Editorial: Non-invasive Delineation of Atrial Electrophysiology in Brugada Syndrome-Another window on arrhythmogenic substrate and risk?

PD Lambiase

Word Count : 1417(Text)

Addresses for Correspondence:

Professor Pier Lambiase
UCL Institute of Cardiovascular Science & Barts Heart Centre
Room 3.20, Rayne Institute
5 University Street
London, WC1E 6JF
United Kingdom
Email: *p.lambiase@ucl.ac.uk*
Word count: Text: 967 Refs: 370
Conflicts of Interest: None
PDL is supported by UCL/UCLH Biomedicine NIHR

Atrial arrhythmias remain a significant issue in Brugada Syndrome (BrS)-even in the first series published by the Brugada group in 1992, 25% of cases had atrial fibrillation. Indeed, AF has been recognised to act as a marker of a more malignant course reflecting abnormal conduction and repolarisation dynamics in ventricles indicative of a more global myocardial pathophysiological process. Sacher et al (1) described the incidence of atrial arrhythmias in a large retrospective series of patients with BrS and ICDs- in 220 patients, 32 demonstrated supraventricular arrhythmias, including atrial fibrillation (AF) in 23 cases (10%). These atrial arrhythmias represent a significant avoidable cause of inappropriate shocks, so predicting who is likely to develop them and mitigating the effects of rapidly conducted AF has important clinical implications. Indirectly, in the Sieira score atrial pathology with sinus node dysfunction was an independent predictor of ventricular arrhythmic events (2).

There are a number of parallels between the mechanisms of ventricular arrhythmias (VAs) and atrial arrhythmias in BrS reflected in detailed studies of murine knock out models and human electrophysiological studies (3). The common finding is loss of conduction reserve and effects of fibrosis promoting conduction delay to enable re-entry and wavebreak resulting in fibrillation whether this be atrial or ventricular. Indeed, vagal tone also has a modulatory influence. The onset of AF is often preceded by fluctuations in autonomic tone, consistent with most AF in BrS occurring at night as in the VAs. Vagal stimulation reduces atrial conduction velocities and shortens the effective refractory period, facilitating the induction of AF. The expression of the cardiac sodium channel gene (SCN5A) has been reported in canine intracardiac ganglia. Loss-of-function mutations in SCN5A may generate an imbalance in the intracardiac ganglia activity and increase vagal tone.

Several genes have been implicated in BrS which is autosomal dominant with variable penetrance, the most common being SCN5A sodium channel mutations identified in 20% to 30% of patient. Rare variants in genes affecting the sodium current (SCN1B, SCN10A) and calcium current (CACNA1C, CACNA2D1, and CACNB2B) are described in a minority of patients (4). These mutations mostly result in qualitative or quantitative alteration of sodium channels. In patients with an SCN5A mutation intra-atrial conduction slowing, reflected as a longer p-wave duration occurs (5). Heterozygote SCN5A knock-out mice

display reduced conduction velocity, impaired AV conduction, and QRS prolongation. They also develop fibrosis and reductions in connexin 40 expression further reducing conduction reserve (6). Interestingly, Kusano et al (7) found no difference in spontaneous AF or VA episodes between patients with and without SCN5A mutations in BrS, suggesting that genetic analysis for this defect is not useful for risk stratification as previously reported in several studies. However, they still found that the interatrial conduction delay was significantly increased in BrS patients with AF, indicating that global atrial myocardium conduction was impaired. Furthermore a greater atrial vulnerability in patients with BrS with VA episodes, indicating a common global electrical vulnerability to fibrillation across the whole heart. The fact fibrosis is found in both the atria and epicardium of Brugada Syndrome patients indicates that other processes e,g inflammation, prior viral infection are an important aetiological factor in this condition and not all cases necessarily have a clearly defined genetic basis.

An interesting study examining concealed Brugada ECG patterns using ajmaline testing, suggests that another SVT: AVNRT and concealed BrS co-occur, particularly in female patients, and genetic variants that reduce sodium channel current may provide a mechanistic link between AVNRT and BrS predisposing to expression of both phenotypes. Hasdemir et al (8) identified a concealed BrS electrocardiogram in 26 of 96 patients with AVNRT (27.1%) and in 3 of 66 control subjects (4.5%) ($P \leq .001$). Genetic screening identified 19 mutations or rare variants in 13 genes in 13 of 17 patients with both AVNRT and BrS (yield = 76.5%). Ten of these 13 genotype-positive patients (76.9%) harbored genetic variants known or suspected to cause a loss of function of cardiac sodium channel current (SCN5A, SCN10A, SCN1B, GPD1L, PKP2, and HEY2). This controversial study raises issues about the specificity of ajmaline testing but gives some insight into understanding the aetiology of supraventricular arrhythmias more widely suggesting that genes affecting Na channel function may have wider implications beyond BrS.

