Universitat de Girona
Facultat de Medicina

FLECAINIDE CHALLENGE IN PEDIATRIC BRUGADA SYNDROME:

ADDING FURTHER DATA TO THIS DIAGNOSTIC TOOL

Final Degree Project

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Pares, per tots aquests anys sent un recolzament constant i per ajudar-me a complir el somni de la meva vida: això està a punt de començar.
A tu, Georgia, per la facilitat i predisposició a deixar-me formar part del teu dia a dia. Ets un referent per mi com a persona i com a doctora, quina gran sort tenir la oportunitat d'aprendre de tu.
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"Simplicity may be beauty in art, but Science is a complex beauty that cannot be reduced into simplicity." – Pere Brugada

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1. LIST OF ABBREVIATIONS

BrS=Brugada Syndrome
ECG=Electrocardiogram
EPS=Electrophysiology Study
ICD=Implantable Cardioverter Defibrillator
RVOT=Right Ventricle Outflow Tract
SCD=Sudden Cardiac Death
SUNDS=Sudden Unexplained Nocturnal Death Syndrome
VF=Ventricular Fibrillation
VT=Ventricular Tachycardia

2. ABSTRACT

BACKGROUND: Brugada syndrome (BrS) is a rare, aggressive and inherited cardiac disease leading to potentially lethal ventricular arrhythmias and sudden cardiac death in young subjects with structurally normal hearts. Its diagnosis requires a Brugada type 1 electrocardiographic pattern, characterized by a coved-type ST-segment elevation in at least one of the right precordial leads. In order to unmask the concealed pattern, the administration of sodium channel blockers drugs (ajmaline, flecainide or procainamide) is stablished as diagnostic test. Little is known about pediatric BrS, as most affected patients are adults.

HYPOTHESES & OBJECTIVES: This cross-sectional study describes the diagnostic approach of pediatric patients with suspected BrS on whom a flecainide challenge has been performed.

METHODS: A registry of the standard diagnostic management of 180 anonymized pediatric patients with suspected BrS was described, including their demographics, clinical characteristics, all diagnostic tests performed and their results. It was analyzed in comparison with their flecainide challenge result.

RESULTS: 180 pediatric patients were included: 112 were asymptomatic and were studied for either familiar screening (71 patients, with five positive flecainide challenges) or ECG abnormalities (41, and 23 had a positive result, with a p-value<0.001). A total of 28 asymptomatic patients had a positive test (25%). The remaining 68 patients were symptomatic (unexplained syncope, febrile seizures or episodes of aborted SCD) and 14 had positive flecainide challenges (21%), without significant associations. The analysis of age and gender with the result of their flecainide test showed p-values of <0.001 and 0.003, respectively. Also, having family history of BrS or positive genetic tests for SCNA5A showed p-values<0.001. Some adverse effects during flecainide challenges were registered: transient photopsies (37), transient pelvic warm sensations (48) and one case of cardiac electromechanical dissociation.

CONCLUSIONS: To our knowledge, this is the largest study of children undergoing flecainide challenge for suspicion of BrS. Most patients were asymptomatic and to diagnose them can be challenging. Basal and febrile ECGs had diagnostic relevance. Also, genetic-related parameters showed an association but without a clear pattern. Symptoms did not show any association with reaching the diagnose. Analyzing age and gender parameters, it might be better to repeat the test after 15 years old, not before this age, due to the hormonal role. A total of 42 patients (23% of the 180 patients studied) were finally diagnosed of BrS thanks to a flecainide challenge, but it is believed that using ajmaline would improve the diagnostic efficiency. However, some acute adverse effects were registered (including a life-threatening arrhythmia), thus it is not a risk-free diagnostic tool.

KEYWORDS: Children, Brugada syndrome, arrhythmia, sudden cardiac death, flecainide challenge.

3. INTRODUCTION

3.1 Definition of Brugada Syndrome

Many years after being introduced by Pedro and Josep Brugada as a new clinical disease (in 1992) (1), the Brugada Syndrome (BrS) has been studied and described as an arrhythmogenic disease which can lead to Ventricular Tachycardia (VT), Ventricular Fibrillation (VF) and Sudden Cardiac Death (SCD) without any structural abnormality. It is included among the channelopathies (2,3), defined as primary genetic electrical disorders caused by alterations in genes encoding for cardiac ion channels or their associated protein, which participate in cardiac cell action potential.

Despite the characteristic life-threatening symptomatology of this syndrome, most patients remain completely asymptomatic and undiagnosed, but they have potential risk of SCD. This situation leads a greatest medical challenge.

3.2 BrS history (4–8)

Twenty-five years have passed since eight individuals had an episode of aborted SCD due to a VF and aroused the curiosity of doctors Pedro and Josep Brugada. This clinical presentation was first described by these two cardiologists as a syndrome when they find out that these patients presented a unique electrocardiographic pattern with a right bundle branch block with ST segment elevation in the right precordial leads with a structurally normal heart. This finding was published in November 1992 in the Journal of the American College of Cardiology under the title of “Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome. A Multicenter Report”.

It was not until 1996, four years later, when this clinical entity was called “Brugada Syndrome”. After its description, many countries found out that this could be the same disease as what they called “Sudden Unexplained Nocturnal Death Syndrome” (SUNDS). It also had different colloquial names in places where BrS is more prevalent: Lai Tai in Thailand, which means “death during sleep”; Pokkuri in Japan, which means “sudden and unexpected phenomena” or Bangungut in Philippines, which means “to rise and moan in sleep”.

In 1998, Ramon Brugada’s research identified genetic mutations involved in BrS, confirming that it was a real new syndrome and showed that BrS was genetically determined. Some related genes were first described, allowing to understand some aspects of its pathophysiology.

From 2000 to 2012, there were lots of advances in diagnostic and therapeutic managements. In 2002, a consensus conference report was published with the first diagnostic criteria for the syndrome, and three years later a second consensus conference reported some risk stratification schemes and approaches

to therapy. Diagnostic criteria have been improved looking for better applicability and diagnostic validity, combining electrocardiography, drugs tests, genetics, and clinical aspects in a multidisciplinary way.

After all these years of scientific progress, the BrS is a well-recognized disease and a focus of continuous research, trying to define better its clinical, genetic, cellular, ionic, and molecular aspects. More and more patients have been identified with the disease and lots of publications describe and formulate theories about its insights. From its epidemiologic data to its therapeutic management; in the pediatric population, adults or in the elderly; the past two decades have witnessed a spectacular literary expansion. In this line, the future (including this study) looks full of new improvements regarding the many facets of BrS that remain still unknown.

3.3 Introduction to pediatric BrS

In the initial description of the disease in 1992, there were reported three cases of affected children who suffered from malignant arrhythmias. Since then, several authors have reported isolated cases of BrS in children, but data of young patients remain scarce (4,9–14).

It is suggested that the prevalence of BrS is lower in children (15) compared with adults because of the influence of male hormones on phenotype expression (4,16). Studies performed in kids with BrS have failed to identify a male predominance (which is clearly defined in adult population), perhaps due to low levels of testosterone in children of both genders. Following this theory, prevalence of this disease could increase from adolescence, especially in male subjects, probably due to the testosterone rise up (17–20). Even so, some cases have been described presenting with malignant clinical expression during childhood (1,2,6,10,13). To find the cause of a SCD in children without an underlying known disease is a challenge, so literature of earlier onset of BrS in pediatrics has grown recently. Moreover, its diagnostic identification in symptomatic or asymptomatic patients (not only finding the cause) is one of the major topics addressed in this study.

3.4 Epidemiology and etiology of BrS

Little is known about the prevalence and natural history of this disease in the pediatric population. BrS is more common among adult men (40 to 45-years old males represent the 80% of all patients) with an estimated prevalence at 0.03-0.05% in adult peopulation and much lower in children (some studies quantified it around 0.0098%, but it is in countries where this disease is endemic, and it could be falsely slanted) (8,13,21,22). It is the cause of 4% to 12% of all SCD and up to 20% of SCD that occur in structurally normal hearts (23,24). Geographical

variability has been observed, being more frequent in certain regions of Southeast Asia.

The multifactorial etiology of BrS has been demonstrated including genetics, hormones, age and environmental components that modify its phenotype. Several mutations in genes encoding subunits of cardiac sodium, potassium and calcium channels, as well as in genes involved in the trafficking or regulation of these channels have been associated to BrS. Around one-third of cases of this disease can be attributed to autosomal dominant mutations with incomplete penetrance in genes encoding the α subunit of SCN5A, (the sodium channel responsible for the rapid sodium current, which generates and propagates the action potential in the excitable cardiac tissues) (4,25,26). Loss-of-function SCN5A mutations can manifest some conduction disorders, so it is one of the most important genes involved in BrS (13).
In the normal heart, sodium channels are responsible for the progression of the electrical potential from the sinus node through all cardiac conduction cells. In this disease, it is thought that the cause could be an accelerated inactivation of sodium channels and a consequent predominance of transient outward potassium current to generate a voltage gradient in the right ventricular layers. This gradient is generated between the epicardium and the endocardium (see *FIGURE 1)*, and it can be detected in the ECG as a J-point elevation and, as the gradient is marked, with negative T waves. This ionic alteration can trigger VT/VF, possibly through a reentrant mechanism (5,24,25). Other pathophysiological theories have been reported, mainly related to depolarization abnormality in the Right Ventricle Outflow Tract (RVOT), providing an arrhythmogenic substrate for this disease, but this theory remains undemonstrated yet.

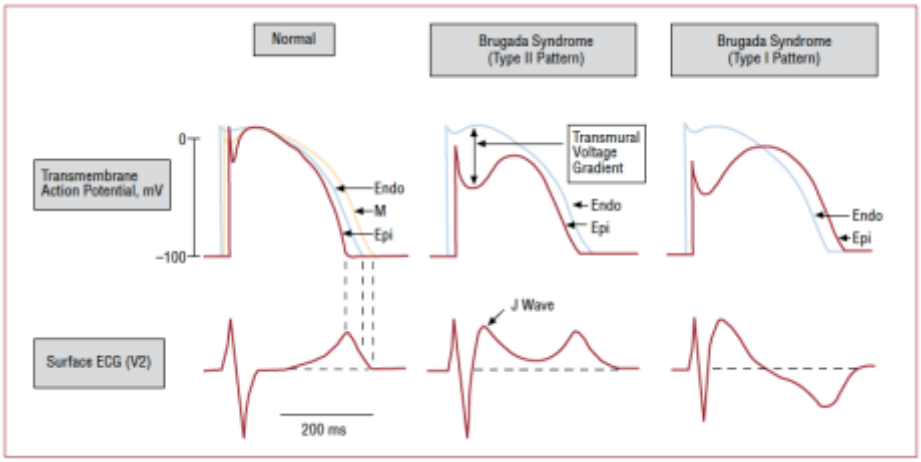

FIGURE 1: Proposed mechanism of ST-segment elevation in BrS. Reproduced with permission from: Benito et al. (24). *Endo=endocardium, Epi=epicardium, M=Myocardium, ECG=Electrocardiogram.*

3.5 Clinical approach

Nowadays, it is understood that there is great variability in clinical presentation of BrS. Clinical or electrical markers for symptomatic BrS can include: unexplained episodes of syncope (a reversible loss of consciousness in absence of prodromal period or other circumstances), and an aborted sudden cardiac death and/or ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation) (8,13).
In many cases, arrhythmia initiation is bradycardia-related (13)(27)(28), and this may contribute to the higher incidence of sudden death at night. A polymorphic VT resembling a rapid Torsade de Pointes is most commonly associated with the BrS, and monomorphic VT (see *FIGURE 2)* is more prevalent in children (4,5,29,30). VT/VF often terminates spontaneously in these patients. These symptoms can be a reason for suspecting a BrS, but they are not enough by themselves to diagnose it.
However, some affected patients can also be completely asymptomatic, giving more importance to an early approach and identification of people at risk.

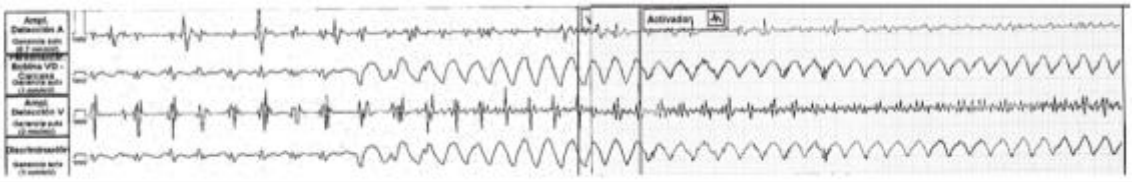

FIGURE 2: Example of a monomorphic VT registered in the intracardiac ECG from an implanted cardiac defibrillator of a pediatric patient from our series.

3.6 Diagnostic management

Which diagnostic tests are important?

Electrocardiogram (ECG) is crucial for the diagnose of BrS. Corcia et al. (28) found out an abnormal baseline ECG in 75% of young patients who presented with lethal events during follow-up, but ECG signs are intermittent. Therefore, further tests are mandatory for uncertain diagnostics or for risk assessment.

What should be found in the ECG? Are there any ECG variations?

The electrocardiographic diagnose requires the coved-type ST segment elevation in one right precordial lead, at baseline or after drug challenge. Different electrocardiographic patterns (1,4,5,23,25,31–33) can be observed, which are summarized in *FIGURE 3*:

- The type 1 pattern (*FIGURE 3*), the only diagnostic pattern. It shows coved-type ST segment elevation, which is more present in V1-V2, but can also be in V3 (less frequently). It presents the following morphologic characteristics: at the end of QRS (which is longer than the QRS of a RBBB), there is an ascending and quick slope with a high take-off ≥2mm followed by concave or rectilinear downslope ST (in comparison to the isoelectric baseline). There is

no clear r' wave and the high take-off often does not correspond with the J point. At 40ms of high take-off, the decrease in amplitude of ST is ≤4mm (in RBBB and athletes could be much higher), and at the end, the ST segment is followed by a negative symmetric T wave.

- Two non-diagnostic patterns:
  - The type 2 (*FIGURE 3*) is a saddleback pattern, which is also more common in V1-V2 and less frequent in V3. After the QRS, the ST segment starts with a high take-off of r'≥2mm (that often does not coincide with J point). The descending arm of r' matches with the beginning of ST, and its ST segment presents an ascent ≥0.5mm. Then, the ST is followed by positive or biphasic T wave in V2 (T peak > ST minimum > 0) and of variable morphology in V1.
  - The type 3 pattern (*FIGURE 3*) is a right precordial ST-segment elevation ≤1mm either with a coved-type or a saddleback morphology.

  In 2012, Bayés de Luna et al. (31) reported that both type 2 and 3 are not diagnostic, and proposed to join them in a single non-diagnostic type 2 Brugada pattern, due to their similarity in morphology and in clinical applications. However, actual literature is still using the type 3 in the terminology, but it does not suppose any clinical or diagnostic difference.

