitartrate	**+**	
Dimenhydrinate (Antihistaminics of first generation) **(69).**	**+**	
Organic and inorganic calcium antagonists**.**	**+**	
Pinacidil (Opener of potassium channel)	**+**	
Cilostazol phosphodiesterase III		Agent that block I_{to} channel in the brugada syndrome.

inhibitors (PDE III inhibitors)		Secondary to the increase in heart and/or increase in Ca2+ current (I(Ca)) due to an elevation of intracellular cyclic AMP concentration via inhibitors of phosphodiesterase activity.

A study carried out in patients and their relatives with post-resuscitation Sudden Unexpected Nocturnal Death Syndrome(SUNDS), concluded that sensitivity of ECG of 12 classical leads increases with the addition of high right precordial leads, in an intercostal space above V_1 to V_3. With this procedure, in some cases, the Brugada sign that remained concealed, appears just with the 12 leads **(70)**. This procedure seems to us solid, since high right precordial leads face the right ventricle epicardium, exactly the place mentioned as presenting electrophysiologic alterations.

7) **T wave:**

The T wave can have a variable configuration: bifid, of alternating polarity or enigmatic **(71)**, of negativity in the terminal portion of V_1 to V_3 and with intermittent normalization.

The negative T wave in the right precordial leads from V_1 to V_3 is considered typical of RV arrhythmogenic dysplasia and not of Brugada syndrome.

Procainamide, an anti-arrhythmic drug of the IA class, administered in endovenous bolus in a dose of 450mg (10mg/Kg in 10') can cause microvolts or visible alternans of the T wave in the V_2 and V_3 leads (TWA: microvolt liable T-wave alternans or TWA) plus stressing ST elevation. When the administration of the drug is interrupted, the T wave microvolt disappears before the elevation of the ST segment returns to leveling. The microvolt of T is not associated with changes in the cycle or with extra-systoles **(72)**.

For detecting T wave microvolt with a useful non-invasive marker for SCD, it is necessary to apply a technology released by the FDA that uses:

1) special multi-segmented electrodes with high resolution power ("high-resolution electrodes") with multi-contact sensors, developed by Cambridge Heart Inc., Bedford, Massachusetts, USA. These electrodes allow to record the fluctuation of Microvolt T-wave Alternans or TWA, virtually invisible in its width variation beat by beat in the ECG.
2) A special conductor gel
3) A computerized system for processing electric signs, based in the method of spectral analysis with reduction of the noise that involves the study of variations of T wave width in microvolts of a large number of beats in sequence (actually 128). This spectral analysis constructs a graph of dominion of frequency recorded in a system of cartesian coordinates.

The criteria for microvolt T-wave alternans positivity are:

1) presence of sustained alternans* of T wave with onset documented in a heart rate inferior to 110bpm or that in rest present it when the HR is higher than 110bpm. The patients in whom the microvolt alternans in rates inferior to 110bpm is recorded, have a higher risk: positives. If the microvolt alternans happens just in values above 140bpm there is no risk of fatal arrhythmias **(73)**: negative.
2) Magnitude above 1.9 mV;
3) Rate or proportion of alternance (**k**) above 3.

Important concepts in microvolt alternans:

*Sustained alternans: it is thus defined the one that in a constant way, and at least for a minute is present in a specific heart rate of onset in the absence of noise, extrasystoles or fall of HR, with V_{alt} > 1.9 microvolts and with a rate of alternans equal or higher than 3.

Onset Heart Rate or OHR is the value of the heart rate when the sustained alternans begins, with noises, extrasystoles or falls of heart rate having been excluded. That is to say, the certainty of "artifact-free data." This certainty is present in cases in which:

1) The percentage of extrasystoles is equal or lower than a 10% of the total of the beats considered (usually 128);
2) The patient is not pedaling 50% of HR;

3) The instantaneous HR variation is less than 30bpm in the complete segment considered (usually 128 beats).

A positive result for microvolt T-wave alternans indicates the need of an electrophysiologic study, of which approximately 50% will have prescriptions for implantation of an automatic cardioverter defibrillator; and treatment with drugs and need of follow-up for the rest **(74)**.

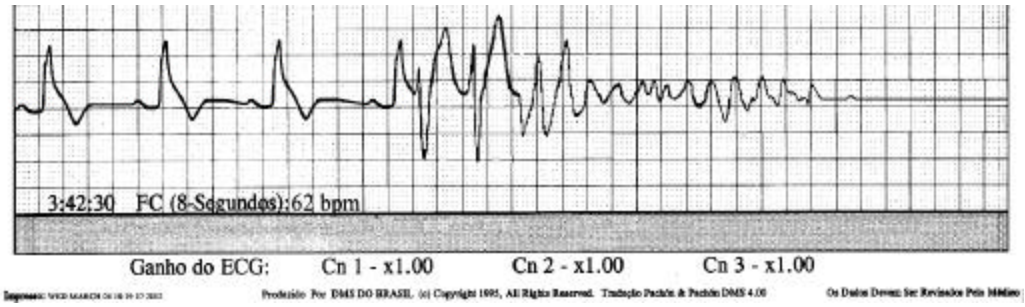
The incidence of microvolt T-wave alternans in patients with Brugada syndrome was not significantly different from normal individuals. So, microvolt T-wave alternans –unlike nearly all other entities– does not constitute a significant non-invasive marker for SCD risk in Brugada syndrome **(75)**.

8) Characteristics of ventricular tachycardia

There are very fast polymorphic ventricular tachycardias (from 260 to 352bpm) with short coupling (an average of 388 +/- 28msec), usually preceded by ventricular extrasystoles, which are identical to the beat beginning the PVT **(76)**, degenerating into VF with syncope or SCD. The arrhythmic events occur in a 93% of cases during the night or by daybreak, and in a 92% of cases when the patients present significant elevation of the ST segment. It has been well established that the degree of elevation of the ST segment is responsible for the arrhythmias. A loss of phase 2 or dome of PAT in the RV epicardium (where the I_{to} channel of initial outflow of potassium is more prominent) and not in the endocardium, produces the ST elevation in the Brugada syndrome. The normal heterogeneity existing between the epicardium and the endocardium is increased in this entity, leading to repolarization abnormalities in ECG, and a higher chance of arrhythmia by reentry in phase 2. These forms resemble very fast torsades de pointes (TdP) observed in patients with normal QTc with morphology of waves in spiral.

FIGURE 04
Name: Y. A . S. Sex: Male Age: 26 years old Race: Yellow Weght: 64 Kg. Height: 1,68 m Date: 03/05/2002 Data: 03/06/2002 Time: 3:42:30 AM
Pacient Sleeping.

LONG-TERM (HOLTER) ELETROCARDIOGRAPHIC RECORDING



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

Exceptionally, onsets of spontaneous monomorphic ventricular tachycardia (MVT) can happen **(77)**, however, the monomorphic form is observed only when induced by drugs. There are references to sustained MVT (SMVT) after the administration of ajmaline. The effect is due to the drug increasing even more the heterogeneity in repolarization in ventricular thickness **(78)**.

In some patients, an automatic mechanism mediated by beta-receptors seems to play an important role in SMVT originated in the RV outflow tract. The place of origin of the event could be very close to the lesion that causes ST elevation **(79)**. In these cases, which can be induced with the drugs that cause MVT, an automatic mechanism originated in a focus of triggered activity by delay after depolarization, located in the RV outflow tract, has been mentioned as the electrophysiologic substrate **(80)**.

