Point of view

1988-2003. Fifteen years after the first Italian description by Nava-Martini-Thiene and colleagues of a new syndrome (different from the Brugada syndrome?) in the *Giornale Italiano di Cardiologia*: do we really know everything on this entity?

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Introduction

The syndrome of right bundle branch block (RBBB), ST-segment elevation and sudden death was first described in 1988 in Italy by Italian doctors from Padua in the *Giornale Italiano di Cardiologia*[1,2], in *Mises à Jour Cardiologiques*[3] and in the *American Heart Journal*[4]. This syndrome is now known worldwide as the "Brugada syndrome", reflecting the name of those who described later the same entity in 1992[5].

At present, 622 papers on this syndrome (excluding our four initial papers) are reported in the Internet site (http://www. brugada.crtia.be). In more than 20% of cases some form of organic heart disease has been recognized, mainly of the right ventricle, while in the vast majority of patients a structural abnormality has not been identified. This may be due to the fact that the investigation was incomplete. This has led to two different theories on the pathophysiology of the syndrome: one relates the precordial ECG to a depolarization abnormality or to an organic heart disease whereas the second ascribed the syndrome to a functional abnormality of repolarization (http://digilander. libero.it/martini_syndrome).

Historical notes

In 1953, Osher and Wolff[6] reported a dynamic ECG abnormality (Osher-Wolff ECG), simulating an acute myocardial infarction, in a healthy man. It is of interest that they wrote: "This is apparently due to prolongation of the depolarization process by right bundle block or possibly focal block with delayed activation of a portion of the right ventricle: unusually early onset of repolarization may also play a role".

A similar ECG pattern, this time associated with an aborted sudden death and occurring in a 42-year-old male while talking with a post officer on the 2nd of October 1984, was seen in Padua, Italy. In the following years incomplete details were given on similar patients[7,8].

A new "syndrome" characterized by a clinical event (sudden or aborted sudden death) associated with the abnormal ECG findings, was first presented at the National Congress of Italian Cardiologists, held in Florence, by Nava, Martini, Thiene and colleagues, working in Padua with Professor Sergio Dalla Volta in 1988[1,2]. Shortly after, Nava et al.[3] published the first ECG characteristic of the syndrome in 1988, which is considered worldwide as the typical ECG of the syndrome, and which is now called the "Brugada sign" (Fig. 1).

One year later, a full description of the syndrome was published in the *American Heart Journal*[4]. It is noteworthy that in our paper we re-published not only "the typical"[9], but most of the ECG variations of the syndrome, namely dynamic or isolated ST-segment abnormalities, incomplete or com-
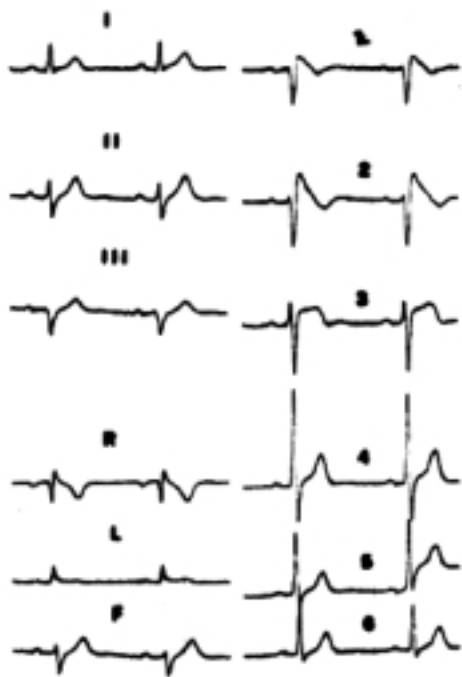
Figure 1. *The syndrome is a clinical ECG association between sudden death, ventricular fibrillation and an ECG pattern of right bundle branch block and ST-segment elevation. This ECG (now called the "Brugada sign") is the first trace of the syndrome published in 1988, 5 years before the article by Brugada.*

plete RBBB, sometimes associated with an atrioventricular and fascicular conduction impairment, and a prolonged HV interval (Fig. 2).

