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Brugada Type 1 Pattern and Risk Stratification for Sudden Death: Does the Key Hide in the ECG Analysis?

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Abstract

Primary prevention of ventricular fibrillation is at the heart of the management of Brugada syndrome. Several recent studies have shown that the analysis of simple electrocardiographic criteria could help to stratify the risk of sudden death. In the present work, 12 markers were studied: spontaneous and permanent type 1 pattern, first-degree atrioventricular block, sinus node dysfunction, wide QRS in V2, aVR sign, fragmented QRS, S-waves in DI, early repolarization pattern, atrial fibrillation, type 1 in peripheral leads pattern, and long Tpeak-Tend interval. These electrical markers reflect abnormalities in conduction, depolarization, and repolarization that may indicate the severity of the disease. In this chapter, we carry out a review of these markers, their method of determination on the surface ECG, and the main studies highlighting their prognostic impact. We also review the main underlying pathophysiological hypotheses of Brugada syndrome.

Keywords: Brugada syndrome, Brugada type 1, primary prevention, risk stratification, ECG markers, ventricular fibrillation, sudden death

1. Introduction

Brugada syndrome is presumed to be a channelopathy causing sudden death by ventricular fibrillation. The diagnosis is based exclusively on the analysis of the surface electrocardiogram.

Today, the challenge is to improve the primary prevention of sudden death. There is a very large heterogeneity of ventricular fibrillation risk among patients and there is no reliable marker to assess this risk.

Beyond the diagnosis based on an accurate analysis of right precordial leads, the ECG phenotype of patients with Brugada syndrome is not unique. Many recent studies have shown that several electrocardiographic markers may indicate a more severe disease with an increased risk of sudden death.

A simple electrocardiographic approach to the risk of sudden death in Brugada syndrome may be worthwhile at a time when risk stratification is being questioned.

In this chapter, we propose to review the main ECG markers and the pathophysiological hypotheses underlying them.

2. Positive and differential diagnoses

2.1. Definition of Brugada type 1 pattern

The diagnosis of Brugada type 1 pattern is based exclusively on the analysis of the electrocardiogram. The panel of experts who elaborated the 2015 ESC recommendations on sudden death prevention [1] has reached a consensus on the diagnosis criteria.

Type 1 pattern is defined by a coved ST segment elevation with a rise of the J-point ≥ 2 mm in at least one derivation between V1 and V2 on a resting surface electrocardiogram (**Figure 1**). It is often accepted [2] that the T waves must be negative in the same lead(s), although this criterion is not included in the guidelines.

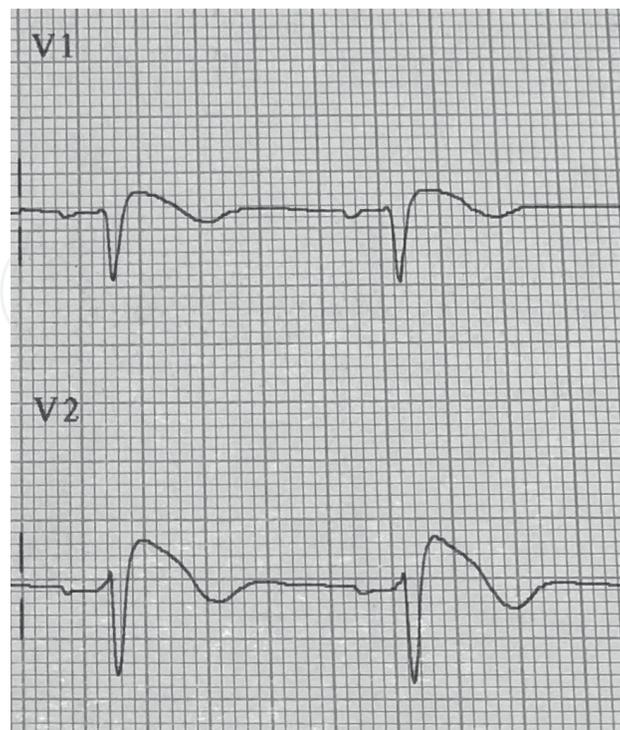


Figure 1. Brugada type 1 pattern.

