

## Drug-Induced Brugada Type 1 ECG Pattern: Concealed Brugada Syndrome or By-Stander Electrocardiographic Sign?

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### Abstract

In the clinical setting, drug testing is currently used to unmask a concealed Brugada Syndrome (BrS) both in patients with unexplained syncope and also in asymptomatic subjects with only suspect ECG signs. Recent studies, however, suggest that the induction of a Brugada type 1 ECG (Br type 1 ECG) by drugs may be an aspecific and/or a by-stander ECG sign. This is no idle hypothesis, as in clinical practice drug-induced Br type 1 ECG and BrS are often used as synonyms, feeding worldwide terror of this disease and resulting in an excess of inappropriate aggressive therapies in otherwise healthy subjects.

**Condensed abstract:** Drug testing is currently used to unmask a concealed Brugada Syndrome in patients with unexplained syncope and also in asymptomatic subjects with suspect ECG signs. Recent studies, however, suggest that the induction of a Brugada type 1 ECG by drugs may be an aspecific and/or a by-stander ECG sign.

**Keywords:** Brugada syndrome; Aborted sudden death; Drug-induced Brugada type 1 ECG; Cardiac arrest; Early repolarization; J-wave syndromes

### Introduction

In 1992, Pedro and Josep Brugada [1] introduced a new clinical and electrocardiographic syndrome named Brugada syndrome (BrS). This syndrome may cause cardiac arrest in the absence of obvious heart disease. The diagnosis of BrS is mainly based on a characteristic electrocardiographic pattern showing J-point elevation of at least 2 mm and down-sloping ST elevation followed by negative T wave (Br type 1 ECG). The first eight cases of BrS that were described displayed a spontaneous Br type 1 ECG [1].

### What's New?

In asymptomatic and symptomatic subjects, a Brugada type 1 ECG (BrS type 1 ECG) during drug testing (ajmaline, pilsicainide etc.) is generally considered indicative of a concealed BrS. However, recent studies, including one by our group, suggest that the induction of a Brugada type 1 ECG by drugs may be an aspecific and/or a by-stander ECG sign. The consequence of the confusion surrounding BrS is worldwide terror of this disease and an unacceptable excess of inappropriate aggressive therapies in otherwise healthy subjects.

### Review

The cause of BrS is debated. Defects of genes encoding or regulating Na<sup>+</sup> channels (SCN5A etc.) have been identified as possible causes [2,3]. This possibility has been validated by laboratory experiments using drugs, such as pilsicainide, which are able to block Na<sup>+</sup> channels [4]. In animal studies, the use of Na<sup>+</sup> channel blockers has proved able to provoke characteristic modifications of the action potential in the subepicardial myocardium of the right ventricular outflow tract (RVOT), reproducing the Br type 1 ECG pattern [4]. These

experimental studies have also reproduced malignant arrhythmias arising from the RVOT.

More recently, an alternative interpretation of the electrophysiologic mechanism of BrS has been proposed in humans. Indeed, in patients with symptomatic BrS, some authors [5], have documented delayed depolarization over the anterior aspect of the RVOT epicardium, and have reported that ablation of this abnormal area normalizes the ECG and prevents the inducibility of ventricular fibrillation by ventricular stimulation. Apart from the mechanism of electrophysiologic alterations, the RVOT site of such alterations explains why, in the clinical setting, a Br type 1 ECG pattern is recorded in V1-V3 leads and/or on positioning the same electrodes over the III and II intercostal spaces.

On the basis of the above-mentioned observations, a drug test (using ajmaline, flecainide, pilsicainide etc.) was introduced into clinical practice, in order to discover a concealed BrS in patients with syncope of unexplained origin [6,7]. In recent years, this pharmacological test has been progressively used worldwide, even in asymptomatic subjects with a suspect ECG pattern (type 2 or type 3 Br ECG or other aspecific ECG alterations). Consequently, a great number of subjects have been found to display a Br type 1 ECG after drug administration (drug-induced Br type 1 ECG) even in the absence of clinical manifestations.