9) QTc:

QTc is normal in the Brugada syndrome; however, after an IPVT event, it is possible for the ECG to show an extension of QTc of about 500msec **(81)**. This verification indicates the existence of a relationship between Brugada syndromes and its allelic mirror image: an LQT3 variant of the long QT syndrome. In a large family of patients, carriers of mixed manifestations, an intrinsic dysfunction was observed in the SA node, along with dromotropic alterations. The implantation of a pacemaker turned out to be an effective prevention for SCD. These facts point out to the possibility of the mechanism of lethal tachyarrhythmias being possibly associated to bradycardia in the Brugada syndrome **(82)**.

10) QTc dispersion

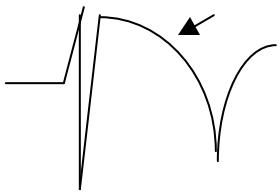
It is defined as the difference between the duration of maximal and minimal QT found in the 12 conventional leads. The measurement must be made at the double velocity of 50mm/s and with alignment of the 12 leads in the vertical, so that the same beat can be analyzed simultaneously. The measurement must be carried out from the first deflection of the QRS complex until the point of return of the T wave to the baseline or in the lowest point between the T and U waves **(83)**. The normal value of QT dispersion is 32 +- 8msec **(84)**. QT dispersion seems higher in men than in women **(85)**, and constitutes a non-invasive marker of myocardial electric instability, and consequently, of SCD risk. So, the higher the dispersion, the higher the risk of severe ventricular tachycardia having the functional reentry mechanism as substrate. The *QT* dispersion is a sensitive indicator for spontaneous or induced ventricular tachyarrhythmias: sensitivity: 88%; specificity of 57% and it was revealed as an independent predictor for cardiac and cardiovascular mortality **(86)**. The QTc dispersion shows variations during the day, being higher during the first hours of the morning, both in normal individuals and in carriers of coronary diseases; QTc dispersion is much lower at night. QT dispersion was not proven to be a significant marker for mortality in the Brugada syndrome in a recent study **(75)**.

Summary of the different electrocardiographic aspects and variants in the Brugada syndrome

- Tendency to atrial arrhythmias: AF and others;
- AV block of first degree by increase of H-V intra or infrahissian;
- ST segment elevation in DII, DIII and aVF;
- Elevation of J point and ST segment, convex toward the top, ST in right precordial leads from V_1 to V_2 or V_3 . Figure 5

ST elevation convex to the top

ST “coved type”

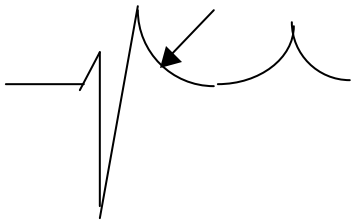


V_1 to V_2 or V_3

- Elevation exclusive of J point, conditioning of inferior convexity of ST segment, showing the aspect of the “saddle type;” Figure 6

ST elevation: saddle type

ST "saddle type"



- Variations of level of ST segment depending on body temperature. Fever can trigger a PVT/VF episode.
- Modification of ECG with administration of three-cycle antidepressants both in therapeutic doses as in excessive doses;
- Increase of elevation of ST or its appearance with anti-malarial agents administration;
- Variability can be observed in the level of the ST segment with circadian variations of the autonomic tone: increase with muscarinic vagal hypertone and decrease with hyper-sympathotonia. This cyclic variation explains the larger number of night events when there is predominance of vagal tone, the shortening of which occurs in phase 2 in the subepicardium but not in the endocardium, with increase of initial outflow of potassium through the I_{to} channel and decrease of inflow of calcium in phase 2 by the slow ICa_L channel.
- Decrease of suppression of elevation of ST segment with beta-adrenergic stimulus just as endovenous administration of isoprenaline, isopreterenol, dobutamine, exercise or hyper-sympathotonia.
- Increase of ST elevation or its appearance with administration of anti-arrhythmic agents of the IA class, ajmaline and procainamide;
- Increase of ST elevation or appearance in right precordial leads, and/or in the inferior wall with administration of anti-arrhythmic agents of the IC class, flecainide, propafenone and pilsicainide;
- Decrease of ST elevation or disappearance in right precordial leads with administration of quinidine by decrease in the initial outflow of potassium through the I_{to} channel;
- Association of Brugada syndrome to Prinzmetal variant angina;
- Appearance of bifid T waves;
- T waves of alternant polarity or enigmatic;
- Normal QTc: lower than 460msec in men and 440msec in women;
- Possible record of extension of QTc after tachyarrhythmic events;
- Onsets of PVT or sustained or non-sustained MVT;
- Mediastinum tumor associated to ECG with Brugada-like pattern;
- Negativity of terminal portion of T wave from V_1 to V_3.

The high resolution electrocardiogram

Late potentials (LP) are those of low amplitude (band of microvolts: μV) and very high frequency that happen in the end of QRS (in ST) and are related to the presence of delayed electric activity and ventricle fractionated conduction ("late fractionated potentials"). The value of these LP as non-invasive markers for SCD has already been proven in many studies of patients with structural heart disease. A recent publication points that the method constitutes a significant non-invasive marker in the identification of patients with high risk of SCD in the Brugada syndrome. These authors found that the high resolution ECG had a sensitivity of 89%, specificity of 50%, positive predictive value of 70%, and a negative one of 77% for the presence of LP. Additionally, the authors did not find a correlation with ST segment elevation and duration of HV **(75)**.

The limitation of high resolution ECG is its compromise in sensitivity in the presence of bundle branch block that extends the duration of QRS, sometimes masking the test. There are no normalized criteria for LP diagnosis in the presence of bundle branch block (left or right); however, the analysis of the dominion of the frequency allows to detect LP in patients with bundle branch block **(87)**.

The positive high resolution ECG indicates the presence of abnormal LP to the end of the filtered QRS. These are present in 0% to 6% among normal volunteers **(88)**.

The criteria of positivity for high resolution ECG are:

1) Square root of mean voltage of the final 40msec of filtered QRS, inferior to 20 microvolts (μV). Normal value: above 20 microvolts (μV). The English-speaking countries call it RMS (Root Mean Square).
2) Total duration of electric signals of low amplitude superior to 40μV to the end of filtered QRS. Known as LAS: from Low Amplitude Signal. Normal: inferior to 40μV if the filters used are from 25 to 250Hz and lower than 35 if the filters used are from 40 to 250Hz.
3) Total duration of QRS complex, filtered in the absence of bundle branch block (QRSD) above 114msec. Normal value inferior to 114msec. Some authors consider this limit as 110msec **(89)**.

The presence of two or more altered variables is considered positive high resolution ECG.
The method is useful in risk stratification for appearance of severe tachyarrhythmias with lethal potential by means of the detection of late potentials (LP) of low amplitude and very high frequency recorded in the end of QRS and at the beginning of ST, non-invasive markers of an arrhythmogenic circuit. This special technique for finding an average, filtering and high gain, results from the reception of the electrocardiographic signal, and uses the time as a variable (time dominion), or the response to the signal frequency (frequency dominion); the results of the former being better established.
The presence of bundle branch block harms the conclusions about LP with high resolution ECG **(90)**.
The presence of LP in the high resolution ECG is present in a 70% of cases of Brugada syndrome.

