Brugada sign: a normal variant or a bad omen? Insights for risk stratification and prognostication

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This editorial refers to "Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada Syndrome" by P. Bordachar et al. on page 879 and "Prevalence and prognosis of subjects with Brugada type ECG pattern in a young and middle-aged Finnish population" by M.J. Junttila et al. on page 874.

Brugada Syndrome is a relatively new clinical electrocardiographic entity with inordinate risk of sudden death in the absence of structural heart disease. However, the Brugada type of ECG changes have been known for almost half a century and observed in many asymptomatic individuals. Recommendations for such individuals in the literature are rather conflicting. Although some authors use the term asymptomatic Brugada syndrome, the relationship between asymptomatic patients with typical ECG abnormalities and clinical cases of Brugada syndrome is not clear. Indeed, the Brugada pattern may also be provoked by right ventricular pathology, by drugs (e.g., Class I A, C anti-arrhythmic drugs, tri-cyclic antidepressants, overdose of psychotropic agents and analgesics that exhibit sodium channel blocking properties) and can be associated with electrolyte abnormalities (i.e., hyperkalaemia and hypercalcaemia).

In Brugada syndrome, affected individuals can usually be detected by the typical ECG pattern, although not all patients have such an ECG and can only be diagnosed by drug challenges with IV ajmaline, flecainide or procainamide.

In a recent review, a systematic literature search was performed in order to identify publications on the Brugada syndrome and the Brugada sign with special emphasis on analysing the outcome data. There have been two kinds of studies on the prognostic value and natural history of Brugada sign. In the first group of studies, the prevalence and outcome of the Brugada sign have been investigated in referred individuals. These patients were referred due to either a personal history of syncope or unexplained ventricular fibrillation, or a familial history of cardiac arrest, and the typical ECG pattern. In these studies the outcome appears to be unfavourable. In the second group, the studies have investigated the outcome of the presence of Brugada-type ECG changes in the general population. These studies have shown that the prevalence of Brugada ECG pattern varies between 0.2% and 6% and that in the general population the outcome is usually benign. The major limitation of those studies, however, is the relatively short duration before follow-up.

In this present issue of the European Heart Journal, Junttila et al., report a follow-up of 2479 healthy male Air Force applicants (18–30 years) and 542 healthy middle-aged subjects (age 40–60). Fifteen (0.61%) subjects in the first population and three subjects in the second population (0.55%) fulfilled the ECG criteria for type 2 or 3 Brugada syndrome, according to the definition suggested by the European Society of Cardiology Consensus Report. Type 1 Brugada abnormality was not detected. None of the subjects with the Brugada sign (saddleback type) died or had life-threatening ventricular arrhythmias during a relatively long follow-up. The authors therefore concluded that type 2 or 3 Brugada ECG pattern in asymptomatic individuals, with no family history of sudden cardiac death, was a benign phenomenon in the Northern European population. These results are interesting from several points; firstly the follow-up duration is relatively longer than the previous population-based studies. However this can not exclude a small risk of sudden cardiac death in the subjects with typical ECG changes if followed for long enough. Secondly, type 1 ECG was not detected and it is believed that the typical coved type ECG pattern is associated with a more serious outcome, compared to the other two patterns. Type 2 and 3 ECG patterns have more subtle changes and can very easily be a normal variant. Therefore the benign outcome reported in this study should be considered in this context. Additionally despite the inclusion of a middle aged group of individuals the sampling error may still be present and the current study may not represent the entire Finnish population.
The data relating to the prevalence of Brugada type ECG pattern in different populations shows that the highest frequency comes from the South-eastern Asian countries. This most probably reflects the geographical genetic distribution of this disease.

The presence of Brugada sign, particularly Type 2 and 3 variants, in most asymptomatic individuals, without a family history of sudden death is likely to be normal variant. Brugada sign in many individuals may also be a transient, non-specific response to different stimuli.

One important issue is how to evaluate an individual with the typical pattern of Brugada sign as it suggests the therapeutic decision of ICD implantation. Determinants of sudden cardiac death in subjects with the ECG pattern of Brugada syndrome and no previous cardiac arrest have been studied by different groups. The role of electrophysiological studies in identifying those who are at risk of sudden cardiac death among individuals who are asymptomatic and have a negative family history is a challenge. The positive predictive value of programmed stimulation in Brugada syndrome varies from 50% to 37%, and negative predictive values vary from 46% to 97% in different reports. Routine genetic screening at this time also has limited value on account of only 15% of patients with a recognised Brugada syndrome testing positive for a SCN5A mutation known to be associated with Brugada syndrome.

This issue also publishes another report on Brugada syndrome by Bordachar et al. In this paper the authors have investigated the occurrence of atrial arrhythmias in 59 consecutive patients with Brugada syndrome and in 31 age and gender-matched controls. These subjects underwent an electrophysiological study and were followed for 34+/−13 months. The incidence of atrial arrhythmias was 20% in Brugada syndrome vs. 0% in controls. Ventricular inducibility was significantly related to the history of atrial arrhythmias. Inappropriate shocks were observed in 14% of patients who received an ICD whereas appropriate shocks were observed in 10.5%. The authors concluded that the presence of atrial arrhythmias was associated with a more advanced disease process in Brugada syndrome. This statement may add to our current knowledge on the prognostic features of Brugada syndrome. However due to the limited data of this particular study, it is too early to consider the presence of atrial arrhythmias as an additional risk factor for developing serious ventricular arrhythmias in patients with Brugada syndrome. More studies are needed to define the value of atrial arrhythmias in the prediction of sudden cardiac death and the relationship between ventricular and atrial arrhythmias during the follow-up. The high frequency of inappropriate shocks due to atrial arrhythmias should lead us to consider carefully programming the ICD, the use of ICDs with advanced features with atrial arrhythmia detection, and possibly dual chamber ICDs for their higher capability of detecting atrial arrhythmias in patients with Brugada syndrome.

In conclusion, currently available data suggest that in most asymptomatic individuals without clinical risk factors such as a family history of sudden cardiac death or South-eastern Asian ethnicity, an incidental finding of Brugada type ECG (particularly type 2 or type 3) does not warrant further diagnostic tests, these individuals can be observed clinically. As we do not have a single strong diagnostic test to predict the risk of developing serious ventricular arrhythmias, in situations when the physician is unsure, the combination of available diagnostic tools including drug challenge with a sodium channel blocker, electrophysiological study and genetic screening should be recommended.

References