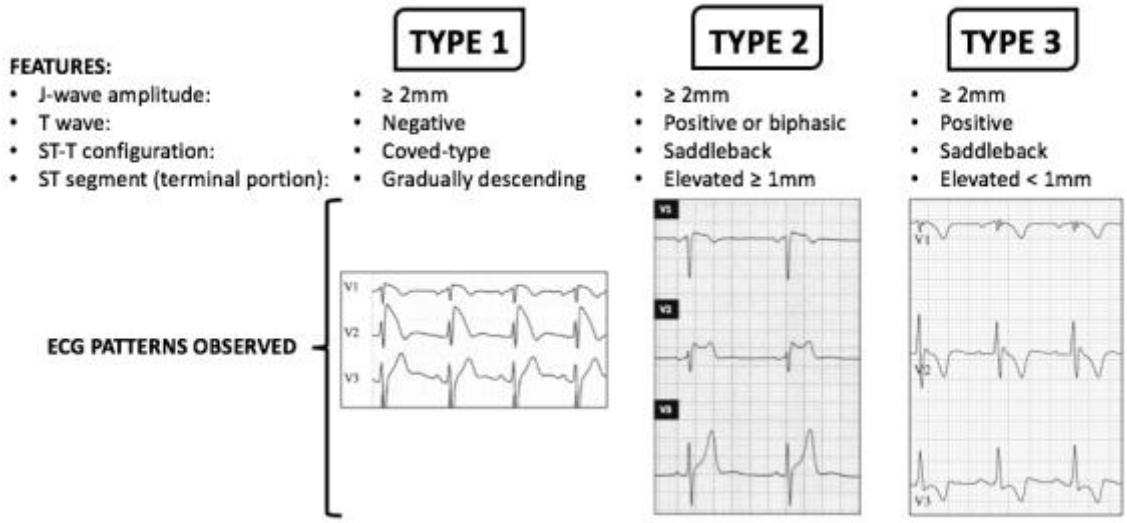

FIGURE 3: Three ECG patterns that can be found in patients with BrS and their main features. *ECG=Electrocardiographic*

Is the diagnostic pattern constant in Brugada patients?

Diagnostic-type 1 Brugada pattern is not always easy to find in Brugada patients. In fact, individuals with confirmed BrS may only display a diagnostic ECG in 20% of their recorded ECGs during their lifetime. Because of these ECG pattern fluctuations, unmasking this pattern is mandatory for the diagnostic (1,5,25,34,35). Fever (36,37) (especially in children) and intravenous

administration of potent sodium channel blockers (1,5,25,38,39) have been described as useful for unmasking concealed (see *FIGURE 5*). Following these findings, it has been proposed to include an ECG during febrile episodes in pediatric patients at study (9,40).
Bradycardia and vagal tone may also contribute to ST segment elevation by decreasing calcium currents, but it has difficult applications in the diagnostic management of these patients.

How can BrS be diagnosed?
In *FIGURE 8,* a diagnostic algorithm has been included to reach the diagnosis of this disease. These ECG patterns have critical importance in the diagnostic of BrS: the type 1 ST elevation (spontaneous or drug induced) is considered diagnostic (5,8,25,31,39,41) when it is found in at least one of the right precordial leads (mainly V1 and V2) without requiring any further evidence of malignant arrhythmias. Clinical features five more consistency to this statement, but they are not necessary for reaching the diagnose:

- Previously documented VF or polymorphic VT, inductility of VT with programmed electrical stimulation, unexplained syncope, febrile seizures and/or an episode of aborted SCD.
- Family history of SCD at younger than 45 years and/or a type 1 ECG pattern in family members.

The diagnosis is also considered positive when a type 2 (saddleback pattern) or a type 3 are observed in at least one right precordial lead under baseline conditions and can be converted to the diagnostic type 1 pattern upon exposure to sodium channel blockers, in addition to one or more of the clinical criteria described above. Drug induced conversion from normal ECG to a type 2 or type 3 pattern is considered inconclusive (5).

How can diagnostic yield be increased?
The ECG protocol has some specificities when it is performed suspecting a BrS. Some studies (5,16,42–45) demonstrated that during the ECG acquisition, the placement of the right precordial leads in a superior position (up to the second intercostal spaces above normal, see *FIGURE 4*) in addition to the standard fourth intercostal space, can increase the sensibility of the ECG detecting the Brugada phenotype in some patients, both in the presence or absence of a drug challenge. False-negative tests can result from not paying attention to these high-placed leads (13).

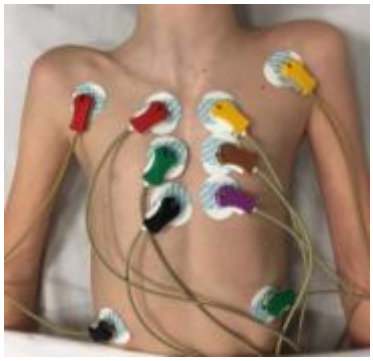

FIGURE 4: Placement of the right precordial leads in the BrS ECG protocol, placing V1 to V6 in second, third and fourth intercostal spaces.

3.7 Sodium channel blockers challenges

As said above, the type 1 diagnostic pattern can be unmasked by administration of some sodium channel blockers (see *FIGURE 5*), such as ajmaline, flecainide, procainamide and pilsicainide (8,38,41,46–53). These drug tests are performed in patients with suspected BrS and non-diagnostic ECG (normal or showing type 2 or 3 patterns) and those with at least one of those characteristics: family history of BrS, family history of unexplained sudden death with abnormal ECG or unexplained syncope, or personal symptoms with suspicious ECG abnormalities (see *FIGURE 8)*. Due to its pro-arrhythmic effects (30,54–58) they are not risk-free diagnostic tests, and some preventive actions should be applied before, during and after their administration.

Comparing all these sodium channel blockers, Probst et al. (59) and Wolpert et al. (60) have concluded that ajmaline and flecainide have the best conduction parameters and low-risk parameters (61). Between these two drugs, several differences have been found (59). In one hand, ajmaline has been shown to be safer and to provide a higher diagnostic yield than the other drugs (positive test seems to be slightly higher). On the other hand, flecainide has the advantage of being able to be administered intravenously or orally (35,62), and in practical terms it is easier to get it from national laboratories.

For these reasons, ajmaline is considered the first option when performing a provocative test in patients with suspected BrS (63,64), but the main problem is its availability. These commercial drug regulations are a strong reason to justify the great interest in finding out more information about the safety and efficiency of flecainide (the second best first-class antiarrhythmic in this indication).

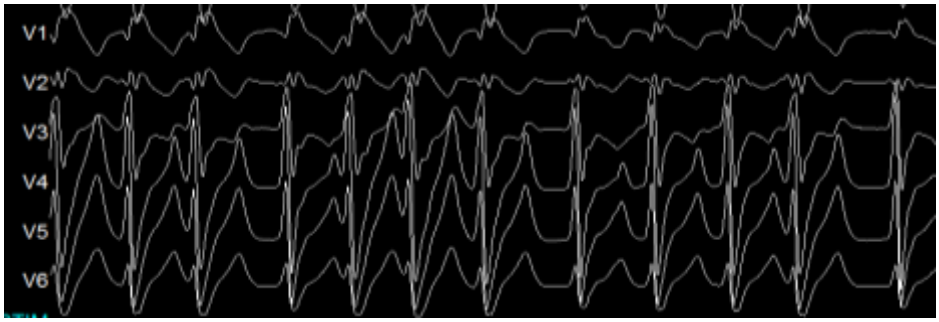

FIGURE 5: Type 1 BrS ECG pattern unmasked by flecainide administration in a provocation test.

3.7.1 Flecainide challenge:

- *FLECAINIDE MECHANISM OF ACTION AND DIAGNOSTIC APPLICATION IN BrS:* Flecainide acetate (*Apocard®)* is a Class IC antiarrhythmic agent (Vaughan-Williams classification, see *ANNEX VII*) which acts as a potent sodium channel blocker. This channel block can facilitate the loss of ventricular epicardial plateau phase by altering the balance of ionic current needed for the action potential. This results in an all or nothing repolarization of the right ventricular action potential and marked abbreviation of the epicardial action potential duration. This loss of the plateau in the epicardium but not in the endocardium creates a voltage gradient that manifests as the typical ST-segment elevation in the right precordial leads of the ECG. For this action mechanism, flecainide can be used as a provocation test in patients with suspected BrS with non-diagnostic ECG. If they have an intrinsic affectation of their sodium channels (caused by this disease), but not enough to affect the basal ECG trace, the flecainide administration (at the dosage explained in the protocol) will increase the blockage of these channels, showing the ST-elevation present in the diagnostic type 1 ECG pattern. This dose (2mg/kg, with a total maximum of 150mg administered) has been proved to be useful in unmasking type 1 ECG pattern in individuals affected with BrS, minimizing the risk of flecainide intoxication and its adverse effects (65–67).
- *FLECAINIDE INDICATIONS:* All indications are therapeutic indications in adult population, so this diagnostic indication as a provocative test in pediatric patients with suspected BrS is an off-label use. This indication is recommended in all meta-analysis (4,5,24,39), consensus reports (8,23,31,38,44), specific studies (35,53,56,60,62,68–71) and has been authorized in this Hospital by the attached protocol in *ANNEX V (CODE: A-COR-PC-0053-01).* Following these citations, sodium channel blockers are considered the best provocative test in patients with suspected BrS: ajmaline as the first option and, if it is not available, flecainide. Nearly a 25% of these challenges may result in a false-negative result, so a repeated test must be

considered during puberty if it was performed during childhood or after puberty if it was performed during this stage of life (4,39,72).

- *FLECAINIDE CONTRAINDICATIONS:* hypersensitivity to flecainide or its excipients (sodic acetate, acetic acid and water), patients with cardiac insufficiency or personal history of myocardial infarction, if cardiogenic shock is present, in patients with chronic atrial fibrillation and/or in patients with hemodynamically significant valvulopathy. The contraindications most related with this study are: patients with confirmed diagnosis of BrS and failure to monitor the patient. The use of flecainide in pediatric population is not contraindicated but should be supervised by an experienced pediatric cardiologist.
- ADVERSE EFFECTS: Adverse effects of this drug (57,67) are explained according to its frequency:
  - Very frequent (≥1/10): transitory dizziness, transitory visual alterations (diplopy). In the personal experience of this Unit, children explain these transitory visual alterations as transient photopsies and they also refer a transient warm sensation in the pelvic zone (not described in the literature).
  - Frequent (≥1/100 but <1/10): pro-arrhythmic effects are the most important and dangerous adverse effects, and they are frequent. Other frequent adverse effects are: dyspnea, fatigue, pyrexia, edema and asthenia, generally seen only in chronic use.
  - Low frequent (≥1/1.000 but <1/100): blood and lymphatic alterations, AV 1:1 conduction in patients with atrial flutter, gastrointestinal alterations, dermatitis and alopecia, generally seen only in chronic use.
  - Rare (≥1/10.000 but <1/1.000): psychiatric alterations, neurologic disturbances, pneumonitis, hepatic enzymes alteration and grave skin affectation, generally seen only in chronic use.
  - Very rare (<1/10.000): immunologic alterations, corneal deposits, generally seen only in chronic use.
  - Unknown frequency: PR and QRS elongations, cardiac AV blocks, hypotension, bradycardia, palpitations, cardiac arrest, pulmonary affectation, hepatic dysfunction.
- *SAFETY:* Administration of intravenous flecainide must be performed in a hospital under cardiologysts supervision and with continuous ECG monitoring. Flecainide must be strictly monitored (using its concentration in patient's plasma) if important hepatic insufficiency or renal insufficiency (creatinine clearance<35ml/min) are present. Accepted and safe plasmatic levels are between 0,2 and 1μg/ml, and before flecainide administration, plasmatic ionic equilibrium must be normal (55,56,67).

In this diagnostic challenge, not exceeding the protocolized dosage is mandatory for safety: the potent sodium channel block could lead to ventricular arrhythmias, the most dangerous adverse effect of this drug (12,46,47,54,57,64,67,68,73). An isoproterenol infusion must be prepared beforehand and ready to administer in case of ventricular arrhythmias: it increases the inward of calcium currents and can revert the VT/VF (24).

- *FLECAINIDE INTERACTIONS:* Flecainide should not be administered concomitantly with other Class I antiarrhythmic drugs and the dose of flecainide should be reduced a 50% if a Class III anthyarrhythmic is also administered. It could be administered concomitantly with Class II and Class IV antiarrhythmics, under strict monitoring. This drug is mainly metabolized by the CYP2D6 (66,67,74) therefore drugs which inhibit this hepatic enzyme (some antidepressants, some neuroleptics, propranolol, ritonavir and some antihistaminic drugs) or stimulate it (phenytoin, phenobarbital or carbamazepine), could rise or decrease, respectively, the plasmatic concentrations of flecainide. The flecainide acetate precipitates in saline solutions (see *FIGURE 6)*, but it is compatible with glucose solutions.

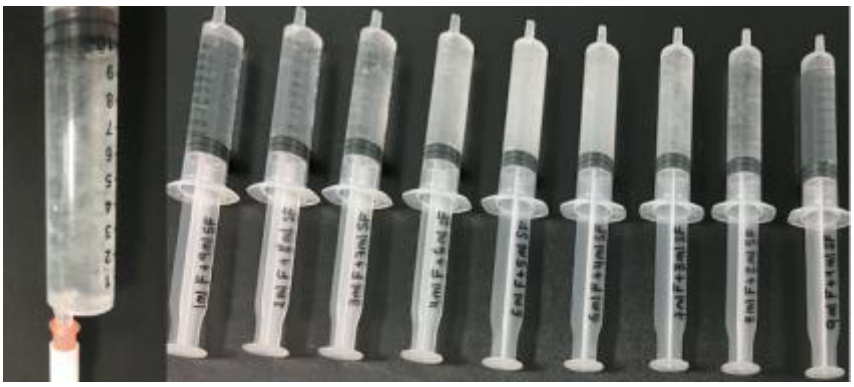

FIGURE 6: Examples of the interaction between flecainide acetate and saline solutions: the flecainide precipitates. On the left, the precipitation reaction itself. On the right, different concentrations of flecainide (F) and saline solutions (SF), showing the precipitation when the concentrations raise.

- *ADMINISTRATION:* The most studied and performed flecainide challenge in patients with suspected BrS uses an intravenous administration (66). Following these references and guides, the protocol used in Hospital Sant Joan de Déu only includes this route of administration. Some studies in countries where intravenous form is not available (mainly in South America) have also described this diagnostic test using oral flecainide, but there is still lack of information about its efficiency and safety. The Latin American Heart Rhythm Society (LAHRS) has validated the oral administration in this

indication, but only in Latin American countries which have access only to oral flecainide.

- *COMMERCIALIZATION:* It can be obtained in Spain for intra-hospital use.
- *TIME*-DEPENDENT RESPONSES: This provocative test performed with flecainide has the peculiarity of time-dependent variability of ECG patterns and intervals. ECG should be recorded in a longer period than in other drug challenges, at least during 120 minutes, to avoid false negative results (74–76). If after 2h the ECG remains normal, the patient can be discharged.