A prolonged PR interval, left axis deviation, some incomplete RBBB and minor ST-segment elevation

were present in patient 4 of our paper. The same patient was re-published by Corrado et al.[10], and that ECG is an excellent example of the dynamic pattern sometimes seen in this syndrome. Despite the typical functional ECG pattern, this patient had anatomical evidence of a right ventricular cardiomyopathy. A complete RBBB morphology was present in patient 1, with only a slight ST-segment elevation in V_1 and V_2. Isolated slight ST/T anomalies/elevation as seen in patients 2 and 5 of our paper[4], 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, was proven both by intracavitary recordings[3] and by signal-averaged ECG[11].

The second description of the syndrome was presented by Aihara et al.[12] in patients without apparent heart disease, and the third by the Brugada brothers[5], 5 years after the initial Italian description.

Further improvements in the evidence-based knowledge of this syndrome came from Naccarella[13] who demonstrated that the typical ECG may occasionally be recorded at a higher precordial level, by Brugada et al.[14] who introduced the class 1C drug challenge and by Chen et al.[15] who reported the first genetic abnormalities[5]. As recently reported by Haissaguerre et al.[16], a possible major step forwards in the cure of this syndrome will be ablation therapy.

The syndrome

The syndrome of RBBB, ST-segment elevation and sudden death is characterized by:
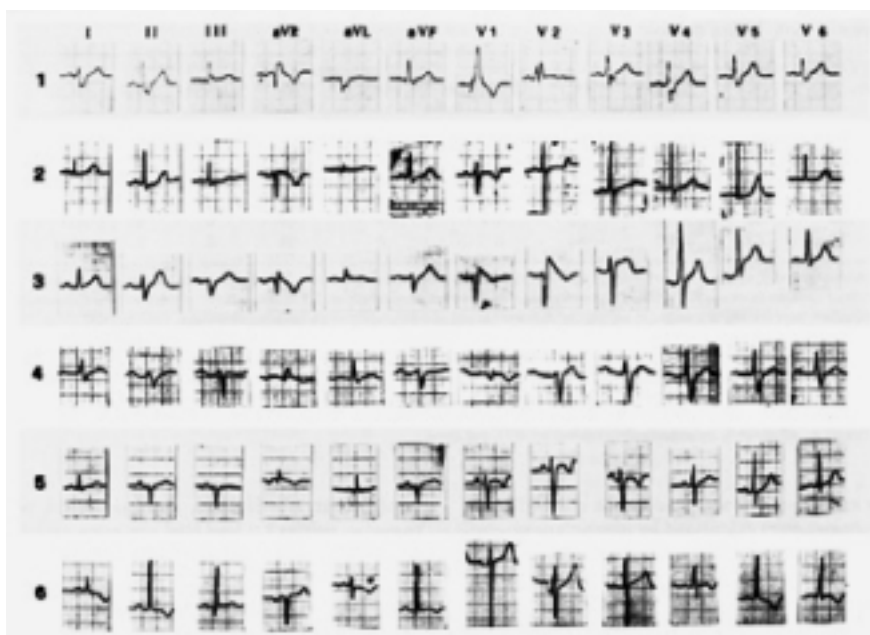

Figure 2. *The ECG of 6 patients with aborted sudden death were reported in 1999. Patient 3 is the same as in figure 1. A prolonged PR interval, left axis deviation, some incomplete right bundle branch block and minor ST-segment elevation were present in patient 4 of our paper[4]. A complete right bundle branch block morphology was present in patient 1, with only slight ST-segment elevation in V_1 and V_2. Isolated slight ST/T anomalies/elevation, as seen in patients 2 and 5, may also be potential markers of the syndrome, possibly modified by drug testing. Patient 6 probably had had a myocarditis.*

• ECG patterns of:

1) different degrees of RBBB and sometimes left axis deviation and a prolonged PR interval[3,4]. The most typical ECG shows an r1 pattern in V_1 (the so-called J wave)[3], followed by a coved ST segment.

