Brugada syndrome and atrial fibrillation: pathophysiology and genetics

Martina Muggenthaler and Elijah R. Behr*

Cardiac and Vascular Division, St George’s University of London, London SW17 0RE, UK

Received 28 February 2011; accepted after revision 28 February 2011; online publish-ahead-of-print 31 March 2011

This editorial refers to ‘Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in Brugada syndrome’ by A.S. Amin et al., on page 968.

In 1992, the Brugada brothers described eight patients with a syndrome of ST segment elevation in electrocardiogram (ECG) leads V1–V3 accompanied by a right bundle branch block appearance and the risk of ventricular fibrillation and sudden cardiac death.1 One patient was an 8-year-old girl with an additional history of paroxysmal atrial fibrillation (AF). She had experienced her first paroxysm soon after birth while her first episode of syncope occurred at 8 years of age. Since this first description a dramatic variability in clinical presentation of the disease has transpired. A high prevalence of AF has, however, remained a feature.2

The genetics of Brugada syndrome

The first gene linked to the Brugada syndrome was SCN5A, which encodes the α-subunit of the NaV1.5 cardiac sodium channel responsible for the inward sodium current. A 20% yield of disease-associated variants has consistently been reported.2 More recently less common mutations in other genes have been associated with the Brugada syndrome including mutations in: GPD1L, involved in the transportation of cardiac sodium channels to the cell membrane; SCN1B and SCN3B, encoding β-subunits of NaV1.5; KCNE3 encoding a β-subunit of the channel responsible for the I(to) current; and CACNA1C and CACNB2b, which both encode subunits of the L-type calcium channel.3 Mutations in SCN5A have also been reported in association with familial AF.4

Atrial fibrillation and Brugada syndrome

The prevalence of AF and atrial flutter in patients with Brugada syndrome is approximately 20%2 compared with 2.3% in the general population above the age of 40.5 Kusano et al. found that 70% of episodes of AF in their Brugada patients occurred at night, suggesting that nocturnal vagal activity and withdrawal of sympathetic activity may play an important role in arrhythmogenesis. Bradycardia due to altered sympatho-vagal balance is also thought to contribute to ventricular arrhythmia initiation, reflecting that most sudden deaths in Brugada syndrome occur at night.6 It has been suggested that atrial arrhythmias are an indicator for more severe disease. Indeed, patients with a spontaneous type 1 ECG pattern, inducibility of ventricular arrhythmias at electrophysiological study or who fulfilled criteria for an implantable cardioverter (ICD) have shown a higher incidence of atrial arrhythmias.7

Pappone et al. found a surprisingly high prevalence of 3.2% of the type 1 Brugada ECG pattern unmasked by class IC anti-arrhythmic drugs in patients with new-onset AF and a prevalence of 5.8% in patients with lone AF. While genetic testing did not identify any SCN5A mutations, one of the patients who had undergone ICD implantation suffered ventricular fibrillation during follow-up. This suggests that some patients with a drug-induced Brugada ECG may develop Brugada syndrome, suffering atrial arrhythmias prior to developing ventricular arrhythmias.8

The effect of SCN5A mutations on atrial fibrillation in Brugada syndrome

Amin et al.9 present a hypothesis based on a study of AF in a large cohort of Brugada syndrome patients. They reason that a reduced number of potentially triggering premature atrial contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may account for AF being no more prevalent in patients with SCN5A mutations than in those without. This is an interesting proposition and seems plausible given the current understanding of the mechanisms initiating and maintaining AF. However, the number of patients with AF in both groups is relatively small and these results will need to be reproduced in larger studies. In addition, given the unresolved and complex issues underlying the pathophysiology of Brugada syndrome, one

The opinions expressed in this article are not necessarily those of the Editors of Europace or of the European Society of Cardiology.

* Corresponding author. Tel: +44 208 725 5939; fax: +44 208 725 3328; Email: ebehr@sgul.ac.uk

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com.
should regard this hypothesis as one potential mechanism of many that influence the prevalence of AF in Brugada syndrome.