Major and minor criteria for Brugada syndrome diagnosis: Gussak criteria **(91)**

Recently, Gussak et al, proposed major and minor criteria for Brugada syndrome diagnosis, moved by the great number of false positives ("waxing ECG signature") and false negatives ("waning ECG signature") observed. The authors posed that the presence of a major criterion and a minor criterion constitute a strong indication for the presence of Brugada syndrome.

Major criteria:
1. Presence of electrocardiographic "Brugada-like" pattern in patients without demonstrable structural heart disease.
2. Appearance of electrocardiographic "Brugada-like" pattern after the administration of sodium channel blockers.

Minor criteria:
1. Family history of SCD
2. Syncope of unknown origin
3. Episode of documented VT/VF
4. Inducibility of VT/VF in the electrophysiologic study.
5. Demonstration of genetic defect (to be defined).

The degree of ST segment elevation and the inducibility of VT/VF in the EPS are the most correct markers to confirm the diagnosis and to stratify the risk in patients with Brugada syndrome.
Pedro Brugada and Peter Geelen from the Cardiovascular Research and Teaching Institute Aalst; Cardiovascular Center, Aalst, Belgium, speak about six SCD predicting electrocardiographic patterns which every doctor should be able to recognize:
1. –Variants of family-inherited long QT syndromes: LQTS
2. –Brugada syndrome
3. –Arrhythmogenic right ventricle dysplasia (ARVD)
4. –Anterior infarction complicated with RBBB
5. –Dilated cardiomyopathy
6. –Hypertrophic cardiomyopathy.

In Latin-America we must add another condition:
7. -Chagas disease.

1. –Variants of family-inherited long QT syndromes

The long QT syndrome (LQTS) can be family-inherited or secondary to the action of drugs and other causes. Within the former, we mention the autosomal dominant Romano-Ward syndrome without deafness, and the cardio-auditory Jervell and Lange-Nielsen with autosomal recessive sensorineural deafness and idiopathic sporadic cases.

Electrocardiographic characteristics of family-inherited long QT syndromes

Heart rate (HR): a tendency to bradycardia can be observed, related to age and in some cases decrease in effort. It has been suggested that this relative bradycardia can be due to a lower sympathetic tone of the right stellated ganglion.
With HR increase, the LQT3 variant shows more shortening of QTc when compared to the LQT1 and LQT2 variants **(92)**.

PR: usually normal, however, we described a family with short PR more than two decades ago **(93)**.

T wave: T wave of late beginning constitutes the typical characteristic of LQT3 variant. In any type of family-inherited LQTS, the T waves from V_2 to V_5 or from V_3 to V_4 can be biphasic or notched, a fact attributed to the subliminal post-depolarization **(94)**.
The alterations of the T wave described in family-inherited LQTS are:

a) T wave of late appearance, specific to the LQT3 variant;
b) Frequent record of micro or macrovolt alternans, i.e., a voltage lower or higher than the T wave alternating with a sequence of the type 1:1 in a pattern called A-B, A-B, much more frequent during emotions and physical activity.
c) "Enigmatic" T waves, characterized by concomitance of T waves that are inverted, with alternated polarity, biphasic, notched, of late appearance and long, can be found in any variant.
d) The T waves with notches and bifid, when found in normal individuals, are only recorded in V_2 and V_3, while in family-inherited LQTS are observed from V_2 to V_5 and with a significantly higher frequency: 65% against 15% **(95)**.
e) The presence of T wave with notches is observed in more than an 80% of patients in the phase of recovery in the ergometer test and with family-inherited LQTS, while only in a 3% of normal individuals.
f) T waves with notches can be recorded after long sinusal pauses that can extend beyond 1.2sec. Frequently, these pauses precede onsets of VT.

U wave:
The U wave is the last, inconstant and lowest deflection of ECG written after the T wave and before P of the following cycle, which corresponds to phase 4 of the transmembrane action potential happening concomitantly to the second noise and during the fast filling or protodiastole **(96)**.
In (the) family-inherited LQTS, the voltage of the U wave is usually of high voltage. The electrogenesis of this fact is attributed to the late repolarization of M cells **(97-98-99-100)**. The voltage of the U wave is always lower than a 50% (of) amplitude of the preceding T and generally between a 5% and 25% of it. Usually, it does not exceed 1mm, with an average of 0.33mm. It is considered high in case it reaches 1.5mm or more; however, there could be normal U waves of up to 2mm (0.2mV) in DII and from V_2 to V_4. The U voltage is inversely proportional to R-R, so when the heart rate reaches 100bpm, the U wave becomes imperceptible.
Habitually, the T wave voltage is accompanied by a proportional voltage of the U wave. Thus, the higher the voltage of T, the higher the amplitude of U.
U waves of increased voltage can present alternating polarity during bradycardia and with pauses.
The normal U wave, in people without long QT, seems to be caused by repolarization of potentials of the His-Purkinje system **(101)**. This hypothesis is founded in that the Purkinje fibers have a longer transmembrane action potential than the rest of the contractile common cells, just like M cells.
The arguments against this hypothesis are:

a) The record of U waves in hearts of batrachians, known to lack Purkinje fibers;
b) Differences between the profile of the U wave and the potential of the Purkinje fibers;

c) Clear dependence of U wave on mechanical phenomena: bradycardia, post-extrasystole pause, physical exercise, use of digitalis and catecholamines, a fact that would not be expected if its origin was in the Purkinje potentials.

QTc

In cases of family-inherited LQTS, QTc is usually prolonged, above the 500msec (2.5 large divisions of ECG paper).

In the allelic LQT3 variation with the Brugada syndrome, there is a very long QTc, higher than in the LQT1 and LQT2 variants; in this variant, the IB class drug mexiletine, significantly shortens QTc, preventing the appearance of TdP. Curiously, the drug does not shorten the long QT of the LQT1 and LQT2 variants, which depend on the involvement of the K^+ channel: KVLQT1 and HERG defects of the I_{ks} K^+ and I_{kr} K^+ channels respectively **(102)**.

The maximal normal value of QTc in men is 446msec and in women 447 msec +- 15% (QT is 10msec longer in the female sex), however, QTc can be normal in the female sex and approximately a 6% of family-inherited LQTS present QTc of normal duration and a 10% develop cardiac arrest **(103)**.

Malignant arrhythmias are more frequent in those patients with very long QT, i.e., those that go beyond 600msec.

Polymorphic VT happens in patients with normal QT, while TdP requires association with long QTc; however, a variant of TdP with QT of normal duration has been recently described, which is triggered by a short coupling extrasystole **(104)**.

QT dispersion:

It is defined as the difference between the duration of maximal and minimal QT found in the 12 conventional leads. Medication must be carried out at double velocity of 50mm/sec, with vertical alignment of 12 leads, so that the same beat can be analyzed simultaneously and from the first deflection of the QRS complex until the point of return of the T wave to the baseline or the lowest point between the T and U waves **(105)**. The normal value of QT dispersion is 32 +- 8msec **(106)**.

QT dispersion or heterogeneity of repolarization constitutes a marker of myocardial electric instability and consequently of SCD risk. Thus, the higher the dispersion, the higher the risk of SCD due to severe VT that have as substrate the reentry mechanism. It is a sensitive indicator of spontaneous or induced VT: sensitivity 88%; specificity 57%, and it was revealed as an independent predictor for cardiac and cardiovascular mortality **(107)**. It shows variations during the day, being higher in the first morning hours.