Overall, a similar ECG may be encountered in 0.11% of healthy individuals, and in 0.23% of males[17-21]. Much concern is devoted to these healthy asymptomatic subjects (not patients), as some of them underwent implantation of a defibrillator because of easily inducible ventricular fibrillation at electrophysiologic study.

With regard to these subjects, long-term data on the predictive accuracy of this approach are not completely available, despite the fact that interesting data should come from the database of implantable cardioverter-defibrillator companies. On-coming guidelines have accepted the concept that asymptomatic subjects with this ECG should not be submitted to invasive cardiac stimulations unless they belong to a family with a high prevalence of sudden death (personal communication). As a personal experience, not a single asymptomatic ECG carrier died in our area, with a population of 173 000 individuals (which should include at least 173 ECG carriers), in the last 15 years. According to a recent review the lethality for asymptomatic subjects occasionally seen with the ECG seems much lower than 1%[22];

2) ST-segment elevation in V_1-V_3 (which can be an isolated pattern), coved, saddle-like or dome-shaped. This pattern may vary in different observations, and may be elicited by the class 1C drugs flecainide, ajmaline, propafenone, or by fever, antidepressant drugs, etc. ST-segment elevation may occur only during arrhythmic events. A dynamic pattern is not so rare, but it is not a proof of a functional abnormality as it is present even in patients with a documented organic heart disease[10];

3) prolonged HV interval, mainly in cases with major conduction abnormalities[4,5];

4) frequent positive late potentials (70%) at signal-averaged ECG. Late potentials may also be recorded at the right ventricular outflow tract (RVOT) level during endocavitary recording, at body surface mapping and at direct epicardial recordings[3,11,23-26].

As a rule, they can be recorded after flecainide challenge[25], demonstrating that this drug could induce a late depolarization rather than an early repolarization abnormality.

Late potentials usually indicate organic heart disease, even though they may occur in subjects without an evident cardiomyopathy. Antzelevitch[26] has recently proposed a new theory: "the second upstroke of the epicardial action potential, thought to be greatly accentuated in the Brugada syndrome, might be capable of generating late potentials when RVOT activation is otherwise normal". This theory needs experimental and clinical evidence-based demonstrations;

• a very low reported prevalence of the syndrome (not of the ECG): only 1:100 000 in Belgium, but a relevant problem in Southeast Asia (up to 66 per 10 000) where it may be the cause of the nocturnal sudden unexplained death syndrome occurring in young males (Pokkurry death, Bangucut disease). The data are however controversial[27];

• juvenile aborted sudden death;

• familial involvement (autosomal dominant with variable expression)[4,5,25,28,29];

• male predominance;

• high recurrence rate of ventricular fibrillation. The lethal arrhythmia may be easily induced even in asymptomatic subjects with the discussed ECG, which raises problems on the specificity and predictive accuracy of invasive electrical stimulation;

• the fatal event is characterized by polymorphic ventricular tachycardia, which degenerates into ventricular fibrillation. Some patients have episodes of ventricular tachycardia of a left bundle branch block morphology[25]. The mechanism of ventricular fibrillation may be reentry but controversy exists regarding whether the circuit is anatomical or functional[9];

• frequent evidence, after detailed examination (including necropsy in rare cases), of some form of latent organic heart disease, particularly of the right ventricle, characterized by lesions within the main conduction system (His and right bundle branch) and atrophy, fibrosis, adiposis of the right ventricular wall, especially of the RVOT[4,10,25,29-41]. Recently, the consensus conference on this disease[42] discussed that there is not a definite border between functional and organic disease, and Antzelevitch[43] reported that structural abnormalities could be present in the syndrome. His interpretation "as we have previously suggested, loss of the action potential dome, because it creates a hibernation-like state, may over long periods of time lead to mild morphological changes, which include lipid accumulation and fibrosis" needs evidence-based data;

• to our knowledge, there is to date no autopsy demonstration of a normal heart underlying the syndrome, even though this cannot be excluded in the future. None of the 622 references available in the Brugada website describe in detail a normal autopsy case. Moreover some patients, in whom an initial diagnosis of a normal heart was made, had later evidence of structural heart disease[44], namely right ventricular dysplasia/cardiomyopathy[45,46];