Summarizing and focusing on the provocative test for BrS suspicion, its efficiency is directly related to its ability to induce or accentuate the typical ECG type 1 pattern. Its safety is referred to its administration in absence of the mentioned undesirable pharmacologic effects, including the previous consideration of possible adverse events (especially potential arrhythmias). It also includes being prepared if dangerous situations appear and prevent further damages to get a useful diagnostic tool with the minimum risk.

3.7.2 Other sodium channel blockers: Ajmaline (12,61,63,64,72,73,77,78), flecainide, procainamide (45,79) and pilsicainide (58,80) have proved to be useful sodium channel blockers in inducing or exacerbating the type 1 ECG Brugada pattern in provocative tests. Ajmaline and flecainide have been used in Europe and they are the most studied drugs in these diagnostic provocative tests. Procainamide has been used in the USA and pilsicainide in Japan.

It is imperative to clarify that a negative provocative test does not exclude the diagnostic of BrS, the patient must be followed-up periodically and re-evaluated (74–76,81).

3.8 Genetic factors and tests

This disease has a typical autosomal dominant inheritance pattern of genetic transmission. Nevertheless, it can be sporadic in a significant proportion of patients, consequently an individual can be affected of BrS in absence of family history related with this disease (24,82).

The first mutations associated with BrS were in the SCN5A gene (3,83–85) which encodes for the α-subunit of the NaV1.5 cardiac sodium channel. This genetic alteration produces a decrease in transmembrane sodium current (Ina) because of a quantitative reduction of these channels or by a qualitative dysfunction. Not all diagnosed patients have a positive SCN5A mutation (only 14-25% have positive genetic test for SCN5A mutation), which indicates that the disease is genetically heterogeneous (3,5,25) (see FIGURE 7). Other genes have been also

associated with BrS: the GPDI-L gene (with the mutation A280V, that can indirectly led to sodium channel loss of function), CACNA1c, CACNB2b and CACNA2D1 genes (encoding calcium channels), the KCNJ8 gene (which encodes for a ß-subunit related with the transient outward potassium currents), but the role for these genes remains unclear, despite it seems that all them could explain a BrS phenotype due to ion current imbalance during phase one of the action potential. Other genes, such as SCN10A, MOG1, MYH7 and HCN4 have also been recently related (4,25).

Despite all these genetic findings, studies showed that gene mutations are not determinant in the diagnostic confirmation or in the risk stratification of this disease: only 20-30% of patients with confirmed diagnose of BrS present a positive genetic test (27,83). However, in cases where there is a diagnostic certainty, genetic testing could be offered to do a family cascade screening, giving the opportunity to identify asymptomatic familiars at risk of being affected.

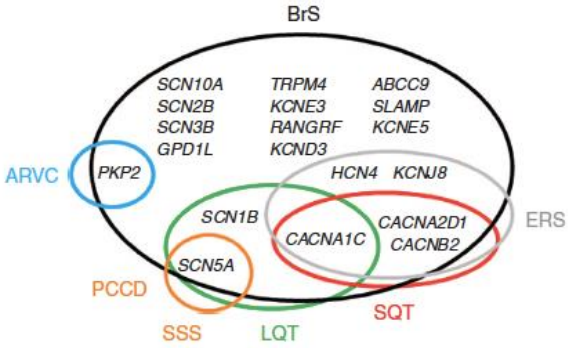

FIGURE 7: Representation of different genes related with BrS and other cardiac diseases, showing their heterogeneity and lack of diagnostic specificity. Reproduced with permission of Sarquella-Brugada from (4). *ARVC=Arrhythmogenic Right Ventricular Cardiomyopathy, ERS=Early Repolarization Syndrome, LQT=Long QT syndrome, PCCD=Progressive Cardiac Conduction Disease, SQT=Short QT syndrome, SSS=Sick Sinus Syndrome.*

3.9 Differential diagnosis and associated diseases

Differential diagnosis of the BrS must be approached with other diseases and ECG abnormalities that can lead to or exacerbate a ST-segment elevation in the right precordial leads (*see FIGURE 8)*. All entities (pathologic or physiologic) that can simulate a Brugada pattern in the ECG, are called Brugada phenocopies, and must be considered during the diagnostic process. At least these clinical entities should be ruled out in the study of patients with suspected BrS: atypical right bundle branch block, early repolarization, left ventricular hypertrophy, acute myocardial infarction, acute pericarditis, hemopericardium, dissecting aortic aneurysm, pulmonary embolism, Duchenne muscular dystrophy, mechanical

compression of the right ventricle or hypothermia, among others (5,24,39,86,87). Ionic imbalances, drugs abuse (71), pectus excavatum, athletes and other confusion factors should be considered and ruled out.

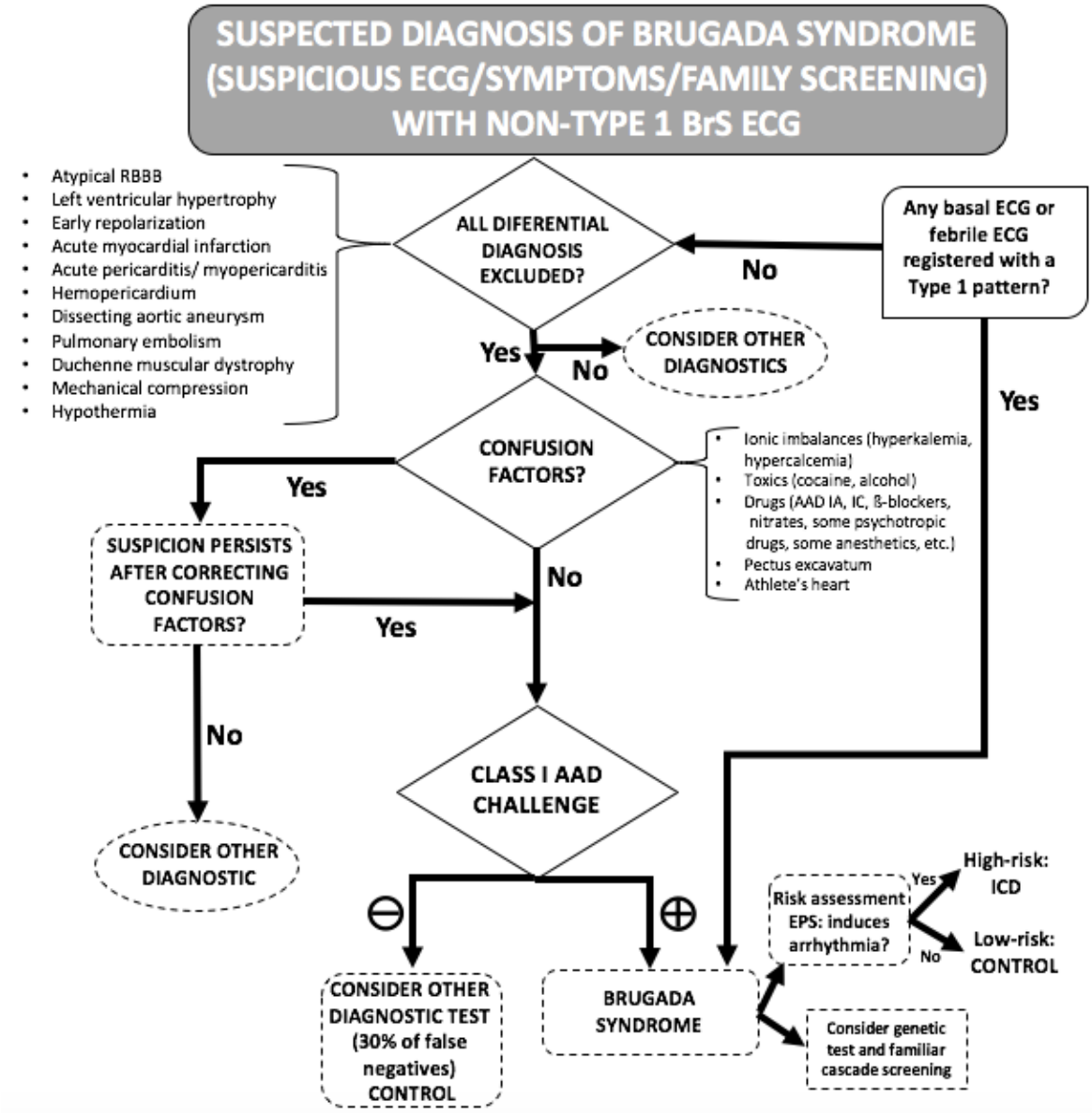

FIGURE 8: Diagnostic algorithm for BrS. Adapted with permission of Brugada (39). A positive result in the Class I AAD challenge requires a type 1 BrS pattern in the ECG. *AAD=Antiarrhythmic Drugs, BrS=Brugada Syndrome, ECG=Electrocardiogram, EPS=Electrophysiology Study, ICD=Implantable Cardioverter Defibrillator, RBBB=Right Bundle Branch Block, SCD=Sudden Cardiac Death, ⊕=positive result, ⊖=negative result.*

The genetic heterogeneity of inherited conduction disorders often show overlapping syndromes. Sarquella-Brugada et al. (4) and Maury et al. (87) found a significant proportion of diagnoses BrS patients in the midst of other diseases: early repolarization syndrome, first degree atrio-ventricular block, sick sinus

syndrome, progressive cardiac conduction disease or Lev-Lenègre syndrome, long QT syndrome type III and atrial fibrillation. They concluded that this association could be explained by the commune affectation of sodium channels in all these disorders, and it reaffirms the importance of a complete physical exploration and asking for other cardiac or neurologic antecedents to consider all these possibly associated pathologies.

3.10 Risk assessment and prevention in children with suspected BrS

Accurate diagnostic evaluation of children at risk is one of the main challenges. Management of a child possibly affected of BrS *(*see *FIGURE 8)* should be divided according to his/her symptomatology:

- *Symptomatic child:* It is not the most frequent situation (usually a child is not the first symptomatic member of a family) but it is known that the presence of symptoms before diagnosis in combination with ECG abnormalities at baseline constitutes a very important risk predictor (85). Clinical or electrical markers for symptomatic BrS (as mentioned before) can be unexplained syncope, an aborted sudden cardiac death, arrhythmias or conduction abnormalities (10). If it is the case of a rhythm abnormality or clinical event, the first diagnostic step consists of an ECG at baseline (of the patient and first-degree family members). It should include a 12-lead ECG and a specific Brugada ECG protocol. It is crucial to obtain new tracings if febrile episodes occur (36,37) and guidelines strongly recommend immediate treatment of fever with local cooling and antipyretics (88). Provocative tests with ajmaline or flecainide are the standard diagnostic methods to unmask the BrS (73). A consensus on the age to start testing children and the safety of the different drugs is not yet well stablished.

  If there is family history related of BrS, genetic tests should be performed. Genotype-positive individuals should be closely followed-up to identify possible clinical manifestations (4,9,13,39).
- *Asymptomatic child:* It is the most frequent condition seen in pediatric arrhythmias units: an asymptomatic pediatric relative with family members at study for or diagnosed of BrS, and it has met with serious debate (4,5,28,89). In this case, the screening should include an annual 12-lead ECG. At least one ECG during a febrile episode should be registered during childhood (36,37). Screening of the asymptomatic offspring in family with known BrS is still controversial. It should include a personal and family history and a physical examination and, in selected cases with a malignant family history, a provocative test could be considered starting at the age of five years (13,39).

When a patient is diagnosed of BrS, genetic testing (including detection of mutations in the SCN5A gene) should be performed in the index case (85), and screening of at-risk family members is recommended after identification of an affected relative. All patients should be followed-up, including those with negative tests. Electrophysiology Studies (EPS) should be performed in every diagnosed patient to stratify his/her risk (21,89), measuring baseline intervals, sinus node recovery time, corrected sinus node recovery time and sinoatrial conduction time (28). If ventricular arrhythmias are induced during the EPS, an ICD is recommended (82).
Moreover, all BrS patients (with confirmed diagnose or at study) should be advised to avoid all drugs that may induce a type 1 ECG and/or trigger VT/VF. The complete list can be consulted at: www.brugadadrugs.org (90).

3.1.1 Therapeutic options

As a treatment, currently the Implantable Cardioverter Defibrillator (ICD) is the only proven effective therapeutic strategy for the prevention of SCD in BrS patients (4,5,8,9,16) and its implantation is a Class 1A indication in patients with BrS and a history of either ventricular arrhythmias or aborted SCD. Meanwhile, ICD implantation for an asymptomatic patient with a family history of SCD is a Class 2B indication. Another therapeutic option is pharmacological treatment to rebalance ionic currents using isoprotenerol (it is only useful when an arrhythmic event appears, during the acute phase) or quinidine (this drug can be useful as a chronic treatment because it acts stabilizing the transient outward ionic currents [Ito] and converting them from polymorphic to monomorphic, improving clinical tolerance of the arrhythmia) being a Class 2A indication. Quinidine can be used as a bridge therapy to ICD, as an alternative to it or in combination with the ICD, depending on the patient's individual risk (39). Recently, epicardial catheter ablation over the RVOT has been suggested in patients with recurring episodes, but this option is not well-defined (41). Levels of evidence in therapeutic studies are attached in *ANNEX VI*.

4. HYPOTHESES AND OBJECTIVES

Due to the cross-sectional descriptive nature of this study, a main hypothesis has not been proposed because the aim of this project is to describe data on the diagnostic flecainide provocation test in children. Despite of this fact, we proposed these secondary hypotheses taking advantage of previous literature about similar studies of adults affected with BrS:

4.1 Secondary hypotheses:

- Hypothesis number one: There will be more pediatric patients with suspected BrS attended in this pediatric Unit for family history of BrS than for symptomatic reasons or ECG abnormalities.
- Hypothesis number two: Pediatric patients whose main reason for suspecting BrS is a related symptom (unexplained syncope, febrile seizures, aborted SCD or documented VT/VF) will show more positive flecainide challenges than asymptomatic patients.
- Hypothesis number three: Asymptomatic pediatric patients with abnormal basal or febrile ECGs will have more positive flecainide challenges than asymptomatic patients with normal ECG.

4.2 Objectives:

- To describe demographical data and clinical characteristics of anonymized pediatric patients with suspected BrS attended in this Unit.
- To describe the main reason for suspecting BrS in this population at study.
- To describe the results of flecainide challenges and other complementary tests performed with diagnostic purposes in these pediatric patients.
- To determine the possible relation with demographics, clinical and diagnostic parameters with the result of flecainide challenges in the studied population.
- To describe the presence or absence of adverse events during the performance of flecainide challenge.
- To determine the possible relation with asymptomatic patients and their different clinical and diagnostic parameters with the result of their flecainide challenges.

