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Monomorphic ventricular tachycardia in Brugada syndrome: True-true but related?

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Brugada syndrome is a genetic arrhythmic disorder with a characteristic electrocardiographic (ECG) pattern associated with a risk of sudden death due to ventricular fibrillation.¹ A typical Brugada ECG pattern includes > 2 mm of coved-type ST segment elevation followed by T-wave inversion in the right precordial leads either spontaneously or after intravenous infusion of Vaughan-Williams class 1 pharmacological challenge. Because of both the low yield (20%–30%) of mutation identification associated with Brugada syndrome² and the plethora of clinical phenotypes associated with sodium channel mutations,³ the foundation of diagnosis is based on ECG characteristics in concert with clinical syndrome⁴ rather than genetic mutations informing the clinical disease.

Arrhythmic sudden death in Brugada syndrome is related to polymorphic ventricular tachycardia (PMVT) from the right ventricular outflow tract (RVOT),^{5,6} which can be heralded by an accentuation of the typical Brugada ECG pattern.⁷ Triggers for arrhythmia are body temperature fluctuations (fever)⁸ and high vagal tone.⁹ Although Brugada syndrome correlates with structurally normal hearts, there is increasing evidence suggesting that slight structural RVOT abnormalities are present and could support arrhythmia substrate in Brugada syndrome.¹⁰ These structural abnormalities have distinct implications with respect to the arrhythmia mechanism.

More generally, tachyarrhythmias occur because of either increased automaticity, triggered activity, or reentry. Increased automaticity refers to abnormal phase 4 diastolic depolarization, resulting in spontaneous depolarization during diastole. Triggered activity refers to oscillations/afterdepolarizations of the membrane voltage that occur after the onset of the action potential. Afterdepolarizations can occur before the action potential has fully repolarized (early afterdepolarizations), or they can occur after the action potential has fully repolarized (delayed afterdepolarizations [DADs]). In either case, an arrhythmia arising from the triggering of an afterdepolarization is said to be a triggered arrhythmia. Reentry involves a circuit that must contain areas with fast and slow conduction velocities, varying refractory periods, and a core (either fixed or functional) about which the circuit moves. Reentry is the most common cause of tachyarrhythmias including atrial fibrillation,

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atrioventricular nodal reentry tachycardia, atrioventricular reentry tachycardia, and some types of ventricular tachycardia (VT).

Reentry has been argued as the dominant arrhythmia mechanism in Brugada syndrome. There is ongoing debate over how the reentrant substrate develops, whether it is due to conduction slowing from primarily depolarization abnormality, repolarization abnormality, or (probably) both.¹⁰ However, there is some consensus that Brugada syndrome–related arrhythmias belie their origin in the heterogeneity in the RVOT¹⁰ and may include structural derangements.¹¹

In contrast, outflow tract idiopathic VT is mechanistically linked to triggered activity due to DADs. DADs result from the overloading of cells with calcium, with calcium transiently re-released into the myoplasm after a depolarization, causing a transient rise in myoplasmic calcium, activating calcium-dependent depolarizing membrane currents that produce a transient depolarization (a voltage oscillation) or a DAD, and if the DAD reaches the threshold voltage, it can initiate an action potential.

In this issue of **HeartRhythm**, Rodríguez-Mañero et al¹² have reviewed implantable cardioverter-defibrillator (ICD) data from 15 institutions between 1993 and 2014 and analyzed a cohort of patients diagnosed with Brugada syndrome. A main finding of their study is that of the studied 834 patients, 35 patients had documented monomorphic ventricular tachycardia (MVT). In addition, MVT was more commonly observed in patients with conduction system disease as evidenced by a wide QRS complex. Rodríguez-Mañero et al conclude that Brugada syndrome should be considered in patients presenting with RVOT MVT and that ICD programming should reflect the presence of MVT in these patients.

