SUDDEN DEATH

Causes, Risk Factors and Prevention

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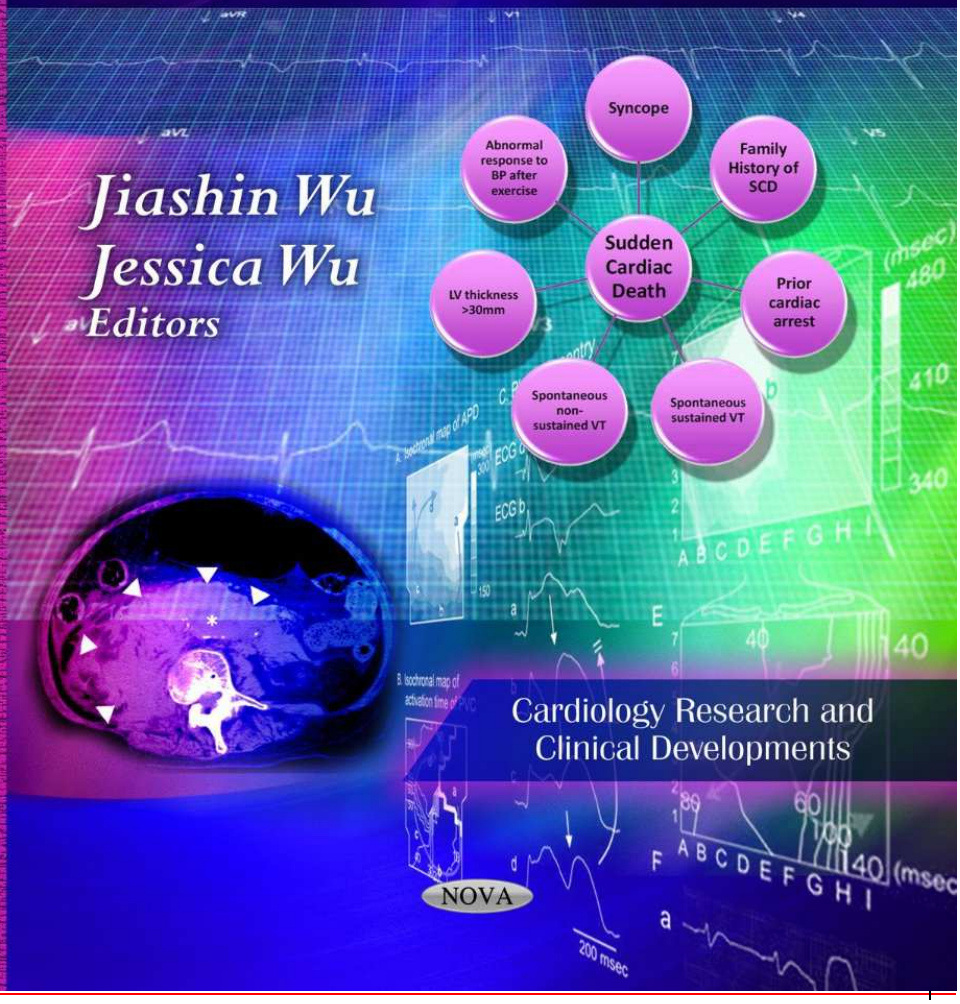

Cardiology Research and Clinical Developments

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Chapter

A RARE LETHAL SYNDROME IN SEARCH OF ITS IDENTITY: SUDDEN DEATH, RIGHT BUNDLE BRANCH BLOCK AND ST SEGMENT ELEVATION

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ABSTRACT

Twenty five years ago a group of doctors from the Padua Medical School described a new familial syndrome characterized by sudden or aborted death, and a strange ECG pattern on the precordial leads, namely an elevated J point and a coved ST segment elevation. A PR interval prolongation, left axis deviation, prolonged HV interval and late potentials at the right ventricular outflow tract (RVOT) clearly indicated a conduction delay. Ventricular fibrillation was easily inducible from the above area. Some minor structural abnormalities of the right ventricle could be evidentiated, and further confirmed by a necropsy study. The syndrome was lately called Brugada syndrome (BS), as more patients with the same ECG pattern and clinical symptoms were identified by these authors, who claimed a new entity not related to a structural abnormality, but with the same phenotypic traits. An explosion of published papers on this topic was seen in the following years, mostly devoted to confirm a functional disease rather than to investigate the underlying etiology; necropsy studies were so rarely described, and not one was consistent with a normal heart. This mistake led to a severe overestimation of the true patients, as the isolated ECG, that is not so rare, was considered itself the disease, following an unjustified J-ICD reflex (ICD implant following the casual detection of a precordial J-ST elevation) in healthy people. Recently, more accurate series are confirming that the true syndrome is so rare, and linked to an underlying right ventricular disease causing a conduction disease at the RVOT. The correct definition of this

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structural anomaly and of its genetic origin, is still needed to transform an ECG into a disease.

Keywords: Brugada syndrome. Sudden death. Right bundle branch block and ST elevation. Ventricular fibrillation. Molecular genetics. Arrhythmogenic Right Ventricular Cardiomyopathy

INTRODUCTION

The syndrome of sudden death, right bundle branch block and ST segment elevation was introduced as a new medical entity 25 years ago [1-5], but became popular after the description by the Brugada brothers [5].

The typical expression describes a middle aged man with a coved ST segment elevation in the precordial leads, and sometime with a family history of cardiac event, that suddenly collapses because of Polymorphic Ventricular Tachycardia (PVT), degenerating into Ventricular Fibrillation (VF). The event occurs usually at rest, sometime at night-time.

Asians are reported to have a high prevalence of this syndrome where it may be the cause of the nocturnal sudden unexplained death syndrome in young males (Pokkurry death, Bangucut disease).

The data are, however, controversial, because of the limited availability of clinical and necropsy studies. The syndrome is still retained a typical expression of a functional idiopathic VF in normal hearts, with an underlying repolarization abnormalities possible linked to genetic disorders of ion channels, especially the sodium and calcium channels.

These latter theories lack of a serious documentation and the evidence based data are little by little confirming that the disorder has some underlying structural and not functional abnormality.

ANECDOTES

On 20 October 1984 a 42 years old healthy and previous asymptomatic cook, quietly talking with the post officer outside his restaurant (http://digilander.libero.it/martini_ syndrome/slide.htm) suddenly collapsed but was so fortunate that an ambulance arrived promptly and a successful defibrillation was performed [1, 2]. The electrocardiogram (ECG) taken showed an ST elevation in the precordial leads (Figure 1), and acute myocardial infarction was diagnosed.

Coronary heart disease was ruled out at angiography. The patient is still alive and asymptomatic on beta blockers therapy. Twenty-eight years later all the interns, fellows and doctors working in the emergency departments are so aware and frightened of this new (lately called) Brugada Syndrome (BS) that they look carefully for similar typical and atypical ECG abnormalities in patients admitted because of syncope.

The entity has become so popular that also Dr. House in his television series has discussed it as one of his brilliant diagnoses, and it also inspired Wes Craven in the film *A Nightmare on Elm Street*.

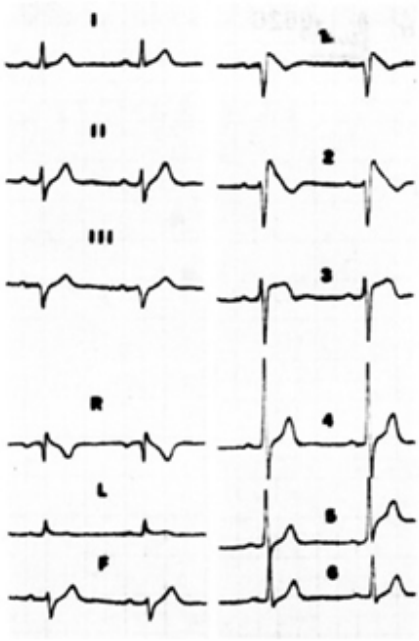

Figure 1. This ECG (now called “Brugada sign”) is the first published trace of the syndrome in 1988, [1]. It shows the most typical pattern: slightly prolonged PR interval, left axis deviation, coved ST elevation starting from the J point, in the precordial leads, with inverted t waves in V1-V2 and reduced s1 wave in V6.