5. METHODS

5.1 Study design and justification

To describe the collected data, a cross-sectional descriptive study of registered cases has been designed. The mentioned registry has data from the 180 pediatric patients on whom a flecainide challenge has been performed and, considering the lack of information in this population of BrS, a description of these cases can be extremely useful to improve knowledge about their diagnostic management in this specialized Unit.

5.1.1 Previous data acquisition in an anonymized registry

It is needed to describe the process for the database register, despite it was done before this study was designed: data was previously collected and registered, as represented in *FIGURE 9*. A completely anonymized (and numerically codified)

registry of the flecainide diagnostic tests was completed between January of 2016 and September of 2017 in Hospital Sant Joan de Déu, Barcelona (at the specialized Unit of Pediatric Arrhythmias of the Cardiology Department, designed as a national reference center in treatment of pediatric arrhythmias by CSUR and European coordinators of the European Reference Network in Rare Cardiac Diseases - subnetwork pediatrics). Data was included by each patient's Doctor in this anonymized registry.

All pediatric patients with suspected BrS attended at the Unit of Arrhythmias of this Hospital were asked to be included in this anonymized registry, with the correspondent informed consents (*ANNEXES I and II)*. These patients were all included in the "Child Life" program of Hospital Sant Joan de Déu (pioneer in this issue) before invasive diagnostic procedures: nurses and psychologists explained to every patient the medical procedures that will be performed. The Child Life program has proven its usefulness in minimizing psychologic damages and fears and contributing to their emotional stability during these tests (91,92). General diagnostic tests were performed first (basal ECG and echocardiography) for excluding any other cardiac disease. Then, if the patient's parents gave their consent (*ANNEX III)*, a flecainide challenge was performed, following its approved protocol (*ANNEX V)*. To register the Unit's activity data with those patients, identification data was not included and it was re-anonymized with a randomized numeric code obtained with an informatics program generator of aleatory numeric codes.

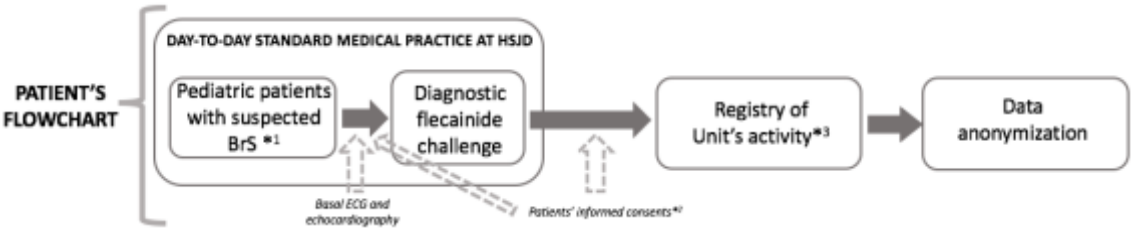

FIGURE 9: A flowchart describing data acquisition process for the registry. **1Suspected BrS criteria is defined in Inclusion criteria, section 5.2. *2Two different informed consents were applied: one for the flecainide challenge (as an invasive procedure, ANNEX III) an another one for collecting data in the registry (ANNEXES I and II). *3The registry included the variables described in section 5.5.5. HSJD=Hospital Sant Joan de Déu, BrS=Brugada Syndrome.*

5.1.2 Study design and chronogram

The chronogram of this study has been represented in *FIGURE 10.* This study begins with the need for describing and publishing the data that has been collected during years in an anonymized registry of the Unit's activity with pediatric patients with suspected BrS. For that reason, a cross-sectional

descriptive study has been proposed. To have access to the registry, a permission to the Ethical Committee of Sant Joan de Déu Research Foundation has been requested. When authorization has been approved, this anonymized data has been analyzed and exposed in this study.

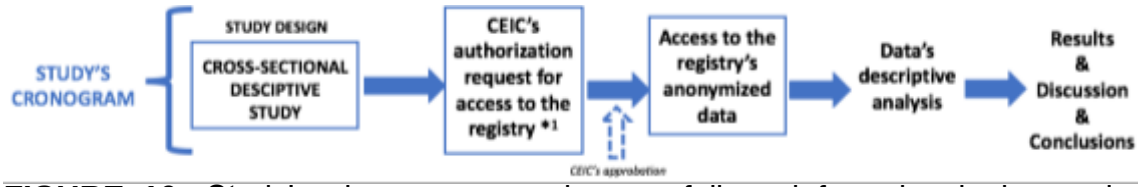

FIGURE 10: Study's chronogram and steps followed from its design to its conclusions. *[1]*This authorization has been included in ANNEX IV. CEIC=Comitè Ètic d'Investigació Clínica.*

5.2 Inclusion criteria

This study includes all data from the mentioned registry, but not all patients were included in the registry. It has anonymized information from patients who meet both A and B inclusion criteria:

A. Pediatric patients (individuals at age less than 18 years old) on whom a flecainide challenge to diagnose BrS has been performed as part of their standard management.
B. Patients suspected to have BrS with at least one of these items:
    - Type 2 or type 3 Brugada patterns in the ECG.
    - Family history of BrS.
    - Patients for whom sodium channel blockers challenges were considered to rule out BrS in the differential diagnosis of their symptomatology.
    - Personal history of aborted SCD or documented VT and/or VF.
    - Unexplained syncope or documented febrile seizures.

5.3 Exclusion criteria

The patients with suspected BrS and with a flecainide test performed which were excluded from the registry were:

A. Patients with spontaneous type 1 Brugada ECG pattern.
B. Patients with contraindications to flecainide (see *section 3.7.1*).
C. Failure to obtain informed consent for participation in this registry.

5.4 Population characteristics

One hundred and eighty patients younger than 18 years old completed a flecainide challenge between 2016 and 2017 in the Pediatric Arrhythmia Unit of Hospital Sant Joan de Déu. Patients were included in a consecutive way (all patients that arrived at this Unit and accomplished the inclusion and exclusion

criteria were asked to participate in this registry). All 180 invited patients agreed to be included in the registry.

Baseline characteristics of the patients are presented in *section 7.1 (demographical results)* and in *TABLE 1.* Their weight and geographical origin has been included to have a complete description of this population, but they have not been analyzed. Weight was registered because it was important during the flecainide challenge to calculate the drug dose to be infused.

5.5 Procedures

To carry out this study, we accessed to data collected in an Excel dataset for Mac (version 15.32, 2017). In this section, some aspects about the previous data acquisition are going to be described: this information was from patients who attended the Unit of Pediatric Arrhythmias of Hospital Sant Joan de Déu, with suspected BrS (see *Figure 2)*. Each patient was initially evaluated with a physical examination, a personal and family medical history, a baseline ECG and an echocardiography. Cardiac and neurologic personal antecedents were registered, because as said in *section 3.9,* there could be some associated diseases. Asking about family history related with BrS, all affected family members up to three generations were registered but in this study only the closest relatives were considered. The presence or absence of underlying structural cardiac abnormalities was checked in all patients using these initial basal ECG and echocardiography, despite a structurally abnormal heart is not an exclusion criteria. If there was still suspicion but not diagnostic confirmation of BrS (and if there were not contraindications), a provocative test with flecainide was performed. A genetic test is considered to all pediatric index cases and if there is a relative with positive genetic test. All acute adverse effects during these diagnostic procedures or during the first two hours after their performance were registered and, in case of showing flecainide adverse effects, were sent in their correspondent yellow card. Most severe adverse effects (such as an arrhythmia) were sent urgently.

5.5.1 ECG protocol and analysis

All patients were connected to a 12-lead ECG machine and ECG was continuously recorded at a speed of 25 mm/s. As explained in *section 3.6,* precordial electrode positition was set V1-V2 in right and left second intercostal space, V3-V4 right and left third intercostal space and V5-V6 right and left fourth intercostal space (see *FIGURE 4*). ECG were recorded and analyzed at baseline and at 1-minute intervals throughout the flecainide test.

All ECGs were analyzed according to ECG diagnostic criteria of BrS by at least three expert pediatric cardiologists of the Unit of Pediatric Arrhythmias, including Georgia Sarquella Brugada and Josep Brugada, experts in this disease.

5.5.2 Flecainide challenge protocol

Before the flecainide challenge, all the procedure was explained to the patient during in the "Child Life" program, explained in *section 5.1.1.*

Previously, general protective equipment was a fundamental requisite before the procedure starts: nonsterile gloves, adequate medical dressing, an adapted room, an appropriate size catheter of 14-25G IV, a non-latex tourniquet, an alcohol swab, antiseptic solution (2% chlorhexidine in 70% isopropyl alcohol), sterile gauzes, paper tape, a sharps container and a topic anesthetic (Lambdalina®) to minimize local pain during the peripheral venous puncture.

Maximum effort was made to prepare a safe environment for this test: life-support equipment and experienced pediatric professionals, two external defibrillators available in the room (*Zoll M Series Defibrillators,* set to an appropriate charge based on the patient's weight, with a dose of two J/kg). A peripheral intravenous access was placed, and flecainide was administered intravenously at a dosage of two mg/kg body weight over 10 minutes, diluted in distilled water with maximum dosage at 150mg. It was not administered orally in any registered case. Flecainide has a prolonged effect and required post-test cardiac monitoring of 30 minutes. The approved protocol for the flecainide test for BrS diagnosis in the Pediatric Arrhythmias Unit of the Hospital Sant Joan de Déu *(code A-COR-PC-0053-01,* see *Annex V)* had the following steps:

1. General previous procedures: to know patient's weight, monitor his/her cardiac rhythm, hemoglobin saturation and arterial pressure.
2. To connect the 12-lead electrocardiograph and register in standard position of electrodes described in *section 5.5.1.*
3. To prepare:
    - FLECAINIDE (*Apocard®* 150mg/15ml, injectable) at a dosage of 2mg/kg of patient's weight (at a maximum dosage of 150mg). It is needed to dilute the flecainide with sterile water to get 20ml (it precipitates with physiologic serum).
    - ISOPROTENEROL (*Aleudrina®* 0.2mg/ml): to prepare 0.4mg of isoprotenerol in 100ml of physiologic serum or with 5% glucose serum. Administer as an antidote in case of severe complications with flecainide.

To administer the flecainide preparation in 10 doses (2ml dose/minute) and to register the ECG in standard position every minute. After 10 minutes, register the ECG placing electrodes in specific positions described above. Experienced

pediatric surgical backup in case of prolonged ventricular arrhythmias that could have required extracorporeal support is mandatory. A procedure's registry (including the timing, drug and dosages administered) was completed.
The flecainide test was considered positive if the ECG registers a type 1 Brugada pattern in one right precordial lead. The flecainide test was finished if the ECG registers a type 1 Brugada pattern or if there is an elevation of the ST-segment ≥5mm in a type 2 Brugada ECG pattern.

5.5.3 Genetic analysis

- Genetic tests were performed (before the flecainide challenge) in pediatric patients with first degree family members diagnosed of BrS with positive genetic mutations.
- If genetic test was performed with negative results in the affected relative, it was not performed in the pediatric patient with unconfirmed diagnosis.
- If the pediatric patient was the first BrS confirmed diagnosis in the family, a genetic test was performed and, if positive, a familiar cascade screening with genetic tests in first grade relatives was proposed.
- Following the Law for ethic procedures in genetic issues, the results were first revealed exclusively to the individual, and then, always with permission, other familiars were involved if there was a medical reason, such as family cascade screening in positive genetic results.

Blood or saliva samples were obtained to extract DNA for genetic analysis. If the patient had a peripheral blood line (for other procedure) when the genetic test was ordered, a blood sample was taken for genetics. If not, a saliva sample was taken to avoid the invasive procedure of blood extraction. Genes studied were all related with BrS (see *section 3.8).* If a saliva sample was needed, a DNA Genotek Oragene 06-500 was used. If it was a blood sample, the described equipment for extracting venous blood from a peripheral vein was used and an EDTA tube as a container.

5.5.4 Other tests performed

- *Basal ECG:* was performed in all patients before the provocative test, using a *CardioTech™ GT-400 ECG Machine.*
- *Fever ECG:* was only performed if a fever episode was presented and it was registered using a *CardioTech™ GT-400 ECG Machine*. If not, it was requested to the patient if it has ever been registered during a febrile episode in the past.
- *Echocardiography:* was performed in all patients before the provocative test, to exclude any structural or functional cardiac disorder. A *Mindray DC-6 Expert Ultrasound System* with 5S probe was used.

- *EPS: were* performed in all patients with a positive result in the flecainide challenge, to assess their risk of developing arrhythmias *(*see *FIGURE 8*). These procedures were performed with *Philips Allura Xper FD20/10 biplane* mixed with cardiovascular X-ray guidance system, and X-ray protection was mandatory in all personal present in the EPS room during the procedure.

5.5.5 Study variables

The different variables included in the registry were obtained as explained in procedures, *section 5.5*.

- Dependent variable: **The result of the flecainide challenge** (positive or negative): it is a categorical dichotomous variable.
- Independent variables:
  - ✓ **Age at study** in years old, as a quantitative continuous variable.
  - ✓ **Sex**: male or female, as a categorical dichotomous variable.
  - ✓ **Geographical origin:** country of origin, as a categorical nominal variable.
  - ✓ **Presence of cardiac and/or neurologic personal antecedents**: It has been registered as a categorical dichotomous variable (yes or not), but in case of having one of those antecedents, the name of the disease has been registered as a categorical nominal variable. The justification of considering these antecedent remains in *section 3.9*, where possibly associated diseases are mentioned.
  - ✓ **Having family history related with BrS:** it was first registered as a categorical dichotomous variable (yes or no), and if the answer was positive, then the affected relative/s was/were registered as a categorical ordinal variable stratified according its familiar relationship (first, second or third grade). In first grade familiars, its personal risk related with the BrS has been asked and registered as a categorical dichotomous variable (high risk or low risk). The high-risk condition is defined as having antecedent of an aborted sudden death or an EPS confirming the inductility of VT/VF.
  - ✓ **Being symptomatic or asymptomatic:** it has been registered as a categorical dichotomous variable (symptomatic or asymptomatic). The concrete symptom was registered as a categorical nominal variable.
  - ✓ **The main reason for suspecting BrS**: have been classified in three groups, being registered as a categorical nominal variable:
    - *Only family history:* if the main reason is a familiar screening (family history related with BrS, with or without genetic tests performed) or a personal genetic mutation related with BrS founded in other circumstances.
    - *Abnormal ECG:* when a suspicious basal ECG or a suspicious febrile ECG exist.

- *Clinical suspicion:* when suspicious symptoms of BrS are present (syncope, febrile seizures, aborted sudden death, etc.).

✓ **Having a basal ECG, a febrile ECG**, **a genetic test** and/or an **EPS performed** and their results: these variables were first registered as categorical dichotomous variables (yes or no), and if it was positive, then the abnormality was registered as a categorical nominal variable.

