Brugada Syndrome versus Congenital Long QT Syndrome type 3 or LQT3: two allelic entities with diverse clinical-electrocardiograph expression

Andrés Ricardo Pérez-Riera

The Brugada Syndrome (BrS) is the mirror image of Congenital Long QT Syndrome (LQTS) variant type 3 or LQT3. Both entities affect, in subtle different ways, the alpha sub-unit of the Na^+ rapid channel of the sarcolemma, and both of them are of autosomal dominant transmission. In about 50% of cases, the BrS is sporadic, and in the other 50%, there is positive family history with an autosomal dominant pattern of inheritance.

The BrS and LQT3 share the same position or locus on a specific chromosome in the diploid cells (chromosome 3p24-p21). That is why they are considered allelic diseases; they only differ in slightly different mutations in the amino acids sequence in the Na+ channel of the sarcolemma ("channelopathies"). Both entities result from different molecular effects: whereas in the BrS, the mutation causes reduced entry of Na+ through the channel, resulting in a fast recovery from the inactivated state. These states correspond to the ST segment in the ECG. On the contrary, the mutation of LQT3 is associated with a gain of its former function with slow and constant entry of Na^+ in phase 2 (prolonged inactivated state), which in turn increases the duration of the ST segment leading to a prolonged QTc at the expense of ST, altogether with the late appearance of the T wave.

A large family has been identified with the mutation SCN5A, and showing mixed electrocardiograph characteristics: elevation of ST segment and prolonged QTc. In some of these cases, flecainide produces elevation of the ST segment, which raises the interrogation whether they could be two aspects of the same disease (1). Despite the great genetic similarity both entities reveal very different clinical-electrocardiograph characteristics but show coincidences that stem from their common genetic nature.

Nowadays, at least 13 variants of the LQTS are already known and 90 % of them among the varieties 1, 2 or 3 denominates as LQT1, LQT2 and LQT3.

The Table 1 shows the three main varieties of LQTS.

Table 1

Disease	Gene	Chromosome and OMIM NO	Ionic Channel Affected
LQT1: JLN* JLN*	KCNQ1 KCNE1 KCNQ1	11p15.5 OMIM NO: 192500 OMIM NO: 176261 21q22.1-q22.2 11p15.5 OMIM NO: 192500	I_{ks}
LQT2 RWS**	HERG KCNH2	7q35-q36 OMIM NO: 152.427	I_{kr}
LQT3, idiopathic ventricular fibrillation and BrS	SCN5A	3p21-24 OMIM NO: 600163.	Na^+

*JLN: Jervell-Lange-Nielsen

** RWS: Romano-Ward Syndrome.

· OMIM NO: refers to the input of the locus at http://www.ncbi.nlm.nih.gov/htbin-post/Omim.

Disease Autosomal dominant	Autosomal recessive	Channel affected	Gene	Effect of mutation	Chromosome

LQT1	JLN1	I_{ks}	KVLQT1	< function	11p15.5
LQT2		I_{kr}	HERG	< function	7q35-36
LQT3		I_{Na^+}	SCN5A	> function	3p21-24

From the clinical point of view, inherited-familiar or congenital variants of LQTS are grouped as follows:

1) Cardio-auditory or deaf-cardiac syndrome (sensorineural deafness) of Jervell-Lange-Nielsen (JLN): autosomal recessive.
2) Romano-Ward Syndrome(RW) without deafness: autosomal dominant.

Observation: every LQT3 corresponds to RWS; but the reverse is not true since the RWS can also be type 4 (LQT4), LQT2 7(HERG) and LQT5 21q22.1 (Mink) (2).

3) Sporadic form, non-familiar or idiopathic.

Comparative aspect**s** of BrS and LQT3 variant

I) Observed differences verified in the Na^+ channel mutations and genetic aspects

The BrS can present mutations in the Na^+ channel, in residue 1620(M1620T), between domains III and IV. The **glutamine amino acid** is exchanged by leucine in codon 567(L 567Q) between domains II and I.
Mutations were described in the gene SCN5A known as “missence mutation”, “splice-donor mutation”, and “frameshift mutation” (3). The first two ones are responsible for the quick recovery of the Na^+ channel from the inactivated state, and the “frameshift mutation”, produces lack of functioning of the channel, which causes a heterogeneous loss of the “plateau”, dome or phase 2, only in the right ventricle epicardium but not on the endocardium (precisely in front of the V_1 to V_3 leads). At the epicardium, the transient outward current or I_{to} channel of phase 1 is the most prominent (because of a larger K^+ outflow). This fact is intensified in the BrS and leads to a marked dispersion of the repolarization and refractivity, ideal substrata for arrhythmias by reentry in phase 2.