In 2004 in “The New York Times” journalist Sandeep Jauhar, reported a scientists note that as many as 12% of all sudden deaths and roughly 20% of deaths in patients with structurally normal hearts were attributed to the disease.

All this uncontrolled informations have created a lot of unjustified nightmares in doctors and their healthy patients with some similar ECG waves. A J-ICD reflex (Implantable Cardiac Defibrillator when a J wave in V1 is seen), is still believed to be a guideline . At the present time however, the evidence-based data have only clarified that this syndrome is an extremely rare lethal disease, characterized by a not so rare, typical or similar healthy ECG pattern. This syndrome is slowly reaching his third decade but we do not yet reliably know the clinical history, the precise ECG pattern, the genetic basis, the patho-physiology, the risk stratification and least but not last, the electrical and anatomic substrate.

HISTORICAL NOTES

In 1953 Osher and Wolff reported a dynamic ECG abnormality, simulating acute myocardial infarction, in a healthy man [7]. It is of interest that they wrote: “This is apparently due to prolongation of the depolarization process by right bundle block (RBBB) or possibly focal block with delayed activation of a portion of the right ventricle (RV): unusually early onset of repolarization may also play a role”. In 1988 Nava, presented a new syndrome characterized by aborted sudden death in a middle aged man with elevated J point and coved ST in the precordial leads (called early repolarization), delayed conduction at the right

ventricular outflow tract (RVOT), and minor structural abnormalities of the right ventricle [1], similar to those found in minor forms of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVC/D) [6]. Most of the clinical and ECG features later discussed nowadays in up to 2,500 papers were completely described in that single patient. This happens frequently in Medicine and in human history, and was well affirmed by Vergilius *"Ab uno disce omnis":* when you see one, you learn all. (Publius Vergilius Maro 70-19 B.C Georgicon II, 64-65)

One year later a full description of the syndrome was published in the American Heart Journal [2]. In that paper it is noteworthy that not only "the typical" but most of the electrocardiographic variations of the syndrome, namely dynamic or isolated ST abnormalities, incomplete or complete right bundle branch block (RBBB), sometime associated with A-V and fascicular conduction impairment, and prolonged HV intervals were described. Prolonged PR interval, left axis deviation, incomplete RBBB and minor ST elevation, was present in patient 4 who had sudden death. The same patient was republished by Corrado, (Figure 1 of reference 8), and that ECG is an example of the dynamic ECG behavior, sometime seen in this syndrome. Despite the typical functional ECG behavior, and a SCN5A genetic anomaly in his family, this patient had anatomical evidence of ARVD/C, with fibrosis of the conduction system [8, 9].

Complete RBBB morphology was present in patient 1, with only a slight ST elevation in V1 and V2. Isolated slight ST/T anomalies/ elevation as seen in patients 2 and 5 of our paper [2] may very well have been a potential marker of the syndrome. Drug testing was not performed at that time. The presence of late potentials, corresponding to ST segment elevation were proven both by intra-cavitary recordings [1] and by signal averaged ECG [4].

The second description of the syndrome was presented by Aihara [3] in patients without apparent heart disease, and the third by the Brugada brothers [5], five years after the initial Italian description. These authors are indeed deserved to be the first who confirmed that the discussed ECG pattern belonged to a new syndrome.

Further improvements in the evidence-based knowledge of this entity came from Naccarella [10] who demonstrated that the typical ECG can occasionally be recorded at a higher precordial level, by Brugada who introduced the class 1c drug challenge [11], by Yan who investigated laboratory models [12], by Chen who reported the first possible genetic abnormalities [13], by Gonzalez-Rebollo who reported the appearance of the ECG during fever [14]. Ablative intervention has been shown to cure this abnormality [15], and as a definitive conclusion of the patho-physiological debate, Shah and Nademanee [16, 17] eliminated the ST elevation by direct ablation of endocardial and epicardial late potentials.

In the future the major challenges will be the identification of the cause of the disease, and more importantly the correct epidemiological and risk stratification of this condition, in order to avoid the indiscriminate abuse of invasive diagnosis and therapies in healthy asymptomatic people.

DEFINITION OF TERMS

A "Syndrome" (from Greek ∑ύνδρομή: σύν = together, δρόμοσ = run) is the association of several clinically recognizable features, signs (observed by someone other than the

patient), symptoms (reported by the patient), phenomena or characteristics that often occur together. Ibn Sina (Avicenna, 980-1037), in "*The Canon of Medicine*", pioneered the idea of a syndrome in the diagnosis of specific diseases.

Some confusion, however, still exists even in recent consensus statement [5]. A "Disease" is the pathological condition of a part, organ, or system of an organism resulting from evidence-based patho-physiologic causes, such as infection, genetic defect, degenerative abnormalities etc., and characterized by an identifiable group of signs or symptoms.

For example the isolate detection of the Parkinson sign: tremor, is neither a syndrome, nor a disease. Parkinson syndrome is any of a group of nervous system signs and symptoms similar to Parkinson disease, marked by muscular rigidity, tremor, and impaired motor control and often having a specific secondary cause, such as the use of certain drugs or frequent exposure to toxic chemicals etc. Parkinson disease is a primary progressive neurologic disorder occurring most often after the age of 50, associated with the destruction of brain cells that produce dopamine., The same occurs for the isolated detection of the ECG "sign" of an atypical right bundle branch block (RBBB) and ST elevation in the precordial leads of an asymptomatic healthy subject. When "symptoms" like syncope or aborted sudden death are absent, a diagnosis of Brugada syndrome based only on an ECG finding is a relevant mistake, with deleterious medical and psychological consequences, often related to a Google rather than a Cardiologist consultation [18-20]. Moreover, at present, a diagnosis of disease for this entity is not possible, as the patho-physiology of the syndrome is still the topic of many interesting but inconclusive studies.

The purpose of this paper is to analyze some evidence based data, on the ECG, clinical, laboratory and patho-physiology underlying the syndrome.

THE "SYMPTOMS" OF THE SYNDROME

Sudden or aborted sudden death, usually typically occurs between ages 35 and 50 years, in a male individual with a similar family history. This event is unfortunately "the gold standard" for an accurate diagnosis of the syndrome. The circumstances of death are usually unrelated to effort or stress, and may occur during sleep, particularly in Asians [21]. Syncope is another major symptom, and is probably due to self-limited episodes of PVT. It is of interest that several studies have confirmed a high frequency (35%) of vaso-vagal syncope in individuals with type 1 ECG [22], which indicates a limited accuracy of these symptoms during risk stratification. Palpitations and chest discomfort before syncope are rare but specific symptoms for the syndrome while vagal prodroms indicate a low risk group for the syndrome [23]. There is a high recurrence rate of ventricular fibrillation and unfortunately this lethal arrhythmia can be easily induced both in symptomatic and asymptomatic people with the discussed ECG, thus limiting its specificity. Symptoms and spontaneous type 1 ECG are the only evidence based predictors of arrhythmic events, whereas gender, familial history of sudden cardiac death (SCD), inducibility of ventricular tachy-arrhythmias during electrophysiological study, and the presence of an *SCN5A* mutation were not predictive of arrhythmic events. [24]. In Finger study, during follow-up, 22 of 62 patients (35%) from the cardiac arrest group, 19 of 313 patients (6%) from the syncope group, and 10 of 654 (1.5%)

patients from the asymptomatic group had an arrhythmic event. The mean event rate per year was 7.7%, 1.9%, and 0.5% [24].

THE "SIGNS" OF THE SYNDROME

The Basal ECG

Since 2002 a new non-evidence-based classification has divided the ECG pattern of the syndrome in three types [25], based on the QRS-T morphology in the first three precordial leads, without any detail for the remaining nine leads. After a "decade of copy and paste" articles very few scientists remember that this classification is simply a case report that described the dynamic precordial ECG-leads of a single resuscitated patient. It has nothing to do with a scientific study that should have analyzed the prevalence of this sign in a relevant series of true patients. Unfortunately this classification has been severely abused, and asymptomatic healthy individuals incidentally found to have one of these three patterns have been submitted to invasive studies and therapies. A new classification has recently been proposed [26], and type 3 has been fortunately erased.

