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Review

Arrhythmogenesis in Brugada syndrome: Impact and constrains of current concepts

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ABSTRACT

Brugada syndrome (BrS), an inherited arrhythmogenic disease first described in 1992, is characterized by ST segment elevations on the electrocardiogram in the right precordium and by a high occurrence of arrhythmias including the life-threatening ventricular tachycardia/fibrillation. Knowledge of the underlying mechanisms of formation of arrhythmogenic substrate in BrS is essential, namely for the risk stratification of BrS patients and their therapy which is still restrained almost exclusively to the implantation of cardioverter/defibrillator. In spite of many crucial findings in this field published within recent years, the final consistent view has not been established so far. Hence, BrS described 20 years ago remains an actual topic of both clinical and experimental studies. This review presents an overview of the current knowledge related to the pathogenesis of BrS arrhythmogenic substrate, namely of the genetic basis of BrS, functional consequences of mutations related to BrS, and arrhythmogenic mechanisms in BrS.

1. Introduction

Brugada syndrome (BrS; [1]) is an inherited arrhythmia with the autosomal dominant trait. It is characterized by a typical electrocardiographic (ECG) configuration consisting of ST segment elevations in the right precordial leads in patients without macroscopic structural changes of the myocardium. An up-to-date consensus report of the diagnostic ECG criteria including a detailed description of typical BrS patterns (Table 1) has been recently published [2]. Arrhythmias including the life-threatening ventricular tachycardia/fibrillation often occur. Except for the endemic occurrence in South East Asia, the worldwide prevalence of BrS is estimated to be 5/10,000 [3] and up to 3.5/10,000 within the European population [4–7]. BrS is responsible for more than 4% of all sudden deaths (SDs) and at least 20% of SDs in patients with structurally normal hearts [3]. Moreover, SD in BrS patients occurs most often during the fourth decade of life [8], at the climax of their working and parental age. Detailed knowledge of pathophysiological mechanisms in BrS plays the key role in the effective diagnostics and risk stratification as well as in the timely prevention of SD and development of new therapeutic tools which are all essential to increase probability of rescue of the affected individuals.

Mutations in the *SCN5A* gene coding structure of α-subunit of the cardiac channel carrying sodium current (I_{Na}), which were first reported in BrS patients by Chen and co-workers in 1998 [9], account for about 11 to 28% cases of BrS [10]. The first BrS-related mutations in another gene were identified lately [11,12]. Since that time, 13 other genes have been detected in BrS patients [13–20]. In many of them, resulting functional changes at the molecular level are known thanks to the availability of the patch clamp technique and development of the molecular genetics providing possibility of cell transfection with the mutant ionic channels. The impact of the mutations on electrophysiological properties of the right ventricular (RV) myocytes or even on the cardiac electrophysiology in RV free wall *en bloc* was suggested in some cases by the mathematical modeling [20–23]. Two generally accepted hypotheses dealing with the arrhythmogenesis in BrS have been proposed [24,25]. However, despite intense study which brings many new clinical and experimental data every year, the final concept of arrhythmogenic substrate in BrS remains incomplete and is still a subject of heated discussion [26].

This review is focused on the overview of the current knowledge related to the pathogenesis of BrS arrhythmogenic substrate, namely on the genetic basis of BrS, functional consequences of mutations related to BrS, and arrhythmogenic mechanisms in BrS.

2. Genetic basis of BrS

In 1998, Chen and co-workers [9] identified the first mutations in patients with BrS, namely in *SCN5A* gene coding structure of *Nav1.5* protein which forms α-subunit of the cardiac I_{Na}-channel. More than 370 mutations in this gene have been reported up to now (http://www.fsm.it/cardmoc/). However, only about 11 to 28% cases of BrS can be assigned to an identified *SCN5A* mutation

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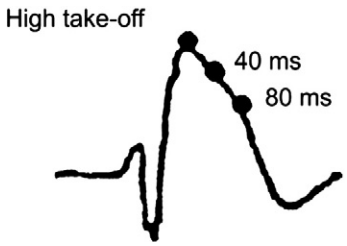
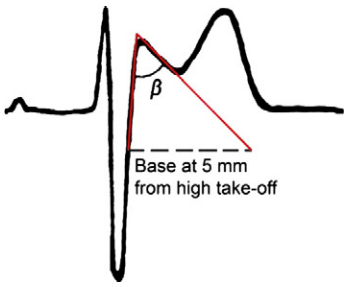
Table 1
ECG patterns of BrS in V1–V2.
Modified with permission from Bayés de Luna et al. [2].

Type 1 — coved pattern	Type 2 — saddle-back pattern
	
Detailed characteristics: a. at the end of QRS, an ascending and quick slope with a high take-off ≥2 mm followed by a concave or rectilinear down-sloping ST (there are few cases of coved pattern with a high take-off between 1 and 2 mm); b. no clear r′ wave; c. the high take-off often does not correspond with the J point; d. at 40 ms of the high take-off, the decrease in amplitude of ST is ≤4 mm (much higher in the right bundle branch block and in athletes); e. ST at the high take-off > ST at 40 ms > ST at 80 ms; f. ST is followed by negative and symmetric T wave; g. a much longer duration of QRS than in the right bundle branch block, and there is a mismatch between V1 and V6.	Detailed characteristics: a. high take-off of r′ (that often does not coincide with J point) ≥2 mm; b. descending arm of r′ coincides with beginning of ST (often is not well seen); c. minimum ST ascent ≥0.5 mm; d. ST is followed by positive T wave in V2 (T peak > ST minimum > 0) and of variable morphology in V1; e. characteristics of triangle formed by r′ allow to define different criteria useful for diagnosis: • β angle; • duration of the base of the triangle of r′ at 5 mm from the high take-off > 3.5 mm; f. the duration of QRS is longer in BrS type 2 than in other cases with r′ in V1, and there is a mismatch between V1 and V6.