The causes extending QT make the same with dispersion, so this is observed in family-inherited long QT syndromes, in sporadic forms and in those secondary to the use of certain drugs. It seems that the electric instability observed in patients carriers of long QT is due to dispersion and not the extension itself. The QT dispersion medication in the family-inherited forms of LQTS reveals a degree of dispersion 20 times higher than normal values **(108)**. The use of beta-blockers and/or left sympaticectomy diminishes it in LQTS. Dispersion persistence in treated patients can identify those patients with higher risk.

Characteristics of VT in LQTS

The VTs observed in LQTS, both family-inherited and acquired, are known as TdP, and are characterized by:

1) They have long or tele-diastolic coupling. Even so, an “R on T” phenomenon due to the bng QT existence is observed;
2) Frequency from 200bpm to 250bpm;
3) QRS complexes of variable amplitude characterized by gradual reduction, followed by a new increase (“spindle-shaped pattern”);
4) Characteristic rotation of apexes along the baseline: “corkscrew effect,” balancing, “swinging pattern” or “twisting appearance.” The changes in the TdP axis can reach 180º;
5) Sequential characteristics of long and short cycles with R-R variations preceding the TdP episodes (“long-short sequences”). The presence of at least three sequences of long and short cycles is called cascade phenomenon;

6) The tachyarrhythmic events can begin after long sinusal pauses that can last more than 1.2sec: VT depending on pauses or during bradycardia.
7) The electrophysiologic mechanism of TdP responds initially to early after depolarizations (EADs) in a subendocardial focus. This automatic arrhythmia causes triggers ("triggered activity") in the final phase of the plateau and at the beginning of phase 3 through the slow calcium channel $ICa^{++}{}_{L}$. However, the subsequent beats are depending of reentry caused by dispersion of repolarization of M cells and Purkinje cells **(109-110)**. In short, the initial mechanism of TdP is automatic, and maintenance responds to reentry.
8) TdP can be triggered by appearance of microvolt alternans **(111)**.

The table 3 below shows the main differences between TdP and the true PVT observed in the Brugada syndrome.

Table 3

Principals differences between the torsade de pointes(TdP) and true polimorphic ventricular tachycardia(PVT)

	TdP	True PVT
In bradycardia	Yes.	No
Onset dependent on pause:	Yes.	No
Heart rate :	200bpm to 250bpm.	Very fast, from 260bpm to 352bpm.
Coupling:	Long.	Short.
QTc:	Long.	Normal.
U wave:	Prominent.	Normal.
Treatment:	1) Drugs; 2) Permanent pacemaker; 3) Left Sympacectomy of the inferior half of the stellated ganglion and of the three or four first thoracic ganglions. (cervicothoracic); 4) Automatic implantable cardioverter defibrillator. 5) Associations.	Automatic implantable cardioverter defibrillator. The eventual onsets of electric storm must include ingestion of isoproterenol, general anesthesia, cardiopulmonary "bypass" and endovenous amiodarone.

2. -Arrhythmogenic right ventricle dysplasia (ARVD). The table 4 below shows the main differences between the Brugada syndrome and the ARVD.

Table 4

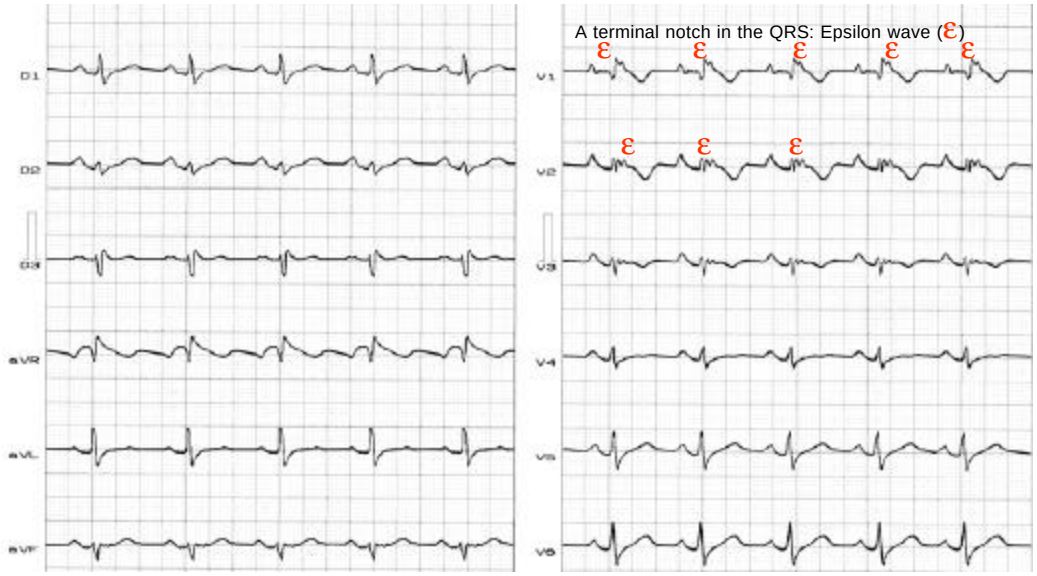
Differential diagnosis between Brugada syndrome and Arrhythmogenic right ventricle dysplasia

Characterization of ECG	**Brugada Syndrome**	**ARVD**
Epsilon wave (ε). They are late potentials of low voltage and short duration, located at the end of QRS and at the beginning of ST (J point) observed in V_1-V_3 and in the frontal plane that is translated as delay in RV activation (*).	Absent.	Present in 30% of cases.

Negative T wave from V_1 to V_4	Absent. Liable waves are described: bifid, biphasic, with notches, alternans and inverted: enigmatic T waves.	Very characteristic when present in children under two years and without RBBB.
Characteristics of VT	Polymorphic, very fast, of short coupling, and that frequently degenerate into VF and SCD. MVT can be present however, induced by drugs. Rarely spontaneous.	SVT or NSVT with morphology of LBBB, indicating its origin in the RV (**). If AQRS is normal or deviated to the right, it indicates that it is originated in RV outflow tract.
High resolution ECG	Sensitivity of 89%, specificity of 50%, positive predictive value of 70% and negative 77% for the presence of LP.	Nearly always abnormal.

(*) Curiously, it has not similarity with the Osborn wave, J wave or camel-hump sign observed in hypothermia and hypercalcemia. These epsilon waves are not observed in the Brugada syndrome and are present in a 30% of ARVD.

TYPICAL ECG OF ARHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (FIGURE 07)



Sinus rhythm, complete RBBB, terminal notch in the QRS (epsilon wave), T wave inversion in V_1 to V_3. The epsilon wave is explaned as a result of slowed intraventricular conduction.

(**) In ARVD, the VT is usually sustained, monomorphic, with LBBB pattern because its origin is in the RV. When they are born in the RV outflow tract, the AQRS is normal or deviated to the right between +90º and +120º (QRS of the "qR" or "QS" type in DI). In rare cases with AQRS deviated to the left, the focus of origin is in the inflow tract, apex or RV inferior wall. A VT with LBBB morphology and AQRS deviated to the left, nearly always indicates underlying organic cardiac disease.

4. -Anterior wall infarction with RBBB

The appearance of RBBB in the course of acute myocardial infarction happens in 2% of cases. This dromotropic complication increases the chances of SCD by VT/VF post-event, particularly if associated to decrease of FE to values under a 40% **(112)**.