Several methods can help in case of borderline aspects.

First, refitting the electrodes to the second or third intercostal spaces can reveal a type 1 pattern. Secondly, when type 1 pattern is not spontaneous but it remains a clinical suspicion of Brugada syndrome (e.g., ventricular fibrillation on an apparently healthy heart, unexplained syncope, family history of Brugada syndrome) or an electrocardiographic suspicion (Brugada types 2 and 3 patterns), it is possible to carry out a pharmacological challenge by blocker of the sodium channels to unmask a type 1 pattern [1]. This pharmacological challenge must be carried out in a specialized cardiological environment under strict supervision. Febrile episodes can also unmask a type 1 pattern and increase the risk of ventricular fibrillation.

Around 40% of Brugada syndrome cases are familial forms, thus linked to genetic mutations [3]. With 20–30% of familial forms, mutations of the SCN5A gene are the most common mutations identified. SCN5A gene encodes the cardiac voltage-gated sodium channel (Nav1.5). These proteins ensure the rapid sodium upstroke, resulting in cellular depolarization [4, 5]. Studies of mutations linked to the development of Brugada syndrome revealed loss of Nav1.5 function, thus indicating a decreased amount of sodium going through the cardiomyocyte membrane. The loss of function appears to be shared by all SCN5A mutations but the molecular underlying mechanism can slightly vary from a trafficking defect to alterations in the biophysical properties. While this does not affect the final result, this is an important characteristic that could in the future determine the appropriate pharmacology.

The loss of sodium channel function is expected to cause an imbalance between depolarizing and hyperpolarizing currents in cardiomyocytes. Furthermore, as shown in the next sections, epicardium and endocardium present different levels of repolarizing currents such as Ito currents. This difference would increase the depolarizing/hyperpolarizing imbalance underlying the ST elevation and promote an arrhythmogenic substrate.

The rationale to the use of Nav blockers to unmask Brugada ECG phenotypes is thus notably supported by the high occurrence of SCN5A mutations. Consequently, in case of SCN5A mutation, the use of a Nav blocker will rapidly unmask the phenotype. In case where a SCN5A mutation is not involved, larger doses of Nav blocker could mimic a SCN5A mutation and thus reveal the phenotype.

The old types 2 and 3, with saddle-back ST segment elevation, no longer allow to make the diagnosis.

The diagnosis of Brugada syndrome remains context-dependent, as illustrated in the next section.

2.2. Phenocopies

A number of pathological conditions can mimic a Brugada type 1 pattern on the electrocardiogram. The works of Baranchuk and Anselm has improved knowledge in this area [6]. These observations are rare and no large series has allowed studying it yet.

Several clinical cases highlight many underlying conditions. Type 1 Brugada phenocopies have been observed in various cardiac diseases (myocardial ischemia such inferior infarction

with right ventricle extension or anterior infarction [7–9], Tako-Tsubo cardiomyopathy [10], cardiac tumors [11], Chagas disease [12]), in pulmonary and mediastinal diseases (acute pulmonary embolism [13], pneumothorax [14], mediastinal tumors [15]), in metabolic and hydroelectrolytic disorders (hypokalemia [16, 17], hyperkalemia [18], hyponatremia [19], hypophosphatemia [20], keto-acidosis [21]), in intoxications (heroin and ethanol overdose [22], propofol [23], propafenone [24], yellow phosphorus [25], lamotrigine [26], phosphine [27]), and various diseases such intracranial hemorrhages [28], hypothermia [29], and electrocution [30]. Pectus excavatum can also mimic a type 1 pattern [31].

According to Baranchuk and Anselm [6], the diagnosis of phenocopy is based on the context, on the normalization of the ECG with the resolution of the cause, and on the negativity of the pharmacological challenge.

The prognostic impact of phenocopies is poorly documented.