5.5.6 Statistical analysis

To describe these data, a univariate analysis was applied: dichotomous variables were represented in absolute and relative frequencies and the only quantitative continuous variable (age) was represented as mean and its standard deviation. To compare all these independent variables with the result of the flecainide challenge (dependent categorical dichotomous variable), a bivariate analysis was applied. First, their normality was calculated with the Kolmogorov test. As these categorical variables did not follow a normal distribution, a Chi-square of Pearson test was used to compare all these independent variables with the dependent variable (also categorical). To analyze the relationship between age (independent quantitative continuous variable) with the mentioned dependent variable, an unpaired *t* test was applied. A p-value <0.05 was considered statistically significant. To perform this statistical analysis, the IBM SPSS software package (version 10; SPSS Inc., Chicago, IL, USA) was used. The sample size was not calculated because it is a descriptive study.

6. ETHICAL CONSIDERATIONS

- Data of BrS patients (diagnosed or under study) were included in a totally anonymized and accepted registry during two years by their Doctors as a day-to-day activity registry. This study uses this previously obtained data, but it does not apply the diagnostic tests, it is a descriptive study of previously registered data (see *FIGURE 9* and *FIGURE 10*). It did not suppose any modification of standard procedures of this disease. The author did not have access to any confidential information of the patients, as they were registered anonymously under non-identifying numeric codes, following the Organic Law 15/1999 of 13 of December about Protecting Personal Data.
- This investigation has not any commercial bias nor interest.
- To have access to these data obtained from anonymized patients, a consent of the Ethical Committee of Fundació Sant Joan de Déu was requested and accepted (see *ANNEX IV*). The Law for observational studies using post-authorization drugs (Order SAS/3470/2009) was considered.
- For the registry, all patients gave informed consent to clinical investigation to use their data under anonymized codes (see *ANNEX I* and *ANNEX II)*. Those

informed consents were in Catalan and in Spanish, because all patients were from Spain. They also signed an informed consent for the flecainide challenge performance, for being an invasive procedure (see *ANNEX III).* All aspects and norms of the Declaration of Helsinki and the Law 14/2007 for invasive procedures were strictly applied. In legally under-age patients (in medical terms, below 16 years old), the legal tutors signed the informed consent. The pediatric patient was also properly informed and his/her agreement was considered. From age seven to 16, patient's agreement was fundamental, because it was considered that they could develop reasoned decisions.

- The use of flecainide for a diagnostic test in pediatric patients does not appear in its indications, so it is considered as for off-label use. For that reason, a request of use was presented in 2013 and accepted by the Hospital's Direction and for the Pharmacy Commission. It explains its protocol of use, which is worldwide accepted and described in many studies and guides of BrS patients' management (see section 3.7). The approved protocol is attached in *ANNEX V.* The insurance policy for covering possible adverse events during this procedure is the standard for this Hospital, as this study does not suppose any modification of day-to-day accepted practices.
- If a genetic test was suggested, all genetic counselling, sample extraction (blood or saliva) and exposition of results to the individuals were applied following the Law for investigation on biologic samples (Law 14/2007 and the Royal Decree 1716/2011). A situation where a child is diagnosed of a rare disease and doctors need to communicate it to the family and to explain them that they should be included in a screening process is a big medical challenge. In this context, communication skills must be extremely careful and must follow these legal and ethical premises.

7. RESULTS

7.1 Demographical results (see *TABLE 1)*

- One hundred and eighty patients younger than 18 years old (mean age 10.3 ± 4.7 years of standard deviation) were included. The mean male patient's age and the standard deviation were 10.1 ± 4.6 years old and in females it was 10.6 ± 4.8 years old.
- Seventy-six were females (42%) and 104 were males (58%).
- All patients registered were Spanish. Most patients were from Catalonia (89% of the total), but 13 boys (12% of all male patients) and six girls (8% of all female patients) were from other communities: two of them came from Valladolid, one from Balearic Islands and 16 from Aragon.
- Their mean weight was 42.1kg with a standard deviation of 20.4kg.

TABLE 1: Demographical characteristics of included patients.

Sex	Number of patients N (%)	Mean age yrs±SD	Mean weight Kg±SD	Catalan origin N (%)
Male	104 (58)	10.1±4.6	43.7±21.1	91 (88)
Female	76 (42)	10.6±4.8	30.6±21.2	70 (92)
TOTALS	**180 (100)**	**10.3±4.7**	**42.1±20.4**	**161 (89)**

SD=Standard Deviation.

7.2 Results concerning the main reason for suspecting BrS

Main reasons for suspecting BrS in all those patients have been classified in these three groups, as represented in *FIGURE 12*:

- **Only family history:** Seventy-one patients were at study only due to family history related with BrS (39%). Five of those 71 patients (7%) were finally diagnosed of BrS.
- **Abnormal ECG:** Forty-one patients were at study for this reason (23%), 29 due to an abnormal basal ECG with a type 2 or a type 3 patterns and 12 with an abnormal febrile ECG. In 23 cases (56%) the BrS diagnose was reached.
- **Symptoms:** it has been the main reason in 68 patients (38%), and 14 of these patients were finally diagnosed of BrS (21% of symptomatic patients). It includes patients consulting for unexplained syncope (42), for febrile seizures (21 cases) and for an episode of aborted SCD (5 patients).

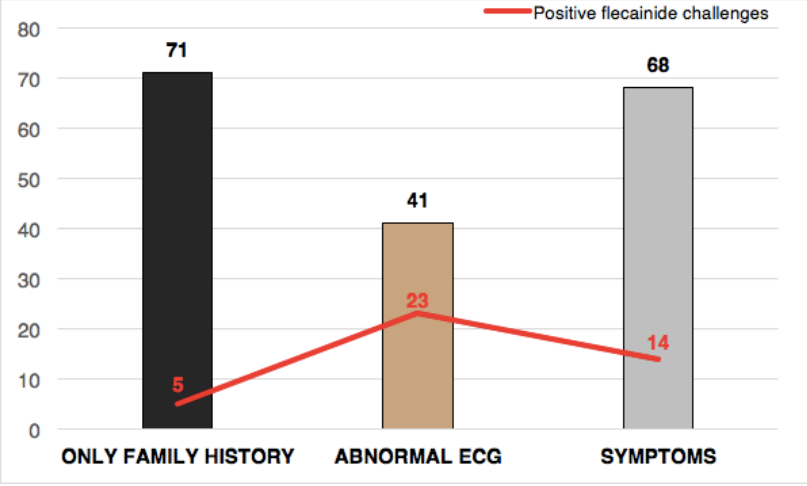

FIGURE 12: Descriptive graphic representing main reasons for suspecting BrS in all included patients and the patients finally diagnosed of BrS in each group. The "only family history" group includes asymptomatic patients with family history and without alterations in the ECG; the "ECG abnormalities" group include patients at study due to abnormalities in basal and febrile ECGs; the "symptomatic group" includes patients who presented unexplained syncope, febrile seizures or an episode of aborted sudden cardiac death. *BrS=Brugada Syndrome, ECG=Electrocardiographic.*

7.3 Analysis of demographics and clinical parameters

7.3.1 Demographical parameters-related results

The relation between gender, age and positive flecainide challenges is represented in *FIGURE 11*. Pediatric patients of both genders were studied in all age ranges from newborns to 17 years old.

- **MALES:** In males, the age ranges with more patients were from nine years old to 10 years old (10 patients), from 11 years old to 15 years old (seven, 11, eight and 11 patients in each year of this interval, respectively) and eight patients of 17 years old. There were positive flecainide challenges in every group except groups of less than one year old, 14 years old and 16 years old, in which all studied boys had a negative result. The groups with more positive tests were 12 years old (five positives) and seven years old (three positive tests), groups of two, five, nine, 10 and 13 years old with three positive tests each and one positive test in the remaining groups.
- **FEMALES:** The highest number of studied females had 15 years old (11 patients), 14 years old (nine) and nine years old (seven). There were positive tests in different age ranges: one positive flecainide challenge in each of these groups: five, six, eight and 11 years old; and two positive tests in females of two, four, 10, 14, 15 and 16 years old).

These demographical independent variables were also analyzed independently with the dependent variable in *TABLE 3:*

- Age differences were analyzed between patients with positive flecainide challenges and those with a negative result: nine years old as mean and a standard deviation of 4.6 years and a mean age of 11.7 years old with a standard deviation of 4.3 (respectively), with a p-value <0.001. Differences between patients younger than 15 years old and older than 15 years old were analyzed: in the younger group, there were 36 positive flecainide challenges (24 males and 12 females) and 106 negatives (63 males and 43 females); in the older group, there were six positives (two males and four females) and 32 negatives (15 males and 17 females). The statistical analysis of differences between them and the result of their flecainide challenge showed a p-value=0.216.
- The 38% of all positive tests were males (16) and the 62% were females (26).

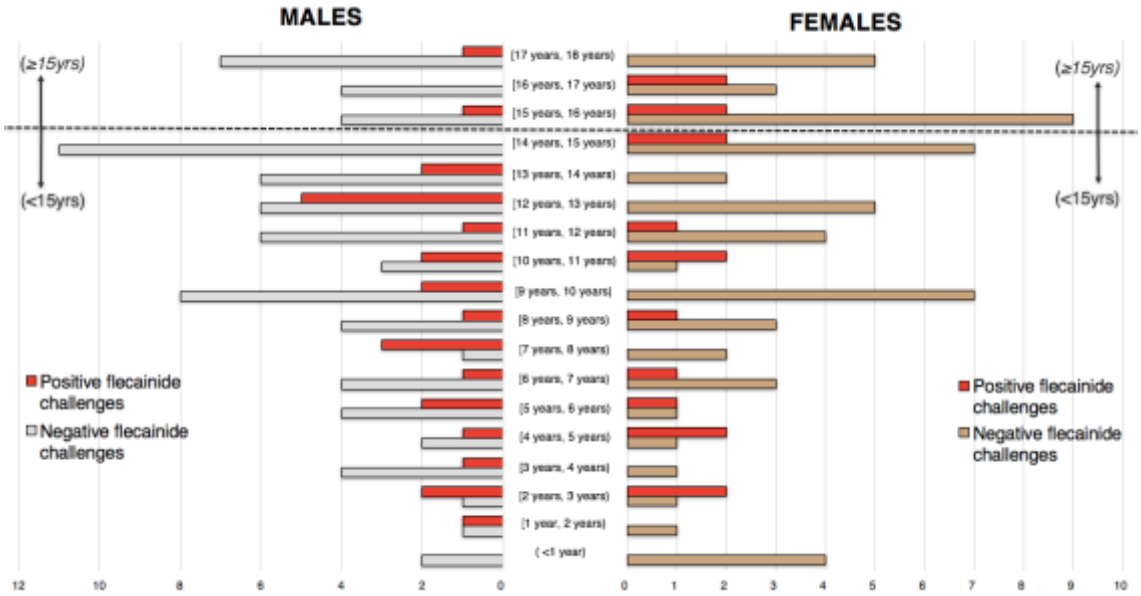

FIGURE 11: Pyramid of study's population classified according to their age and sex and the result of their flecainide challenge (positive or negative). The dashed line separates these groups in younger than 15 years old (below) and older than 15 years old (above), to analyze possible differences between them.

7.3.2 Diagnostic tests applied and their results *(see TABLE 2 and TABLE 3)*

- A basal ECG was performed to all 180 patients before the flecainide challenge. One hundred nineteen of these were completely normal, in sinus rhythm without any abnormal ECG wave or interval abnormalities. Sixty-one showed an abnormal basal ECG: in 29 cases a non-diagnostic type 2 or 3 ECG patterns were found (23 of those had a positive flecainide test, obtaining a p-value<0.001), 23 individuals presented a Right Bundle Branch Block pattern (8 had a positive challenge, with a p-value=0.165), in two basal ECG a short PR alteration was found (with one positive test and a p-value=0.370), four showed a QT alteration (two long QT and two T wave morphology alterations, one of those with a positive flecainide challenge, p-value=0.936) and three atrio-ventricular blocks were detected (two positives and one negative result, with a p-value=0.074).
- An echocardiography was performed to all 180 patients before the flecainide challenge. Any other structural or functional cardiac diseases were found in these patients.
- A total of 14 patients had a previous febrile ECG or presented a fever episode during the interval of diagnostic study and it could be registered. In two cases the febrile ECG was normal and 12 of these patients showed a non-type 1 ECG abnormalities. Flecainide challenges were performed in all these patients, with 10 positive results and four negatives, showing a p-value<0.001.

- A flecainide challenge was performed to all 180 patients. Of these 180, 138 patients had a negative provocative test and 42 had a positive test inducting a type 1 ECG BrS pattern. Positive tests represent the 77% of all patients.
- A genetic test looking for mutations related with BrS was requested in 30 patients: 18 showed a positive SCN5A mutation (with 14 positive flecainide challenges, p-value <0.05), five expressed these other mutations: two MOG1, one MYH7, one KCNJ8 and one HCN4 (with two positive flecainide challenges, p-value=0.372) and seven genetic tests were negative.
- EPS were indicated for risk assessment and performed in 42 patients with a positive flecainide challenge: seven of those presented an episode of inducible VT/VF, the rest had a normal result.

TABLE 2: Description of all tests performed and their results.

TESTS PERFORMED	RESULTS			TOTAL
	Normal/ negative	Abnormal/positive		
Basal ECG	119	*Non-type 1 ECG pattern*	29	**180**
		RBBB	23	
		AV block	3	
		Short PR alteration	2	
		QT alteration	4	
Echocardiography	180	0		**180**
Febrile ECG	2	12		**14**
Flecainide challenge	138	42		**180**
Genetic test	7	*SCN5A positive*	18	**30**
		Other mutations	5	
EPS	35	7		**42**

In genetic tests, other positive mutations include these genes: MOG1, MYH7, KCNJ8 and HCN4 without SCN5A mutation. *AV=Atrio-Ventricular, ECG=Electrocardiogram, EPS=Electrophysiology Study, RBBB=Right Bundle Branch Block.*

7.3.3 Clinical parameters-related results *(see TABLE 3).*

- Of 180 studied patients, 112 were asymptomatic and 28 of them presented a positive flecainide challenge (67% of all positive results). Of all those asymptomatic patients, 84 had a negative result. The statistical comparison of asymptomatic and symptomatic with their test results had a p-value=0.497.
- The remaining 68 patients were at study due to their symptomatology related with BrS. Forty-two had an unexplained syncope (nine of them presented a positive flecainide challenge, with a p-value of 0.739), 21 had at least one episode of febrile seizures (four of those had a positive result, with a p-value=0.621) and five had an aborted sudden cardiac death, with one positive test (showing a p-value of 0.858).
- Focusing in their personal antecedents, three patients had a previous diagnose of a third grade atrio-ventricular block, and two of those had a

positive result (p-value=0.074). Eight patients had personal history of a neuropathy (one case of Neurofibromatosis type 1, three mental retardations and four cases of epilepsy) and three of those presented a positive result (p-value=0.332).