Furthermore, other factors such as strain, autonomic stimulus, neurogenic "triggers", fever, antiarrhytmic classes IA and IC, antimalarials, antidepressants, hyperglycemia and other external influences can trigger the onset of fast polymorph ventricular tachycardia (PVT) degenerating into ventricular fibrillation (VF) in the BrS.
The LQT3 presents deletion in nine nucleotides bases, resulting in the loss of three amino acids in the protein channel: lisine (K), proline (P) and glutamine (Q). This mutation is known as DKPQ (4). In addition, a mutation was observed in aspargine, at position 1325, exchanged **by** serine (N1325); arginine at position 1644 is exchanged **by** histidine (R1644H) and finally another **one in the** residue 1623 (R1623Q) between domains III and IV of the Na^+ channel.
In both entities (BrS and LQT3) the gene involved is the SCN5A alpha sub-unit and **share** the same position or locus in the genetic map: 3p24-p21, which gives them the allelic characteristic (4-5).
The LQT3 and the idiopathic ventricular fibrillation (IVF) have OMIM NO number 6000919(*). Since probably 50% of the IVF correspond to the BrS, we infer that this last entity would have to share this number. In another word, a considerable proportion of the IVF is BrS. There are elements that orient us to ascertain that the BrS and IVF are, in a certain percentage, the same entity: both are more frequent in middle-aged men without structural cardiopathy (6), both affect the same gene (SCN5A) and share the same locus (3p24-p21).
A recent publication remarks that in order to make this percentage more accurate, it is important to define the diagnostic criteria used to catalogue patients with IVF as being BrS, since it depends on the diagnostic criteria used (7).
(*) The OMIM NO refers to the locus entry at http://www.ncbi.nlm.nih.gov/htbin-post/Omim(8).

II) Sex:
The BrS shows greater male predominance: 8:1 to 10:1 and on the contrary, LQT3 predominates among women (9).

III) Structural Cardiopathy:
Both entities do not reveal **APPARENT** structural cardiopathy and only molecular alterations in the structural Na^+ channel genetically conditioned and non-detectable without genetic tests.

IV) Phenotypic Characteristics:
There are no special somatic changes described in the BrS. At the LQT3 there is a reference of association with syndactyly (10).

V) Electrocardiographs modifications:

1. **Rhythm:** Sinus rhythm is found in both entities. In the BrS the arrhythmogenic substratum may not be circumscribed at the ventricular level. Therefore, temporary atria fibrillation has been referred in Brazil by Villacorta H et al (11). There was an initial description of the Brugada brothers and a recent publication by Eckardt L, et al (12). This last group of researchers point to the presence of supraventricular tachyarrhythmias in 29% of the cases of BrS and AV reentrant supraventricular tachycardia.
2. **Heart Rate**: The BrS does not reveal special characteristics in this item, but the LQT3 shows a tendency to bradycardia related to age and, in some cases, a decrease during rising efforts. It has been suggested that this may be caused by a decrease in the sympathetic tonus of the right stellated ganglion. When the heart frequency increases, LQT3 shows a shorter QTc, compared to variants LQT1 and LQT2 (13).
3. **PR interval (PRi**: In the BrS, PRi can be prolonged at the cost of H-V. The electrocardiograph PRi represents the sum of the intervals P-A, A-H and H-V of the Electrogram. There can be a prolonged H-V or intra-hissian block with PRi still within normal values (less than 200ms) because depolarization **of** His bundle (H) is very short: it represents less than 10% of the whole of PRi (15 to 20ms. until 30ms.). In this cases the diagnostic is only possible through Electrogram showing His split. In the LQT3, PR is usually normal. Nevertheless, we have related the first short PRi case in a family over two decades ago (14).
4. **SÂQRS**: An eventual deviation to the left is described in the BrS. There are no references to deviations of QRS the axis in the LQT3.
5. **QRS**: Pseudo Right bundle branch block (RBBB) or right ventricular conduction delay in RVOT territory, with atypical characteristics, constitutes the hallmark of BrS. Broad terminal S-wave in left leads DI, aVL, V5 and V_6 and final large R in aVR typical of RBBB is seen in 28% of cases and the QRS duration is usually only prolonged on right precordial leads. Diagnoses of RBBB should not be made in the absence of such an S wave at left leads and abnormal QRS widening in all leads. ECG terms, such as “pseudo-RBBB”, “RBBB-like”, and “RBBB-pattern” **have** been **non** help. We believe that the vectorcardiogram **can** enlighten **this** doubt.There is no reference to a major incidence of RBBB at LQT3.
6. **J point and ST segment**: In the BrS we observe gross alteration of ventricular repolarization in right precordial leads V_1 to V_2 or V_3 consisting in persistent elevation of the J point and the ST segment usually convex towards the top (“coved type”) followed by negative

symmetrical T wave. Another so considered morphology of ST in the same leads is the elevation of ST with a horse saddle aspect ("saddle type"), with the convex side inferior as a consequence of the exclusive elevation of the J point associated a positive T wave. Modifications in the leveling of the ST segment are observable during oscillation of the autonomous nervous system. It was thus verified that vagotonia increases the ST segment elevation and the sympaticotonia decreases it. (15). This hypothesis was reinforced by eventual disappearance of the ST elevation with isoprenaline and exercise during the exercise stress testing as well. Therefore, the selective beta-adrenergic and muscarinic stimulation accentuates the ST elevation while the alpha blocking and the alpha-adrenergic stimulation diminish it. Antiarrhythmics of group 1A and 1C, fever, tricycles antidepressants, antimalarials and hyperglycemia can accentuate the ST elevation, beyond the fact of being potential accelerators of tachyarrhythmias. (16-17). There is a description of elevation of the ST segment in the inferior leads DII, DIII and aVF and multiple modifications in the morphology of the ST segment (18). A characteristic prolongation of ST duration is described in LQT3, causing late appearance of T **wave** and long Qt. (19-20-21). Flecainide can induce elevation of the ST segment in variant LQT3, signaling the genetic relationship between the BrS and the LQT3 (22).