The incidence of malignant ventricular tachyarrhythmias associated to the acute phase of myocardial infarction is directly related to its extension **(113)**.

When the acute infarction is complicated with the appearance of right bundle branch block, it indicates the possibility of proximal obstruction of the anterior descending artery and consequently an extensive infarction with high risk of arrhythmic SCD. In these cases, the implantation of a prophylactic cardioverter defibrillator is indicated **(114)**.

In case of acute myocardial infarction complicated with RBBB, it could be identified without problems by ECG, since the necrosis modifies the initial portions (QRS initial 40 msec) and the RBBB at the end of the ventricular depolarization. Thus, the ECG sensitivity for diagnosis of acute myocardial infarction associated to RBBB is the same as that without dromotropic disorder **(115)**.

The electrocardiographic criteria for RBBB associated to antero-septal infarction are:

1) V_3R, V_1 and V_2: QR or qR.
2) V_5-V_6, RS
3) Transitional leads V_3 and V_4: QS.

RBBB associated to antero-lateral infarction shows QS in $\mathbf{V_5}$ and $\mathbf{V_6}$ or from $\mathbf{V_4}$ to $\mathbf{V_6}$ associated to elevation of ST segment, convex toward the top, and symmetric and negative T waves with long base.

Patients who survived acute infarction with ejection fraction lower than 35, who present sustained VT (SVT) during the electrophysiologic study, not reverted with endovenous procinamide, constitute those patients of choice for implantation of prophylactic cardioverter defibrillator **(116)**.

Patients with SVT badly tolerated, or well tolerated, but in which the drugs prove inefficient, must receive the prophylactic automatic cardioverter defibrillator associated to amiodarone or beta-blocker.

5. -Dilated cardiomyopathy.

Low voltage in leads of limbs and standard with preservation of voltage in precordial leads, is usually an indication of severe left ventricular dilatation in the absence of coronary disease. These patients have high risk of SCD. In some cases the low voltage can be secondary to pericardial effusion.

In 24h Holter in 50% of cases onsets of NSVT or SVT can be recorded, and eventual episodes of VF with SCD. The causes for this higher tendency to ventricular tachyarrhythmias are:

1) Depression in parasympathetic cardiac activity and sympathetic predominance;
2) Tendency to originate late potentials in the high resolution ECG **(117)**;
3) Tendency to originate higher QT time dispersion **(118-119)**. In patients waiting for transplantation, it was observed that *QT* dispersion constituted the main predictor for sudden cardiac death. Thus, patients with *QT* dispersion > *140msec* present approximately twice the mortality than those with *QT* lower than this figure.

6. -Hypertrophic cardiomyopathy (HC)

This is a polymorphic entity from the genetic point of view. In clinical practice the diagnosis is suggested by anamnesis, physical examination and ECG; the confirmation being done by echocardiogram.

The factors mentioned in literature associated to SCD and poor prognosis in HC are:

1) Septal thickness with important increase: more than 30mm;
2) Estimation of mass highly increased;
3) Positive family history for SCD;
4) Abnormal response of blood pressure (hypotension) with or without syncope in the effort test, particularly in young people (< 30 years);
5) Progression in the narrowing of left ventricular wall associated to significant increase of size of cavity and involvement of systolic function;
6) History of recovery from SCD;
7) Recurrent syncope in children;
8) Presence of NSVT in the Holter record;
9) Presence of NSVT in Holter monitoring in patients with loss of conscience;
10) Significant bradyarrhythmia and hidden conduction;
11) Confirmation of certain genetic mutations knowingly malignant. E.g.: Type I, located in locus1q of the long arm of chromosome 14. This variant affects the heavy chain of beta-myosin (β-MyHC). It has a high penetration, severe hypertrophy and SCD in 50% of those affected. Forms type I that are considered malignant: 1) mutation Arg403Gin, which presents 50% of rate of SCD before 40 years; 2) Arg453Cys, (substitution of the amino acid arginine by cysteine in the 453 position) and Arg719Trp (substitution of amino acid arginine by triptophan in the 719 position). Type II: (15%) affects the chromosome 1 in the 1q3 locus. This variant causes the modification of cardiac T troponine (cTnT) and the patients do not have significant hypertrophy; however, there is a high rate of mortality in young people. ***Notes:*** in patients with genetic identification of malignant forms or those who survived SCD, the prophylactic implantation of cardioverter defibrillator is indicated **(120)**.
12) Acute atrial fibrillation with fast worsening of functional class reaching class IV;
13) Induction of SVT in EPS;

The ablation procedure is indicated in supraventricular arrhythmias causing SCD.

7. -Chagas disease

ECG alterations are the rule in the course of this entity. Complete RBBB associated to antero-superior fascicular block and to polymorphic ventricular extrasystoles, constitute the most frequent aspects of the chronic form of the disease.

Syncope and SCD are constant threats in individuals in productive age, and they could happen in the absence of cardiomegaly (arrhythmic forms).

The following facts indicate a poor prognosis or reveal SCD:

1) The presence of VT induced by EPS. This type of arrhythmia is more frequent in patients with dromotropic disorders, low FE, apical aneurysm, atrial fibrillation, and accentuated cardiomegaly **(121)**;
2) Bradycardia not sensitive to atropine sulfate in 0.004mg/kg doses, associated to trifascicular block (RBBB + antero-superior fascicular block + AV block of first degree);
3) Presence of alternating block;
4) Presence of total AV block with or without Stokes-Adams episode;
5) Apical aneurysm associated to left ventricular dilatation **(122)**.

Conclusions

The classical ECG of 12 leads used for more than a century, constitutes a diagnostic resource for tracing, very useful due to the simplicity to perform it, the low cost, and due to its huge capacity to allow raising a suspicion of the presence of an entity with high risk of SCD, especially in the Brugada syndrome, in family-inherited LQTS and others already mentioned above. We believe that the knowledge of these simple electrocardiographic features by clinicians, family doctors, pediatricians, and even cardiologists could surely save many lives.

The association of RBBB and the elevation of the J point and the ST segment from V_1 to V_2 or V_3 corresponding to the antero-septal wall, occurring in a male patient in productive age of yellow or white race with normal QTc in the absence of provable organic heart disease, constitutes a key element for suspicion.

Because of the already furnished data, we have the conviction that the entity represents a much larger universe than what is currently attributed to it. The disease represents the most frequent cause for death in young adult men in Thailand.

There are about 300,000 new cases of SCD recorded per year in the USA (1 death per 1000 inhabitants/year). SCD happens in patients with structural heart disease in 85% of cases (265,000 cases/year) while the remaining 15% (45,000 cases/year) occur in patients without demonstrable structural heart disease. In the latter, the possible causes are: idiopathic ventricular fibrillations (IVF), family-inherited long QT syndromes and Brugada syndrome. From these, in turn, 24,000 cases/year are secondary to idiopathic ventricular fibrillation. If we believe that a 20% to 40% of IVF correspond to Brugada syndromes, it can be deduced that in the great Northern country, 4.800 to 8400 SCD/year happen as a consequence of Brugada syndrome.