3. Electrocardiographic risk markers

3.1. Type 1 pattern

3.1.1. Spontaneous type 1 pattern

The spontaneous nature of the ECG type 1 pattern (contrary to the drug-induced type 1) seems to indicate an increased risk of ventricular fibrillation. This was demonstrated in 2005 by Eckardt et al. [32] and has since been found in several large studies, particularly in the FINGER cohort [33] involving 1029 patients, where a spontaneous type 1 pattern was predictive of a greater risk of sudden death with a hazard ratio (HR) of 1.8 (CI 1.03–3.33, $p = 0.04$).

A study by Cerrato et al. [34] has shown that the use of the 24-h holter ECG monitoring can help with spontaneous type 1 diagnosis, which is more common during the sleep. This method could be an alternative to avoid the risks related to the pharmacological challenge.

3.1.2. Duration of type 1 pattern expression

Similarly, Extramiana et al. [35] showed by holter ECG monitoring that permanent type 1 expression was associated with an increased risk of syncope and/or ventricular fibrillation.

The 24 or 48 h-holter ECG monitoring could therefore be an interesting tool in the stratification of patients' risk.

Two opposed theories [36] can explain the electrocardiographic and rhythmic abnormalities observed in the Brugada syndrome: a so-called depolarization theory and a so-called repolarization theory. The abnormalities of depolarization and repolarization explain a number of ECG changes that may indicate a poor prognosis.

3.2. Depolarization and conduction disorders

3.2.1. Supraventricular level

3.2.1.1. Sinus node dysfunction

The sinus node dysfunction (**Figure 2**) frequently observed in Brugada syndrome is the conjunction of two phenomena secondary to the reduction of sodium current: an alteration of sinus tissue function and a sino-atrial functional block [37]. Sinus node dysfunction is more frequent in case of mutation on the SCN5A gene [38].

A study conducted on 400 patients by Siera et al. [39] showed that sinus dysfunction was a predictor of ventricular fibrillation risk. The same observation was also made on a cohort of children [40] and a cohort of women [41] with Brugada syndrome (**Table 1**).

3.2.1.2. First degree atrioventricular block

Maury et al. [42] showed in a study of 325 patients with Brugada type 1 that the presence of first-degree atrioventricular block (**Figure 3**) was significantly associated in multivariate analysis with increasing risk of ventricular fibrillation (OR 2.41, 95% CI 1.01–5.73, $p = 0.046$) (**Table 2**).

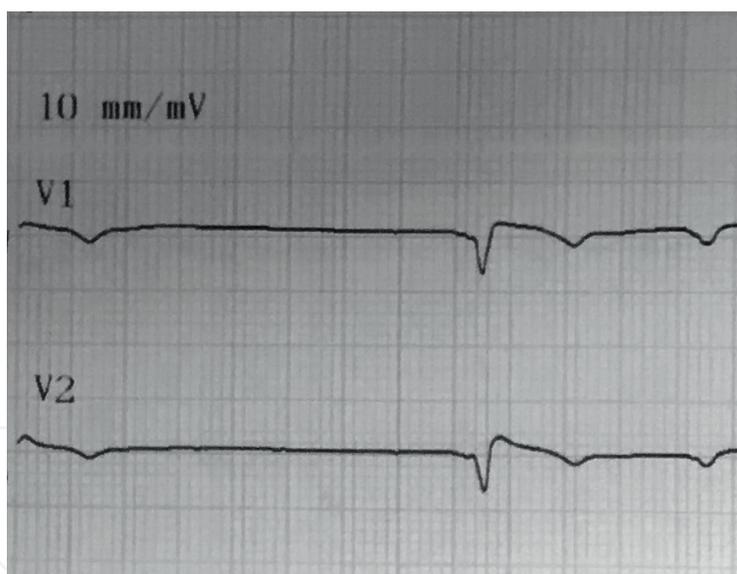


Figure 2. Sinus pause in a 54-year-old woman with Brugada type 1 syndrome and recurrence of syncope.