7. **T wave**: They are described as variants of the BrS bifid T waves; of alternating polarity or "enigmatic". We call "enigmatic ECG" those presenting themselves with an unstable T wave: large, inverted, alternating, biphasic, bifid and/or with notches. It describes terminal portion of negative T from V_1 to V_3. T waves of late beginning are the hallmark of variant LQT3. In every kind of LQTS, the T wave from V_2 to V_5 or from V_3 to V_4 can be biphasic with notches attributed to precocious subliminal post-depolarization (23). The T wave alterations in LQTS have grouped in three degrees, according to the notches: a) The late appearance proper of the LQT3 variant; b) Alternations beat by beat; c) Long T waves, of late appearance, inverted, alternating, biphasic, bifid with notches are responsible for the so-called "Enigmatic ECG" that can be found in any LQTS variants.
8. **U wave**: There are not references of alterations in the U wave in BrS. The U wave **can be** prominent in **many** cases of LQT3. It would follow a late repolarization of the M cells. It can increase during bradycardia and within pauses; and presents with alternating polarity.
9. **QTc**: is normal or prolonged only in right precordial leads in BrS, i.e., less than 0,46 in men and 0,46 in women. The QTc is of normal duration because the mutations influence in only less of the initial 1ms;

afterwards the channel closes. On the contrary, in the LQT3, QTc is long, because the mutation DKPQ brings about a small but persistent entry of Na^+ in phase 2 with late re-opening, which explains the QTc prolongation and the late start of T wave. The QTc of the LQT3 is very long, the longest within the LQTS: more than the LQT1 and LQT2 variants. The QTc can be normal in the female sex (24). Approximately 6% of the LQTS present QT of normal duration and 10% of them present cardiac arrest (25).

10. **QT dispersion**: It is defined as the difference between the maximum and the minimum QT duration found on the 12 conventional leads. The measurement must be done at the double speed of 50mm/s and vertical alignment of the 12 leads so that the same heartbeat can be simultaneously analyzed. It will show from the first deflection of the QRS complex until the point return **point of T wave** to the base line or the lowest point between the T and U waves (26). Dispersion is not so significant in the BrS, but it is of major importance in LQTS (27). The effective use of beta-blockers or in left sympaticectomy lessens the dispersion in LQTS. Measurements taken at the congenital LQTS verify a QT dispersion twenty times greater than normal: 645ms + - 32ms(28). The persistence of dispersion related to the treatment may identify high-risk patients.
11. **Ventricular Tachycardia (VT) Characteristics**: VT in the BrS is almost always polymorph, (PVT) very fast (between 260 to 352bpm) and with short coupling or protosystolic. The ones induced by drugs can be monomorphic (MVT). The electrophysiological mechanism of the PVT in the BrS can be called “re-entry in phase 2” characterized by a shortening of phase 2 between 40 % and 70 % only in the epicardium and abolition of the plateau or dome, which causes a marked dispersion of repolarization, originating arrhythmia. The factors leading to this type of mechanism are the use of K^+ openers, pinacidil (29), flecinide (30), and metabolic inhibition (31) and ischemia simulation. The block of the channel of I_{to} by 4-aminopyridine restores homogeneity and abolishes re-entry in phase 2 in all cases (32). VT of the LQT3 is characteristically known as torsade de pointes (TdP). They are characterized by: a) Long coupling or Tele-diastolic; nevertheless, a belated “R on T” phenomenon is observed by the long QT (relatively late);b) Lower frequency (between 200 and 250bpm);c) Variable amplitude complex with a graduate reduction followed by a new increase (“spindle-shaped pattern”);d) VT aspect: with fast rotations of the apexes along the base line: “corkscrew effect”, balancing, “swinging pattern” or “twisting appearance”. The changes along the VT axis can reach up to 180^0;e) Characteristic sequences of long and short cycles