New criteria have however been proposed using "angles and index" that should require a more severe validation according to scientific principles.

At present time, the only serious way to discuss this topic is go back to the analysis of the published pathological cases that provide the following evidences:

1. The vast majority of the true patients show in the precordial leads QRST patterns resembling a right bundle branch block (RBBB) [1-5] and a coved ST elevation (Figure 1, 2). Differently from RBBB an S wave is reduced or absent in V6 [27], leading to a longer QRS duration in the precordial leads with a mismatch between V1 and V6 QRS duration. When this S wave is present and pronounced in V6 the QRS morphology and duration in V1 becomes similar to a RBBB pattern. A prolonged PR, HV interval and left axis deviation is not so rare in the true patients [1-5]; all indicate a conduction disturbance underlying the ECG. The most typical (type 1) ECG shows an high take-off coved ST pattern in V1 (the so called precordial early repolarization described by Wassenburg [28] with an occasional small sharp notch wave at the J point (the QRS-ST junction). This ECG pattern is, erroneously called but better known as a J wave, forgetting that is however so different from the true J wave described by Osborn [29-31].

2. The most typical ST segment has a coved ST morphology that continues with asymmetric inverted T waves in V1-V2, rarely in V3. Increased ST elevation can rarely precede the arrhythmic events [32], and spontaneous ECG alterations may predict VF recurrence [33]. Type 1 morphology induction at drug testing is retained a necessary condition to make a diagnosis of BS, but this assumption is controversial [18-20].

In occasional cases [34-36] the J point can be fragmented, both spontaneously and after ajmaline infusion [37], (Figure 5), which closely resemble the epsilon waves described by Guy Fontaine [38, 39]. A fragmented terminal QRS (f-QRS) can be documented in up to 43% [40, 41] of individuals, more frequently in those with type 1, and in those with prolonged HV intervals and in those with VF. The fragmentation (both isolated and multiple), can be recorded all around the end of the QRS [40] (Figure 3). An f-QRS can be better recorded at higher intercostals spaces. A similar f-QRS can be recorded in the isolated canine RV tissue

model of the syndrome, obtaining a large phase 1 notch of the action potential in epicardium and a local activation delay in the epicardium [40].

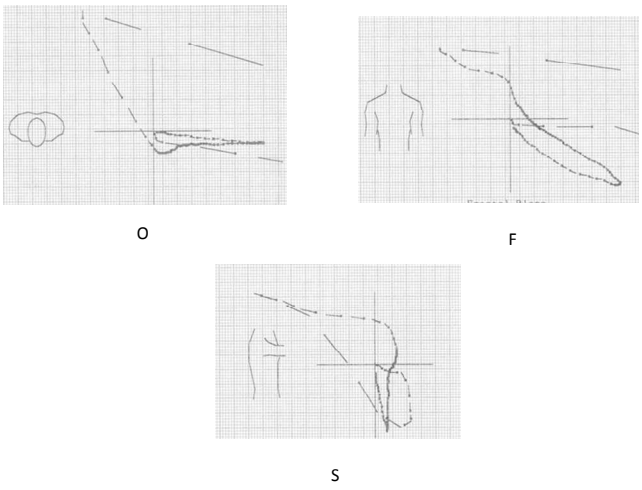

Figure 2. Vectorcardiographic analysis of terminal (amplified) QRS of the same patient (type 1 pattern) : The end of the QRS loop does not coincide with its beginning, and its distance depends on the degree of ST elevation. There is right superior and posterior conduction delay that probably suggests a partial block of fibers that approach the right ventricular outflow tract.

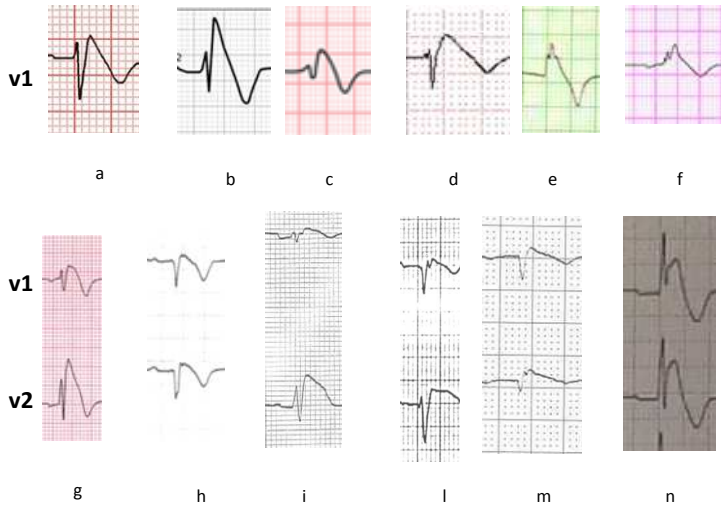

Figure 3. Precordial ECG traces in 12 different cases. In the first six cases (a-f), only V1 is showed. These cases a-f shows a progressive 1) disappearance of S wave 2) slowing of the final QRS and 3) smoothing of the J point that becomes fractionated. Similar progressive fractioning of J point is present in g-m, leading to typical epsilon waves. Fractioning can be present in lead V1 (g,i,l), or better seen in lead V2 (h and m). Case n is a rare example of a true J wave so similar to the one described by Osborn. It belongs to a patient treated with amiodarone intra-venously.

Increasing the cutoff frequency of the low-pass filter from 35 to 150 Hz, more spikes are visible [42]. Magnetocardiographic recordings increase the detection of f-QRS [43].

3. The ST segment elevation may also show a saddle-back configuration (so called type 2 and 3). These patterns un-rarely spontaneously change to type 1 in serial observations of the true patients, while have very limited relevance in the asymptomatic population. A "dome shaped" or up-looping ST elevation, without a high ST-QRS takeoff is unusual in the syndrome, and is a typical pattern in healthy athletes [44, 45].

This spontaneous change between saddle-back to coved ST elevation, unfortunately also occurs in asymptomatic individuals not rarely inducing the J-ICD reflex. This change can be elicited by positioning the precordial leads in the third intercostals spaces, by the class 1c drug challenge, by antidepressant drugs, etc.

Recently, Holst has reported a 4.7% non-specific prevalence of type 2 and 9.4% of type 3, by recording at different intercostal spaces among 340 healthy European individuals [46]. These data were also confirmed in Turkey [47].

A Saddle back but also coved ST elevation in inferior and lateral leads has been described in patients with major cardiac event especially when there is a fragmentation of the terminal QRS [48-50]. Up to 11% of subjects with precordial type 1-2 ECG have an infero-lateral J point elevation [51]. Recently the presence of a J wave in multiple leads and horizontal ST-segment morphology after J wave may indicate a highly arrhythmogenic substrate in patients with BS [253]. It has not been demonstrated yet, that these ECG pattern truly belongs to the same syndrome. The proposed new groups of "J wave syndromes" or "early repolarization syndromes", share some limited ECG abnormalities but do not have yet any common evidence-based genetic and patho-physiologic substrate [50-52].

4. A febrile state of different etiologies can induce a type 1 pattern [14], and laboratory experiments confirmed a relationship between the discussed ECG and temperature [53, 54]. Many reports have been published on this topic raising the question if the ECG pattern is related to the body temperature or to the syndrome. In a highly selected group [55], fever was the cause of inducible type 1 ECG in 16 of 47 subjects.

In another series 18% of patients with the true syndrome [56], had symptoms associated with fever. SCN5A and other different genetic abnormalities of the ion channels may concur to heart arrhythmias during fever [57, 58]. In healthy people with the ECG abnormality only during a febrile state the data are still controversial, but usually the prognosis is favorable [59].

Healthy subjects with fever-inducible type 1, should however be clinically followed, as the phenomenon is not usual. Erdogan recently conducted an important survey on 2011 male subjects with fever ≥38 °C. This study demonstrated that when the ECG was recorded at the fourth intercostals level, no subject developed type 1 pattern, whereas almost 10% revealed type 2 or 3 pattern at higher intercostals level [60].