-
- clinical-electrical criterion with correlation between symptoms (faintness, syncope) and a documented event among sinus bradycardia, sinus arrest, sick sinus syndrome, and chronotropic incompetence;
 - A Holter ECG was practiced in case of doubt to correlate electrical events and symptoms; and
 - electrophysiological exploration of the sinus node was also performed.
-

Table 1. Criteria of sinus node dysfunction in Siera et al. study [41].

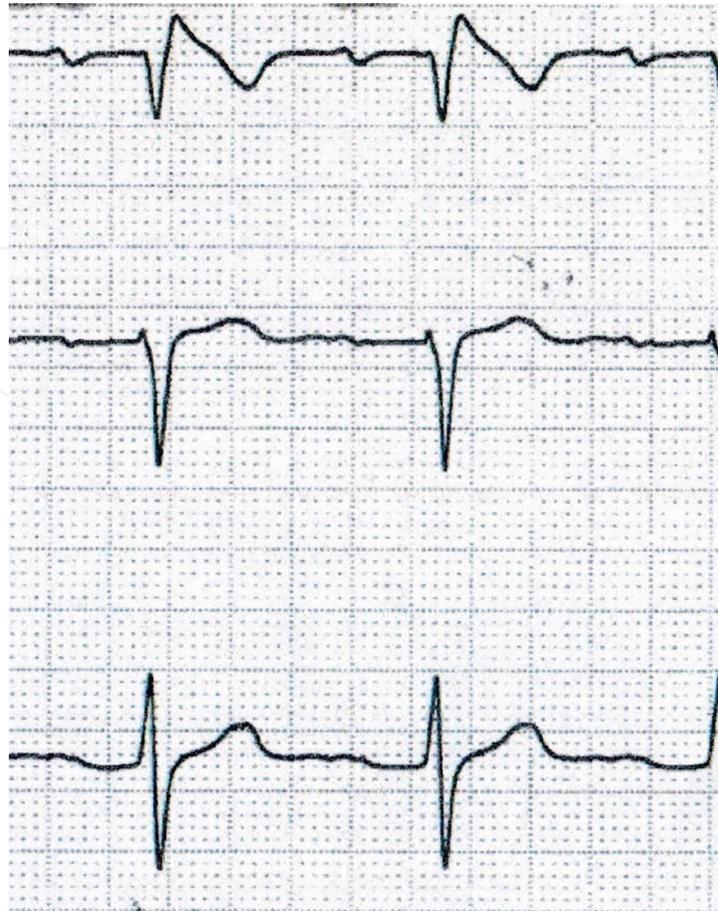


Figure 3. First-degree AVB in a woman with Brugada type 1 pattern.

In addition, Smits et al. [38] demonstrated that atrioventricular conduction abnormalities were significantly increased in the case of SCN5A gene mutation. A PR interval ≥ 210 ms would be a good predictor of a mutation in the SCN5A gene in Brugada syndrome. Previous observations [43, 44] have shown that sodium channels genes mutations are also implicated in conduction disturbances in Lev/Lenegre disease.

3.2.2. Ventricular level

3.2.2.1. Pathophysiology

Cardiac imaging tests (transthoracic echocardiography, angiography, MRI) are usually normal in Brugada syndrome, so it was long believed that this pathology did not lead to heart structural abnormalities. Several recent studies question this dogma.

PR interval ≥ 200 ms

Table 2. First-degree atrioventricular block criterion in Maury et al. study [42].

Functional studies using surface ECG mapping [45], tissular Doppler imaging [46], and endo- and epicardial electrophysiology [47, 48] show that there is an abnormally long conduction delay in the epicardium of the right ventricular outflow tract. This conduction delay is sometimes accompanied by late ventricular potentials [48].

Several factors may explain these abnormalities of conduction. On the one hand, the decrease of the incoming sodium current reduces the intramyocardial conduction velocity [49], while on the other hand, histological and histochemical studies [50, 51] reveal the abnormally large presence of fibrosis deposits in the epicardium of the right ventricle outflow tract, these deposits are accompanied locally by a reduction in expression of gap-junctions. An experimental model in the mouse showed that these two abnormalities could be the consequence of the decrease of SCN5A gene expression [52].