The usefulness of this test in unselected asymptomatic subjects, however, has been questioned by many authors [8-14]. Indeed, a number of prospective studies have demonstrated that asymptomatic subjects with a drug-induced Br type 1 ECG have an excellent prognosis [8,11,13,15]. In particular, in a multicenter study that included our group [13], subjects with a drug-induced Br type 1 ECG who did not undergo ICD implantation, in the absence of major risk factors, showed a risk of SD during follow-up that was very low, being similar to and slightly lower than that of the general population. Consequently, the doubt that a drug-induced Br type 1 ECG is always a sign of a concealed BrS appears reasonable. On the contrary, the

above-cited data suggest that a drug-induced Br type 1 ECG may be an aspecific ECG sign in the majority of cases.

In contrast with these reassuring data, in the real world too many asymptomatic patients with drug-induced Br type 1 ECG undergo ICD implantation [9] or RVOT ablation [15]. In patients with idiopathic aSD (and non-diagnostic resting ECG), drug testing has also been employed in order to unmask a concealed BrS as a possible cause of the potentially lethal event. In subjects with aSD and a positive drug test, a BrS is currently considered the cause of cardiac arrest. In this case, too, however, many doubts arise.

In a recent paper [16], we analyzed 243 cases of aSD published by various authors and also collected by us (Italian cohort). In these 243 patients, a BrS was considered the cause of cardiac arrest on the basis of a spontaneous or drug-induced Br type 1 ECG. Interestingly, we found that, while in patients enrolled by Brugada et al. before 2002 [17], the prevalence of drug-induced Br type 1 ECG was only 14%, in those enrolled in more recent years by us [16], and by Probst et al. [18] the prevalence rose to 42%-50%.

The high number of drug-induced Br type 1 ECG in patients with aSD in our study [16], certainly depended on the progressive diffusion of drug testing in patients with idiopathic cardiac arrest. However, these data are at least surprising. Indeed, according to all prospective studies [8, 19-24], patients at highest risk of malignant arrhythmias are those with a spontaneous Br type 1 ECG, while those with a drug-induced Br type 1 ECG have a significantly lower risk. Consequently, if a BrS had really been the cause of aSD in this population, we should have expected a much higher number of patients with a spontaneous Br type 1 ECG than a drug-induced Br type 1 ECG. Specifically, in the Italian cohort (26 cases) 42% of patients had a drug-induced Br type 1, while less than 10% displayed a spontaneous Br type 1 ECG during follow-up [16].

This striking discrepancy between prospective and retrospective studies is not easy to explain. However, a recent paper by Nagayama et al. [25], offers an intriguing interpretation. These authors collected 44 cases of aSD which was attributed to BrS. Indeed, 29 patients had a spontaneous Br type 1 ECG, while in the remaining 15 the Br type 1 ECG was induced by pilsicainide. A fragmented QRS was also recorded in right precordial leads in 69% of patients with spontaneous Br type 1, but in no case in those with drug-induced Br type 1 ECG. By contrast, in patients with a drug-induced Br type 1 ECG, on basal ECG early repolarization in inferior leads was present in 87%, as opposed to 10% of those with a spontaneous Br type 1 ECG. In addition, in 26 cases, the ECG was recorded immediately after ventricular fibrillation (VF).

Interestingly, in 75% of patients with a spontaneous Br type 1 ECG just after VF, ST elevation in leads V1-V3 was increased (in comparison with the basal resting ECG). By contrast, in those with a drug-induced Br type 1 ECG after VF, no ST elevation in right precordial leads was observed, while clear early repolarization in inferior leads was visible in 90% of cases. In one of these latter patients, VF recurred during hospital monitoring; just before VF, enhanced early repolarization was visible in concomitance with very premature ventricular beats which triggered VF.