[10]. Such a low efficiency of identification of mutations in BrS patients was expected to be at least partly due to nonidentified *SCN5A* mutations in the promoter region, cryptic splicing mutations, or the presence of gross rearrangements that are not a part of the routine investigation. In recent years, several such disorders have been detected in BrS patients [27–31]. At any rate, mutations in other genes have been anticipated.

Since 2007, when the first mutations in a non-*SCN5A* gene were identified in BrS patients [11,12], the number of genes related to BrS rapidly grows. Hedley and co-workers [13] reviewed the papers focused on the genetic basis of BrS and established 7 subtypes of BrS in 2009. Up to now, mutations in additional 7 genes have been detected in BrS patients, thus, 14 subtypes of BrS (BrS subtypes 1–14) may be determined (Table 2). Identification of a mutation in most of these newly BrS-related genes is, at least in the meantime, rare with the exception of mutations in *CACNA1C* a *CACNB2b* genes (BrS subtypes 3 and 4) which were estimated to account for about 11–12% cases of BrS [32]. For an overview of the functional consequences of the mutations see Section 3.

Similar to other inherited arrhythmogenic syndromes, the clinical symptoms of BrS might be further modified by an associated polymorphism or mutation, either in the sense of their aggravation [33] or reduction [34,35].

In many BrS patients, an effort to detect a causal mutation is still failing. In 2009, Gaborit and co-workers [36] provided a study targeted at the transcriptional profile of BrS patients with and without *SCN5A* mutation evaluated from the endomyocardial biopsies. They showed that BrS patients exhibited a signature of a common ionic channel molecular expression independent of the presence of *SCN5A* mutation. The authors hypothesized that a putative ionic channel expression pattern might contribute to BrS symptoms or, in the presence of appropriate electrophysiological modifiers, may be even sufficient to cause BrS by itself. Similarly, Probst and co-workers [37] stated that *SCN5A* mutations were not directly causal to the occurrence of BrS ECG pattern and suggested a powerful role of the genetic background in BrS pathophysiology. It seems to be desirable to take the data related to the genetic background into account in the following studies aimed at BrS arrhythmogenesis (namely if the mathematical modeling is used) and not to concentrate merely on the changes owing to the mutant channel itself.

Table 2
Subtypes of BrS according to the genetic basis.

Subtype	Gene	Protein	Ionic current	Dysfunction	First referred by
BrS 1	*SCN5A*	*Nav1.5*	I_{Na}	Decrease	[9]
BrS 2	*GDP1L*	*GDP1-L*	I_{Na}	Decrease	[11,12]
BrS 3	*CACNA1C*	*Cav1.2* (*Cavα*$_{1c}$)	$I_{Ca\text{-}L}$	Decrease	[61]
BrS 4	*CACNB2b*	*Cavβ*$_{2b}$	$I_{Ca\text{-}L}$	Decrease	[61]
BrS 5	*SCN1B*	*Navβ.1*	I_{Na}	Decrease	[54]
BrS 6	*KCNE3*	*MiRP2*	I_{to}	Increase	[68]
BrS 7	*SCN3B*	*Navβ.3*	I_{Na}	Decrease	[58]
BrS 8	*KCNH2*	*hERG1*	I_{Kr}	Increase	[14]
BrS 9	*KCNE2*	*MiRP1*	I_{to}	Increase	[15]
BrS 10	*KCNJ8*	*Kir6.1*	$I_{K(ATP)}$	Increase	[16]
BrS 11	*CACNA2D1*	*Cavα*$_2$*δ-1*	$I_{Ca\text{-}L}$	Decrease	[17]
BrS 12	*MOG1*	*MOG1*	I_{Na}	Decrease	[18]
BrS 13	*KCNE5*	*MiRP4*	I_{to}	Increase	[19]
BrS 14	*KCND3*	*Kv4.3*	I_{to}	Increase	[20]

I_{Na}, sodium current; $I_{Ca\text{-}L}$, L-type calcium current; I_{to}, transient outward potassium current; I_{Kr}, fast delayed rectifier; $I_{K(ATP)}$, ATP-sensitive potassium current.

3. Functional consequences of mutations related to BrS

In addition to the identification of the first mutations in patients with BrS, Chen and co-workers [9] also analyzed the impact of these mutations on function of the affected ionic channel. Nowadays, a lot of analogical studies are available. In the case of some mutations, their functional consequences for RV cellular electrophysiology or even for RV electrophysiology *en bloc* have been suggested using tools of the mathematical modeling. Such data should help us to resolve the arrhythmogenic mechanisms in BrS more precisely in the future.