The authors' identification of arrhythmias besides PMVT in patients with Brugada syndrome is not new, as a relatively high incidence of 10%–13% of supraventricular tachycardia^{13,14} and atrial fibrillation¹⁵ has been well recognized. In addition, although more rare, MVT has been reported in Brugada syndrome¹⁶ and is noted to occur more commonly in children.¹⁷

The association of MVT in adults in this Brugada cohort begs several questions: Is MVT and PMVT in Brugada syndrome related to the same mechanism? Or, do MVT and PMVT occur as independent mechanisms and MVT noted only as an epiphenomenon? Or lastly, are we observing Brugada mimickers subject to misclassification bias in this cohort?

A careful examination of the cohort presented in Rodríguez-Mañero's article reveals some heterogeneity in their presentation, which may, in turn, affect their MVT arrhythmia mechanism. The data in Table 2 demonstrate that in the MVT cohort, only 14 patients had clinical PMVT while 21 patients had only MVT (some had PMVT induced during the electrophysiology study). There is an unfortunate paucity of VT characterization since only 10 of 35 cases had MVT morphology available and there is no data on clinical symptoms such as syncope associated with MVT.

Importantly, the cohort contains several factors supporting a comprehensive arrhythmia mechanism for both PMVT and MVT. Most MVT morphology was noted to be RVOT in

origin, when ECG was available, supporting regionalism of disease in Brugada syndrome.^{5,6,10} In line with a reentry hypothesis, MVT noted in 3 patients occurred only after the initiation of quinidine (triggered activity and functional reentry) and 2 patients had MVT only after ablation. In addition, 2 patients with conduction system disease and *SCN5a* mutations (*SCN5a* mutation Arg367Cys; *SCN5a* splice site mutation c. 4813+6_4819+9dupGGGT) had bundle branch reentry, thus demonstrating an observed disease continuum between Brugada syndrome and conduction system disease in association with *SCN5a* mutations.¹⁰

In contrast, some cases suggest that MVT and PMVT occur as independent mechanisms. Several cases manifested MVT from a location distinct from the RVOT. In addition, some cases required infusion of isoproterenol for MVT induction, a drug classically given to patients with Brugada syndrome during VF storm, which has been shown to normalize Brugada ECG patterns as well.¹ Even so, exercise-induced MVT has been reported in Brugada syndrome¹⁸ but may be mechanistically distinct from PMVT in substrate mechanism.¹⁹

Because of the high percentage of patients who presented clinically with only MVT without clinical PMVT, it is curious as to whether this cohort inadvertently included patients without Brugada syndrome, such as those with arrhythmogenic right ventricular cardiomyopathy, a limitation conceded by the authors. Of significant importance in context of Rodríguez-Mañero's article is the fact that reentry in the right ventricle also underlies arrhythmias related to arrhythmogenic right ventricular cardiomyopathy as well as a similar genetic linkage to *SCN5a* mutations.²⁰ However, such is an inherent limitation of this retrospective data base analysis: strengthened by the incorporation of an impressive 834 patients and weakened by the lack of control of the cohort composition. Misclassification bias is also easily understood given both the abstract nature of the cohort construction and misdiagnosis of even trained cardiologists in accurately interpreting Brugada ECG patterns.²¹

Given these considerations, we can probably say that MVT may be more common in adults with Brugada syndrome than initially recognized, particularly in patients with associated conduction system disease, even with the caveat that there may be some heterogeneity within the cohort. In addition, with respect to ICD selection and programming, single zone programming for VF to avoid inappropriate shocks²² has long been relied upon for patients with Brugada syndrome.⁴ Rarely, however, programmed ATP will have the opposite effect (of avoiding shocks), and such programming options as well as consideration for subcutaneous vs transvenous ICD should be carefully evaluated in this context.

What still remains unclear is whether the association of MVT in this cohort of adults diagnosed with Brugada Syndrome is (1) mechanistically similar to that of PMVT, (2) a distinct disease-related entity, (3) true but patients have been subject to misclassification bias, or (4) an epiphenomenon. Moreover, what is made increasingly clear by this study is the need for further mechanistic characterization and careful clinical phenotyping to drive clinical management.

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