- The 81% of patients with family history (being or not their reason of suspicion) obtained a positive flecainide challenge (34), 27 of those having a first-grade relative with high-risk of having the BrS, five with a first-grade relative with low-risk and three with a second and/or third relative related with BrS. Comparison between family history and flecainide challenges showed a p-value <0.001 for first-grade relatives and 0.124 for second and/or third grade.

TABLE 3: Comparison of demographics, clinical and diagnostic parameters with the result of the flecainide challenge.

	PARAMETERS		Flecainide challenge ⊕ N=42 (%)	Flecainide challenge ⊖ N=138 (%)	p-value
DEMO-GRAPHICS	**Age yrs±SD**		9±4.6	11.7±4.3	**<0.001**
	≥14yrs		8	50	**0.040**
	<14yrs		34	88	
	Male sex		16 (38)	88 (64)	**0.003**
	Female sex		26 (62)	50 (36)	
		TOTAL	**42**	**138**	
CLINICAL PARAMETERS	**Asymptomatic**		28	84	0.497
	Symptomatic	*Unexplained syncope*	9	33	0.739
		Febrile seizures	4	17	0.621
		Aborted SCD	1	4	0.858
		TOTAL	**42**	**138**	
	Personal history	*Cardiac pathology*	2	1	0.074
		Neurologic pathology	3	5	0.332
		NO personal history	37	132	0.073
		TOTAL	**42**	**138**	
	Family history	*1st grade low-risk*	5	71	**<0.001**
		1st grade high-risk	26	17	**<0.001**
		Only 2nd and/or 3rd grades	3	23	0.124
		NO family history	8	27	0.941
		TOTAL	**42**	**138**	
DIAGNOSTIC TESTS	**Basal ECG abnormal**	*Non-type 1 ECG pattern*	23	6	**<0.001**
		RBBB	8	15	0.165
		AV block	2	1	0.074
		PR alteration	1	1	0.370
		QT alteration	1	3	0.936
	Febrile ECG abnormal		10	4	**<0.001**
	Genetic test positive	*SCNA5A mutated*	14	4	**<0.001**
		Other mutations	2	3	0.372

In genetic tests, other positive mutations include these genes: MOG1, MYH7, KCNJ8 and HCN4 without SCN5A mutation. *AV=Atrio-Ventricular, ECG=Electrocardiogram, EPS=Electrophysiology Study, SCD=Sudden Cardiac Death, SD=Standard Deviation, RBBB=Right Bundle Branch Block, ⊕=positive result, ⊖=negative result.*

7.4 **Analysis of asymptomatic-related results** (see TABLE 4)

- Thirty-nine of all asymptomatic patients presented an abnormal basal ECG, associating a positive flecainide challenges in 14 of these patients (36%). Twenty-nine patients with an abnormal basal ECG had a family history related with BrS and 12 of those presented a positive test. There were two asymptomatic patients with an abnormal basal ECG and with a positive flecainide challenge, without having family history. Considering these tests separately in asymptomatic patients with positive flecainide challenges, the statistical analysis showed a p-value=0.050 for having an abnormal basal ECG and a p-value=0.287 for having an abnormal febrile ECG.
- The 10 asymptomatic patients who had an abnormal febrile ECG and a positive flecainide challenge also had an abnormal basal ECG, and the statistical analysis between these previously abnormal ECGs and their positive flecainide test showed a p-value<0.001.
- Genetic tests were performed in 22 of 28 asymptomatic patients with positive flecainide challenge. Eleven had a positive genetic test, having both positive (genetics and the flecainide challenge). Five patients had a positive genetic test but a negative flecainide challenge.
- Considering only family history related with BrS, 100 of these asymptomatic patients had antecedents and 25 presented a positive flecainide challenge.

TABLE 4: Comparison of asymptomatic patients and their clinic and diagnostic characteristics with their result of the flecainide challenge.

	PARAMETER	Flecainide challenge ⊕ N=28	Flecainide challenge ⊖ N=84	p-value
ASYMPTOMATICS	*Abnormal basal ECG* *Normal basal ECG*	14 14	25 59	0.050
	Abnormal febrile ECG *Normal febrile ECG*	10 1	2 1	0.287
	Positive genetic test *Negative genetic test*	11 5	5 1	0.494
	With FH *Without FH*	25 3	75 9	1
	With FH + basal ECG abnormal	12	17	0.012
	Abnormal basal ECG + abnormal febrile ECG	10	0	<0.001

ECG=Electrocardiogram, FH=Family History, ⊕=positive result, ⊖=negative result.

7.5 **Acute adverse effects-related results** (see *TABLE 5*)

- Any acute adverse effects during the procedure of basal ECGs, echocardiographys, febrile ECGs and genetic tests were documented.
- During the flecainide challenges, some acute adverse effects exposed in *section 3.7.1* were registered: 37 patients explained visual alterations as

transient photopsies, 48 experimented a transient warm sensation in the pelvic zone where the puncture was performed, seven had transitory dizziness and three patients referred local pain in the peripheral venous access. Other documented adverse effects were three cases of prolonged stay in the hospital with constant monitoring due to persistent ECG abnormality, one case of chest pain or discomfort and one patient presented a cardiac electromechanical dissociation during the procedure.

- Referred to EPS, any patient had an arrhythmia in the time interval between after de procedure and before being discharged. Clinically, seven patients presented chest pain or discomfort, six patients had local pain at the puncture site and five referred transitory dizziness before the procedure. Any case of cardiac arrest was registered.

TABLE 5: Acute adverse effects registered during the performance of the different tests.

Basal ECG	Echocardio-graphy	Febrile ECG	Flecainide challenge		Genetic test	EPS	
0 adverse effects were registered	0 adverse effects were registered	0 adverse effects were registered	*Arrhythmia and/or cardiac arrest*	1	0 adverse effects were registered	*Early post-test arrhythmia*	0
			Transitory dizziness	7			
			Transient photopsies	37		*Cardiac arrest*	0
			Transient warm sensation in the pelvic zone	48		*Local pain at the puncture area*	6
			Persistent ECG abnormality (>2h) and consequent prolonged stay	2		*Chest pain or discomfort*	7
			Local pain in the injection area	3		*Transitory dizziness*	5
			Chest pain or discomfort	1			

ECG=Electrocardiogram, EPS=Electrophysiology Study.

8. DISCUSSION

To our knowledge, this is the largest study of children undergoing flecainide challenge for suspicion of BrS. In this cross-sectional descriptive study, we analyze data of a significant number of patients presenting with suspicion of this disease. In 42 of these 180 patients (23%), a flecainide challenge had a positive result and finally reach the diagnose.

As it has been described in adult population, significant differences between genders were observed in positive flecainide challenges in this pediatric population. Following the theory of the hormonal role in this syndrome (described in *section 3.3*) we did not expect any significant difference in children due to their low levels of testosterone. This result made us think that older patients (adolescents with high levels of testosterone) could be a confusion factor. For that reason, results were analyzed dividing them in younger than 15 years old and older than 15 years old. This age limit was determined from the statistical

analysis: it did not show any statistical difference between genders stratifying the results in these two age groups. The lack of differences in patients older than 15 years could be explained because there were few patients in this age range, but this result in younger patients was based on a large number of patients, thus it is more reliable. These results agreed with our first impression about the hormonal role, and they could be a reason for proposing to repeat the flecainide challenge when the patient is older than 15 years rather than before, to control possible false negatives in the first test performed.

Reasons that give rise to complete a flecainide challenge include family history related with BrS and/or positive genetic tests performed in affected familiars, an electric suspicion due to abnormalities in a basal ECG and/or in fever ECGs or having symptomatology related with BrS (mainly unexplained syncope, febrile seizures in infancy and/or an episode of aborted sudden cardiac death).
The main reason for suspecting BrS in this population was a genetic reason: 39% of all studied patients were at study due to familiar screening, but only five of these 71 patients were finally diagnosed of BrS. It supports the affirmation that this disease could have a heterogenic genetic pattern of transmission that could be important in considering familiar screening in relatives of individuals affected. Apart from that, 68 patients were consulted for related symptomatology. Positive challenge results could be observed in all mentioned symptoms but any statistical association was found. The last reason was an abnormality in the ECGs (basal or febrile), supposing the main reason for 41 patients and obtaining a final BrS diagnose in 23 of those, the highest proportion of final diagnoses (55%) according to the main reason of study. These results in this population showed that ECG abnormalities could suppose an important parameter in determining the patient's risk of being affected of this disease, and the statistical analysis confirmed a relationship between finding a non-type 1 ECG pattern in these ECGs (basal or febrile) with a positive result in the challenge. Other findings in the ECG (such as RBBBs, atrio-ventricular blocks and alterations in the duration of PR and QT intervals) did not seem to be associated, despite some studies described the possible association between atrio-ventricular blocks and BrS. Likewise, the genetic finding of SCNA5A mutation showed an association with a positive flecainide challenge: regardless genetics are heterogeneous they could play a more important diagnostic role. EPS was not included as a diagnostic tool because it is applied in positive flecainide challenges to assess their risk of having life-threatening arrhythmias (it is explained in *section 3.10*). Seven of these 42 patients with a positive flecainide challenge had a ventricular arrhythmia during their EPS, hence they were considered as high-risk BrS and an ICD was applied as a recommended therapeutic measure.

Moreover, the relation between cardiac and/or neurologic personal antecedents with the positivity of flecainide challenges was analyzed. Any relationship between these parameters was found in this population of study, despite there are some studies performed in adults that found a strong relationship with some associated diseases and overlapping syndromes (it is described in *section 3.9*).

Asymptomatic patients (it means that their reason for suspecting BrS is an abnormal base ECG and/or family history) were considered and described separately due to their clinical importance and diagnostic difficulties. The most associated parameters of these subjects with a positive challenge were having a basal ECG abnormal and a febrile ECG abnormal. None of the other factors that could contribute to the diagnostic management showed a significant association, so the great debate in these asymptomatic patients is still open. These results agree with the proposal of performing an ECG in all individuals with BrS suspicion, symptomatic or asymptomatic, and to give more importance to febrile ECGs.

All acute adverse effects registered during the procedure or in the first two hours after performing these diagnostic tests were exposed, and it is mandatory to discuss the most severe adverse effect seen in these 180 patients: a case of a cardiac electromechanical dissociation during the performance of a flecainide challenge. It was a six years old male patient at study due to abnormal basal and febrile ECGs (with a non-diagnostic type 2 Brugada pattern and an intermittent atrio-ventricular block). He had symptoms (episodes of unexplained syncopes), but he did not present any family history. During the flecainide infusion for the challenge, a monomorphic VF was presented at 32 seconds of starting the infusion, which led to a cardiac electromechanical dissociation. The flecainide infusion was immediately stopped and the previously prepared isoprotenerol infusion was administered with a single electric cardioversion using the previously prepared and charged at 2J/kg defibrillator. These procedures reverted the process and took the heart back to sinus rhythm while thoracic compressions were performed. The flecainide challenge was immediately stopped and the patient was admitted to the Intensive Care Unit of the hospital with continuous heart monitoring to prevent further damages. During this monitoring, a type 1 pattern was found in the basal ECG and the patient was finally diagnosed of BrS. An ICD was immediately placed, because the previously induction of VF and the cardiac electromechanical dissociation rated him/her of having a high-risk BrS. The patient was discharged after 48 hours without presenting any other

complication. During follow-up, polymorphic ventricular tachycardia was observed at the monitor of the ICD, therefore, quinidine was started.

9. STUDY LIMITATIONS

Due to the cross-sectional descriptive nature of this study, many limitations should be mentioned:

- This kind of studies are not very useful in research of rare diseases (such as the BrS in children), but this problem has been solved selecting this Hospital Pediatric Unit of Arrhythmias, where most of affected or possibly affected patients come, regardless of their geographical origin or area of residence.
- Cross-sectional descriptive studies use to be prevalence studies, however it was not the objective of this concrete project because a reference Unit in pediatric arrhythmias such as the BrS was used and lots of cases are followed, despite the mentioned low prevalence of this disease, so extracting a prevalence number of this data would be totally biased. In consequence, prevalence was not calculated, and the description of these patients was the main important concept. It was done to avoid the Healthcare access bias.
- It is difficult to control confusion factors in observational studies, but we tried to minimize the possible bias ruling out all confusion factors in the ST-segment elevation (described in *section 3.9*) in each patient and considering them as exclusion criteria.
- A consecutive sampling was used, therefore all pediatric patients with suspected BrS which accomplish inclusion and exclusion criteria were asked to participate in the registry. This fact generates an important selection bias but it avoids the spectrum bias of including only the well-defined cases. In consequence, conclusions of this cross-sectional descriptive study should not be generalized in all populations.
- Data obtained from these patients cannot be modified and other parameters cannot be asked to them, because of the double anonymization and the cross-sectional nature of the study. Cause-effect relationships between risk factors and the disease cannot be exactly determined because any temporal sequence was followed, each patient was only registered once in a concrete moment. Even so, to describe the real standard management of these patients gives an interesting practical value to the obtained results.
- Long-term adverse effects were not registered (it is not a prospective study). However, the most important and most referenced adverse effects are acute.
- Some variables were registered during the performance of diagnostic tests, which are measured with the correspondent instruments (described in *section 5.5)* that could present measurement biases. Some aspects were considered to minimize these errors: firstly, all instruments were calibrated periodically

(as part of the standard activity of the Hospital). Besides, expert doctors in this syndrome participated in all medical procedures (Josep Brugada and Georgia Sarquella Brugada, for example) and each result was analyzed by at least three expert cardiologists. To avoid this bias during the data computerization, the Department of Medical Informatics supervised the correct functioning and safety of the dataset.

- The fact that data was registered before this study was designed helped to avoid the observer bias because these doctors did not know the hypotheses and objectives of this study.
- Due to the anonymization, if any irregularity in the diagnostic management of a registered patient was found, it could not be solved directly with the patient because they remain unknown. To solve this, their doctors (in their normal medical activity, independently of this study) revise periodically all his/her patients related with BrS to assess that the management proceeding has been done properly. Moreover, no irregularities were found in the registry but it was a considered issue.
- In this study, a flecainide challenge was applied in all patients as a diagnostic tool. Sensitivity and specificity could not be calculated because there is no "gold standard" diagnostic test to compare with, and it would be other kind study. In this way, it would be interesting to perform a clinical trial comparing ajmaline and flecainide challenges in each pediatric patient (to determine which one is better). Thus, only the parameters found in every positive or negative challenges were described.
- As explained in *section 3.7.1*, flecainide challenge could present nearly a 25% of false negative results, so the test was proposed to be repeated in every patient with a negative result after a few years. As it is not a prospective study, it has not been possible to register the results of their second test, but we are planning to start a retrospective descriptive study when all them have it performed.

10. CONCLUSIONS

The main purpose of this study was to describe data included in the registry: this could be the largest pediatric population undergoing a flecainide challenge. Further information about the diagnostic management of pediatric patients with suspected BrS is being added with this project.

