REVIEW ARTICLE

Electrocardiographic methods for diagnosis and risk stratification in the Brugada syndrome

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The Brugada syndrome (BrS) is a malignant, genetically-determined, arrhythmic syndrome manifesting as syncope or sudden cardiac death (SCD) in individuals with structurally normal hearts. The diagnosis of the BrS is mainly based on the presence of a spontaneous or Na + channel blocker induced characteristic, electrocardiographic (ECG) pattern (type 1 or coved Brugada ECG pattern) typically seen in leads V1 and V2 recorded from the 4th to 2nd intercostal (i.c.) spaces. This pattern needs to be distinguished from similar ECG changes due to other causes (Brugada ECG phenocopies). This review focuses mainly on the ECG-based methods for diagnosis and arrhythmia risk assessment in the BrS. Presently, the main unresolved clinical problem is the identification of those patients at high risk of SCD who need implantable cardioverter-defibrillator (ICD), which is the only therapy with proven efficacy. Current guidelines recommend ICD implantation only in patients with spontaneous type 1 ECG pattern, and either history of aborted cardiac arrest or documented sustained VT (class I), or syncope of arrhythmic origin (class IIa) because they are at high risk of recurrent arrhythmic events (up to 10% or more annually for those with aborted cardiac arrest). The majority of BrS patients are asymptomatic when diagnosed and considered to have low risk (around 0.5% annually) and therefore not indicated for ICD. The majority of SCD victims in the BrS, however, had no symptoms prior to the fatal event and therefore were not protected with an ICD. While some ECG markers such as QRS fragmentation, infero-lateral early repolarisation, and abnormal late potentials on signal-averaged ECG are known to be linked to increased arrhythmic risk, they are not sufficiently sensitive or specific. Potential novel ECG-based strategies for risk stratification are discussed based on computerised methods for depolarisation and repolarisation analysis, a composite approach targeting several major components of ventricular arrhythmogenesis, and the collection of large digital ECG databases in genotyped BrS patients and their relatives.

Keywords: Brugada syndrome, Electrocardiogram, Sudden cardiac death, Risk stratification, Genetic arrhythmic syndromes

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Contents

Introduction

The Brugada syndrome (BrS) is a malignant arrhythmia syndrome manifesting as recurrent syncope or sudden cardiac death (SCD) due to polymorphic ventricular (VT) or ventricular fibrillation (VF) in the absence of overt structural heart disease or myocardial ischemia [1,2]. The prevalence of the syndrome is estimated at around 15 per 10,000 in South East Asia, including Japan and around 2 per 10,000 in the Western countries [3,4]. One study on a southern Turkish population suggested that the prevalence of BrS in the Middle East may be lower than in South East Asia and higher than in the West [5]. The BrS may be responsible for up to 4% of all sudden cardiac deaths (SCD) and at least 20% of SCDs in patients with structurally normal hearts [6]. It is eight to ten times more prevalent in males than in females [7]. In South East Asia, the BrS is the leading cause of non-traumatic death in men younger than 40 years [8]. The purpose of this article is to briefly summarise current knowledge about the electrocardiography (ECG) based methods for diagnosis and assessment of the risk of malignant arrhythmias in patients with the BrS. Before that, the cellular and genetic mechanisms of the BrS are discussed briefly.

Abbreviations

AP	action potential
ARI	activation-recovery intervals
BrS	Brugada syndrome
ECG	electrocardiogram
EPS	electrophysiology study
ICD	implantable cardioverter-defibrillator
IHD	ischaemic heart disease
LBBB	left bundle branch block
MAP	monophasic action potential
MI	myocardial infarction
PCA	principal component analysis
RVOT	right ventricular outflow tract
SAECG	signal-averaged electrocardiogram
SCD	sudden cardiac death
SNP	single-nucleotide polymorphism
VF	ventricular fibrillation
VT	ventricular tachycardia
WT	wavelet transform

Genetics and cellular mechanisms

BrS has been considered a heritable autosomal dominant disease [9] and more than 390 mutations have been identified in the SCN5A gene encoding the α-subunit of the cardiac I_{Na}-channel [10]. However, presently SCN5A mutations are found only in 11–37% of the genotyped patients [11,12]. Many patients with the BrS have no family history, presumably due to under-diagnosis in other family members, low penetrance, or sporadic disease [13]. Recent data has suggested that heritability may not be strictly monogenic, but may in fact relate to common genetic variation [14].

The cellular basis of the BrS is still not completely clear [15]. According to the repolarisation theory, genetically determined or drug-induced reduction of the inward Na+ current leads to unopposed transient outward (I_{to}) current in some (but not all) epicardial regions of the right ventricular outflow tract (RVOT), which causes either delayed expression of the action potential (AP) dome and epicardial AP prolongation or loss of the dome and AP shortening. The net effect is magnification of repolarisation dispersion between the RVOT endo- and epicardium, and between different RVOT epicardial regions, which is potentially arrhythmogenic. The repolarisation theory was initially promoted on the basis of experimental studies [16–18]. It was later supported by clinical studies, which demonstrated a 'spike and dome' configuration with deep notching of monophasic action potentials (MAP) from the RVOT epicardium but not endocardium [19], paradoxical shortening of the RVOT epicardial activation-recovery intervals (ARI) during augmentation of Brugada-type ST segment elevation