with R-R variations preceding the VT ("long-short sequences"). The presence of at least three sequences of long and short cycles is called cascade phenomenon's) It can start after long pauses: VT pause depending on characteristics of variant LQT3; The electrophysiological mechanism of the TdP responds to the precocious early after depolarization (EADs). These are automatic arrhythmias caused by deflagrated or triggered activities ("triggered activity") in late phase 2 and initial of phase 3 via $ICa^{++}{}_{L}$ channel by activation time and voltage dependent preferably on **M and Purkinje** cells (33-34). This channel contributes to the "plateau" or phase 2 in the atria and ventricular contractile cells and the Hiss -Purkinje system, being the "trigger" for the Ca^{++} exit of the sarcoplasmatic reticulum (SR) or longitudinal channel. This is an membranous intracellular system; when activated by the transmembranous potential of action (TPA) of the former, sets Ca^{++} free to the sarcoplasm to the intra-citoplasmic fluid of the muscular cell ($Ca^{++\ freeing}$ channel). Quickly, a Ca^{++} pump, also located in the SR membrane transports the Ca^{++} again to the interior of the SR (Ca^{++} capture pump) so as to induce the precocious EADs, in phase 3 or bradycardic dependents. As such, it has a relevant role in the automatic arrhythmias. The phenomenon occurs because of the existence of a marked transmural dispersion (heterogeneity) of the ventricular repolarization whose ionic base is of greater duration of the **M cells** (34) as a consequence of possessing the weakest slow channel of K^{+} at the end of phase 3 of the TAP ("delayed rectifier current"): $I_{Ks,\ which}$ contributes to a longer TAP. The duration of the TAP of these cells increase in greater measure when compared to the subepicardial and subendocardial before the effects of antyarrhythmic agents class III Ex: d-sotalol, eritromicine, ATX-II and anthopleurin and during bradyarrythmias. Additionally, the epicardium and middle myocardium cells where there are M cells the I_{to} **channel** is very abundant, being responsible for the prominent notch in phase 1and absent in endocardium: I_{to} channel absent and therefore inexistence of phase 1 with notch. The **basic ionic** of the EADs is maintained by non-homogeneous ventricular repolarization, which originates a facilitator window of the classical re-entry (arguable).

12. **Predominant moment in the occurrences of tachyarrhythmic episodes: Regarding** BrS altogether with the LQT3 syndrome the events occur predominantly during sleep or in rest. In the BrS the events occur in the activity in only 15% of the case (36).In LQT3 the tachyarrhythmic events occur during sleep and the rest in 61% of the instances (37). On the contrary, the LQT1 variant occurs almost exclusively in cases of effort or stress.

13. **Effect of flecainide and Class IC antiarrhythmics** This group of drugs has a potent action effect in the Na^+ channel because it has slowed kinetic of union with it. Additionally, flecainide in larger doses block the transient outward current or I_{to} and $I_{Ca^{++}L}$ channels.Flecainide is administered in the dose of 10mg/Kg weigh in 10'. In the BrS the drug increases in a pronounced form the elevation of ST segment, the duration of QRS and can break out the occurrence of ventricular extrasystoles (38). Flecainide and pilsicainide can induce the elevation of both the right precordial (39) and the low leads where they can simulate ischemia (40) and trigger an episode of VT. The sodium blockers normalize repolarization in LQT3; they produce the appearance of more precocious T waves and shorten the QTc (41). A great family with SCN5a mutations has been reported and mixed electrocardiograph pattern: long Qt. and elevation of the ST segment. In these cases, flecainide occasions elevation of ST in some patients with a LQT3 syndrome. The presence of an intermediate phenotype suggests that the clinical manifestations can depend on a single mutation (1).
14. **Effect of mexiletine and antiarrhythmics class IB:** These drugs have a light action in the Na^+ channel because of their quick kinetic of union and liberation. They act mainly by means of inhibition of the inactivated state of the channel (42). This inhibition occurs in much lower concentrations than in the open or Rest State of the channel. They do not change or shorten the duration of TPA; they slightly reduce the $V_{max.}$ And do not affect the QRS and the JT interval. In the BrS Mexiletine does not cause any special effect in the ECG. On the contrary, in the LQT3 syndrome this drug shortens the QT In low concentrations they act blocking the late inflow of Na^+ into the Na^+ channel because they inhibit its late opening (42)thus avoiding the appearing of TdP. They do not shorten the QT of LQT2 that affects the K^+ channel (HERG defect of the K^+ channel). Also the drug does not shorten the LQT1. Even being more adequate for the LQT3 form, mexiletine produces reduction of repolarization dispersion either in the LQT2 or in LQT3 and LQT1 by shortening TPA of the M cells in a larger extent than the subendocardic and subepycardic cells, causing homogenization of ventricular repolarization (44).

The annual mortality rate

The annual mortality rate in BrS is extremely high: 10%average per year without intervention. There are cases with characteristic ECG in asymptomatic patients without family history of sudden death (SD) that present a relatively benign course. In these, the VF induction seems rare

(45). Professor Pedro Brugada divides the patients in several groups according to a decreasing mortality rate scale: **a)** Patients with altered VF e ECG with 81% inductibility present an annual mortality rate of 15%. The channel has a 50% degree of damage. **b)** Patients with syncope, altered ECG and 66% inductibility present na annual mortality rate of 10%.The channel has a 25% degree of damage;**c)** Asymptomatic patients with altered inducible ECG. Annual mortality of 5%. **d)** Asymptomatic patients, with disturbed ECG not inducible present an annual mortality of 05,% and channel has 25% degree of damage; **e)** Asymptomatic patients, altered ECG after drugs inductibility of 18% present an annual mortality of 0,01%; Normal persons present SD with an annual mortality rate of 0,01% and no degree of channel damage. In the LQT3 syndrome the annual mortality rate is lower that in BrS. About 5% per year. Rises to 10% in children with previous symptoms. The LQT3 variant has less number of tachyarrhythmic events. Nevertheless, more lethal than LQT1 and LQT2.