The shift created between the depolarization (and thereby, secondarily, the repolarization) of the right ventricular outflow tract and the other segments of the ventricles could thus explain the ST segment elevation and the negativity of the T waves [36].

Several studies show that the importance of these conduction abnormalities is highly variable between patients with Brugada syndrome and is correlated with the risk of ventricular fibrillation [53].

These findings are supported by several interventional studies highlighting the lower recurrence of ventricular rhythmic events after radiofrequency ablation in the right ventricular outflow tract [54].

It is therefore important to estimate the importance of impairment of right ventricular conduction in patients to determine their level of risk of sudden death. Several ECG markers can help with a non-invasive evaluation.

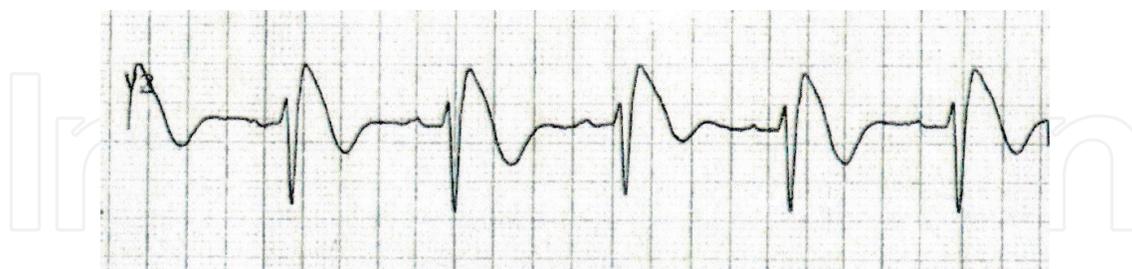


Figure 4. Wide QRS in lead V2 in a patient with a Brugada type 1 pattern.

In lead V2, width of QRS \geq 120 ms

Table 3. Wide QRS criterion on Ohkubo et al. study [55].

3.2.2.2. Wide QRS in lead V2

Wide QRS in lead V2 (**Figure 4**) is the most obvious marker of alteration of right ventricular conduction. The widening of the QRS in V2 classically demonstrates a slowdown of conduction in the right ventricle.

Ohkubo et al. [55] found, in a cohort of 35 patients with Brugada syndrome, a significant association between wide QRS in lead V2 and ventricular fibrillation and/or syncope (**Table 3**).

3.2.2.3. S-waves in lead DI

Based on the assumption that S-waves in lead DI are the translation of the third vector resulting from the depolarization of right ventricular outflow tract and the basal parts of the two ventricles, Calò et al. [56] demonstrated an electroanatomical correlation between the epicardial activation time of the right ventricular outflow tract and the importance of S-waves in DI.

The same team has shown in a multicentric study [56] of 347 patients with spontaneous type 1, that significant S-waves in lead DI (**Figure 5**) represent a strong marker of risk of sudden death, with a sensitivity of 90.6% and a specificity of 62.2% for the depth of the waves and a sensitivity of 96.9% and a specificity of 61.1% for the duration of the waves (**Table 4**).

The right ventricular outflow tract is notably the last structure responsible to eject the blood to the pulmonary artery. This is notably ensured by a delay in action potentials. While such delay constitutes a physiological need, it also creates a first-degree heterogeneity between this specific structure and the right ventricle. In the background of a SCN5A mutation, such heterogeneity would be even more pronounced, making the right ventricular outflow tract a pro-arrhythmogenic area.

3.2.2.4. The aVR sign

The positivity of the QRS complexes in lead aVR (**Figure 6**) may reflect a right ventricular conduction delay responsible for a right axial deviation of the QRS.

Babai Bigi et al. [57] found in a prospective cohort of 24 patients with a Brugada type 1 pattern a significant association between the presence of significant R-waves in aVR and the risk of syncope and/or ventricular fibrillation (**Table 5**).