ECG variations may also related to food-consumption: Nogami [61] demonstrated that glucose and insulin infusion or an oral glucose tolerance test augments morphologic changes in ST-T waves in patients with syndrome but in none of the patients in the control group. Patients who showed coved-type ST elevation before the glucose load exhibited positive ECG changes more frequently than patients with saddleback-type elevation or transiently normalized ST.

A full stomach test has been proposed [62] as a test to identify high risk patients, but is rarely applied.

Prevalence of the ECG Pattern and of the Syndrome in Different Populations

Male predominance is an evident character of the syndrome, accounting for more than 80% of cases. Although the mechanism for the male predominance is not fully understood, it is believed that testosterone is also involved. A study suggests that higher testosterone level associated with lower visceral fat may have a significant role in the male predominance in Brugada syndrome [63].

Since the pioneer paper of Tohyu [64], the true prevalence both of the ECG and of the true syndrome is still controversial. In a large series, approximately 16 out 10,000 European individuals older than 18 years might have a spontaneous type 1 pattern [65]. Holst in a recent Danish registry has collected 1.1 true patients /100,000 inhabitants (67% had a type 1 pattern) [66]. However, other large series in northern Europe [67-69] did not find any type 1 ECG in non-selected populations, whereas type 2 and 3 were also rare (0.6%).

Interestingly, despite the rare finding of the typical ECGs in these European populations, many papers have described a relevant number of patients with the syndrome in this geographic area.

In south-east Asian population the isolated prevalence of the ECG was retained to be higher but controversial data are described, probably due to a limited availability of the health system for most of the people. In Korea [70], type 1 was not found in soldiers (0.9% had type 2-3). In the Philippines a 0.2% of type 1 and 1.8% of type 2-3 ECG has been reported [71]. Recently type 1-3 ECG was found in 0.1% of 18,476 young male conscripts [72]. Black people with the syndrome, both living in Africa or in western countries are only anecdotally reported [73, 74].

In Japanese infants [75] the prevalence is very low for type 1 (0.005%), and an age dependence of the discussed ECG has been shown [76]. When serial ECG are taken during a long term follow up to these individuals, 56% shows normalization or fluctuation between type 1-2 and 3 [76].

For what concern the prevalence of the true syndrome (symptoms+signs), Wilde and Brugada reported that the syndrome affects 3-5 in 10,000 people [77] while Ackermann [78] established a prevalence of 1 in 5,000 to 10,000. A possible relevant problem was anecdotally reported in Southeast Asia (up to 66 patients per 10,000 inhabitants) where it may be the cause of the nocturnal sudden unexplained death syndrome in young males (Pokkurry death, Bangucut disease). The data are, however, controversial [79], because of the limited availability of clinical and necropsy studies. A recent large study in Southeast Asian refugees has shown a high prevalence of sleep disorder, paralysis and apnea [80], that might be the cause of nocturnal sudden death or a concurrence in Brugada syndrome [81]. These data need serious epidemiological reconsideration, as probably 1.1 true cases in 100,000 people is a more convincing prevalence [66], at least in Caucasians.

Class 1c Drugs Challenge

The use of ajmaline introduced by Brugada [11], and all class 1c drugs, to elicit a syndrome in an asymptomatic or mildly symptomatic cohort has a very poor predictive value

. A type 1 pattern can be elicited in up to 50% of Italian and in 85% of German-French healthy, asymptomatic individuals with a type 2 or 3 pattern [82-84].

It is interesting to note that there was more positive tests in asymptomatic subjects than in symptomatic or familial cases, which raises scientific, ethical and legal questions on these, sometime unsafe, challenges [85-87].

In these and other published studies, severe limitations are noted because of the low prevalence of the true syndrome, the low event rate and the short follow up period [83].

A correlation of the drug challenges with genetic abnormalities has no evidence: Brugada [11] initially proposed a 100% correlation between SCN5A carriers and the spontaneous or drug inducible ECG pattern, but this assumption was not confirmed [88]. Priori demonstrated, that the test might be negative in as many as 80% of asymptomatic gene carriers [89-90]. These drugs are not specific for the syndrome, as normal subjects, and patients with right ventricular cardiomyopathy may show similar ECG changes [27, 91-92].

A simpler explanation for the effects of Flecainide does not involve repolarization or ionic channels but drug-induced conduction abnormalities, as documented in an old study[93]. When Flecainide is injected in these subjects with a possible latent conduction disturbance, the first thing to be expected is a maximal deterioration of depolarization with conduction delays, and not a repolarization abnormality. This is simply and well demonstrable by recording late potentials after the drug is given. [27, 94].

In four true patients with type 1 ECG, Miyazaki [95] demonstrated that ST elevation was augmented by selective stimulation of alpha adrenoceptors or muscarinic receptors or by class 1A drugs, but was mitigated by beta-adrenoceptor stimulation or alpha-adrenoceptor blockade. Other limited experiences with adrenergic drugs have partially confirmed these data [96].

The ECG during Effort

Sumiyoshi [21] reported syncope after effort in a female patient with the syndrome, with late VF during sleep. Since the historical paper by Douard [97], little interest has been devoted to the study of effort-related symptoms and the syndrome. At present time there is not a single published report of sudden death during effort in a patient with the syndrome.

One athlete had sustained monomorphic ventricular tachycardia during sport activity [98] but no symptoms during exercise stress test in hospital, where the J-ST pattern increased significantly during recovery. Another athlete with type 1 ECG had syncope and palpitation during cycling [99], but nothing during exercise test.

Also in non-athlete, symptoms are almost never related to efforts, and ventricular tachycardia during stress test has been only anecdotally reported [100]. Despite these limited evidences all guidelines and consensus paper discourage people with the discussed ECG to practice sports [101].

For what concern the ECG pattern (both in patients and asymptomatic subjects), Nademanee observed that during exercise stress test the ECG normalized in 25% of type 1 ECG, and then reappeared at the recovery phase [102]. Guevara Valdivia [103], observed a similar pattern with normalization during the effort, and reappearance of the ST elevation during the recovery phase. In another subject, the ST anomaly occurred during effort and disappeared at the recovery phase. Amin [104] evidentiated that QRS duration and both J

point and coved ECG were enhanced during peak exercise (representing a stress induced conduction abnormality) and further during recovery in subjects with spontaneous or induced ECG; this pattern was not related to SCN5A abnormalities. No arrhythmias were induced in this population. Another conspicuous series confirmed that in 37% of type 1 ECG, this pattern is augmented at early recovery, and might have some negative predictor for future events [105]. Unmasking of type I Brugada ECG only in the recovery phase of exercise and during vaso-vagal reaction, has been described [106]. It is however of relevant interest that patients with right ventricular cardiomyopathy may also show ST elevation during exercise stress test [107].

Similar ECG in Different Situations

A recent review summarized the same or similar ECG patterns that have been recognized in different pathological, physiological or drug induced conditions [108]. In this and other review it is of relevant interest that the same ECG patterns are not so rare in patients with a definite diagnosis of ARVD/C [109-111].

These patients may also show similar ST modification after ajmaline [92].

Further Non–Invasive and Invasive ECG Evaluations

Since its first presentation [1], vectorcardiographic analysis is rarely performed but it shows some interesting features: The end of the QRS loop does not coincide with its beginning, and its distance depends on the degree of ST elevation. There is right superior and posterior conduction delay that probably suggests a partial block of fibers that approach the right ventricular outflow tract (Figure 2). This nowadays forgotten cultural approach to the electrical activity of the heart, helps to differentiate type 1 ECG from incomplete RBBB [4, 112]. Vectorcardiography provides informations on the terminal QRS, and indicates the presence of delayed depolarizations or late potentials (LP) caused by an organic heart disease. LP are however better recorded at signal averaged ECG study, where they are frequently positive (up to 70%) [113] (Figure 4). Late potentials may also be recorded at right ventricular outflow tract (RVOT) level during endocavitary recording, at body surface mapping, and at direct epicardial recordings [114-116]. Positive late potentials are more frequently found in patients with subsequent arrhythmic events [117].