Mechanisms of arrhythmogenesis

The pathophysiology of AF in general has been extensively studied and the current understanding includes the interplay of triggers, the arrhythmogenic substrate and modulating factors such as the autonomic nervous system or inflammation. In this context Makiyama et al. studied a family with autosomal-dominant inherited AF and identified a novel gain-of-function mutation in SCN5A. Family members presented in their teens with palpitations secondary to PACs, which later progressed to paroxysmal and ultimately persistent AF. Catheter ablation was performed in one proband and increased excitability in the right atrium with multiple repetitive atrial tachycardias noted. A second ablation was required and the patient remained symptomatic with episodes of paroxysmal and persistent AF. They speculated that the gain-of-function mutation in SCNSA might cause triggered activity due to failure of repolarization or early after-depolarizations leading to PACs and AF. This is consistent with Amin et al.’s description of reduced PACs in patients with SCNSA loss-of-function mutations.

While a number of groups have reported structural changes in the right ventricle in Brugada syndrome, less is known about such changes in the atria. Toh et al. found significantly prolonged atrial conduction times and increased left atrial volumes in Brugada patients with SCNSA mutations compared to those without. Similar to Amin et al.’s findings, however, left atrial diameter was not significantly different between the two groups. This reflects that left atrial volume may be a more accurate measurement of asymmetric remodelling of the atrium. Increased atrial structural remodelling in SCNSA loss-of-function mutation carriers compared with non-carriers would also be consistent with the observation by Amin et al. that the prevalence of persistent AF tended to be higher in the former group. This view of the substrate is supported by experiments in mice with a single null allele of the SCNSA gene. They demonstrate age-related development of myocardial fibrosis and progressive slowing of atrial and ventricular conduction. Furthermore, a 50% reduction in the expression of atrial Connexin 40 was observed, which, in addition to reduced sodium current, might be responsible for the slowing of atrial conduction.

The onset of AF is often preceded by fluctuations in autonomic tone, consistent with most AF in Brugada syndrome occurring at night. Vagal stimulation reduces atrial conduction velocities and shortens the effective refractory period facilitating the induction of AF. Scornik et al. demonstrated the expression of SCNSA in canine intracardiac ganglia. Loss-of-function mutations in SCNSA may therefore generate an imbalance in the intracardiac ganglia activity and increase vagal tone.

Management of atrial fibrillation in Brugada syndrome

Treatment of AF in Brugada syndrome is challenging as many antiarrhythmic drugs have sodium channel blocking properties that exacerbate the Brugada ECG pattern potentially provoking ventricular arrhythmias. In addition beta-blockers have been reported to promote transmural dispersion of repolarization, unmasking ST segment elevation, as have calcium channel blockers and both should therefore also be avoided. The safety of amiodarone in Brugada syndrome is not established. Quinidine, a class IA antiarrhythmic, however, reduces the Brugada ECG pattern and inducibility of VF. This effect is thought to be due to its vagolytic and significant I(1) blocking properties. Quinidine is known to be an effective treatment in AF and might be a safe pharmacological agent in Brugada syndrome. Kusano et al. observed that two patients with AF treated with quinidine and bepridil for recurrent episodes of ventricular fibrillation did not experience any episodes of AF while taking these drugs either.

Controlling AF is all the more important as it commonly causes inappropriate ICD therapy in patients with Brugada syndrome. In recent studies, up to 14% of patients received inappropriate shocks per year due to atrial arrhythmias. In view of the difficulties with pharmacological management of AF in Brugada syndrome, catheter ablation might therefore be an attractive choice of treatment. Yamada et al. published a small series of six patients with Brugada ECGs and paroxysmal or persistent AF who underwent pulmonary vein isolation. One of the patients required a repeat procedure, but after a follow-up period of 11 ± 6 months all were free of symptoms without antiarrhythmic medication. An interesting observation was a lack of pulmonary vein ectopics raising the possibility that the triggers originate from elsewhere in the atria in Brugada syndrome. Nevertheless, pulmonary vein isolation without any additional lesions seemed to be effective in preventing AF during a limited follow-up period.

Conclusion

Despite huge advances in our understanding of the Brugada syndrome there remain many unanswered questions. It is likely that the underlying mechanisms for AF are a culmination of multiple lesions, genetic and acquired that impact upon cardiac conduction, atrial structure, autonomic function, and other unknown factors. The elucidation of these mechanisms will also be likely to impact on our understanding of AF in general.

Conflict of interest: E.R.B. receives research grants form Boston Scientific and Biotronik.

References