• the autonomic tone plays a role in this syndrome, and may be responsible for the dynamic pattern of the ECG. This suggests a functional abnormality. Most of the sudden deaths in South-East Asia occurred at nighttime. This is not, however the case of other populations. Elegant data have been proposed[28,47]. Patients with clear organic heart disease may also share a dynamic pattern, possibly elicited by the influence of the autonomic tone[10,48];

• 58 mutations of SCN5A, a gene on chromosome 3, have been proposed to date, as the pathophysiological explanation of the syndrome. Up to a 50% prevalence

of this finding was initially described[15]. Despite the fact that the term channellopathy to classify the syndrome is becoming popular, it has been admitted in the recent consensus[42] that SCN5A gene abnormalities may be found, not in the vast majority of patients, but only in a small proportion (10-20%), sometimes reaching zero even in high-risk groups[49]. SCN5A abnormalities have also been described in the long QT syndrome, in atrioventricular block, and a recent study has claimed that this abnormality is widespread in some populations[50-52].

Priori[22] recently wrote: "Despite the initial reports rather consistently indicate that Brugada syndrome mutations bear a loss of SCN5A function, more recent data show that they may also be associated with a more heterogeneous phenotype ... *in vitro* expression of such genetic defects was (and still is) not able to gather data fully explaining the link with the clinical phenotype". This opinion confirms that evidence-based correlations between the molecular and laboratory data and the clinical picture are lacking, and again that these mutations in any case do not exclude a coexistent structural heart disease. The patient, submitted to necropsy study in our initial report[4], had a right ventricular cardiomyopathy and SCN5A abnormalities (also present in his family).

Other genetic abnormalities have been detected, including the isolated demonstration of mapping in the same loci of right ventricular cardiomyopathy[53-55]. Thus, the genetic analysis of the disease must be considered as an on-going process;
• laboratory data on this disease have limited evidence-based clinical correlation. The elegant experiments conducted by Yan and Antzelevitch[56,57], who studied the J wave (Osborn wave) as seen in the left precordial leads in conditions of cold temperature and vagotonia, demonstrated that this wave is induced in the left ventricle by the I_{to} abnormality and "provide the first direct evidence in support of the hypothesis that the heterogeneous distribution of a transient outward current-mediated spike-and-dome morphology of the action potential across the ventricular wall underlies the manifestation of the ECG J wave. The presence of a prominent action potential notch in the epicardium but not endocardium is shown to provide a voltage gradient that manifests as a J (Osborn) wave or elevated J-point in the ECG". Again Yan and Antzelevitch[56] "found the spike-and-dome morphology of right ventricular epicardial action potentials to be more accentuated than that of the left ventricular epicardium. Despite the larger notch, the right ventricular epicardium might be expected to make only a minor contribution to the J wave under normal conditions. Because of a thinner ventricular wall and a briefer activation time, the right ventricular epicardial action potential notch occurs during the QRS. Thus, during normal excitation, these cells would be expected to contribute little to the manifestation of the J wave".

According to this assumption the right J wave cannot be recorded at surface ECG without a marked conduction delay.

"The idiopathic J wave has been linked to life-threatening ventricular arrhythmias such as the Brugada syndrome". The loss of the action potential dome (plateau) in the epicardium but not endocardium causes elevation of the ST segment or early repolarization syndrome, similar to that found in patients with the Brugada syndrome. Because the loss of the dome is caused by an outward shift in the balance of currents active at the end of phase 1 of the action potential (principally I_{to} and I_{Ca}), autonomic neurotransmitters such as acetylcholine facilitate loss of the action potential dome by suppressing I_{Ca}, whereas beta-adrenergic agonists restore the dome by augmenting it. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome. The appearance of ST-segment elevation only in the right precordial leads is also consistent with the observation that loss of the action potential is usually observed in the right but not left ventricular epicardium. These observations point to a depressed right ventricular epicardial action potential dome as the basis for ST-segment elevation and phase 2 reentry as a trigger for episodes of ventricular fibrillation in patients with the Brugada syndrome. These hypotheses remain to be investigated".