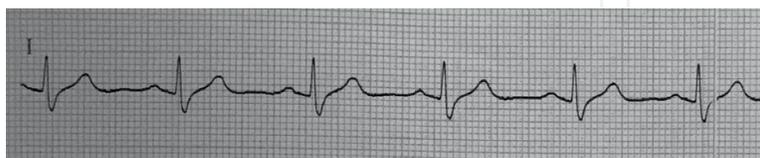


Figure 5. Significant S-waves in lead DI.

In lead DI, S-waves with a depth of at least 0.1 mV and/or a width of at least 40 ms

Table 4. Criteria of S-waves in Calò et al. study [56].

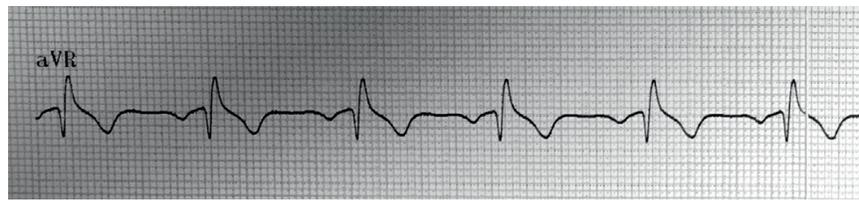


Figure 6. aVR sign.

In lead aVR, R-wave ≥ 0.3 mV and/or R/q ratio ≥ 0.75

Table 5. Criterion of aVR sign in Babai Bigi et al. study [57].

3.2.2.5. Fragmented QRS

Fragmented QRS (**Figure 7**) were first described in ischemic cardiomyopathies [58], where they are a sign of significant fibrotic scars and lead to a risk of malignant ventricular arrhythmias by macro-reentry. They could also testify of the importance of right ventricular fibrosis in Brugada syndrome. Morita et al. [49] also showed the existence of a dynamic part to this pattern, varying according to the conditions of conduction.

The same team showed [49], with a cohort of 115 patients with Brugada syndrome, that fragmented QRS were significantly more frequent in the ventricular fibrillation group (**Table 6**).

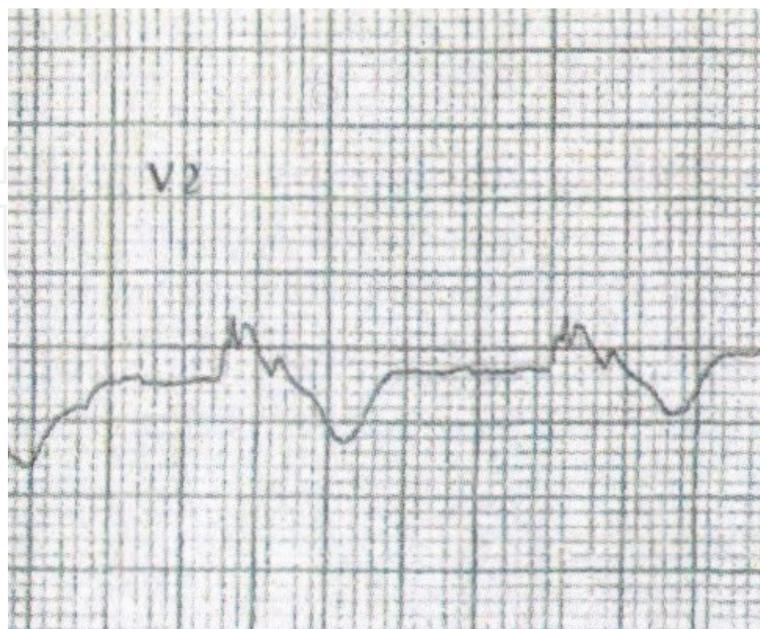


Figure 7. Fragmented QRS in a patient with a Brugada type 1 pattern.