Focusing on secondary hypotheses, the objectives to assess them were followed properly: demographics, clinic and diagnostic parameters were described and their statistic comparison with the result of the flecainide challenge was analyzed, to obtain these answers:

- Hypothesis number one: In frequency terms, in this pediatric Unit there were more patients with suspected BrS at study because of family history than because of their symptoms: (71, which represents the 39% of the total), thus this hypothesis has been confirmed. However, there was few differences between this group and the clinical suspicion, which include 68 subjects (38%). Symptoms and familiar screening were two important reasons for suspecting BrS these patients attended this Unit.
- Hypothesis number two: Pediatric patients whose main reason for suspecting BrS is a related symptom did not show more positive flecainide challenge than those 112 asymptomatic patients: symptomatic subjects (68) represent the 38% of the totals and had 14 positive flecainide challenges. Asymptomatic patients were 112 and obtained 28 positive tests, the 67% of all positive flecainide challenges). Consequently, this hypothesis has been refused.
- Hypothesis number three: It was a complex hypothesis with different aspects to comment: asymptomatic pediatric patients attended at his Unit with abnormal basal ECG had the same number of positive flecainide challenges than those asymptomatic with a normal basal ECG (14), thus this part of the hypothesis has been refused. In febrile ECGs, there were more positive tests when it was abnormal (10) than when it was normal (one), but this relationship did not show significant relevance. This unexpected result could be explained because only 14 patients could register a febrile ECG. Patients with both basal and febrile ECGs abnormal presented 10 positive flecainide challenges and a statistical significance was found.

The hormonal role remained unclarified, but results suggested that it might be better to repeat the challenge when the patient is adolescent (around 15 years old, considering the hormonal change), to minimize false negatives.

This registry showed that 42 patients were finally diagnosed and treated of BrS in this Unit thanks to the performance of a provocative flecainide test (23%). Most importantly, 28 of those were asymptomatic and identifying them supposed a great medical challenge. In this way, and without extrapolating it to the general population, it can be assured that in these cases the flecainide challenge has been a useful diagnostic tool.

The willing of presenting all acute adverse effects registered (including the discussion of this life-threatening adverse effect) is to demonstrate that these provocative tests could be useful but have some risks that must be considered and avoided. Some of them are non-severe (luckily, the most frequent seen), but a single case of cardiac electromechanical dissociation in 180 patients due to the flecainide administration is more than enough to consider the high-risk of this

procedure. Therefore, provocative test should only be performed in a high-specialized center.

More studies about flecainide challenge in pediatric patients with suspected BrS should be performed in the future to assess its efficacy, efficiency and safety and to improve the validity of these results. A clinical trial study with flecainide challenges in pediatric population would be ideal, but this kind of studies in children are very difficult to perform due to ethical aspects. At this moment, we are confident to add information about this diagnostic test in this large pediatric population with suspected BrS, because there is an important lack of information and any data can provide useful knowledge in this topic.

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12. ANNEXES

12.1 ANNEX I: Registry's informed consent (Catalan)

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INFORMACIÓ PER AL PACIENT I FORMULARI DE CONSENTIMENT INFORMAT

REGISTRE ANÒNIM D'ACTIVITAT DIAGNÒSTICA EN PACIENTS PEDIÀTRICS AMB SOSPITA DE SÍNDROME DE BRUGADA.

- *Responsable principal*: Doctora Georgia Sarquella Brugada
- *Entitats responsables:* Unitat d'Arítmies Pediàtriques, Electrofisiologia i Mort Sobtada, Departament de Cardiologia de l'Hospital Sant Joan de Déu, Barcelona.

En el present document i conforme a la normativa vigent actualitzada el 2013 de la Declaració de Helsinki de la AMM sobre els principis ètics per investigacions mèdiques en éssers humans, es presenta la següent informació:

1. *Naturalesa i objectiu del registre:*
   - 1.1 L'objectiu d'aquest registre d'activitat mèdica de la Unitat d'Arítmies Pediàtriques és obtenir informació totalment anònima de tots els pacients pediàtrics que s'atenen en aquesta unitat sota la sospita diagnòstica de Síndrome de Brugada.
   - 1.2 Es pretén aconseguir dades anònimes que puguin aportar dades del maneig diagnòstic d'aquesta malaltia en la població pediàtrica.
   - 1.3 Les variables a obtenir dels subjectes participants seran:
     - 1.3.1 Dades demogràfiques (sexe, edat, nacionalitat, comunitat autònoma d'origen en Espanyols).
     - 1.3.2 Dades antropomòrfiques (talla, pes, etc.)
     - 1.3.3 Antecedents personals cardíacs i neurològics.
     - 1.3.4 Antecedents personals de simptomatologia relacionada amb la Síndrome de Brugada i altres síndromes arítmiques cardíaques (sincopes, convulsions febrils, espasmes del plor, etc.), així com el motiu clínic de sospita de la malaltia, si és que n'hi ha.
     - 1.3.5 Antecedents familiars, anònims, de Síndrome de Brugada, mort sobtada (recuperada o no) i d'altres patologies relacionades.
     - 1.3.6 Resultat del test de provocació amb flecainida, així com el registre d'efectes adversos presentats durant el procediment.
     - 1.3.7 Resultat d'altres proves diagnòstiques realitzades, així com el registre d'efectes adversos presentats durant els procediments.

2. *Propòsit:*
   Aquest consentiment té el propòsit de sol·licitar la seva informació per a participar en aquest registre d'activitat diagnòstica en pacients pediàtrics sota sospita de Síndrome de Brugada.

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3. *Procediment del registre:*
   3.1 Les variables requerides seran preguntades al pacient i/o al seu tutor/a legal per la responsable d'aquest registre a la consulta mèdica corresponent.
   3.2 El registre es realitzarà en una base de dades protegida informàticament i confidencial, sense emmagatzemar cap dada identificadora del pacient.
   3.3 Aquestes dades anònimes tornaran a ser anonimitzades posteriorment assignant un codi numèric aleatoritzat no identificador.
   3.4 Un cop realitzat el registre d'activitat mèdica, futurs estudis podran utilitzar aquestes dades anònimes per a ser analitzades i publicades.
   3.5 El registre de les dades es realitzarà un sol cop per pacient i no comportarà cap intervenció extraordinària en el seu maneig diagnòstic o terapèutic, simplement es farà un registre del/s procediment/s estàndard acceptat/s que s'hagi realitzat.
   3.6 Si vostè (com a pacient o com a tutor/a del/la pacient) accepta participar-hi, se li sol·licitaran les dades explicades als apartats anteriors.

4. *Riscs associats a la participació en el registre::*
   4.1 La seva participació en aquest registre de dades no implica cap risc físic ni moral per a la seva pròpia persona, d'acord a la *resolució R.D. 1090/2015* i a les *Normes BPC/CPMP/ICH/135/95* establertes en investigacions realitzades en éssers humans, tal com s'expressa a la *Declaració de Helsinki*.
   4.2 La part més important és la **confidencialitat de les seves dades**, que serà registrada i mantinguda sota **total anonimat** i que **en cap cas serà revelada a ningú més que al propi pacient i/o al seu tutor/a legal.**

5. *Beneficis associats a la participació en el registre:*
   La seva participació en el corresponent registre d'activitat mèdica suposa una valuosa font de dades anònimes que podran ser utilitzades per a millorar el maneig de pacients pediàtrics amb sospita de Síndrome de Brugada.

6. *Confidencialitat de dades:*
   6.1 La informació del participant serà mantinguda de manera **confidencial i anònima**, sota custodia del responsable del registre.
   6.2 **No es registrarà cap dada identificadora del pacient** i després es tornaran a anonimitzar utilitzat un codi numèric aleatori.
   6.3 En qualsevol cas, es complirà l'establert en la *Llei Orgànica 15/1999 de 13 de desembre de Protecció de Dades de Caràcter Personal.*

7. *Voluntarietat:*
   7.1 La participació en aquest registre ha de ser **NECESSÀRIAMENT de forma LLIURE DE COACCIÓ.**
   7.2 Els subjectes participants i/o els seus tutors/es legals tenen la possibilitat de consultar amb altres persones (familiars, amics, el seu metge, etc.) el fet d'atorgar aquest consentiment abans d'acceptar-lo.

8. *Conflicte d'interès del responsable:* No hi ha cap conflicte d'interès per part del responsable d'aquest registre.

Jo, _____, amb DNI _____ i com a participant d'aquest registre he entès la informació que s'exposa en aquest consentiment i se m'han respost els dubtes i inquietuds sorgides.

Per a constància, signo el ___ de/d'_____ de 20__

_____
Signatura del/la participant

Jo, _____, amb DNI _____ i com a tutor/a legal del/la participant d'aquest registre, he entès la informació que s'exposa en aquest consentiment i se m'han respost els dubtes i inquietuds sorgides.

Per a constància, signo el ___ de/d'_____ de 20__

_____
Signatura del tutor/a legal

9. *Declaració del responsable:*
Com a responsable d'aquest registre d'activitat mèdica certifico que he explicat a aquest pacient i al seu tutor legal la naturalesa i objectiu del registre i que aquesta persona entén completament en què consisteix la seva participació, els possibles riscs i beneficis implicats i tots els apartats numèrics corresponents a aquest consentiment informat.
Totes les preguntes que s'han formulat han estat contestades de manera adequada.
Aixi mateix, he llegit i explicat adequadament les parts d'aquest formulari de consentiment informat i sóc conscient de totes les meves responsabilitats de custodia de dades mèdiques expressades en els apartats anteriors.
Faig constar amb la meva firma l'1 de gener de 2016

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12.2 ANNEX II: Registry's informed consent (Spanish)

Sant Joan de Déu
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INFORMACIÓN PARA EL PACIENTE Y FORMULARIO DE CONSENTIMIENTO INFORMADO

REGISTRO ANÓNIMO DE ACTIVIDAD DIAGNÓSTICA EN PACIENTES PEDIÁTRICOS CON SOSPECHA DE SÍNDROME DE BRUGADA.

- *Responsable principal*: Doctora Georgia Sarquella Brugada
- *Entidades responsables:* Unidad de Arritmias Pediátricas, Electrofisiología y Muerte Súbita, Departamento de Cardiología del Hospital Sant Joan de Déu, Barcelona.

En el presente documento y conforme a la normativa vigente actualizada el 2013 de la Declaración de Helsinki de la AMM sobre los principios éticos para investigación médica en humanos, se presenta la siguiente información:

1. *Naturaleza y objetivo del registro:*
   - 1.1 El objetivo de este registro de actividad médica de la Unidad de Arritmias Pediátricas es obtener información totalmente anónima de todos los pacientes pediátricos que se atienden en esta unidad bajo sospecha diagnóstica de Síndrome de Brugada.
   - 1.2 Se pretende conseguir datos anónimos que puedan aportar información del manejo diagnóstico de esta enfermedad en la población pediátrica.
   - 1.3 Las variables a obtener de los participantes serán:
     - 1.3.1 Datos demográficos (sexo, edad, nacionalidad, comunidad autónoma de origen en españoles).
     - 1.3.2 Datos antropomórficos (talla, peso, etc.)
     - 1.3.3 Antecedentes personales cardíacos y neurológicos.
     - 1.3.4 Antecedentes personales de sintomatología relacionada con el Síndrome de Brugada y otros síndromes arrítmicos cardíacos (síncopes, convulsiones febriles, espasmos del llanto, etc.), así como el motivo de sospecha de la enfermedad.
     - 1.3.5 Antecedentes familiares, anónimos, de Síndrome de Brugada, muerte súbita (recuperada o no) y de otras patologías relacionadas.
     - 1.3.6 Resultado del test de provocación con flecainida, así como el registro de efectos adversos presentados durante el procedimiento.
     - 1.3.7 Resultado de otras pruebas diagnósticas realizadas, así como el registro de efectos adversos presentados durante los procedimientos.

2. *Propósito:*
   Este consentimiento tiene el propósito de solicitar su información para participar en este registro de actividad diagnóstica en pacientes pediátricos bajo sospecha de Síndrome de Brugada.

3. *Procedimiento del registro:*

3.1 Las variables requeridas serán preguntadas al paciente y/o a su tutor/a legal por parte del responsable de este registro, en la consulta médica correspondiente.

3.2 El registro se realizará en una base de datos protegida informáticamente y confidencial, sin almacenamiento de ningún dato identificador del paciente.

3.3 Estos datos anónimos volverán a ser anonimizadas posteriormente asignando un código numérico aleatorizado no identificador.

3.4 Una vez realizado el registro de actividad médica, futuros estudios podrán utilizar estos datos anónimos para ser analizados y publicados.

3.5 El registro de los datos se realizará una sola vez por paciente y no comportará ninguna intervención extraordinaria en su manejo diagnóstico o terapéutico, simplemente se hará un registro de el/los procedimiento/s estándar aceptado/s que se haya/n realizado.

3.6 Si usted (como paciente o como tutor/a del/la paciente) acepta participar, se le solicitarán los datos explicados en los apartados anteriores.

4. *Riesgos asociados a la participación en el registro:*

4.1 Su participación en este registro no implica ningún riesgo físico ni moral para su persona, de acuerdo con la *resolución R.D. 1090/2015* y a las *Normas BPC/CPMP/ICH/135/95* establecidas en investigaciones realizadas en humanos, tal y como expresa la *Declaración de Helsinki*.

4.2 La parte más importante es la **confidencialidad de sus datos,** que será registrada y mantenida de forma **totalmente anónima** y que **en ningún caso será revelada a nadie más que al propio paciente y/o a su tutor/a legal.**

5. *Beneficios asociados a la participación en el registro:*

Su participación en el correspondiente registro de actividad médica supone una valiosa fuente de datos anónimos que podrán ser utilizados para mejorar el manejo médico de pacientes pediátricos con sospecha de Síndrome de Brugada.

6. *Confidencialidad de datos:*

6.1 La información del participante será mantenida de forma **confidencial y anónima**, bajo custodia del responsable del registro.

6.2 **No se registrará ningún dato identificador del paciente** y después se volverán a anonimizar utilizando un código numérico aleatorio.

6.3 En todo caso, se cumplirá lo establecido en la *Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal*.

7. *Voluntariedad:*

7.1 La participación en este registro debe ser **NECESARIAMENTE de forma LIBRE DE COACCIÓN.**

7.2 Los participantes y/o sus tutores legales tienen la posibilidad de consultar con otras personas (familiares, amigos, otros médicos, etc.) el hecho de otorgar este consentimiento antes de aceptarlo.

8. *Conflicto de intereses del responsable:* No hay ningún conflicto de interés por parte del responsable de este registro.

_____, con DNI _____ y como participante en este registro, he entendido la información que se expone en este consentimiento y se me han respondido las dudas e inquietudes surgidas.

Para constancia, firmo el ___ de_____ de 20__

_____
Firma de el/la participante

_____, con DNI _____ y como tutor/a legal de el/la participante en este registro, he entendido la información que se expone en este consentimiento y se me han respondido las dudas e inquietudes surgidas.