It is not easy to demonstrate a link between these experiments and clinical evidence[58]. Direct epicardial and endocardial recordings do not confirm the laboratory data: "Monophasic action potential recordings from the endocardium with special focus on the RVOT could not demonstrate any morphological abnormalities in three Brugada patients"[59];
• drug 1C challenge in the syndrome. It has been shown that the intravenous administration of the class 1C antiarrhythmic agents ajmaline and flecainide may unmask the presence of the ECG pattern in patients affected by the syndrome[14]. Brugada initially proposed a 100% correlation between SCN5A carriers and the spontaneous or drug inducible ECG pattern. This assumption was not confirmed by others, and was recently re-discussed[9,42]. Priori et al.[51,60,61] demonstrated that the test may be negative in as many as 80% of asymptomatic gene carriers. It is also debated whether these drugs are specific for the syndrome, as normal subjects and patients with right ventricular cardiomyopathy may show similar ECG changes[25,53].

The observations by Brugada, however, have introduced the extensive utilization of flecainide (or other class 1C agents) to induce the typical J-ST abnormalities. These are ascribed by Brugada to repolarization disorders linked to the shortening of the right epicardial action potential because of drug-induced alterations of the Na^+ channels.

Contradicting this hypothesis, in the perfused right ventricular wedge Yan and Antzelevitch[57] demonstrated that flecainide and ajmaline reduced the notch, and in-

creased the dome, without any J wave or ST-segment elevation. This latter abnormality could be produced only by adding acetylcholine but we know that the clinical ECG pattern is occasionally dependent on vagal drive. Thus, the hypothesis that flecainide induces a repolarization abnormality lacks demonstrable evidence.

A simpler explanation for the flecainide effect does not involve the ionic channels but conduction abnormalities, as documented in an old work by Joseph Brugada[62] in 1992. Clinically, most of the patients with the syndrome have conduction disorders, namely a prolonged PR interval, axis deviation, a prolonged HV interval, and positive late potentials[4,11,25,26]. When flecainide is injected in these patients, the first thing to be expected is a maximal deterioration of depolarization with conduction delays, and not a repolarization abnormality. This is well demonstrable by recording the late potentials before and after the drug, which confirms that flecainide induces major depolarization rather than repolarization abnormalities[25,63];

• risk stratification is a major concern in this population, especially in symptom-free individuals[9,25,42,48,60-65]. Registries are needed to clarify the problem. Therapy with implantable cardioverter-defibrillators is recommended in symptomatic patients, but interesting results have been recently seen with quinidine and with ablation. Some anecdotal patients treated with beta-blockers or amiodarone did not have any relapse[4,25].

Controversial

In our initial papers, not referenced in the European consensus conference[42], we demonstrated for the first time that at least some patients affected by sudden cardiac death because of ventricular fibrillation and a peculiar ECG had an underlying structural heart disease. The first reported patient with the syndrome who had a necropsy study had atrophy, fibrosis and adiposis of the right free wall[4]; 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 disorder fitted well with a septal and parietal conduction abnormality. Many patients, even in the Brugada series, had a diseased right bundle branch with a prolonged PR interval and a left anterior fascicular block. In these patients, the HV interval is frequently prolonged (indicating a His bundle lesion); to date, no functional disease that induces a prolonged HV interval is known.

The free wall lesions, particularly at the infundibular level, well fit with a second conduction disorder, at the end of ventricular depolarization. This is well documented by the intracavitary recording of a late QRS activity at the infundibular level (coincident with ST-segment elevation), and by the presence of positive late potentials. A late activity may be recorded at the RVOT level even during surface mapping and by direct epicardial recording. Simply, the ECG pattern may be revealed by recording the right precordial leads at the third intercostal space[13].

Thus, the RBBB (in our hypothesis) may be explained by a His bundle lesion, and ST-segment elevation by late depolarization of the RVOT. It is not easy to accept that ST-segment elevation in this syndrome is a depolarization abnormality of the RVOT, but the presence of late potentials cannot be ascribed to anything else. In these patients late potentials may be induced by class 1C drugs, which may induce or enhance a conduction abnormality and not a repolarization abnormality.