Echocardiography

In the BrS the echocardiogram has always been normal, up to now. In the LQT3 it was verified in the mode M in ventricle parasternal long axis section a rise in the thickness in the precocious contraction phase of ($Th^1/_2$) and the presence of a slow movement in the late phase of thickening with plateau morphology (TSTh) drawing a second peak: morphology with double peak (46). 42 patients with congenital LQTS were studied and compared to 42 healthy individuals, of equivalent sex, age, weight and height, with the following abnormalities among carriers: 1) a rise in the thickening rate in the initial phase of contraction ($Th1/_2$); 2) presence of a slow movement in the late phase of thickening of the wall with a “plateau” morphology eventually followed by a second peak. Those abnormalities were more frequent in the symptomatic LQTS (77%) than the asymptomatic (19%). Three years **later**, the same group of researchers (47) demonstrated, in a group of 10 patients, that the calcium antagonist verapramil causes echocardiograph abolition of the slow movement in the late phase of thickening with “plateau”-like morphology in the LQTS patients. This verification suggests that the intimate mechanism of change of movement of alterations in the walls is a consequence of the increase of cytosolic calcium since the drug, by blocking the entrance of the cation, diminishes the calcium liberation stimulus of the reticulo-sarcoplasm (RS) for the cytosol, therefore preventing the appearance of the more vigorous contractile event The same explanation is given to the arrhythmia trigger of the TdP by precocious EADs or in phase 2 and 3 (deflagrated or triggered activity).

Exercise Stress Testing

The BrS can reveal occasional tendency to normalize alterations of ventricular repolarization produced by sympathetic predominance (48). It can equally happen in the LQT3 variant. In variants LQT1 and LQT2 the test of effort can trigger tachyarrhythmic events.

Programmed right ventricular stimulation

In BrS induction happens in 80% of the cases. Inducibility of sustained VT is a good predictor of outcome in BrS. In asymptomatic individuals, a prolonged H-V interval during sinus rhythm is associated with a higher risk of developing arrhythmic events during follow-up. Symptomatic patients require protective treatment even when they are not inducible. Asymptomatic patients can be reassured if they are noninducible.(49).The LQTS usually are not inducible.

Treatment

In the BrS the Automatic Implantable Cardioverter Defibrillator Therapy is the only safe option at the present time. Professor Dr. Pedro Brugada described the occasional occurrence of "electrical storms": repetitive episodes of twenty or more for a day or four or more per one hour requiring repeated defibrillation. Treatment of electrical storms may include isoproterenol, general anesthesia, and partial cardiopulmonary bypass. The LQTS must be treated in all cases, whether they are symptomatic or asymptomatic, once 35% of cases SD occur as a first manifestation (50). The therapeutic arsenal counts on the following resources:**a)** Drugs; **b)** Permanent Cardiac Pacing; c) Left High Sympacectomy (LHS) of the lower half of the stellate ganglion and the first three or four thoracic ganglions (cervicothoracic); d) Automatic Implantable Cardioverter Defibrillator (ICD); **e)** Associations.

1) Drugs: beta-blockers in high dosages (the higher tolerated): 3 to 5mg/Kg/ day of propranolol. Propranolol elixir is used for children under the age of 2 years. The experts recommended use of long-acting beta-blockers such as nadolol or atenolol, which require once-daily administration.

Beta-blockers can cause excessive bradycadia in LQT3 variant and induce precocious EADs and may not always be efficient in this variant of LQTS (51).

Drugs are indicated In patients with: a) Clinical classes I or II; b) Familiar history positive for SD; c) Presence of complex ventricular arrhythmias; d) Patients with one syncope episode (risk of SD less than 3%); e) Asymptomatic, because its drugs prevent the first episode of SD. It is calculated in 8%; f) **Asymptomatic women that plan to have babies by high risk of arrhythmias in the first year after-delivery.**

The drug of choice in LQT3 is mexiletine, which significantly shortens the QTc thus avoiding the appearing of the TdP (51). The drug does not shorten the

long QT of the LQT2 of the congenital QT HERG that affects the K^+ channel (46).
In-patients with recurrent class III symptoms (syncope): association of beta-blockers with class IB drugs can to be used.