References

1) Remme CA, Wever EF, Wilde AA, et al. Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. Eur Heart J 2001; 22:400-409
2) Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, and Chaitman BR. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol 1999; 33:5-15
3) Cau C. The Brugada syndrome. A predicted sudden juvenile death. Minerva Med 1999 Sep;90(9):359-64
4) Hari P, Chemiti GK, Joshi A. Brugada syndrome also linked to sudden cardiac death. Postgrad Med 2001; 109:18
5) Butler JM. Brugada . syndrome--the missed epidemic. J Accid Emerg Med 2000; 17:426-8
6) Futterman LG, Lemberg L. Brugada. Am J Crit Care 2001; 10:360-364
7) Matsuo K, Kurita T, Inagaki M, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J 1999;20:465-70
8) Matsuo K, Akahoshi M, Nakashima E, et al. The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol 2001; 38:765-70
9) Brugada J, Brugada P, Brugada R. The syndrome of right bundle branch block ST segment elevation in V1 to V3 and sudden death--the Brugada syndrome. Europace 1999 Jul;1(3):156-66
10) Monroe MH, Littmann L. Two-year case collection of the Brugada syndrome electrocardiogram pattern at a large teaching hospital. Clin Cardiol. 2000;23:849-51
11) MacKenzie R.: The Brugada syndrome--an electrocardiogram with important mortality implications. J Insur Med 2001; 33:106-9
12) Gussak I, Antzelevitch C, Bjerregaard P, et al. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol 1999; 33:5-15

13) Priori SG, Napolitano C, Giordano U, et al. Brugada syndrome and sudden cardiac death in children. Lancet 2000; 355(9206):808-9
14) Towbin JA, Ackerman MJ. Cardiac sodium channel gene mutations and sudden infant death syndrome: confirmation of proof of concept? Circulation 2001;104:1092-3
15) Antzelevitch C. Molecular biology and cellular mechanisms of brugada and long QT syndromes in infants and young children. J Electrocardiol 2001;34:177-81
16) Naccarelli GV, Antzelevitch C. The Brugada syndrome: clinical, genetic, cellular, and molecular abnormalities. Am J Med 2001; 110:573-81
17) Balser JR. Sodium "channelopathies" and sudden death: Must you be so sensitive? Circ Res 1999; 85:872-874
18) Takenaka S, Kusano KF, Hisamatsu K, et al. Relatively benign clinical course in asymptomatic patients with Brugada-type electrocardiogram without family history of sudden death. J Cardiovasc Electrophysiol 2001; 12:2-6
19) Boveda S, Albenque JP, Baccar H, et. al. Prophylactic value of automatic implantable defibrillators: a case report of a patient with asymptomatic Brugada syndrome. Arch Mal Coeur Vaiss 2001; 94:79-84
20) Corrado D, Buja G, Basso C, et al. What is the Brugada syndrome? Cardiol Rev 1999; 7:191-5
21) Izumi T, Ajiki K, Nozaki A, et. al. Right ventricular cardiomyopathy showing right bundle branch block and right precordial ST segment elevation. Intern Med 2000;39:28-33).
22) Scheinman MM. Is the Brugada syndrome a distinct clinical entity? J Cardiovasc Electrophysiol 1997; 8:332-336
23) Lee KL, Lau CP, Tse HF, et al. Prevention of ventricular fibrillation by pacing in a man with Brugada syndrome. J Cardiovasc Electrophysiol 2000;1: 935-7
24) Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 1992, 20: 1391-1396
25) Villacorta H, Faig Torres RA, Simões de Castro IR, Lambert H. de Araujo Gonzáles Alonso R.: Morte súbita em paciente com bloqueio de ramo direito e elevação persistente do segmento ST. Arq Bras Cardiol. 1996; 66:(N^{0}4) 229-231
26) Itoh H, Shimizu M, Ino H, Okeie K, Yamaguchi M, Fujino N, Mabuchi H; Hokuriku Brugada Study Group. Arrhythmias in-patients with Brugada-type electrocardiograph findings. Jpn Circ J 2001; 65:483-6
27) Eckardt L, Kirchhof P, Loh P, et al. Brugada Syndrome and Supraventricular Tachyarrhythmias: A Novel Association? J Cardiovasc Electrophysiol 2001; 12:680-685
28) Kobayashi T, Shintani U, Yamamoto T, et al. Familial occurrence of electrocardiographic abnormalities of the Brugada-type. Intern Med 1996;35:637-640
29) Kyndt F, Probst V, Potet F, et. al. Novel SCN5A Mutation Leading Either to Isolated Cardiac Conduction Defect or Brugada Syndrome in a Large French Family. Circulation 2001; 104:3081-3086
30) Myerburg RJ, Castellanos A. Cardiac Arrest and Suden Cardiac Death In. Heart Disease: a texbook of cardiovscular medicine. Editors: Braunwald E, Zipes DP, Libby P. 6th 2001; Chapter 26 p: 890-931
31) Wang DW, Viswanathan PC, Balser JR, et al. Clinical, Genetic, and Biophysical Characterization of SCN5A Mutations Associated With Atrioventricular Conduction Block. Circulation 2002 ;105:341-346
32) Atarashi H, Ogawa S, Harumi K, et al. Idiopathic Ventricular Fibrillation Investigators. Three-year follow-up of patients with right bundle branch block and ST segment elevation in the right precordial leads: Japanese Registry of Brugada Syndrome. Idiopathic Ventricular Fibrillation Investigators. J Am Coll Cardiol 2001;37:1916-20
33) Gussak I, Antzelevitch C, Bjerregaard P, et al. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol 1999; 33:5-15
34) Matsuo K, Akahoshi M, Nakashima E, et al. The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol 2001; 38:765-70
35) Gussak I, Antzelevitch C. Early repolarization syndrome: Clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol. 2000;33:299-309
36) Bianco M, Bria S, Gianfelici A, et. al. Does early repolarization in the athlete have analogies with the Brugada syndrome? Eur Heart J 2001; 22:504-510
37) Preito Solis JA, Martin Duran R.: Multiples changes of the morphology of ST segment in a patient with Brugada syndrome. Rev Esp Cardiol 2000; 53: 136-138