In the journal, Bisignani et al (9) utilised ECG Imaging (ECGI) to study atrial conduction in 43 consecutive BrS patients and 40 controls and related this to atrial tachycardia events (ATs). Both total activation conduction time (TACT) and Local activation CT (LACT) were significantly prolonged in BrS patients compared with controls. Ajmaline also significantly lengthened these conduction parameters in BrS patients carriers of a

pathogenic/likely pathogenic SCN5A variant versus controls. After a mean follow-up of 40.9 months, 6 patients experienced a first AT occurrence (all in the BrS group, 13.9%). TACT was the only independent predictor of ATs with a cut-off of > 138.5 ms. There were no differences between BrS patients with a history of spontaneous type I Brugada ECGs vs BrS patients without spontaneous type I in TACT and LACT before and after ajmaline challenge.

These findings certainly reflect the observations of abnormal atrial electrophysiology in BrS as outlined above and studies cited in the manuscript. There are a number of limitations to the study, particularly in relation to the nature of the arrhythmias described, it would be useful to know if these were re-entrant or focal atrial tachycardias or indeed atrial fibrillation. The duration of episodes is also not described simply >30s. Furthermore, the control group was not consistently followed-up with rhythm monitoring and the fact that 90% of the Brugada group had ICDs implanted means there is a reporting bias in arrhythmia detection, and so it is unclear whether these events are more frequent than would be expected in a matched cohort for age, sex and cardiovascular risk factors. Indeed, even the control group had a history of ventricular ectopy (with normal cardiac MRIs). Although this did not have a bearing on the direct ECGI comparisons, it does not necessary reflect a truly normal control population as these patients may have atrial conduction anomalies linked to the ectopy.

Nevertheless, the utilisation of ECG Imaging (ECGI) in this context is instructive and could inform the actual effects of BrS on atrial arrhythmias. ECGI provides the advantages of instantaenous non-invasive global atrial mapping and has an accuracy of 13.5±9 mm for focal activation localisation, although it can be subject to error depending on rotational alignment and geometry co-regisitration on CT/MRI (10). In this context, it is a suitably accurate technique to address the global conduction hypothesis in this study. It would have been useful if these patients were having EP studies utilising atrial pacing restitution S_1-S_2 pacing protocols to examine conduction reserve and interrogate for the development of lines of functional block versus controls and induce atrial tachycardias. This would delineate the atrial arrhythmia mechanisms and relate these to sites of conduction abnormalities or electrogram fractionation. These data could be of value in understanding atrial fibrillation mechanisms more widely, especially in SCN5A mutation

carriers. It would provide an elegant human model of the effects of Na channel dysfunction in atrial fibrillation. With the advent of higher resolution MRI and CT enabling deeper interrogation of the structural atrial substrate, the effects of fibrosis in BrS and atrial fibrillation could also be examined in detail. It would have important clinical implications to enable tailoring of therapy for BrS patients in the first instance. By predicting AF vulnerable patients, one could ensure optimal medications and ICD programming to prevent rapidly conducted AF triggering inappropriate shocks or VT/VF or being more proactive with anti-arrhythmic therapy such as quinidine in higher risk cases.

The other issue alluded to in the paper is whether atrial electrophysiology could give insights into VA and sudden death risk stratification. The study did not evaluate differences in patients with VAs and those without, but since the atria may represent a "window" on the myocardial substrate in this disease and indeed rapidly conducted atrial arrhythmias may act as triggers for sudden death events, it would be an interesting line of enquiry to systematically examine such differences in the atria aswell as the ventricular electrophysiology where conduction and repolarisation abnormalities in the right ventricle have already been described.

In conclusion, Bisignani et al should be commended in utilising ECGI informatively to open new directions to study BrS arrhythmogenic mechanisms providing opportunities to characterise the atrial substrate in a more dynamic & widely applicable approach that could have implications beyond BrS.

References

1. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation. 2006;114:2317-2324.

2. J. Sieira, G. Conte, G. Ciconte, et al. A score model to predict risk of events in patients with Brugada Syndrome. Eur Heart J, 38 (2017), pp. 1756-1763

3. Takla M, Edling CE, Zhang K, et al. Transcriptional profiles of genes related to electrophysiological function in Scn5a+/- murine hearts. Physiol Rep. 2021 Oct;9(19):e15043.
4. Cerrone M, Costa S, Delmar M. The Genetics of Brugada Syndrome.Annu Rev Genomics Hum Genet . 2022;23:255-274.

5. Amin AS, Boink GJ, Atrafi F, et al. Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in Brugada syndrome. Europace. 2011;13:968-975.

6. Derangeon M, Montnach J, Baro I, Charpentier F. Mouse models of SCN5A-related cardiac arrhythmias. Front Physiol. 2012;3:210

7. Kusano KF, Taniyama M, Nakamura K, et al. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. J Am Coll Cardiol. 2008; 51:1169-1175.

8. C. Hasdemir, S. Payzin, U. Kocabas, et al. High prevalence of concealed Brugada syndrome among patients with atrioventricular nodal re-entrant tachycardia. *Heart Rhythm*, 12 (2015), pp. 1584-1594.

9 Bisignani, et al JACCEP

10. Graham AJ, Orini M, Zacur E, Dhillon G, et al. Simultaneous comparison of electrocardiographic imaging and epicardial contact mapping in structural heart disease. Circ Arrhythm Electrophysiol. 2019; 12:e007120. doi: 10.1161/CIRCEP.118.007120