2) Permanent Cardiac Pacing (PCP): Indicated for patients with malignant VT dependent on sinus pauses or bradyarrhythmias. These pause-dependents episodes are more frequently observed at the LQT3 variety. PCP is the resource with better results in its variant.
PCP is choice therapeutic in severely affected newborns in the neonatal period and in children who have remained with syncope even after drugs in correct dosages.
PCP must to be implanted with greater frequency that natural and almost always associated to beta-blockers: and/or:

3) Left High Sympathecthomy (LHS) of the half-lower part of the stellate ganglion and of the three or four chest ganglions (cervico-thoracic) this is a less used resource because a well-trained team is needed. It is not necessary the extirpation of the cephalic portion of the left stellate ganglion. This is how the syndrome of Horner is avoided.
It is accepted that, in part, genesis of VT obeys to a “sympathetic imbalance”, traduced by hypertonus of the left sympathetic hypertonus and relative right hypotonus that affects the functional affected channels. Thus, extirpation of the right star ganglion occasions QT prolongation.
Ablation of the left stellate ganglion does not shorten the QTc and consequently the antiarrhytmic effect of this therapeutic measure can only be explained by the autonomous affectation of the channel function (53). This therapeutic resource partially diminishes the sympathetic tone contributing to an increase the heart rate variability (HRV). The sympathetic hypertone increases the cardiac frequency and diminishes the HRV. The rise of the sympathetic tone diminishes the HRV increasing the risk of SD by electric instability.
The anterior wall of the left ventricle is innerved by the right sympathetic and in these patients, it has a longer delayed ventricular repolarization, in relation to the inferior and posterior wall innerved for the left sympathetic. This non-homogeneous repolarization between the anterior and inferior and posterior wall would be partially responsible for the perpetuation of the arrhythmia by the mechanism of re-entry, increasing a myocardial instability (54).

4) Automatic Implantable Cardioverter-Defibrillator (ICD)
Indicated only in those unmanageable cases shish remain in recurrent clinics class III (syncope) or IV even with the use of drugs in adequate doses,

pacing, sympaticectomy and other associated measures and recovered from SD secondary to VF or VT that would require resuscitation or in those whom the first event was a cardiac arrest. In those cases, it is the safest alternative.
Sustained pause-dependent VT
The LQT3 variant is characterized by showing a smaller number of events, but with more serious significance may require the use of this resource in a greater proportion, so much that new tendencies point out that the BrS and LQT3, because of their high rate of mortality, would be both better treated with the ICD.
An additional risk of the ICD would be the pain occasioned by the shock that could increase an adrenergic discharge and constitute itself in an electrical triggered of TdP (55). **For** this reason, implantation of the device must always be followed in all cases by the concomitant use of beta-blockers. Inadequate shocks can cause gigantic T waves. (56).

Differential diagnoses of TdP observed in LQT3 and true PVT of the BrS.

	TdP	**True PVT**
Related to bradicardia	Yes	No
Onset of arrhythmia related to pauses:	Yes	No
Cardiac Frequency:	200 **to** 250bpm.	260 to 352bpm.
Coupling:	Long.	Short.
QTc:	Long.	Normal *.
U wave:	Prominent.	Normal.
Treatment of choice:	Mexiletine and others drugs, pacing, left sympaticectomy	Automatic Implantable Cardiac Defibrillator

* There is recent reference to BrS with a long QTc (1)

I) Elements of significant concordance between the BrS and the LQT3

1) They share the same gene: SCN5A;
2) They lack apparent structural cardiopathy;
3) They affect the rapid Na^+ channel at the alpha subunit;
4) They have frequent positive familiar antecedents;
5) They **can have** autosomal dominant inheritance;

6) Both have the VT episodes predominantly during sleep and/ or rest;
7) Vagotonia can harm them and sympaticotonia can improve them;
8) Both can to have enigmatic T waves ("Enigmatic ECG");
9) Both have a very high annual mortality rate: superior at LQT3 than the other LQTS variants;
10) They can benefit in greater measure with the ICD. The LQT3 in relation to the other variants of LQTL and clearly the BrS.

II) Significant discordant elements between the BrS and the LQT3

1. Male predominance in the BrS and female in the LQT3;
2. Tendency to bradycardia in the LQT3 : lower cardiac frequency for age and normal in the BrS;
3. Normal PR or short in the LQT3 and normal or prolonged in the BrS;
4. Characteristic atypical RBBB or right conduction delay in BrS and absence in the LQT3;
5. QTc: BrS does not modify it. LQT3 prolongs it;
6. QT dispersion: LQT3 significant; the BrS no;
7. Triggering extra-systole: short in the BrS and late in the LQT3;
8. Electrophysiologic mechanism of VT: BrS re-entry in phase 2 and LQT3 precocious initial post – depolarization;
9. VT usual frequency: extremely fast in BrS and slower in LQT3;
10. Different VT morphology: polymorph TdP in LQT3, but without the characteristic aspect of the former ones;
11. The drug of choice, mexiletine, for the LQT3, does not provide any benefit for the BrS.
12. Permanent cardiac pacing benefits only the LQT3;
13. In LQT3, like in all the LQTS the M cells constitute a fundamental cause of heterogeneity in the ventricular thickness and for the lengthening of QTc, the abnormal aspect of the T wave, the prominent U waves and the appearance of TdP (30-56). In the BrS the tendency to rapid PVT depends on the shortening of the action potential in the right ventricular subepicardium.