38) Antzelevitch Ch, Yan GX, Shimizu W, Burashnicov A. Electrical Heterogeneity, the ECG, and Cardiac Arrhythmia. In. Cardiac Electrophysiology From Cell to bedside. Zipes DP & Jalife J. Third Edition 2000, Chapter 26, p:222-238
39) Chinushi M, Kuroe Y, Ito E, et. al: Vasospastic angina accompanied by Brugada-type electrocardiographic abnormalities. J Cardiovasc Electrophysiol 2001; 12:108-111
40) Nakamura W, Segawa K, Ito H, et al. Class IC antiarrhytmic drugs: flecainide and pilsicainide, produce ST segment elevation simulating inferior myocardial ischemia. J Cardiovasc Electrophysiol 1998; 9: 855-85
41) Tarin N, Farre J, Rubio JM, et al. Brugada-like electrocardiographic pattern in a patient with a mediastinal tumor. PACE 1999; 22:1264-12660
42) Rouleau F, Asfar P, Boulet S, et al. Transient ST segment elevation in right precordial leads induced by psychotropic drugs: relationship to the Brugada syndrome. *J Cardiovasc Electrophysiol* 2001; 12:61-5
43) Tada H, Sticherling C, Oral H, et. al.: Brugada syndrome mimicked by tricyclic antidepressant overdose. J Cardiovasc Electrophysiol 2001; 12:275
44) Ortega-Carnicer J, Bertos-Polo J, Gutierrez-Tirado C. Aborted sudden death, transient Brugada pattern, and wide QRS dysrrhythmias after massive cocaine ingestion. J Electrocardiol 2001; 34:345-9
45) Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? J Cardiovasc Electrophysiol 2000;11:95-8
46) Dumaine R, Towbin JA, Brugada P, et al. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res 1999; 85:803-9
47) Gonzalez Rebollo JM, Hernandez Madrid A, et al. Recurrent ventricular fibrillation during a febrile illness in a patient with the Brugada syndrome. Rev Esp Cardiol 2000; 53:755-7
48) Scheinman MM. Is the Brugada syndrome a distinct clinical entity? J Cardiovasc Electrophysiol 1997; 8:332-336
49) Fischer S, Reinhold S, Kettner W. Kardiologische Abteilung der Medizinischen Klinik, Stadtisches Klinikum Magdeburg, Krankenhaus Altstadt Med Klin 2001; 96:485-8
50) Fujiki A, Usui M, Nagasawa H, et al.: ST segment elevation in the right precordial leads induced with class IC antiarrhytmic drugs: Insight into the mechanism of Brugada syndrome. J Cardiovasc Electrophysiol 1999; 10:214-218
51) Shimizu W, Antzelevitch C, Suyama K, et al. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11:1320-9
52) Brugada R, Brugada J, Antzelevitch C. et al. Sodium channel blockers identify risk for sudden death in-patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000; 101:510-515
53) Brugada R. Use of intravenous antiarrhythmics to identify concealed Brugada syndrome. Curr Control Trials Cardiovasc med 2000; 1:45-47
54) Brugada J, Brugada P, Brugada R. Ajmaline unmasks right bundle branch block-like and ST segment elevation in V1-V3 in-patients with idiopathic ventricular fibrillation. PACE (abstract) 1996; 19:599
55) Shimizu W, Kamakura S. Catecholamines in children with congenital long QT syndrome and Brugada syndrome. J Electrocardiol 2001; 34:173-5
56) Asenjo R, Madariaga R, Morris R, et al. Sudden death due to recuperated ventricular fibrillation: Brugada syndrome? Rev Med Chil 1998; 126:814-821
57) Tanaka H, Kinoshita O, Uchikawa S, et al. Successful prevention of recurrent ventricular fibrillation by intravenous isoproterenol in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2001;24:1293-4
58) Chalvidan T, Deharo JC, Dieuzaide P, et al. Near fatal electrical storm in a patient equipped with an implantable cardioverter defibrillator for Brugada syndrome. Pacing Clin Electrophysiol 2000; 23:410-2
59) Araújo N, Godinho F, Maciel W, et al. Pesquisa de Portadores Assintomáticos da Síndrome de Brugada Através do Teste da Ajmalina e Dobutamina. LIV Congresso Brasileiro de Cardiologia Tema Livre 084 Hospital Universitário Clementino Fraga Filho - UFRJ; Clínica São Vicente Rio de Janeiro-RJ Brasil).
60) Guevara-Valdivia ME, Iturralde Torres P, de Micheli A, et al. 'Brugada syndrome' Arch Cardiol Mex 2001;71:66-72
61) Lee KL, Lau CP, Tse HF, et al. Prevention of ventricular fibrillation by pacing in a man with Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11:935-7

62) Butler JM. Brugada syndrome--the missed epidemic. J Accid Emerg Med 2000 Nov;17(6):426-8
63) Litovsky SH, Antezelevitch C.: Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetilcholyn in ventricular myocardium. Circ Res 1990; 67:615-627
64) Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. The antiarrhthmic effect of 4-aminopiridine. Cardiovasc Res 1996; 32:593-603
65) Zygmunt AC, Goodrow RJ, Antzelevitch C. Sodium effects on 4-aminopyride-sensitive transient outward current in ventricular cells. Am J Physiol.272: H1-H11, 1997
66) Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol 2001; 24:1420-2).
67) Imaizumi Y, Giles WR: Quinidine-induced inhibition of transient outward current in cardiac muscle. Am J Physiol 1987; 25:H704-H708
68) Fujiki A, Usui M, Nagasawa H, Mizumaki K, Hayashi H, Inoue H. ST segment elevation in the right precordial leads induced with class Ic antiarrhythmic drugs: Insight into the mechanism of Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:214-218
69) Pastor A, Nunez A, Cantale C, et al. Asymptomatic brugada syndrome case unmasked during dimenhydrinate infusion. J Cardiovasc Electrophysiol 2001;12:1192-4
70) Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, et al. Right ventricular electrocardiographic leads for detection of Brugada syndrome in sudden unexplained death syndrome survivors and their relatives. Clin Cardiol 2001; 24:776-81
71) Bjerregaard P, Gussak I, Antzelevitch C. The enigmatic ECG of the Brugada Syndrome. Letter to the Editor. J. Cardiovasc. Electrophys. 9: 109-111, 1998)
72) Chinushi M, Washizuka T, Okumura H, Aizawa Y.: Intravenous administration of class I antiarrhytmic drugs induced T wave alternans in a patient with Brugada syndrome. J Cardiovasc Electrophysiol 2001; 12:493-5
73) Hohnloser SH, Klingenheben T, Zabel N et al. T wave alternans during exercise and atrial pacing in humans. J Cardiovasc Electrophysiol 1997; 8:987-93
74) MTG Newsletter. Special Report: T-Wave Alternants Test, October 1999/Vol.6, N.10
75) Ikeda T, Sakurada H, Sakabe K, et al. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. J Am Coll Cardiol 2001; 37:1628-34
76) Kakishita M, Kurita T, Matsuo K, et al. Mode of onset of ventricular fibrillation in patients with Brugada syndrome detected by implantable cardioverter defibrillator therapy. J Am Coll Cardiol 2000; 36:1646-53
77) Sastry BK, Narasimhan C, Soma Raju B. Brugada syndrome with monomorphic ventricular tachycardia in a one-year-old child. Indian Heart J 2001; 53:203-5
78) Pinar Bermudez E, Garcia-Alberola A, Martinez Sanchez J, et. al.: Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2000; 23:407-9
79) Shimada M, Miyazaki T, Miyoshi S, et al. Sustained monomorphic ventricular tachycardia in a patient with Brugada syndrome. Jpn Circ J 1996; 60: 364-70
80) Ogawa M, Kumagai K, Saku K. Spontaneous right ventricular outflow tract tachycardia in a patient with Brugada syndrome. J Cardiovasc Electrophysiol 2001; 12:838-40
81) Martinez Sanchez J, Garcia Alberola A, Jose Sanchez Munoz J, et al. Concurrent Long QT and Brugada Syndrome in a Single Patient. Rev Esp Cardiol 2001; 54:645-648
82) Maarten P, van den Berg MD; Arthur AM. et al. Possible Bradycardic Mode of Death and Successful Pacemaker Treatment in a Large Family with Features of Long QT Syndrome Type 3 and Brugada Syndrome J Cardiovac Electrophysiol 2001; 12: 630-636)
83) Lepesckin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram, Circulation 1952; 6:378-88
84) Pye M, Qinn AC, Cobbe SM,: QT-interval dispersion: a non-invasive marker fo susceptibilility to arrhytmias in patients with sustained ventricular arrhytmias?. Br Heart J 1994; 71:511-14
85) Fei L, Statters DJ, Camm AJ. QT-interval dispersion on 12-lead electrocardiogram in normal subjects: its reproducibility and relation to the T wave. Am. Heart J. 1994; 127:1654-55
86) Battur MK, Aloseyed S, Oto A, et al. Circadian variations of QTc dispersion: is it a clue to morning increase in sudden cardiac death? Clin. Cardiol 1999;22:103-6