As a rule, they can be recorded after Flecainide challenge [27], demonstrating that this drug could induce a late depolarization rather than an early repolarization abnormality. Late potentials are less frequent in type 2 and 3 ECG patterns that might indicate a true functional origin of these ST abnormalities. Nademanee [17] has highly enhanced the role of late potentials by simply demonstrating that the ablation of late depolarization waves (obviously linked to an organic substrate), at the epicardial surface of RVOT, eliminated the ST segment elevation. Thus the initial hypothesis by Osher [7] that the delayed repolarization at the RVOT level was responsible for an unusual ECG pattern has been confirmed after 50 years of heavy discussions. T Wave Alternans (TWA), indicating a repolarization abnormality, is positive only in 16% [118]. T wave alternans (both spontaneous or drugs/fever induced) and random T wave changes have been described in the syndrome, and their origin has been

attributed to heterogeneity of infundibular action potentials [119, 120] not excluding a local conduction disturbance. A controversial exist on their clinical usefulness [121].

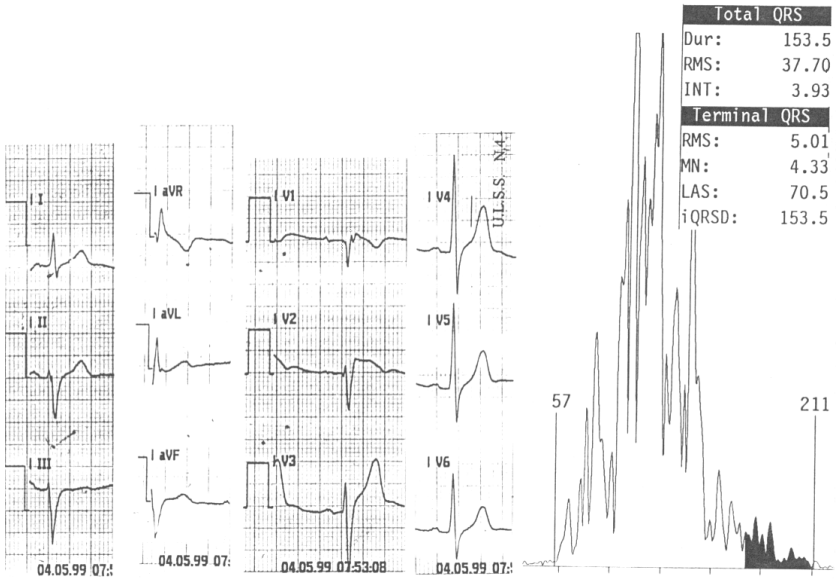

Figure 4. Basal ECG and Late Potentials study in a familial case of the syndrome associated to SCN5A homozigotic abnormality and structural heart disease. The ECG trace shows a prolonged PR interval, left axis deviation and a fragmented J point very similar to an epsilon wave and ST elevation. At signal averaged ECG study, there is a marked prolongation of depolarization, coincident with J point fragmentation.

Arrhythmias Linked to the Syndrome

Patients with the true syndrome develop VF or polymorphic VT. Repetitive monomorphic premature ventricular contractions (PVCs), mostly of LBBB morphology (with superior or inferior axis) are observed initiating ventricular tachyarrhythmias in more than 2/3 of cases [32]. Before the onset of VF, these PVC increase their intensity, and this is sometime associated also with increased ST segment elevation. There were no seasonal differences in cardiac arrest in the patients but a higher incidence of this event can be observed from midnight to 6:00 AM at least in Asian population [122]. In this population however, serious sleep disorders can be recorded, that indicate that the sudden nocturnal death syndrome has not yet a clarified mechanism [80, 81]. The long coupling interval (usually 300-380 milliseconds) of triggers, or their Purkinje origin, does not support epicardial phase 2 reentry [32]. These PVC, are usually abolished during exercise, or with adrenergic stimulation. Endocardial mapping of these PVCs can detect the earliest ventricular activation within the right Purkinje system or from the right ventricular outflow tract. Ablation of these PVCs can successfully abolish recurrences [15]. Severe arrhythmic storms are a rare but dramatic occurrence [123], and seems to well respond both to isoproterenol and quinidine [96, 97,124]. Cardiac Transplant is the last resource [125].

Sustained VT is a rare but well described arrhythmia [126] in this syndrome, clearly associated to a structural reentry circuit. Most of the cases show a LBBB morphology, and different axis [34]. RBBB morphology is not so rare [127].

The patients with major ventricle arrhythmias may have few premature contractions during Holter monitoring. The morphology of these ectopics is usually LBBB, mainly with an inferior axis, but RBBB morphology may also be recorded, with some correlations with genetic abnormalities [128].

Atrial arrhythmias [130] can be encountered in up to 20% of the true patients [130-131], and can be simply associated with a more advanced disease andto common genetic abnormalities[132]. It is not proven that patients with persistent atrial fibrillation and in whom a type 1 or 2 ECG pattern is induced after class 1C therapy have the syndrome [133]. Recent series still however include these patients in the syndrome [134].

Intra-Cavitary ECG Recordings and Stimulation Studies

Investigations evidentiated a prolonged HV interval as a frequent finding, mostly in the cases with major conduction abnormalities [1-3]. Prolonged HV interval is always a pattern of organic heart disease of the conduction system. Marked fibrosis of the conduction system has been shown to underlie this finding [8, 9]. Activation maps during stimulation from the AV nodal area in another patient with histological proven heart disease showed a normal rapid spread of activation of the left septal endocardium and of the LV; in the RVOT, crowding of isochrones indicated slowed conduction. The entire RV wall (endocardium and epicardium) was activated relatively late [125]. High resolution Electro- anatomic mapping, has further confirmed these underlying structural right heart diseases [135, 136], but this technique is unfortunately rarely used during routine electrophysiological study, which is mainly devoted to induce ventricular arrhythmias rather than understanding their origin and underlying mechanism (Figure 5).

Few but relevant studies have however indicated that this mapping reliably documents areas of slow conduction, particularly at the RVOT level [137-140] (Figure 5). In this area most of the isolated premature contractions have origin [128], and it is the best site to induce VF with premature electrical stimulation (PES) [2].

In this area radiofrequency ablation can be “curative” both experimentally [114, 140] and clinically [16, 17]. RVOT is a complex embryological structure [141], where different structures fuse together, creating a mixture of structural and physiological properties, uncommonin other myocardial regions.

From these area where depolarization and repolarization peculiarities can simultaneously be present [120, 142,] both benign [143] and lethal ventricular arrhythmias originate. VF and/or PVT are easily inducible both in symptomatic patients and asymptomatic subjects with the discussed ECG. Brugada could induce VF in 73% and 33% respectively [144], but some Japanese studies reported higher percentages of 92 and 64% [145].

The PES protocol and site of stimulation probably explain why the percentage of asymptomatic individuals with inducible VF was (much) higher in the Japanese studies.

Significantly more patients and subjects with inducible VF have their arrhythmia induced from the RVOT [145]. A prolonged HV interval is more frequent in inducible patients.

At present time the value of EP-studies, particularly in asymptomatic patients, is not robust enough to guide therapy. It is unclear why PES has only prognostic value in asymptomatic patients with a spontaneous type 1 in the hands of the Brugada brothers [146].