Conclusions

The BrS and the variant LQT3 of LQTS can, due to their common origin, present significant concordant elements and very different clinic-electrocardiograph manifestations, typical of the slight differences in the genetic manifestations occurred in the protein of the Na^+ channel.

References

1) Cerrone M, Crotti L, Faggiano G, De Michelis V, Napolitano C, Schwartz PJ, Priori SG.[Long QT syndrome and Brugada syndrome: 2 aspects of the same disease]? Ital Heart J 2001; 2(3Suppl):253-257

2) Priori SG, Barhanin J, Hauer RNW, et al: Genetic molecular basis of cardiac arrhythmias: impact on clinical management. Circulation1999; 99:518

3) Cheng Q, Kirsch GE, Zhang D, et al: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998; 392:293-296

4) Wang Q, Li Z, Shen J, Keating MT: Genomic organization of human SCN5A gene encoding the cardiac sodium channel. Genomics 1996; 34:9-16

5) George AL Jr, Varkony TA, Drabkin HA, et al: Assignment of the human heart tetrodotoxin-resistant voltage-gate Na+ channel alpha-subunit gene (SCN5A) to band 3p21. Cytogenet Cell Genet 1995; 68:67-70

6) Belhassen, Viskin S,: Idiopathic ventricular tachycardia and fibrillation. J Cardiovasc Electrophysiol 1993; 4:356-369

7) Remme CA, Wever EF, Wilde AA, Derksen R, Hauer RN,: Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. Eur Heart J 2001; 22: 400-409.

8) Pyeritz RE, in Braunwald E, Zipes DP, and Libby P. 6th Edition. Heart Disease. A Texbook of Cardiovascular Medicine. W.B. Saunders Company. 2001. Molecular Biology and Genetics. Chapter 56; p: 1981

9) Locati EH, Zareba W, Moss AJ, et. al: Age and Sex-related differences in clinical manifestations in patients with congenital long QT syndrome: Finding from the international LQTS Registry. Circulation 1998; 97:2237-41

10) Marks, M. L.; Whisler, S. L.; Clericuzio, C. et. al.: A new form of long QT syndrome associated with syndactily. J Am Coll Cardiol.1995; 25:59-61

11) 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; 66:229-231

12) Eckardt L, Kirchhof P, Loh P et al: Brugada Syndrome and Supraventricular Tachyarrhythmias: A Novel Association? J Cardiovasc Electrophysiol 2001; 12:680-685

13) 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

14) 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

15) Miyazaki T Mitamura H, Miyoshi S, et al.: Autonomic and antiarrhythmic modulation of ST segment in patients with Brugada syndrome. J Am Coll Cardiol 1996; 27:1061-1070

16) Yan G,& Antzelevitch C.: Cellular basis for the electrocardiographic J wave Circulation 1996; 93: 372-379

17) Grant AO: Cardiac Arrhythmias.50th Annual Scientific Session of the American College of Cardiology 2001

18) Prieto-Solis JA, Martin Duran A: Múltiples cambios en la morfologia del segmento ST en un paciente com síndrome de Brugada. Rev Esp Cardiol 2000; 53:136-138

19) Moss AJ, Zareba W, Benhorin J. et al: ECG T waves patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995; 92:2929-22934

20) Zareba W, Benhorin J, Moss A, et al. Phenotypic characteristics of long-QT syndrome patients with different mutations of the SCN5A sodium channel gene. Eur Heart J 1999;20:344 (abstract).

21) Moss AJ, Anderson ME. Prolonged QT syndrome: from cell to bedside. Program and abstracts of the American College of Cardiology 50th Annual Scientific Session; March 18-21, 2001; Orlando, Florida. Meet the Experts Session 222.

22) Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. Circulation 2000 ;102:945-947

23) 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

24) Merri M, Benhorin J, Alberti M, et. al: Electrocardiographic quantitation of ventricular repolarization. Circulation 1989; 80:1301-1308

25) Schwartz PJ, Moss AJ, Locati E, et al: The long QT syndrome international prospective registry[abstract]. J Am Coll Cardiol 1989; 13(Suppl A):20A

26) Lepesckin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram, Circulation 1952; 6:378-88

27) De Ambroggi L, Negroni MS, Monza E, et al: Dispersion of ventricular repolarization in the long QT syndrome. Am J Cardiol 1991; 68:614-620

28) Day, C. P.; McComb, J. M.; Campbell, R. W.: QT dispersion: an indication of arrhythmia risk in patients wtih long QT intervals. Br Heart J 1990; 63:342-344

29) Di Diego JM, Antzeleitch C: Pinacidil induced electrical heterogeneity and extrasystolic activity in canine ventricular tissues: phase 2 reentry? Circulation 1993; 88:1177-1189

30) Krishnan SCm Antzelevitch C: Flecainide induced arrhythmia in canine ventricular epicardium; Phase 2 reentry? .Circulation 1993; 87:562-573

