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Brugada syndrome : clinical and pathophysiological aspects

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Brugada syndrome is an intriguing syndrome responsible for sudden cardiac death (SCD) at young age. In around 30% of the subjects affected by Brugada syndrome, a mutation in the *SCN5A* gene is found. The hallmark of Brugada syndrome is a typical ECG pattern, consisting of ST segment elevation in the right precordial leads whose form and severity can vary even daily in the same patient. The fluctuations of the ST segments on the ECG's make the diagnosis of Brugada syndrome often difficult to achieve. The management of Brugada syndrome patients is also challenging since standard risk stratification tools do not provide certainties in determining the prognosis of affected patients. The best therapeutic strategy in Brugada syndrome is nowadays still a highly debated matter, especially in asymptomatic patients.

The principal **aim** of this thesis is to provide a detailed description of the clinical phenotype, including clinical characteristics in different subgroups of Brugada syndrome patients. Secondly, the value of diagnostic drug testing using flecainide is studied. Moreover, this thesis aims to examine the genotype-phenotype relationship in the patients that are carriers of a *SCN5A* mutation. Finally, there is an attempt to clarify the mechanism underlying this syndrome, with a critical review of all data from the literature.

Outline

11

As outlined in the introduction (**Chapter 1**), Brugada syndrome is increasingly recognized worldwide as an important cause of SCD at young age, in the absence of clear structural cardiac abnormalities. Death arises because of fast polymorphic ventricular tachycardia, which occurs at rest, especially while asleep. The prevalence of Brugada syndrome in Europe is not as rare as initially thought. Familial forms of Brugada syndrome are inherited as autosomal dominant trait. In 1998, an association was found with mutations in the *SCN5A* gene, encoding the α -subunit of the cardiac sodium (Na^+) channel protein. Since then, progression has been made in finding other genes linked to the Brugada syndrome phenotype. Interestingly the same mutations can be associated with overlap syndromes, often between the Brugada syndrome and Progressive Cardiac Conduction Disorders

(PCCD). The Brugada syndrome is characterized by a typical ECG pattern consisting of ST segment elevation in the right precordial leads and in leads positioned in the third intercostal space. These leads register the electrical activity from the right ventricle outflow tract (RVOT), which is considered to be the place of origin of the arrhythmias in Brugada syndrome. The diagnosis of Brugada syndrome requires the presence of a type I ECG and often necessitates the performance of drug challenges since the baseline ECG fluctuates daily. Sodium channel blockers are the drug of choice for these provocation tests. **Chapter 2** reports the results of a retrospective study where the diagnostic value of drug testing, performed with the administration of flecainide (class IC Vaughan-Williams), has been investigated. The results of this study are of importance in clinical practice since it is demonstrated not only that provocation testing has a high diagnostic yield, but also that it can be safely conducted. As a result of a detailed ECG analysis, we have been also able to present additional ECG criteria for the diagnosis of Brugada syndrome. **Chapter 3** manages the controversial theme of the pathophysiological mechanism underlying this syndrome. A comprehensive review dealing with the two predominant theories regarding the genesis of the typical ECG features and the development of arrhythmias in Brugada syndrome is reported. The first theory (mainly supported by the experimental work of Dr. Antzelevitch and co-workers) suggests that a repolarization disorder, i.e., unequal expression of the transient outward potassium current I_{to} between the epicardial and endocardial layers of the right ventricle is responsible for the genesis of the ECG alterations in Brugada syndrome. Equally, also all the evidence supporting the second theory has been reviewed. This theory states that ST elevations in Brugada syndrome are due to a depolarization disorder, i.e., a delay in the onset of the action potential in the region of the RVOT.

12

Both theories are compatible with the presence of mutations in the *SCN5A* gene, leading to a loss-of function of the cardiac sodium channel.

A genotype-phenotype relationship in Brugada syndrome exists and previous studies have resulted into a better elucidation of the clinical characteristics of *SCN5A* mutation carriers. ECG parameters related to conduction disorders help to distinguish mutation carriers from non-carriers. We hypothesized that it might

be possible to predict the prognosis of the mutation carriers by analyzing the type of *SCN5A* mutation.

Up to now, standard risk stratification tools include the presence of syncope/familial death and clinical investigations such as ECG data, electrophysiological study (EPS), and signal average ECG (SAECG) for the presence of late potentials. We sought to explore the value of genetic data as a new tool for risk stratification. The results of this genotype-phenotype analysis in *SCN5A*-positive patients are provided in **Chapter 4** of this thesis.

It is known that patients affected by Brugada syndrome are at risk for SCD from fast polymorphic VT, especially at rest. We also know that the penetrance and the expressivity disease expressivity are very variable, from totally asymptomatic patients to SCD at young age as first presentation. Moreover, male patients are more symptomatic than females. In **Chapter 5**, the clinical presentations in different categories of patients is described: firstly in children, who are more susceptible to fever-induced symptoms and secondly in symptomatic women, whose ECGs show less degree of ST segment elevation than men. One of the most intriguing clinical properties in Brugada syndrome is that affected patients have a higher arrhythmic risk during fever. In chapter 5 we also report the results of a systematically conducted work on the prevalence of fever-triggered cardiac events. Furthermore, a unique case report is included to underlie the role of body temperature on clinical presentation in a resuscitated man affected by Brugada syndrome.