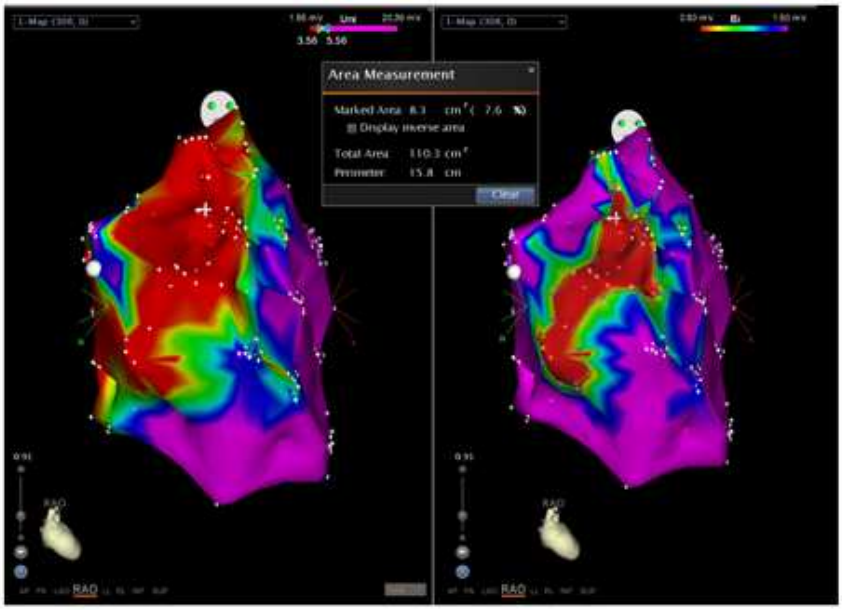

Figure 5. Electroanatomic mapping of the RV (RAO view, unipolar and bipolar recordings), show significant scares at the RVOT, consistent with a structural abnormality that underlies a conduction disturbance. (Courtesy of Dr. Marras, Corò and Delise).

2D Echocardiogram, Nuclear Magnetic Echocardiography, Resonance Studies (NMR), Radionuclide Angiography and Electron Beam Tomography

2D echocardiography usually excludes a structural heart disease in almost all series, but the accuracy of this investigation in the detection of subtle abnormalities is operator dependent [147]. A very careful analysis [148, 149] can however detects subtles abnormalities. A cardiac NMR study was firstly reported by D'Onofrio [150], who documented a fatty replacement of the RVOT in one patient with a true syndrome. Nine years later Papavassiliu confirmed an enlargement of the right ventricle, particularly of the RVOT and localized fatty replacement. These findings however did not reached significance in the first paper, but were relevant in the second study where only type 1 patients were enrolled [151], similarly to what found by Catalano [152] and Van Hoorn [153]. Other series [154] recently reached different conclusions, but these latter included subjects with a limited probability of having the true syndrome (females and drug induced ECG). According to Santangeli [155] however, Late Gadolinium Enhancement is significantly less sensitive than Electro Anatomic Mapping in identifying RV cardiomyopathic substrates (small scars), particularly at the RVOT level. Electron beam tomography has also been rarely used to study the RV in this population by Tada [156] and Takagi [157], and again RVOT and RV abnormalities were detected. At Radionuclide Angiographic study, Rouzet [158] assessed that

RVOT contraction was delayed in patients with BS, and RV contraction heterogeneity increased according to the pattern of ST-segment elevation, without impairment of the amplitude of contraction.

RV volumes were greater in patients with BS compared with control subjects, without impairment of the ejection fraction, whatever the ST-segment elevation pattern or the magnitude of contraction heterogeneity.

Cardiac Angiography

Despite the extensive use of invasive electrophysiologic study in these subjects, limited data are available regarding the angiographic study of the left, and especially the RV, where some minor abnormalities were initially described [1-2], and recently confirmed by Durthoit [159]. A diagnosis of normal versus abnormal right angiography is often controversial in those frequent cases in which the anomaly is much localized.

A relevant role in the study of the RV is the operator experience and to the protocols utilized [160]. The first published image of a diagnostic angiography by Proclemer [161] was highly criticized by Brugada [162]. It is of notice that in the report by Remme [163] RV was retained normal in patients with a subsequent diagnosis of ARVD/C at necropsy study. As suggested by high experience colleagues, [159, 160], a single postero-anterior view has a limited accuracy in detecting minor abnormalities of the right ventricle, and multiple views, are required for a correct diagnosis. A correlation between any detected anomaly and electro-anatomic mapping, highly increases the accuracy [135-139].

Genetic Studies

The disease is clearly an autosomic dominant entity with variable expression, mainly affecting males, and possibly more frequent in Asia [1, 5, 164]. After the paper from Chen [13], a rush in the genetic studies has described hundreds SCN5A abnormalities, leading to authoritative classification of the syndrome among the channellopathy, without any clear evidence-based data. Specific genetic mutations of ion channels are not yet part of the diagnostic criteria of the Syndrome according to fair admission by leading authorities.

According to Hoogendick [165], and despite biologist, geneticist-cardiologist and industry pressure, a causative role of genes in the patho-physiology of the syndrome is still a hypothesis. The disorder and/or the ECG are clearly familial in a relevant number of patients but a Mendelian autosomal dominant pattern of transmission cannot explain the syndrome. Chen in 1998 identified SCN5A missense mutations in three out of six families with idiopathic ventricular fibrillation and the abnormal spontaneous or drug- induced ECG in some members [13].

Thus far, more than 300 mutations in 12 genes have been associated with the syndrome [165, 166]. Most of these mutations reduce the cardiac sodium current (I_{Na}) and are located in *SCN5A* [13], the gene encoding the cardiac sodium channel, its β-subunits *SCN1B* and *SCN3B* or in *GPD1L* and *MOG1*, which are thought to impair trafficking of the cardiac sodium channel to the cell membrane [167-170]. Other mutations associated with the Brugada syndrome reduce the L-type calcium current (I_{CaL}) and are located in *CACNA1C*, *CACNB2b*

and *CACNA2D1*, which encode the α1-, β2b-, and α2δ-subunit of the L-type calcium channel [171, 172].

Lastly, mutations in *KCNE3* which encodes MiRP2, a β-subunit of several potassium channels, in *KCNJ8* encoding the ATP-sensitive potassium channel, and HCN4 that cause a reduction of pacemaker current, have been associated with the Brugada syndrome [173, 174].

What is evidenced from the published studies is that SCN5A-related patients (especially the younger [17, 177] have greater defects in impulse propagation (longer PR, HV, QRS duration), more severe QRS fragmentation and late potentials [40, 178-180]. Patients and relatives with a truncated protein might have a more severe phenotype. It is relevant that 2-5% of healthy individuals host missense SCN5A variants, leading to a potential conundrum in the interpretation of genetic results [181-183]. In blacks (that are so rarely affected by the syndrome), SCN5A variation are common [183], and can be related to PR prolongation [184]. Mutations of SCN5A genes have been found in patients with Long and short QT Syndromes [185-186], Early Repolarization Syndrome, Lev-Lenegre Disease, Idiopathic Ventricular Fibrillation, in dilated cardiomyopathy, in sinus node dysfunction and in atrial fibrillation [187-189].

Van Hoorn [153] reported that mutations were associated with increased cardiac dimensions and reduced contractility. Interestingly, the patient submitted to necropsy study in our initial report [2, 9] had both ARVD/C and SCN5A abnormalities present in his family. Frustaci [190] reported one more case. In the presence of an anatomic substrate (an area with slow conduction in RVOT), SCN5A abnormalities could have a strong role [77].

Only one family has been reported with a novel SCN5A missense mutation, R814Q, in homozygous, and this was associated with a coved ST, epsilon waves, sustained ventricular tachycardia of left bundle branch block morphology and structural right ventricular abnormalities [34]. A homozygous mutation has also been reported in a severe, recessive type of cardiac conduction disease [191], but without the discussed ECG. SCN5A mutations accounts for 75% of global anomalies [78], while the calcium channel mutations account for 10-15% of the published papers.

These mutations have been suggested to increase repolarizing currents activated early during the action potential, but clinical and laboratory role that these mutations play in the syndrome is subject of debate. Nine of the 11 genes other than SCN5A currently believed to be associated with the syndrome have been identified by the candidate gene approach, in the absence of linkage-analysis and definitive familial segregation and their disease-causation, suggested by the absence of the specific rare variants from control.

Patch-clamp studies could not clarify how SCN5A mutations can be responsible for such a large spectrum of disease and genetically modified mice are proposed as an interesting but still promising and non-specific tool [192]. This scientific mess caused by geneticist-cardiologists needs new evidence based rules. The major problem is that data are so lacking in the population with the true syndrome (spontaneous type 1 ECG and severe symptoms), as most of the reported series deals with unselected populations including true patients and healthy individuals with overt, masked and induced similar ECGs. In Kapplinger's report [182], the most common (missense) mutations, which possible pathological significance are poor [193], are located in *SCN5A and* can be identified in approximately 21% of people "accepted for genetic testing simply if the referring physician had made a clinical diagnosis of either possible or definite syndrome, and also if "an ECG was not always available" [182]. In

this poorly selected population, positive genotype alone is not an independent risk factor for lethal events.