Our report describing the association between a clinical ECG pattern and an organic heart disease of the right ventricle has been extensively confirmed at autopsy, at *in vivo* examination, and at diagnostic investigation. In the medical literature, it is reported that angiography, nuclear magnetic resonance imaging, electron beam computed tomography, endomyocardial biopsies and echocardiography have extensively documented the presence of organic heart disease, mainly of the right ventricle.

We cannot be sure whether we are dealing with the typical right ventricular cardiomyopathy, as most of the patients do not have the typical features, including genetic study. At present, only one of our patients with the typical ECG, had a family history of right ventricular cardiomyopathy associated with an arrhythmogenic right ventricular dysplasia/cardiomyopathy chromosome 14 involvement[53].

The series of Brugada includes patients with the same ECG patterns: complete RBBB, a prolonged PR interval, left axis deviation, a prolonged HV interval, positive late potentials. The clinical presentation was also similar[5].

The presumption of a functional syndrome derives from the absence of evident organic heart disease in all their patients. Not rarely, however, these patients have "non-specific abnormalities" at angiography and biopsy, but even some patients considered to be healthy are later recognized as being affected by structural heart disease[44]. At present, there is no autopsy proven case of a normal heart in a patient who died because of the syndrome. We cannot exclude the possibility of an underlying functional heart disease or channellopathy in patients with the syndrome, as a lot of outstanding physicians failed to demonstrate any clinical or investigational heart disease in a considerable portion of these patients.

The theories of Brugada and Antzelevitch have constituted the basis for the discussion of this problem over the years:
• 1992: prolonged HV interval suggests His-Purkinje disease, marked dispersion of refractory periods or extreme anisotropic conduction;
• 1994: disorder related to "M cells";

• 1996: I_{to} channel involvement;
• 1998: mutations of SCN5A genes inducing heterogeneity in the epicardial and endocardial action potentials in 50% of patients with the ECG;
• 1998: the available data suggest that the Brugada syndrome is a familial primary electrical disease caused by a defect in an ion channel gene, resulting in premature repolarization of some right ventricular epicardial sites;
• 2001: the morphological abnormalities could be secondary to an electrical conduction defect and abnormal repolarization;
• 2002: loss of the action potential dome, by creating a hibernation-like state, may over long periods of time lead to mild morphological changes, which include lipid accumulation and fibrosis.

The hypothesis of a functional syndrome is mainly proposed because of the dynamic ECG changes[9,10]. The patients may sometimes have a normal ECG and then a typical abnormal one. ST-segment elevation can change from coved to saddle-like to dome shaped. Physical activity and various drugs modify the ECG: propranolol, acetylcholine and class 1C drugs amplify the ECG pattern, while isoproterenol and atropine normalize the ECG. ST-segment elevation may occasionally increase before the onset of the ventricular arrhythmia. This has led to the hypothesis that the ECG abnormality could be linked to a repolarization abnormality. This theory may provide an explanation for ST-segment elevation but does not fully explain the right bundle branch disorder.

Highlights to this theory have been provided by the Antzelevitch experiments, but the conclusions derived from this study do not clearly connect to clinical evidence[22].

Relevant support has been given to the functional theory by the discovery of a Na^+ channel gene abnormality in some of the patients with the syndrome. The initial paper described a 50% prevalence of the abnormality, but recent articles report only 10-20% of positive results, which appears to be the usual prevalence in some non-affected populations[50].

Conclusions

Nava-Martini-Thiene and colleagues, in Italy, initially described the syndrome of RBBB and ST-segment elevation.

Despite the fact that most of the reports have not identified any structural heart disease, evidence-based clinical and investigational data have sometimes documented that not rarely this syndrome has a subtle organic substrate. Despite past controversy, even Antzelevitch and Brugada have discussed the possibility that the ECG pattern may be due to abnormal depolarization, and that structural anatomic abnormalities of the right ventricular wall may be present in some of these patients[9]. This shortens the distance between a functional and organic syndrome[4,5,66].

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