Risk stratification of patients with Brugada syndrome remains a significant challenge. Cardiac event rates vary from 1.9 to 8.8% per annum, even in patients with a spontaneous type 1 pattern on the electrocardiogram (ECG) and a history of syncope, depending on the patient population. Although spontaneous type 1 coved J point and ST-segment elevation, history of syncope or cardiac arrest, and male gender are recognized as the main predictors of risk, a more refined approach is required. A family history of arrest is recognized as the main predictors of point and ST-segment elevation, history of syncope or cardiac arrest, and male gender are recognized as the main predictors of risk, a more refined approach is required.

This editorial refers to ‘T_peak–T_end interval and T_peak–T_end/QT ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype’ by K.P. Letsas et al., on page 271.

Risk stratification of patients with Brugada syndrome remains a significant challenge. Cardiac event rates vary from 1.9 to 8.8% per annum, even in patients with a spontaneous type 1 pattern on the electrocardiogram (ECG) and a history of syncope, depending on the patient population. Although spontaneous type 1 coved J point and ST-segment elevation, history of syncope or cardiac arrest, and male gender are recognized as the main predictors of risk, a more refined approach is required. A family history of sudden death and genetic profile, specifically the presence of an SCN5A mutation, is not predictive. The clinical use of programmed electrical stimulation studies remains controversial because of conflicting results with respect to the positive predictive accuracy, which may be a reflection of variations in the stimulation protocols used and the different underlying risk profile of the population studied.

A recent meta-analysis concluded that induction of ventricular tachycardia (VT) or ventricular fibrillation (VF) by programmed stimulation was of low positive predictive accuracy in identifying high-risk subjects with Brugada syndrome. This observation has prompted a renewed search to identify other risk markers to prevent sudden death associated with Brugada syndrome.

Although a structurally normal heart is required as a diagnostic criterion for Brugada syndrome, there is emerging evidence that this is not necessarily the case. A number of studies have demonstrated that fibrosis of the right ventricle may be present in patients with Brugada syndrome, suggesting a degenerative process that may be genetic, inflammatory, or infective in origin. Fibrosis of the right ventricle may be due to premature ageing of myocytes arising from abnormal ion channel kinetics as described in the SCN5A heterozygotic mouse. It may explain recent magnetic resonance imaging data suggesting right ventricular outflow tract dilatation in patients with Brugada syndrome as the resolution of imaging modalities has improved. This fibrotic process would promote conduction delay in the right ventricle and may explain the presence of a coved ST-segment elevation pattern independent of specific ion channel mutations promoting transmural repolarization gradients. Invasive mapping studies of the right ventricle in patients with Brugada syndrome have confirmed the presence of significant conduction delay, and computer simulations incorporating these delays can reproduce the characteristic surface ECG features. These conduction abnormalities could also increase arrhythmogenicity of the substrate through promoting conduction block and re-entry or causing destabilization of VT into VF. This may help to explain significant variations in presentations and risk of sudden death in this condition.

Letsas et al. presented data addressing the problem of refining non-invasive risk stratification in patients with Brugada syndrome. They demonstrated that an increased T_peak–T_end interval in leads V2 and V6 and T_peak–T_end/QT ratio in lead V2 were associated with VT/VF inducibility in patients with Brugada syndrome with spontaneous or ajmaline-induced type 1 ECG patterns. The T_peak–T_end interval-related repolarization parameters were measured in all precordial leads. The T_peak–T_end/QT ratio now arrives in the context of the recent description of the fragmented QRS and late potentials as other high-risk markers in Brugada syndrome. These surface ECG parameters may reflect common features of the arrhythmogenic substrate and may have the advantage of being non-invasive and capable of tracking progressive changes in the Brugada heart over time.

However, there is some controversy as to what the T_peak–T_end interval interval represented
dispersion of repolarization of the whole heart including the entire left and right epicardial surfaces. Repolarization time of the right ventricular epicardium was the shortest in normal conditions, but prolongation of repolarization time at the right ventricular epicardium in Brugada syndrome reduced dispersion of repolarization of the whole heart, resulting in a short $T_{peak} - T_{end}$ interval. This prolongation in the epicardial repolarization time may be explained by local slowing in conduction leading to more prolonged local diastolic intervals and hence, longer local action potential duration on the flatter portion of the action potential restitution curve. Thus, both $T_{peak} - T_{end}$ interval shortening and the fragmented QRS indicated marked conduction delay in the myocardium, creating the ideal opportunity for conduction block and re-entry with the degeneration of VT into VF.

It is of interest to compare data from Sangawa et al. who recently examined dynamic $T_{peak} - T_{end}$ intervals and $T_{peak} - T_{end}$/RR slopes in patients with Brugada syndrome with and without VF as opposed to patients with inducible VT/VF reported by Letsas et al. They showed that individuals with VF had shorter $T_{peak} - T_{end}$ intervals (measured in lead V5 only) at slow heart rates and longer intervals at fast heart rates compared with patients without VF. These differences in the $T_{peak} - T_{end}$ intervals were equivalent to those between patients with inducible and non-inducible VT/VF reported by Letsas et al. Longer $T_{peak} - T_{end}$ values measured by Letsas et al. were similar in magnitude to those recorded by Sangawa et al., at 100 b.p.m. The $T_{peak} - T_{end}$/QT ratio was also increased at fast heart rates in patients with VF compared with controls and reduced at slow heart rates in the population reported by Sangawa et al. Significantly longer $T_{peak} - T_{end}$/QT ratios were recorded in lead V6 by Letsas et al. in subjects with inducible VT/VF. Although there are no data on heart rates at which these measurements were made to make direct comparisons with Sangawa’s data, one can calculate that the study by Letsas et al. was performed at 72 b.p.m. The data from the Letsas’s study are likely to be compatible with findings by Sangawa et al., indicating that the $T_{peak} - T_{end}$ measurements corrected for the QT interval or heart rate, respectively, may yield useful information about arrhythmogenicity of the substrate. However, the lack of patients who developed clinical VF in the study by Letsas et al. means that it is underpowered to establish whether the $T_{peak} - T_{end}$/QT ratio is a useful predictor of clinical events. Given the controversy surrounding the predictive accuracy of programmed stimulation, this should be acknowledged.

These ECG data suggest that significant changes in intramyocardial repolarization may occur in patients with Brugada syndrome and dynamic changes in repolarization gradients may form the basis for ventricular arrhythmogenesis. These dynamic changes would also emphasize the role of increased vagal tone promoting ventricular arrhythmia in Brugada syndrome since they may slow conduction and reduce the $T_{peak} - T_{end}$ interval at slow heart rates to promote subsequent conduction block and facilitating VT/VF.

Therefore, these data provide further insight into arrhythmogenesis in Brugada syndrome and may lead the way to more useful non-invasive predictors of VF in an evolving substrate that is not easily detectable by programmed electrical stimulation. The challenge is to co-ordinate international registries of these populations similar to the landmark studies in long-QT syndrome. Such ECG data need to be prospectively collected in genotyped cohorts of patients who are phenotypically evaluated and followed in a systematic fashion to provide reliable risk stratification and prognosis in the wider populations with Brugada syndrome.

Conflicts of interest: none declared.

References