87) Ruskin JN. Role of invasive electrophysiology testing in the evaluation and treatment of patients at high risk of sudden cardiac death. Circulation 1992; 85(suppl I):1152-1159
88) *Zipes DP. Genesis of cardiac arrhytmias electrophysiological considerations. In: Braunwald E. Heart Disease. Philadelphia: WB Saunders, 1997*
89) Simsom MB, and MacFarlane PW. In Comprehensive Electrocardiology. Theory and Practice in Heath and Disease. Volume 2. The Signal-Averaged Electrocardiogram. Chaper 33 p:1204. Pergamon Press, 1989
90) Buckingham TA, Thessen CC, Stevens LL, et al. Effect of conduction defects on the signal-averaged electrocardiographic determination of late potentials. Am J Cardiol 1988; 61:1265-71
91) Gussak I, Hammill SC.: Clinical diagnosis and risk stratification in patients with Brugada syndrome * J Am Coll Cardiol 2001; 37:1635-1638
92) Priori SG, Napoliano C, Cantu F, et al: Differential response to Na+ channel blockade, beta-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long QT syndrome. Circ Res 1996; 78:1009-1015
93) Pérez Riera AR, et al. "SÍNDROME DO QT LONGO FAMILIAR SEM SURDEZ (ROMANO WARD) COM PR CURTO, VARIANTE DA SÍNDROME. 36 Congresso Brasileiro de Cardiologia Recife 1980
94) Lehmann MH, Suzuki F, Fromm BS, et al: T waves “humps” as a potential electrocardiographic marker of the long QT syndrome. J Am Coll Cardiol 1994; 24:746-754
95) Malfatto G, Beria G, Sala S, et al: Quantitative analysis of T wave abnormalities and their prognostic implications in the idiophatic long QT syndrome. J Am Coll Cardiol 1994; 23:296-301
96) Lepesckin, E.: Physiologic basic of the U Wave, in Schlant, R. C.; and Hurst, J.W. (eds.): Advances in Electrocardiography(New York: Grune&Stratton, Inc.,1972
97) Antzelevitch C and Sicouri S. Clinical relevance of cardiac arrhythmias generated by afterdepolarizations. Role of M cells in the generation of U waves, triggered activity and Torsade de Pointes. J Am College Cardiol 1994; 23:259-277
98) Antzelevitch C, Zipes DP. What causes the U wave. NASPETAPES 5 (2), 1996
99) Antzelevitch C, Nesterenko VV, Yan G-X. The role of M cells in acquired LQTS, U waves and Torsade de Pointes. (Invited) J Electrocardiol 1996; 28: 131-138
100) Shimizu W, Antzelevitch C. Cellular Basis for the T Wave. The Role of M cells. Jpn J Electrocardiology 2001; 21:101-108
101) Watanabe Y: Purkinje repolarization as a possible cause of the U wave in the electrocardiogram. Circulation 1975; 51:1030-1037
102) Priori SG, Napolitano C, Paganini V, et al: molecular biology of QT long syndrome; Inpact on management Pacing Clin Electrophysiol 1997; 20:2052-2057
103) Schwartz PJ, Moss AJ, Locati E, et al: The long QT syndrome international prospective registry [abstract]. J Am Coll Cardiol 1989; 13(Suppl A):20^{A}
104) Leenhardt A, Glaser E, Burguera M, Nurnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. Circulation 1994; 89:206-215
105) Lepesckin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram, Circulation 1952; 6:378-88
106) Pye M, Qinn AC, Cobbe SM. QT-interval dispersion: a non-invasive marker fo susceptibilility to arrhytmias in patients with sustained ventricular arrhytmias?. Br. Heart J 1994; 71:511-14
107) Battur MK, Aloseyed S, Oto A, et al. Circadian variations of QTc dispersion: is it a clue to morning increase in sudden cardiac death? Clin. Cardiol 1999;22:103-6
108) Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients wtih long QT intervals. Br Heart J 1990; 63:342-44
109) January CT, Riddle JM, Salata JJ: A model for early afterdepolarizations: induction with the Ca^{2+} channel agonist BAY K 8644, Circ Res 1988; 62:563-71
110) Burashnikow A, Antzelevitch C: Acceleration-induced early depolarizations and triggered activity [abstract]. Circulaton 1995; 92:5-432
111) Zareba W , Modd SJ, Le Cessie S, et al. T-wave alternans in idiopathic long QT syndrome. J Am Coll Cardiol 1994; 23:1541-6

112) Lamas GA, Mueller JE, Turi AG, et. al. A simplified method to predict occurrence of complete heart block during acute myocardial infarction. Am J Cardiol; 1986 57: 1213-18
113) Geltman EM, Ehsani AA, Campbell MK, et al.: The influence of location and extent of myocardial infaction on long-term ventricular dysrhythmia and mortality. Circulation 1979; 60:805-10
114) Brugada P, Wellens F, Andries E. A prophylactic implantable cardioverter-defibrillator? Am J Cardiol 1996; 78 (suppl 5A):128-133
115) Rosembaum MB, Girotti LA, Lazzari JO, et al.: Abnormal Q waves in rigth side chest leads, provoked by onset of rigth bundle branch block in patiens with anteroseptal infarction. Br Heart J 1982; 47:227-31
116) Moss Aj, Hall J, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular tarrhtmia. N Engl J Med 1996; 335:1933-40 (MADIT study)
117) Grimm W, Winzenburg J, Knop V, et al. Incidence and clinical significance of ventricular late potencials in idiopatic dilated cardiomiopathy compared to coronary artery disease.1997; ANE2: 20-26
118) Maia IG, Drumond Neto C, Montera M, et al. Avaliação do perfil arritmogênico ventricular de pacientes com miocardiopatia dilatada e fração de ejeção diminuída. Arq Bras Cardiol 1998; 70:237-241
119) Korhonen P, Vaananen H, Makijarvi M, Katila T, Toivonen L. Repolarization abnormalities detected by magnetocardiography in patients with dilated cardiomyopathy and ventricular arrhythmias. J Cardiovasc Electrophysiol 2001; 12:772-7
120) Bart BA, Shaw LK, Mc Cants CB, et al. Clinical determinants of mortality in patients with angiographically diagnosis ischemic and nonischemic cardiomyopathy. J Am Coll Cardiol 1997; 30:1002-1008
121) Primo J, Geelen P, Lorga F° A, Wellens F, Brugada P. Hypertrophic cardiomyopathy: Role of the implantable defibrillator in the prevention of sudden death. Eur Heart J 1997;18:467(abstract)
122) Bestetti RB, Dalbo CM, Arruda CA, et al. Predictors of sudden cardiac death for patients with Chagas' disease: A hospital-derived cohort study. Cardiology 1996;87:481
123) Bestetti RB, Dalbo CM, Arruda CA, et al. Predictors of sudden cardiac death for patients with Chagas' disease: A hospital-derived cohort study. Cardiology 1996;87:481-6