-
- In leads V1, V2, and V3: ≥ 4 spikes in a derivation and/or ≥ 8 spikes in these 3 leads
 - The filters must be kept to a minimum so that they do not erase the spikes, especially with a high frequency cut-off (around 150 Hz). This explains why fragmented QRS are often missing on standard ECG.
-

Table 6. Criteria of fragmented QRS in Morita et al. study [49].

3.3. Repolarization disorders

3.3.1. Pathophysiology

The repolarization theory was mainly developed in the works of Antzelevitch [59–61].

The right ventricular outflow tract epicardial cells hold more I_{to} potassium channels than other myocardial cells. In the Brugada syndrome, the reduction of the sodium current accentuates locally in the right ventricular outflow tract the shortening duration of the action potentials induced by the important activity of the I_{to} channels. A voltage gradient is thus created between the endocardium and the epicardium, resulting in the dome-shaped ST elevation observed on the ECG. Brugada syndrome thus carries a risk of ventricular fibrillation by Phase 2 reentry mechanism.

This theory is usually opposed to the theory of conduction described earlier [62].

3.3.2. *Tpeak-Tend interval, QT*

The three types of ventricular myocardial cells have different repolarization durations [61]. The epicardial cells are the most rapidly repolarized, then the endocardial cells, and finally the M-cells. Thus, the peak of the T waves corresponds with the moment when the epicardial cells are completely repolarized and the end of the T waves coincides with the end of the repolarization of the M-cells. Therefore, the $Tp-e$, corresponding with the interval between the vertex and the end of the T waves, is considered by many authors [63] as proportional to the importance of the transmural dispersion of repolarization in the ventricular myocardium. A wide dispersion of repolarization increases myocardial vulnerability and therefore the risk of arrhythmia. An elongated $Tp-e$ would thus translate into a high risk of sudden death by ventricular arrhythmia.

Maury et al. [64] showed in 2015 with a large retrospective cohort of 325 patients, that a maximum $Tp-e$ in precordial leads greater than or equal to 100 ms was significantly and independently associated with an increased risk of ventricular fibrillation in Brugada syndrome (**Table 7**).

Similarly, a study by Castro Hevia et al. [65] highlighted a correlation between a $Tpeak-Tend$ dispersion (difference between $Tpeak-Tend$ maximum and minimum in precordial shunt) > 20 ms and a risk of ventricular fibrillation.

QT interval prolongation may also mean a worse prognosis in Brugada syndrome [65].

3.3.3. Early repolarization

Haïssaguerre et al. [66] have recently individualized the early repolarization syndrome, which associates an early repolarization pattern (**Figure 8**) with malignant ventricular

Maximum Tpeak-Tend adjusted to heart rate among leads V1–V4 ≥ 100 ms

Tpeak-Tend measurement method:

- From lead V1 to lead V4
 - Measurement of the interval between the peak of the T wave and the tangent between the downward slope of the T wave and the isoelectric line
 - Average of three consecutive complexes by derivation
 - Correction of the heart rate according to the Bazett method ($Tp-e$ corrected = $Tp-e/\sqrt{RR}$)
-

Table 7. Criteria of prolonged maximum Tpeak-Tend interval in Maury et al. study [64].

arrhythmia. Antzelevitch and Yan [67] have shown that the pathophysiology of this syndrome is close to the repolarization theory of Brugada syndrome: a large repolarization heterogeneity in the left ventricle could lead to a risk of ventricular fibrillation by Phase 2 reentry. The association of both syndromes would result in repolarization heterogeneity in both the right ventricle and the inferior lateral parts of the left ventricle with a high risk of ventricular fibrillation [67, 68].

Kawata et al. [68] showed, in a cohort of 49 patients with Brugada type 1 syndrome and a history of ventricular fibrillation, that the presence of a permanent early repolarization pattern (HR 4.88, 95% CI 2.02–12.7) or intermittent (HR 2.50, 95% CI 1.03–6.43) was significantly ($p = 0.043$) associated with a higher risk of recurrence of a fatal rhythmic event (**Table 8**).