31) Antezelevitch C, Sicouri S, Lukas A, et. al.: Clinical implications of electrical heterogeneity in the heart: The electrophysiology and pharmacology of epicardial, M and endocardial cells. In Podrid PJ, Kowey PR,eds; Cardiac Arrhytmia: Mecahnism, Diagnosis and Management Baltimore, William and Wilkins, 1995; pp 88-107

32) Lukas A, Antezelevitch C: Phase 2 reentry as a mechanism of iniciation of circuls movement reentry in canine epicardium exposed to simulated ischemia. The antiarrhythmic effects of 4-aminopyridine, Cardiovasc Res 1996; 32: 593-603

33) Viskin S, Alla SR, Barron HV, et al: Mode of onset of torsade de pointes in congenital long QT syndrome. J Am Coll Cardiol 1996; 28:1262-66

34) Krause PC, Rardon DP, Miles WM, et al: Characteristics of Ca (2+)-activated K+ channels isolated from the left ventricle of patients with idiopatic long QT syndrome. Am Heart J.1993; 126:1134 -1141

35) Sicouri S, Antzelevitch C: Drug-induced after depolarization and triggered activity occur in a discrete subpopulation of ventricular muscle cells (M cells) in the canine heart: Quinidine and digitalis. J Cardiovasc Electrophysiol 1993; 4:48-54

36) Futterman LG, Lemberg L. Brugada. Am J Crit Care 2001;10:360-364

37) Zareba W, Moss AJ, Schwartz PJ. et al: Influence of genotipe on the clinical course of the long QT syndrome. International Long-QT syndrome Registry Research Group. N Engl J Med 1998; 339:960-965

38) 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;11:1320-1329

39) 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

40) Nakamura W, Segawa K, Ito H, et al.: Class Ic antiarrhytmic drugs: flecainide and pilsicainide, produce segment elevation simulating inferior myocardial ischemia. J Cardiovasc Electrophysiol 1998; 9:855-858

41) Wang DW, Yazawa K, Makita N, et al: Pharmacological targeting of long QT mutant sodium channels. J Clin Invest 1997; 99:1714-1720

42) Priori SG, Napolitano C, Paganini V, et al: molecular biology of the long QT syndrome: Impact on management Pacing Clin Electrophysiol 1997; 20:2052-2057

43) Shwartz PJ, Priori SG, Locati EH, et al: Long QT syndrome patients with mutations of the SCN5A and HERG genes have different responses to Na+ channel blockade and to increases in hear rate. Implications for gene-specific therapy [se comments] Circulation 1995; 92:3381- 3386

44) Shimizu, Antzelevitch C: Sodium channel block with meixiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. Circulation 1997; 96:2038-2047

45) Takenaka S, Kusano KF, Hisamatsu K, Nagase S, Nakamura K, Morita H, Matsubara H, Emori T, Ohe T: Relatively benign clinical course in asymptomatic patients with Brugada-type electrocardiogram without family history of sudden death. J Cardiovasc Electrophysiol 2001;12:2-6

46) Nador F, Beria G, De Ferrari GM, et. al: Unsuspected echocardiographic abnormality in the long QT syndrome: Diagnostic, prognostic, and pathogenetic implications. Circulation 1991; 84: 1530-42

47) De Ferrari GM, Nador F, Beria G, et al: effect of calcium channel block on the wall motion abnormality of the idiopatic long QT syndrome Circulation 1994; 89:2126-2132

48) Antzelevitch, C.; Brugada, P.; Brugada, J. et. al. In:Camm, A . J. E. Clinical Approaches to Tachyarrhytmias (vol 10) Armok; Futura, 1999

49) Brugada P, Geelen P, Brugada R, Mont L, Brugada J. Prognostic value of electrophysiologic investigations in Brugada syndrome. J Cardiovasc Electrophysiol 2001; 12:1004-7

50) Vincent GM: The molecular basis of the long QT syndrome: Genes causing fainting and sudden death. Ann Ver Med 1998; 49:263-274

51) Priori SG, Napolitano C, Paganini V, et al: molecular biology of QT long syndrome; Impact on management Pacing Clin Electrophysiol 1997; 20:2052-2057

52) Schartz PJ, Priori SG, Locati EH, et al: Long QT syndrome patientes with mutations pf the SCNA and HERG genes have differential responses to Na+ channel blockade and to increases in heart rates. Impliclations for gene-specific therapy. Circulation 1995; 92:3381-3386

53) Schwartz PJ, Locai EH, Moss AJ, et al: Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome: A worldwide report. Circulation 1991; 84:503-509

54) Yanowitz, F, Preston, JB, Abildskov, JA: Functional distribution of right and left stellate innervation to the ventricles. Production of neurogenic electrocardiographic changes by unilateral alternation of sympathetic tone. Circ. Res 1996;18:416-421

55) Saxon LA, Shannon K, Wetzel GT, et al: Familial long QR syndrome: Electrical strom and implantable cardioverter devise therapy. Am Heart J 1996; 131:1037-1039

56) Perry GY, Kosar EM: Problems in managing patients with long QT syndrome and implantable cardioverter defibrillators: A report of two cases. Pacing Clin Electrophysiol 1996; 19:863-867