

Risk Stratification in Asymptomatic Brugada Patients

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Introduction

Brugada syndrome is an arrhythmogenic disorder characterised by ST elevation in the precordial leads, which predisposes individuals to ventricular fibrillation. It is primarily an electrical disorder, without any associated structural abnormalities (1) and has a prevalence of 5 in 10000, but is considered to contribute to 4-12% of sudden cardiac deaths (2,3).

Diagnosis

According to the J-wave syndrome expert consensus conference report, the diagnosis of Brugada Syndrome requires the presence of a Type 1 Brugada ECG. This is defined as coved ST elevation ($\geq 2\text{mm}$ at the J point) followed by negative T waves in at least one of the right precordial leads (V1,V2) placed in either the 2nd, 3rd or 4th intercostal spaces. The presence of a spontaneous type 1 Brugada pattern, in the absence of another known cause (Brugada phenocopies), should be considered as Brugada syndrome.

Where the Type 1 Brugada ECG is not spontaneous, but rather induced after drug administration, then a diagnosis of Brugada Syndrome can only be made if one of the following is also present: documented ventricular arrhythmia, arrhythmogenic syncope, family history of sudden cardiac death before age of 45 (with negative autopsy) or nocturnal agonal respiration(4).

Pathophysiology

There are two proposed mechanisms to explain why the underlying ECG changes occur. The Repolarization theory is developed from experiments on arterially perfused wedges of canine right ventricles. It has been demonstrated that increased activity of I_{to} channels in the cardiac epicardium cause a transmural gradient, subsequently producing the ST elevation in the precordial leads (5). The Depolarisation theory is based on the suggestion of slow conduction in the right ventricular outflow tract (RVOT) in comparison to the right ventricle (RV) generates a difference in membrane potential, subsequent driving current from the RV to the RVOT leading to ST elevation (6).

Managing Asymptomatic Patients

The current consensus is that individuals with Brugada syndrome, who have suffered from an aborted sudden cardiac death or syncope deemed to be arrhythmogenic are candidates for an ICD since the annual risk of further ventricular arrhythmias is 8% (7,8).

However, according to the multi-registry FINGER trial, approximately 64% of patients with Brugada Syndrome are asymptomatic at diagnosis. These patients have a 0.5% rate per year of ventricular arrhythmic events (9), consistent with other large ICD registries of patients with the Brugada ECG phenotype (10,11).

It is disconcerting that asymptomatic individuals are not completely risk free when it comes to from sudden cardiac death. However, ICD implantation must be performed with caution given that the FINGER registry also identified a 37% prevalence of inappropriate shocks and 29% occurrence of lead failure, in Brugada patients who were implanted with an ICD. Additional tools are therefore required to decipher, which group of asymptomatic individuals are at a significantly high risk of sudden cardiac death to warrant ICD therapy.

Predicting Risk

Brugada patients who have previously suffered from syncope have 1-1.5% per year risk of VF, which is 4 times higher compared to asymptomatic individuals (9). In this group of patients it can be difficult to differentiate between arrhythmogenic and neural mediated syncope. Previously studies have attempted to categorise syncopal episodes on clinical history with a high degree of accuracy, they have proceeded to emphasise prodromal features such as blurred vision, nausea/vomiting or sweating are more associated with vasovagal syncope, but abnormal respiration or urinary incontinence is affiliated with arrhythmogenic syncope (12).

It has been shown in large registries that there is an almost seven fold increase risk of sudden cardiac death in men compared to women in asymptomatic patients, although there is a bias of predominance of males in the asymptomatic cohort (13). Another cohort of asymptomatic Brugada patients consisting of 42% women displayed lower incidence of serious events in the female group(14). These prospective studies suggest men experience a more malignant form of the condition.

Brugada syndrome is strongly associated with SCN5A gene, which encodes for the cardiac sodium channel and on screening it is believed 10-15% of patients have a variant of this gene that results in change in channel function (15). It was therefore theorised these individuals are at a higher risk, but the FINGER and PRELUDE trials failed to confirm this association after multivariant analysis (9,10). A large Japanese registry of Brugada patients demonstrated mutations in the channel's pore region compared to other areas corresponded to higher cardiac event rates along with conduction abnormalities (16).

It has been previously demonstrated that sudden cardiac death in a family member below the age of 45 is a strong independent predictor of poor prognosis(17) but this has not manifested in larger registries (9), where SCD in the family was not

statistically predictive of events in either symptomatic (3.3% vs 3.0%) or asymptomatic patients(0.5%vs 0.6%).

The Electrocardiogram and Risk

It has been consistently emphasised that patients with the spontaneous Brugada ECG are at a greater risk of arrhythmic events than those who develop it after medication administration (18). Caution should be exercised when screening family members of Brugada patients since drug induced Brugada Type 1 ECG currently does not lead to definitive therapy. A recent study by Sieira et al followed asymptomatic patients with drug induced Type 1 Brugada ECG and found a low incidence of cardiac events over a 5 year follow up, this was even lower in patients who have no ventricular arrhythmias induced during an electrophysiology study(19).