Para constancia, firmo el ___ de_____ de 20__

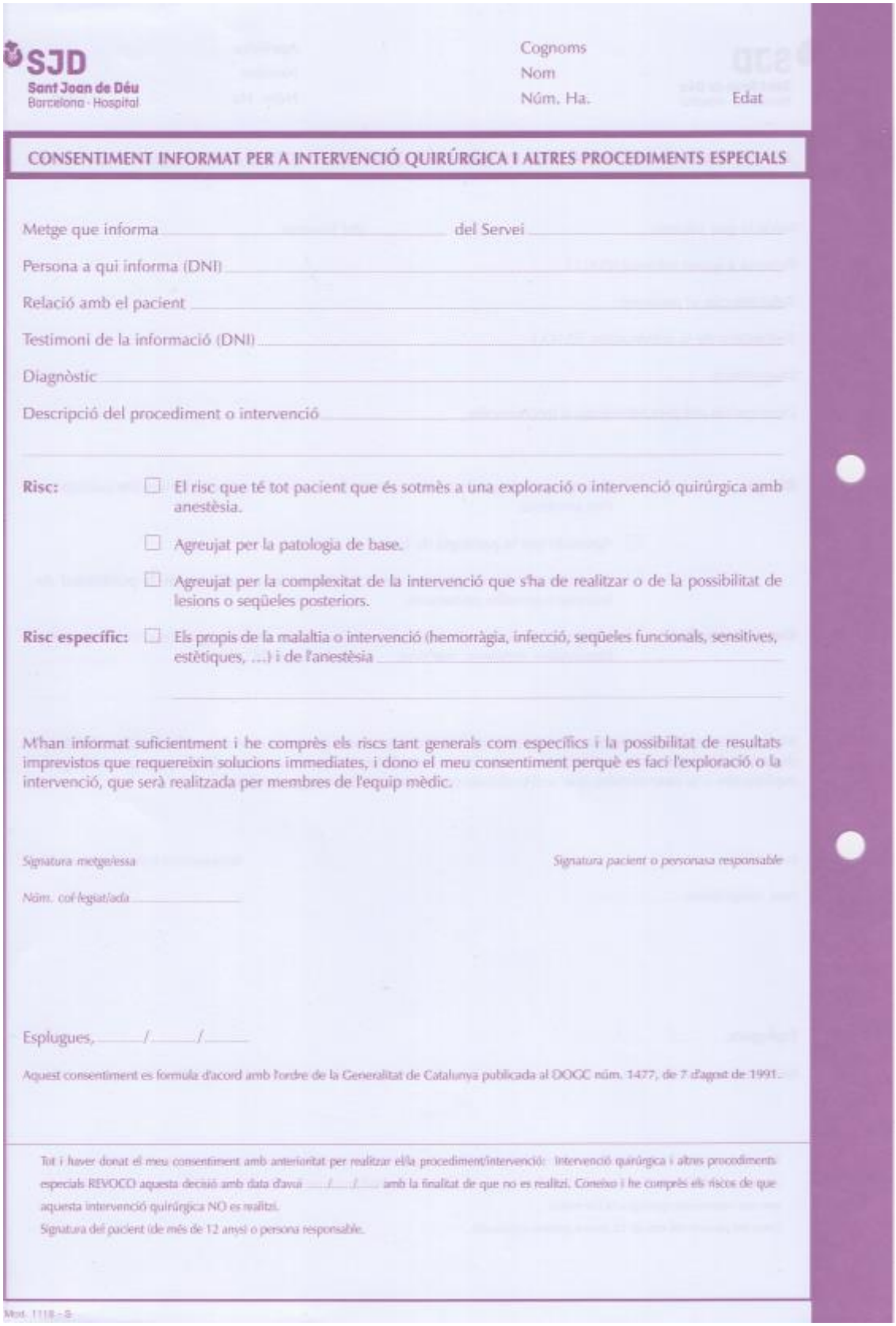
_____
Firma del tutor/a legal

9. *Declaración del responsable:*
Como responsable de este registro de actividad médica, certifico que he explicado a este paciente participante y a su tutor legal la naturaleza del registro y que esta persona entiende completamente en qué consiste su participación, los posibles riesgos y beneficios implicados y todos los apartados numéricos de este consentimiento informado.
Todas las preguntas que se han formulado han sido contestadas de forma adecuada.
Así mismo, he leído y explicado adecuadamente las partes de este formulario de consentimiento informado y soy consciente de todas mis responsabilidades de custodia de datos médicos expresados en los apartados anteriores.
Hago constar con mi firma, el 1 de enero de 2016.

Dra. Georgia Sarquella Brugada
georgia@brugada.org

Unidad de Arritmias Pediátricas, Electrofisiología y Muerte Súbita
Departamento de Cardiología..
Hospital Sant Joan de Déu, Barcelona

12.3 ANNEX III: Informed consent for invasive procedures (in Catalan and in Spanish)



SJD
Sant Joan de Déu
Barcelona · Hospital

Cognoms
Nom
Núm. Ha. Edat

CONSENTIMENT INFORMAT PER A INTERVENCIÓ QUIRÚRGICA I ALTRES PROCEDIMENTS ESPECIALS

Metge que informa _____ del Servei _____

Persona a qui informa (DNI) _____

Relació amb el pacient _____

Testimoni de la informació (DNI) _____

Diagnòstic _____

Descripció del procediment o intervenció _____

Risc:
- ☐ El risc que té tot pacient que és sotmès a una exploració o intervenció quirúrgica amb anestèsia.
- ☐ Agreujat per la patologia de base.
- ☐ Agreujat per la complexitat de la intervenció que s'ha de realitzar o de la possibilitat de lesions o seqüeles posteriors.

Risc específic:
- ☐ Els propis de la malaltia o intervenció (hemorràgia, infecció, seqüeles funcionals, sensitives, estètiques, ...) i de l'anestèsia _____

M'han informat suficientment i he comprès els riscs tant generals com específics i la possibilitat de resultats imprevistos que requereixin solucions immediates, i dono el meu consentiment perquè es faci l'exploració o la intervenció, que serà realitzada per membres de l'equip mèdic.

Signatura metge/essa *Signatura pacient o persona responsable*

Núm. col·legiat/ada _____

Esplugues, ____/____/____

Aquest consentiment es formula d'acord amb l'ordre de la Generalitat de Catalunya publicada al DOGC núm. 1477, de 7 d'agost de 1991.

Tot i haver donat el meu consentiment amb anterioritat per realitzar el/la procediment/intervenció: Intervenció quirúrgica i altres procediments especials REVOCO aquesta decisió amb data d'avui ____/____/____ amb la finalitat de que no es realitzi. Conec/o i he comprès els riscos de que aquesta intervenció quirúrgica NO es realitzi.

Signatura del pacient (de més de 12 anys) o persona responsable.

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Apellidos
Nombre
Núm. Ha. Edad

CONSENTIMIENTO INFORMADO PARA INTERVENCIÓN QUIRÚRGICA Y OTROS PROCEDIMIENTOS ESPECIALES

Médico que informa ..... del Servicio .....

Persona a quien informa (D.N.I.) .....

Relación con el paciente .....

Testimonio de la información (D.N.I.) .....

Diagnóstico .....

Descripción del procedimiento o intervención .....

.....

Riesgo:

- ☐ El riesgo que corre todo paciente sometido a una exploración o intervención quirúrgica con anestesia.
- ☐ Agravado por la patología de base.
- ☐ Agravado por la complejidad de la intervención a realizar o de la posibilidad de lesiones o secuelas posteriores.

Riesgo específico:

- ☐ Los propios de la enfermedad o intervención (hemorragia, infección, secuelas funcionales, sensitivas, estéticas, ...) y de la anestesia .....

.....

Me han informado suficientemente y he comprendido los riesgos tanto generales como específicos y la posibilidad de resultados imprevistos que requieran soluciones inmediatas, y doy mi consentimiento para que se haga la exploración o la intervención, que será realizada por miembros del equipo médico.

Firma médico ..... *Firma paciente o persona responsable* .....

Núm. colegiado/ada .....

Esplugues, ... / ..... / .....

Este consentimiento se formula de acuerdo con la orden de la Generalitat de Catalunya publicada en el DOGC núm. 1477, de 7 de agosto de 1991.

Pese a haber dado mi consentimiento con anterioridad para realizar el/la procedimiento/intervención: Intervención quirúrgica y otros procedimientos especiales REVOCO esta decisión con fecha de hoy ..... / ..... / ..... con la finalidad de que no se realice. Conozco y he comprendido los riesgos de que esta intervención quirúrgica NO se realice.

Firma del paciente (de más de 12 años) o persona responsable.

12.4 ANNEX IV: CEIC's authorization

Fundació Sant Joan de Déu

CEIC Fundació Sant Joan de Déu

Informe Dictamen Favorable
Proyecto Investigación Biomédica
C.I. PIC-134-17
26 de octubre de 2017

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

CERTIFICA

1º. Que el CEIC Fundació Sant Joan de Déu en su reunión del día 26/10/2017, ha evaluado la propuesta del promotor referida al estudio:
Título: "Flecainide challenge in pediatric Brugada syndrome: a diagnostic tool with limitations"
Código Interno: PIC-134-17
IP: Georgia Sarquella Brugada

Considera que:

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

2º. Por lo que este CEIC emite un **DICTAMEN FAVORABLE**.

3º. Este CEIC acepta que dicho estudio sea realizado en los siguientes CEIC/Centros por los investigadores:
- **HOSPITAL SANT JOAN DE DEU. Georgia Sarquella Brugada.**

Lo que firmo en Esplugues de Llobregat, a 26 de octubre de 2017

Fdo:

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

12.5 ANNEX V: Flecainide test protocol

Sant Joan de Déu

Test farmacológicos de flecainida y isoprenalina		
Tipo Documento: Procedimiento	**Código:** A-COR-PC-0053-01	
Autores: Dra. G. Sarquella, Dr. Brugada		**Ámbito:** Hospital
Fecha aprobación: 2013	**Fecha revisión:**	

1. Indicaciones

TEST DE FLECAINIDA para Síndrome de Brugada

Fármaco antiarrítmico(clase Ic). Actúa inhibiendo los canales rápidos de Na, provocando una prolongación del potencial de acción cardíaco (aumenta el tiempo de repolarización).

TEST:

1. Conocer el peso del paciente
2. Monitorizar: Ritmo cardíaco, SatHb y presión arterial
3. Canalizar una vía venosa periférica
4. Colocar ECG de 12 derivaciones y registrar
   - Posición estándar
   - V1 y V2 en 3º espacio intercostal
   - V1 y V2 en 2º espacio intercostal
5. Preparar:
   - **FLECAINIDA** (*Apocard® 150mg/15ml*): **Dosis 2mg/Kg** (dosis máxima 150mg). Diluir la dosis de Flecainida hasta completar un volumen de 20ml con agua estéril (precipita con suero fisiológico). Administrar en 10 dosis (2ml/dosis).
   - **ISOPROTERENOL** (*Aleudrina® 0.2mg/ml*): Preparar 0.4mg de Isoproterenol (2 ampollas) en 100ml de suero Fisiológico o suero Glucosado al 5%. Se utilizará como antídoto de la Flecainida en caso de complicaciones.
6. Administrar la preparación de Flecainida en 10 dosis (dosis/minuto) y registrar ECG en posición estándar cada minuto.
   En el minuto 10 realizar ECG en posición estándar y con V1 y V2 en 3º y 2º espacio intercostal.
7. El test se considerará positivo:
   - ECG con morfología de Síndrome de Brugada Tipo 1 en mínimo 2 precordiales derechas (↑ 1mm Segmento ST en V1, V2 o V3).

Se suspenderá el test en caso de:

- Aparición en el ECG de morfología Síndrome de Brugada Tipo 1
- ↑ del segmento ST ≥5mm en Síndrome deBrugada tipo 2

Alternativas farmacológicas a la Flecainida:

- *Ajmalina*: 1mg/Kg EV en 5 minutos (No aprobado su uso en España)
- *Procainamida*: 10mg/Kg EV en 10 minutos

TEST DE ISOPROTERENOL para Síndrome de QT largo

Fármaco β-adrenérgico no selectivo. Efecto inotrópico y cronotrópico positivo. Elevación de la presión arterial sistólica y disminución de la presión arterial diastólica por su efecto vasodilatador (sistémico y pulmonar). Disminuye el periodo de refracción del nodo AV.

Inicio de acción	Efecto máximo	Eliminación
Inmediato	1 minuto	2-6 minutos

Su perfusión es utilizada en: Bradicardia, Bloqueo AV de 3º Grado, Intoxicación por β-Bloquers, Shock y T.Piontes.

Utilizada también en pruebas funcionales hemodinámicas y electrofisiológicas:

- **Diagnóstico de síndrome QT largo**
- **Inducción de taquicardia durante el estudio electrofisiológico**
- Desenmascarar taquicardias catecolaminergicas
- Asegurar actividad ventricular(ritmo de escape) mientras se implanta un marcapasos provisional o se recambia la batería del generador de marcapasos.

TEST:

1. Conocer el peso del paciente
2. Monitorizar: Ritmo cardiaco, SatHb y presión arterial
3. Canalizar una vía venosa periférica

4. Colocar ECG de 12 derivaciones y registrar.
5. Preparar:
   - **ISOPROTERENOL** (Aleudrina® 0.2mg/ml): Preparar 0.4mg de Isoproterenol (2 ampollas) en 100ml de Suero Fisiológico o Suero Glucosado al 5%. (4mcg/ml).
     Dosis pediátrica: 0.05-2 mcg/Kg/min (Dosis media 0.2mcg/Kg/min)
6. Administrar ajustando la dosis para conseguir FC= 150% de FC máxima (220-edad).
7. El test se considerará positivo (síndrome de QT largo) si no hay un correcto acortamiento del QT relacionado con un aumento de la FC.

12.6 ANNEX VI: Levels of evidence in therapeutic studies

Levels of evidence for therapeutic studies, extracted from the Centre for Evidence-

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Based Medicine: http://www.cebm.net

12.7 ANNEX VII: Vaughan-Williams classification of anthyarrhythmic drugs

Class	Basic Mechanism	Comments
I	sodium-channel blockade	Reduce phase 0 slope and peak of action potential.
IA	- moderate	Moderate reduction in phase 0 slope; increase APD; increase ERP.
IB	- weak	Small reduction in phase 0 slope; reduce APD; decrease ERP.
IC	- strong	Pronounced reduction in phase 0 slope; no effect on APD or ERP.
II	beta-blockade	Block sympathetic activity; reduce rate and conduction.
III	potassium-channel blockade	Delay repolarization (phase 3) and thereby increase action potential duration and effective refractory period.
IV	calcium-channel blockade	Block L-type calcium-channels; most effective at SA and AV nodes; reduce rate and conduction.

Abbreviations: APD, action potential duration; ERP, effective refractory period; SA, sinoatrial node; AV, atrioventricular node.

Extracted from Cardiovascular Pharmacology: http://www.cvpharmacology.com/antiarrhy/Vaughan-Williams