3.4. Other electrocardiographic markers

3.4.1. Atrial fibrillation

Calò et al. [56] showed through a multivariate analysis of 347 patients that the occurrence of atrial fibrillation (**Figure 9**) episodes in Brugada type 1 patients was a significant and independent risk marker for ventricular fibrillation.



Figure 8. Early repolarization pattern (notching).

J-point elevation at least 1 mm in at least two inferior or lateral leads (either notching or slurring pattern)

Table 8. Early repolarization criteria in Kawata et al. study [68].

In at least one peripheral derivation (aVR included):

- coved ST segment elevation with J-point rise ≥ 2 mm
 - and negative T waves in the same derivation.
-

Table 9. Criteria of type 1 in peripheral lead pattern in Rollin et al. study [69].

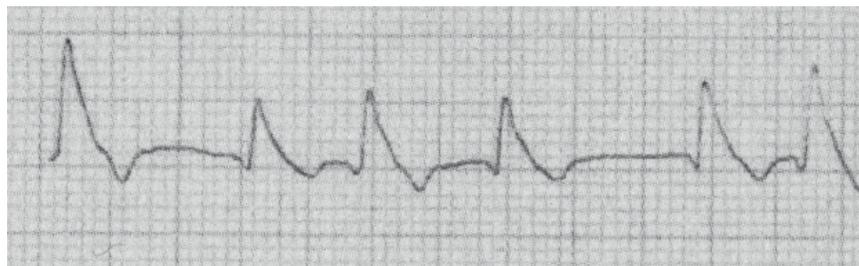


Figure 9. Atrial fibrillation in a patient with Brugada type 1 pattern.

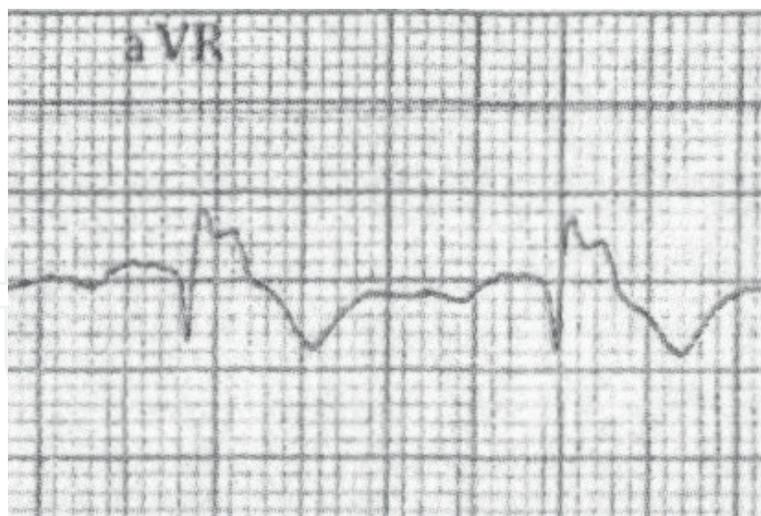


Figure 10. Type 1 pattern in peripheral lead (aVR).

3.4.2. Type 1 in peripheral leads

In a study by Rollin et al. [69] conducted on 323 patients, a type 1 pattern in peripheral leads (**Figure 10**) appears to be an independent marker of high risk of ventricular fibrillation (**Table 9**). In total, 27% of patients with type 1 in peripheral leads showed malignant

ventricular arrhythmia, compared to 6% for other patients. The multivariate analysis confirms a strong correlation (OR 4.58, 95% CI 1.7–12.32, $p = 0.025$).

The pathophysiological significance of this aspect still needs to be clarified.

4. Conclusion

The surface electrocardiogram is the key examination in Brugada syndrome. It is currently the only means to allow diagnosis and it could help stratification of the ventricular fibrillation risk. In the last few years, numerous publications highlighted several electrocardiographic markers testifying to a more severe disease and a potentially unfavorable prognosis. These markers also contributed to the improvement of knowledge of the physiopathology of this syndrome. However, studies are still needed to determine their use in daily practice.

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