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Brugada syndrome : clinical and pathophysiological aspects

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Summary

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Although impressive progress has been made since the year of recognition of the Brugada syndrome in 1992, many aspects of this intriguing disease remain unknown and are still a matter of international debate. In this thesis, different clinical aspects of the Brugada syndrome are handled, from its diagnosis to the peculiarities of the clinical characteristics in different sub-groups of patients and its therapeutic approach. Particular attention is also given to the genetic background, represented by mutation in the *SCN5A* gene, encoding the main subunit of the cardiac sodium channel protein.

Chapter 1 collects all the known demographic and clinical data on Brugada syndrome, giving an overview of the general characteristics starting from the geographical area where the syndrome is endemic, its typical electrocardiographic pattern (including the differential diagnosis and the effect of certain drugs on the ECG) and providing a comprehensive description of the clinical phenotype. Up to now, the major role in the genetic background associated with Brugada syndrome is played by the *SCN5A* gene. The protein encoded by this large gene has a crucial function for the initiating phase of the cardiac action potential. The sodium channel protein, in fact, with its voltage sensor, gives rise to the depolarizing forces that represent the beginning of the activation of the cardiac myocytes and is responsible for the propagation of the electrical signal within the heart. More recently, mutations in other genes have been discovered in families with Brugada syndrome. Interestingly, these genes, like *GPD1L*, can modify the sodium current (I_{Na}) amplitude, in a similar fashion as mutations in the *SCN5A* gene. Alternatively, mutations are found in genes encoding for calcium channels (*CACNA1c/CACNB2b*) and potassium channels (*KCNE3*) that are active during the first part of the action potential.

Chapter 2 revolves around the diagnostic work-up in Brugada syndrome patients. The value and the safety of the provocation challenge to unmask the peculiar ECG pattern (type I ECG) in affected patients are studied. In a population of 160 patients, who underwent the drug test with flecainide, a class IC sodium channel blocker, we found that the diagnostic test is safe, provided that it is performed in accordance with the guidelines of the First Consensus paper. That means that

we have not recorded any case of dangerous ventricular arrhythmias, although some cases of incessant ventricular tachycardia during infusion with sodium channel blockers were reported in the literature. The reason for this apparent discrepancy could reside in the selection criteria of the patients to expose to drug challenge and in the criteria to stop the infusion of flecainide. We also found that flecainide testing has a good diagnostic yield, with a very high positive predictive value (96%) and a sensitivity and specificity of 77% and 88%, respectively. These results were obtained in a population of 110 genotyped patients, using genetic analysis as gold standard. Finally, we found a high percentage of positive tests by ECG investigation at the third intercostal space, a simple method through which the sensitivity of the diagnostic tests can be increased. In **Chapter 3** a highly debated issue is discussed: the mechanism by which the ECG alterations and arrhythmogenesis are generated in Brugada syndrome. Two main theories are generally proposed to explain right precordial ST elevation and both of them are comprehensively described in this chapter. Both are also compatible with the I_{Na} reduction caused by *SCN5A* mutations and favor reentry as mechanism for the development of ventricular arrhythmias. The first theory proposes that an inhomogeneous shortening of the action potential (AP)/loss of AP dome in the right ventricle exists due to the unbalance between I_{Na} and I_{to} during phase 1 of the AP. There is evidence that I_{to} expression is unequal in the transmural layers of the right ventricle and this explain why only epicardial cells show a drastic shortening of the AP, while in the endocardial cells the original AP duration is maintained. This difference in AP morphologies causes a voltage gradient from endocardium to epicardium generating the characteristic ST segment deviation in leads close to the RVOT.

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The second theory states that ST elevations in Brugada syndrome are the result of conduction slowing in the RVOT. That means that epicardial and endocardial cells activate asynchronously. The presence of conduction slowing in all heart compartments is truly a very common finding in Brugada syndrome patients, especially the carriers of a *SCN5A* mutation. In experimental settings, all studied *SCN5A* mutants linked with Brugada syndrome showed reduction of peak I_{Na} due to reduced density of the channel in the cell membrane or to changes in the

activation/inactivation process of the channel. We hypothesized that the type of *SCN5A* mutation could significantly influence the severity of the clinical phenotype. In **Chapter 4** we report the results of a retrospective international study, in which we studied the association between the type of mutation, either a truncation mutation or a missense mutation, and the clinical condition of 147 *SCN5A* mutation carriers. We found that subjects carrying a truncation mutation are at a higher risk of becoming symptomatic and express a more severe phenotype with the presence of a drastic reduction in conduction reserve at parity with the amount of ST segment elevation. It seems, therefore, that the degree of conduction disorders is not only a by-stander, but also significantly affects the prognosis of the Brugada syndrome patients. This might be of crucial importance especially in those patients in whom the ST elevations are less pronounced, i.e., women. In **Chapter 5** we collected the results of three clinical studies and one distinctive case report that describe the main clinical features of the Brugada syndrome in different groups of patients.

We first investigated whether the Brugada syndrome was present in children, a category of patients in which the presence of ECG alterations and/or ventricular arrhythmias may be underestimated given the fact that routine ECGs are performed less frequently in young individuals (defined as <16 years of age). We collected data on 30 affected children from 13 tertiary hospitals in the Netherlands, France and Germany and we found that, similarly to adult male subjects, the presence of a spontaneous type I ECG is associated with a high risk of developing ventricular arrhythmias. Also, children are more prone to fever illnesses and that is associated with a high arrhythmic risk. Therefore, it is crucial that the parents of affected children are well informed about the importance of promptly treating fever. In the case of loss of consciousness, pediatricians should think of hemodynamic instability due to VT and not only to more common and benign diseases like febrile seizures. As far as gender disparities in Brugada syndrome are concerned, we can conclude that this is not present at such a young age yet. Later on, with the hormonal changes, men and women affected with the Brugada syndrome develop distinct clinical features. Affected women are generally thought to be less prone to develop symptoms in comparison with men. From the results of the study presented in

Chapter 5.2, conducted on severely symptomatic women, we conclude that women do have indeed a lower arrhythmic risk than men. Interestingly, the incidence of Brugada syndrome in women may also be underestimated due to the different clinical and electrocardiographic presentations. The coved-shaped type I ECG is less common in women, and the degree of ST segment elevation is usually less, compared to men. Even preceding an arrhythmic event, the ST segment elevation does not seem to increase or to change shape, like described for men. A remarkable property in Brugada syndrome is that the severity of the phenotype is strongly influenced by body temperature. Chapter 5.3.1 reports data on the prevalence of fever-induced symptoms in the Brugada syndrome population at our institution. Similar to what we showed for the affected children, we demonstrate here that fever plays a key role in precipitating cardiac arrhythmic events. This seems to be related to temperature-induced changes in the gating properties of the Na⁺ channel, more than to the presence of tachycardia due to fever.

Finally, this chapter encloses a unique case report of a young man who has been resuscitated at night and in whom therapeutic hypothermia masked the electrocardiographic hallmark of Brugada syndrome.