Introduction

After its recognition in 1992 as a distinct clinical entity, Brugada syndrome has increasingly been recognized worldwide as an important cause of sudden cardiac death (SCD) at a young age, in the absence of structural cardiac abnormalities. Patients affected with Brugada syndrome are at risk for SCD from fast polymorphic ventricular tachycardia (VT)/ventricular fibrillation (VF), especially at rest. Brugada syndrome is characterized by a typical electrocardiographic (ECG) pattern consisting of ST segment elevation in the right precordial leads and in leads positioned in the upper intercostal spaces, \( \text{(Figure 32–1)} \). The large number of case reports and clinical/experimental studies lately published about Brugada syndrome indicate its increasing weight and interest for its still not completely known aspects, such as the underlying pathophysiological mechanism, its genetic background, and its prognosis and treatment.

The pathophysiological mechanism underlying this syndrome remains controversial, with two predominant theories regarding the typical ECG features and the genesis of the arrhythmias: (1) a repolarization disorder, i.e., unequal expression of the transient outward potassium current \( I_{to} \) between the epicardium and the other transmural layers, or (2) a depolarization disorder, i.e., a delay in the onset of the action potential in the region of the right ventricle outflow tract (RVOT).

In 2002 a First Consensus Report was published to define the diagnostic criteria for this syndrome. Three repolarization patterns of ST-segment elevation (with two different shapes) were recognized as potential manifestations of Brugada syndrome. The coved-type morphology (type I) is characterized by a coved-shaped J wave elevation \( \geq 2 \text{ mm} \), followed by a negative T wave. A type I ECG is required for the diagnosis, while a saddleback-shaped ST elevation or a coved-type \(< 1 \text{ mm} \) (types II–III) are indeterminate forms that necessitate pharmacological challenge (Figure 32–2).

The diagnosis is posed when a type I ECG, spontaneously or after provocation with sodium channel blockers, is present in more than one right precordial lead in the absence of structural abnormalities, and in association with one of the following conditions: (1) documented VF or polymorphic VT, (2) a family history of SCD at a young age or a type I ECG in family members, (3) otherwise unexplained syncope, or (4) inducibility of VT/VF with programmed electrical stimulation (EPS). Spontaneous occurrence of a type I ECG has prognostic implications, representing a condition with increased risk for malignant arrhythmias and, if present in conjunction with Brugada syndrome-associated symptoms, conferring an indication for implantation of an implantable cardioverter defibrillator (ICD).

Risk stratification and indications for ICD implantation are extensively discussed in the Second Consensus Report paper, published in 2005. This topic and other important aspects to consider in the interpretation of ECG patterns in Brugada syndrome are presented later in this chapter.
Brugada syndrome is inherited as an autosomal dominant trait. In 1998, it was linked to mutations in the SCN5A gene, encoding the α subunit of the cardiac sodium channel protein. Up to now, more than 80 mutations correlating with the Brugada syndrome phenotype have been found (inherited Arrhythmia Database: http://www.fsm.it/cardmoc/) (Figure 32–3). It is estimated that SCN5A mutations account for 20–30% of all Brugada syndrome cases. Discovery of new genes is still ongoing.

A linkage to a second locus on chromosome 3 was demonstrated in a large Brugada syndrome family and direct sequencing of that region led very recently to the identification of a novel mutation in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L). The exact function of the product of the GPD1L gene is still unknown, but most likely the mutant protein causes Brugada syndrome through a reduction in Na⁺ inward current, as well as the other Brugada-linked SCN5A mutations.

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**Figure 32–1.** Four ECG traces of a resuscitated Brugada syndrome patient showing most severe ST-T abnormalities in leads positioned over the second and third intercostal space (right two panels) where a coved-type ECG is present (arrows). Intermediate ST-T abnormalities (saddleback-type) are recorded in the fourth intercostal space (leads V2–V3). Calibrations are given. (Courtesy of Dr. Wataru Shimizu.)

**Figure 32–2.** Precordial leads ECG of a resuscitated patient with three types of ST segment elevation described in Brugada syndrome. Within a few days the ECG changed from type I (left panel) to type II (middle) and type III (right panel). For explanation see text. The arrows indicate the J waves. Calibrations are given. (Modified from Wilde et al.)

**Figure 32–3.** Representation of the α subunit of the voltage-gated SCN5A sodium channel showing the locations of the mutations associated with Brugada syndrome (circle). (Courtesy of Dr Andre Linnenbank, Department of Experimental Cardiology, AMC, The Netherlands.)