The authors therefore concluded that, in their population, spontaneous Br type 1 ECG and drug-induced Br type 1 ECG were probably two distinct clinical conditions. Indeed, in patients with spontaneous Br type 1 ECG, a BrS was clearly the cause of aSD, and the source of malignant arrhythmias was located in the outflow tract of the

right ventricle. By contrast, in patients with drug-induced Br type 1 ECG, the cause of cardiac arrest was presumably an early repolarization syndrome (ERS), in which the source of malignant arrhythmias is generally located in the inferior aspect of the right or left ventricle [26]. In this paper, however, no hypothesis was proposed to explain the role of a drug-induced Br type 1 ECG in association to ERS in the genesis of malignant arrhythmias.

On the basis of these data, an important question arises: in subjects with resuscitated cardiac arrest and drug-induced Br type 1 ECG, is the Brugada ECG pattern a contributory cause (concealed BrS) in conjunction with ERS, or might it be only a by-stander ECG finding?

The possibility that a drug-induced Br type 1 ECG might be a contributory cause is supported by the observation that both BrS and ERS may be provoked by dysfunctions of Na<sup>+</sup> channels (J-wave syndromes) [3]. However, it is difficult to explain why, both in our paper and in that of Nagayama, only 20% of patients with aSD and drug-induced Br type 1 ECG had SCN5A gene mutations. The hypothesis that a drug-induced Br type 1 ECG is a by-stander finding in patients with idiopathic aSD and non-diagnostic basal ECG therefore emerges as a possible explanation.

To test this hypothesis, the prevalence of a drug-induced Br type 1 ECG should be compared in a large population of patients with idiopathic aSD and in an asymptomatic general population with normal basal ECG. If the prevalence of a drug-induced Br type 1 ECG were higher in patients with idiopathic aSD than in the general population, a causative/contributory role of BrS would be suggested. By contrast, if the prevalence of a drug-induced Br type 1 ECG were similar in patients with idiopathic aSD and in the general population, a by-stander role of drug-induced Br type 1 ECG should be hypothesized. Unfortunately, no such study has ever been conducted. Thus, in patients with idiopathic aSD and a drug-induced Br type 1 ECG, the contributory role of a concealed BrS cannot be supported; likewise, the possibility that a drug-induced Br type 1 ECG is a by-stander finding cannot be ruled out.

Whether a drug-induced Br type 1 ECG may be a by-stander finding and not always proof of a concealed BrS is not an idle question in clinical practice, particularly in asymptomatic subjects or in those with syncope of uncertain origin. Indeed, in clinical practice, the terms drug-induced Br type 1 ECG and BrS are often used as synonyms, and current guidelines identify the Brugada Syndrome with the Br type 1 ECG, whether spontaneous or drug-induced [27]. Our opinion, and that of other authors [12], is that this is not correct, as all available data suggest that only a minority of patients with a drug-induced Br type 1 ECG really do have a BrS, while the vast majority of them have no risk of SD.

In the history of medicine, similar mistakes have been made many times in the past when an ECG sign has been equated to a disease. For example, more than 60 years ago, negative T waves were defined by the Mexican School [28] as "ischemia" and this ECG anomaly was identified with coronary artery disease. This error was corrected only after many decades, when it was demonstrated that negative T waves were not always a manifestation of myocardial ischemia; rather, they may be an aspecific finding or may be due to various heart diseases (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, etc.). The consequence of the confusion surrounding BrS is worldwide terror of this disease and an unacceptable excess of inappropriate aggressive therapies in otherwise healthy subjects [29-31].

## Conclusion

In patients with aSD, too, the hypothesis that a drug-induced Br type 1 ECG is a by-stander finding is not idle. Indeed, if the real cause of cardiac arrest in these cases is ERS and not Brugada Syndrome, then the electrophysiologic substrate of VF is not located in the RVOT but at other sites (i.e., inferior aspects of ventricles), and ablation of the RVOT is useless. Brugada syndrome and Br type 1 ECG pattern is not always the same thing.

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