Roden [194] asked in an editorial note: What causes the syndrome in the remaining 79 %? In a more selected high risk (Japanese) population, an anomaly was found in 15% (195). Also Probst [196] in his series utilized a spontaneous or induced ECG as major diagnostic criteria, and found SCN5A anomalies in 26% of type 1 ECG. Thirteen of them belonged to 13 families with 115 carriers.

Eight individuals had type 1 ECG but not mutations. Type 1 ECG was spontaneous only in 18% of these, reaching 61% after drug challenge.

A family history of sudden death was present only in 3/12 families, and the probands did not have a severe clinical history. With this unclear selection the results created confusion between positive and negative phenotype and genotype; the only possible conclusion is that 26% of individuals (not syndromes!) with a spontaneous or induced ST elevation have some SCN5A abnormality.

As pointed out by Marian [197]: "by definition, the causal mutation cannot be absent in family members with the phenotype.
Expression of the Brugada phenotype in family members without the index *SCN5A* mutation, nonetheless, necessitates considering the possibility of another causal gene". In a following paper, Probst [24] increased his series to 808 individuals with spontaneous (43%) or induced type 1 ECG. He reported SCN5A mutations in 24% of survivors of cardiac arrest (spontaneous type 1 only in 50%), in 26% of syncope group (spontaneous type 1 in 54%), and 30% of asymptomatic individuals (spontaneous type 1 in 41%). In the screened families the prevalence of the gene abnormalities (not associated with the syndrome or the ECG) was 52%.

Hermida [198] and Santos [199] recently respectively reported a 43% and 40% familial prevalence of the gene anomalies (not the syndrome!!), with more pronounced conduction abnormalities in the carriers. In another, mostly ECG-based study Bai [176] had a positive genotype only in 13%. This author calculated that the cost per one positive genotyping was US $ 21,441. This should discourage indiscriminate use of this test, until evidence based data on its utility are available.

According to the hypothesis that the syndrome could be the cause of otherwise unexplained cases of sudden death, a "molecular autopsy" has been proposed, but cardiac channelopathies associated with structurally normal hearts such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and BS, leave no major evidence to be found at autopsy [200].

Thus, despite the term channellopathy to classify the syndrome is so popular, and it has been admitted that SCN5A gene abnormalities may be found only in a small proportion of patients [201], genetic testing however is still a Class I recommendation for family members and appropriate relatives following the identification of the BS-causative mutation in an index case [78], while it is a Class IIa recommendation (limited to SCN5A genes mutations) for any patient in whom a cardiologist has established a clinical index of suspicion for BS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype. Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG patterns [78].

The rush for new SCN5A gene abnormalities has forgotten other genetic abnormalities, including isolated demonstration of mapping in the same loci of right ventricular cardiomyopathy [91, 202]. Thus, the genetic analysis of the disease must be considered as an on-going process.

Experimental Findings

The pioneer experimental study of Yan and Antzelevitch [13, 203], proposed to ascertain the lacking patho-physiologic basis of the syndrome, and completing the pathway to the promotion of a "syndrome" to a "disease" status. These outstanding studies derived from their research to explain the J wave of early repolarization in the "precordial leads" on a "left" ventricular wedge. As left J wave was similar to right precordial elevated J point, their subsequent studies were mainly devoted to this pattern, assuming that the two entities belonged to the same patho-physiologic pattern. The theory of impaired repolarization proposed in 1999 [203] was based on a non-homogeneous expression of the transient outward potassium current (I_{to}) between epicardium and endocardium. I_{to}, which is responsible for the early repolarization phase (phase 1 notch) during action potential (AP), is more strongly expressed in the epicardium, contributing to a "spike and dome" in AP. The phase 1 notch deepens in the presence of a loss or reduced function of the sodium channels. Progressive deepening of the phase 1 notch can first delay the activation of I_{CaL}, leading to a prominent dome and late repolarization. Further deepening of the phase 1 notch can prevent the activation of I_{CaL}, abbreviating AP. These effects on AP are more evident in the epicardium layer of RVOT, where the I_{to} is the strongest, resulting in simultaneous presence of APs with and without a phase 2 dome and long and short AP duration in the epicardium and across the wall of RVOT [118, 141]. A discrepancy in the AP shape between the endocardium and epicardium result in the surface BS ECG patterns. Abnormalities in the surface ECG are proportional to the discrepancy in the AP, creating slight ECG alterations (saddle-back ST elevation, J point <0.2 mv) or marked ECG alterations (cove type, J point >0.2 mv) according to the degree of sodium channel damage and the different I_{to} expression. Male hormones enhance I_{to}, thus, contributing to a male prominence of BS. Temperature modulates the shape and duration of AP, promoting the expression of BS type ECG at hypothermia and occurrence of arrhythmias at hyperthermia [54]. The conduction of the AP dome from sites where it is maintained to sites where it is lost provokes local re-excitation via a phase 2 reentry mechanism with a closely coupled extrasystole occurring during the vulnerable period. These PVC may then trigger malignant ventricular arrhythmias. Despite the well-known assumption that a "wedge is not a heart" this theory has become very popular among scientists, leading to a so relevant number of correlated experiments that have not been confirmed in the entire heart [125], .

Embryologic Studies

Elizari has recently conducted an outstanding embryologic study on the RVOT, and has proposed a theory, based on the abnormal expression of the neural crest on myocardial development of the RVOT and surrounding structures [141].

During embryogenesis, the cardiac neural crest plays a critical role in morphogenesis of the RVOT, which comprises the free wall and the aorto-pulmonary septum, and the great arteries.

A population of cardiac neural crest cells migrates toward the arterial pole of the embryonic heart leading to myocardial cell proliferation, differentiation and RVOT myocardialization. A second population of migratory cardiac neural crest cells enters the heart via the venous pole and plays a crucial role in the formation of the AV node, the His bundle, the beginning of the bundle branches, and atrial tissue. This pivotal study is very important as it enhance the embryological complexity of the RVOT that could lead to different structural abnormalities and to many different ventricular arrhythmias originating from this area [143, 204-207]. A detailed analysis of this structure [207] will limit in the future the so called cases of “idiopathic” ventricular arrhythmias.

Bioptic Studies and Autopsy

The "gold standard" investigation, to make a correct diagnosis and to quantify both the specificity and sensitivity of other different investigations is still necropsy study, while biopsy seems less important due to the impossibility or to dangerousness to examine only pathological localized areas of the right ventricle, namely the RVOT. Nowadays there are very few cases of autopsy in these patients (Table 1), and all have evidentiated both fibro-fatty substitution mainly of the RVOT and some conduction system disease [8, 9, 125, 156, 163, 208-210]. Biopsy study (Table 1) has been reported more frequently, with controversial results [2112-219]. Anecdotal studies by Gotoh and Kirshner [220-221] evidentiated significant histological lesions of the conduction system in the vast majority of Asians died suddenly at night (in whom the syndrome could retrospectively been suspected). Nowadays a normal heart belonging to a patient with the syndrome has never been reported. Our first reported patient with the syndrome had atrophy, fibrosis and adiposis of the right free wall [8, 9]; this patient also had an unusual lesion of the conduction system characterized by sclerotic interruption of the right bundle branch and by severe fibrosis of the bifurcating bundle. The right ventricular free wall showed bundles of viable myocardium. According to these findings, the conduction disturbance fit well with a septal and parietal conduction abnormality. The free wall lesions, particularly at the infundibular level, are compatible with a second conduction disturbance, at the end of ventricular depolarization.

Thus the right bundle branch block (in our hypothesis), might be explained by a His an Right bundle lesions, and the ST segment elevation by late depolarization of the RVOT. It was not easy until recently to accept that the ST elevation in this syndrome is a depolarization abnormality of the RVOT, but the presence of epsilon waves, f-QRS and late potentials could be ascribed to nothing else.