The presence of multiple spikes (> 4) in a QRS complex is categorised as a fragmented QRS complex, if present in the precordial leads it is a significant predictive marker for arrhythmic events in Brugada patients. A study compared incidence of fragmented QRS between symptomatic and asymptomatic Brugada patients. They identified fragmented QRS complexes in 80% of Brugada patients who have previously experienced VF compared to 34% in the asymptomatic group(20). There was a similar finding in the PRELUDE study and by Junnttila et al, a group that recognised that 94% of patients with Brugada and VF had fragmented QRS complexes, with 58% of patients with fragments QRS suffered from recurrent syncope(21).

If the R wave is $\geq 0.3\text{mV}$ or $R/q \geq 0.75\text{mV}$ in lead aVR this is defined as an aVR sign, but only in one small trial this was a segregate marker for development of ventricular arrhythmias(22) that unfortunately was not replicated in other trials(10,21)

Conduction delay is one of the fundamental theories regarding the arrhythmogenic mechanism of Brugada hence it is not surprising there is a higher incidence of Late Potentials in symptomatic patients. Late potentials can be identified on signal averaged ECGs and represent delay in ventricular conduction. A study enrolled 43 patients with Brugada Syndrome and differentiated them into symptomatic and asymptomatic patients, 91% of patients in the symptomatic group had late potentials on their ECG, while only 36% in the asymptomatic had late potential on their ECG(23). Ikeda et al processed signalled average ECGs from 124 Brugada patients with no previous history documented arrhythmia, only 24 patients had syncope and discovered statistically higher incidence of late potentials on group that suffered from ventricular arrhythmia during follow up(24).

Early Repolarisation pattern demonstrated by J Wave or Horizontal ST segment has a higher prevalence in symptomatic than asymptomatic patients, especially in the inferolateral leads(25). A recent meta-analysis validated this finding, but showing an increased incidence of cardiac events in patients with Brugada and Early repolarisation in the inferolateral leads (Odds Ratio 3.29)(26).

The above ECG markers give us some inclination of their role in risk stratification but it is imperative to emphasise significant number of trials were processed with small number of patients or have failed to be replicated in other studies (2).

Programmed Electrical Stimulation and Risk

The role of Electrophysiology Study (EPS) in risk stratification of asymptomatic Brugada patients is highly controversial. Initially Brugada et al. reported only a small percentage of patient with a negative EPS going on to develop ventricular fibrillation after a negative EPS during a 3 year follow up (27). This was correlated by Delise et al, but this group then proceeded to use other clinical factors such as family history, spontaneous type 1 ECG and syncope, and discovered that 30% of patients with all the above factors and a positive EPS went on to experience arrhythmogenic event (28). The major contradiction to this data arrived from the PRELUDE study which revealed 9 of 14 cardiac events occurring in the non-inducible group (10).

One of the largest multi-centre studies, consisting of 800 asymptomatic Brugada patients, failed to demonstrate a relationship between a negative EPS and future cardiac events, even when combined with other factors such as family history (9).

Fauchier et al, a meta-analysis of 13 clinical trials incorporating over a 1000 asymptomatic Brugada patients. Their analysis illustrated asymptomatic patients with inducible VT/VF with an EP study had a higher incidence of cardiac events, which was homogenous across multiple studies (11). A recent similar meta-analysis reiterated a positive EPS study in asymptomatic brugada patient corresponded to increased risk of ventricular arrhythmias particularly if induced with fewer extra stimuli, but a negative EPS did not necessarily correlate with a complete exemption from cardiac events(29)

The disparity between studies reviewing the utilisation of EPS in risk stratification is likely due to difference stimulation protocols i.e. number of stimuli, coupling intervals and site of pacing.

The development of clinical scoring models may enhance risk stratification for physicians. A recent scoring tool founded on following factors: on spontaneous type 1 ECG, Syncope, VF/VT inducibility on EPS, aborted sudden cardiac death, sinus node dysfunction and familial sudden cardiac death had a predictive ability of 0.81 in an asymptomatic group (30). More importantly this group undertook a lengthy follow up and had a sensitivity of 96.9% in the group scoring 0-1. These individuals probably represent Brugada patients identified during routine pre-operative testing or family screening but this needs to be validated over a lengthy follow-up.

Non Device Management

All asymptomatic patients should be advised to treat fevers with anti-pyretics, avoid pro-arrhythmic drugs, and to avoid both excessive alcohol and heavy meals.

Quinidine, an anti-arrhythmic drug which is sometimes employed in patients who have declined or been unsuitable for ICD implantation, should not be utilised in the asymptomatic group as a prophylactic measure. The QUIDAMI study reviewed the efficacy of hydroquinidine in Brugada patients but had to be terminated prematurely due to high rate of discontinuation hence its efficacy has not been proven in the asymptomatic group and may fail due to its side effect profile(31).

Conclusions

The management of asymptomatic Brugada patients remains a conundrum for physicians due to inadequate evidence of long term follow up in clinical trials, and the high prevalence of ICD related complications in this cohort. When consulting these low risk patients it is instrumental to provide them with all the information available and to evaluate all obtainable clinical information to inform upon that individual's risk of sudden cardiac death.

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