We have never been sure if the diseased right ventricle was a typical right ventricular cardiomyopathy, as most of the patients do not have the other typical features, including genetic profile. At the present time only one of our patients with the typical ECG, had a family history of right ventricular cardiomyopathy associated with an ARVD/ C chromosome 14 involvement [91].

It must be admitted however that the detailed and authoritative pathologic examination of a heart is not the rule, and some relevant different opinions between pathologists may exist

according to their experience [210]. As written before, biopsy is an interesting but a very controversial investigation that has led to so different findings (Table I), possibly due to different population examined, but also to different techniques.

Table 1. Patients with the syndrome and some structural abnormality at biopsy, autopsy

Author	Number of patients/sex	Ecg type	Biopsy	Autopsy
Martini [2]	2 M,1 F	2 type 1, 1 type 3	2 Fibro/fatty susbstitution	1 ARVC/D
Sumyoshi [21]	1 F	Type 1	Fibrosis	
Brugada [211]	16	Type 1-2	"non specific abn."	
Tada [118]	2 M	Type 1	6/6 EMB negative but ARVD in one direct biopsy during open heart surgery	1 ARVD/C
Morgera[212]	1 M	Type 1	Fibro-fatty replacement	
Izumi [213]	1 M	Type 1	Fibrosis	
Remme [163]	9	Incomplete RBB + inverted t wave V1	All negative	1 ARVD/C: 1 pt with incomplete RBBB and inverted t waves
Corrado [8]	13 M, 1 F	ST segment elevation		all patients had ARVC predominant fatty replacement of the right ventricular anterior wall (92%) except one, who had no evidence of structural heart disease
Morimoto [208]	22+3	?	8/22 byopsy: Fatty infiltration in. Minor abnormalities in the remaining	3 autopsy: marked fatty infiltration (2 in the RVOT)
Buob [214]	1	Type 1		
Coronel [125]	1	Type 1 (drug 1c)		Right ventricular hypertrophy and fibrosis with epicardial fatty infiltration
Frustaci [215]	15 M, 3	Type 1-2	right ventricular myocarditis in 14 patients, viral genomes in 4; ARVD/C in 1; and cardiomyopathic changes in 3	
Morimoto [209]	1 M	Type 1		fatty replacement of the rvot. FF of sinus node
Kim [216]	14	Type 1	7/14 had fibro-fatty sustitution	
Fontaine [210]	1 M	?		1 ARVD/C
Marras [217]	1 M	Type 2	fibro-fatty replacement	
Zumhagen [218]	16 M, 5 F	type 1 (11 only after ajmaline)	Fibro-fatty replacement in 75%	
Ohkubo [219]	24 M, 1F	Type 1-2	Fatty replacement in 47.6%	

Biopsy does not seem so relevant for the detection of some structural heart disease, as noninvasive investigations like late potentials, electro-anatomic mapping and nuclear magnetic study can probably provide accurate data [157], also if different opinion on their significance has been proposed [222].

Other Clinical Features of the Syndrome: Role of the Autonomic Tone

Autonomic tone plays a role in this syndrome, and might be responsible for the dynamic behavior of the ECG, and for the high prevalence of event at rest or at night time, that highly suggested a functional abnormality [21, 73, 223, 224]. Further confirmation derives from ST segment elevation after effort of drug challenge and after meals, and in response to autonomic drugs, as being previously discussed. Differently from Miyazaki [9], an abnormal 123I-MIBG uptake can be found in patients with Brugada syndrome, indicating presynaptic sympathetic dysfunction of the heart [225-228]; he also demonstrated with heart rate variability study that high vagal tone and low sympathetic tone are specific properties of symptomatic BS. Yokokawa [22] recently confirmed that 35% of patients with type 1-2 ECG showed vaso-vagal responses during the Head Up Tilt Test. This should discourage to include syncope (unless a neuro-mediated reaction can be clearly excluded), in the risk stratification of the syndrome.

Risk Stratification and Therapy

Annual rate of lethal event ranges from 4.1% in Brugada series [229, 230], to 1.1-1.6% in recent series (0.5% event per year for both spontaneous and induced type 1 ECG (in 60%), in the Finger and other studies, [24, 41, 231].

The peak incidence of symptoms is in the third and fourth decades of life [232]. Indicators of high relative risk of sudden death associated with the syndrome include a personal history of aborted SCD or syncope (RR 3.51), the spontaneous presence of a type 1 ECG pattern (as opposed to a drug-induced type 1 pattern) (RR4.65), male gender (RR 3.47), and South-East Asian origin. A family history of sudden death and SCN5A mutation status do not carry an increased risk of sudden death. Many asymptomatic subjects have been and are still submitted to ICD implantation only because of a spontaneous or drug induced type 1 ECG, because of doubtful symptoms, family history, abnormal cardiac stimulation study, genetic abnormalities, etc., with very low consideration of the high rate of procedure related-complications [233]. After a relevant metanalysis [234], this asymptomatic healthy population has been deserved of major attention, and most of the authors now agree that ICD implantation should be a class 1A indication only for aborted sudden death or arrhythmic related syncope, in patients with a spontaneous type 1 ECG [235]. The electrophysiologic study, particularly, has not more a relevant predictive value for most of the authors, although different respectable opinions still consider this test as highly necessary. Registries and not personal series are needed to clarify the problem. Interesting results have been recently seen with quinidine [124] and with ablation [15, 17]. Some anecdotal patients treated with beta-blockers or amiodarone did not have however any relapse [1, 27]. A limited number of cases with electrical storms have been successfully treated with isoproterenol infusion [236].

CONCLUSION

This rare and sometime lethal syndrome is still in search of its identity, after having lost his paternity soon after birth [1, 5]. The initial theory that this new familial syndrome was related to a conduction disorder mainly at the RVOT level [1, 2, 9], after two decades of heavy discussions and criticism [237-241] has received recently authorital confirmations [114, 137, 138, 242-248]. Surface ECG, late potentials, HV interval, endocavitary recordings and mapping clearly indicated this electrical abnormality. The rare but increasing number of evidence based data confirms that the conduction delay may predominantly be related to a structural fibro-fatty substitution of the RVOT, histologically similar to ARVD/C, but mainly localized to the RVOT and the conduction system, and with a different genetic substrate. It is well known that different heart diseases can affect the RV, and that these different entities can produce similar structural lesions. The research in this syndrome should be addressed to the identification of minor structural abnormalities rather than to defend aggressively the theory of an idiopathic syndrome, only because some functional factors, the autonomic system, fever and drugs undoubtedly concur to the clinical picture. The future evidence-based definition of the cause of these structural abnormalities will be the last frontier that will transform a syndrome into a disease [249]. The oncoming studies should clarify the role of embryology [141, 250], the similarity with ARVD, the importance of new genetic abnormalities different from those well-known (SCN5A), but inconclusive. The roles of geneticist-cardiologist and that of wedge preparations will maintain importance, but they should not prevaricate the clinical work. A wedge is not a heart. Well controlled clinical and epidemiological surveys must clarify the true prevalence of a strange ECG and its role in inducing a so rare lethal event. The ECG interpretation should not start from a classification in types, angles, index etc. , but should review all the true published clinical case, avoiding those drug induced. We all are so ignorant on this rare but now popular “Media” syndrome, but we cannot passively accept the statements of hundreds of published papers where some authors apply a “copy and paste” procedure rather than trying to think with their own mind and give personal experience and contribution.

This common ignorance (mine first!)does not further justify the extensive use of drugs challenge, invasive investigations and consequent invasive therapies [251, 252]. The J-ICD reflex must be abandoned, and asymptomatic people must let live a normal life, do their sport activity, avoid the frightening consultations provided by Google and to see from time to time their wise cardiologist who is in charge to reassure these healthy individuals and not to terrify them, passively accepting the suggestions of the last published uncontrolled paper. A clinical follow up and noninvasive risk stratification is the only serious approach suggested at present time. We need to learn more before to cure a healthy individual, who so rarely needs a therapeutic intervention that can be at induced higher risk [234] than the estimated 0.5% per year risk of a spontaneous serious clinical event [24].

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