Are all CPVT Patients Equal??

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disease characterized by exercise- or stress-induced ventricular tachyarrhythmias, leading to syncope or sudden cardiac death (SCD) [1]. The latter could be the first manifestation in some patients. Typically, CPVT patients have no evidence of structural heart disease. In fact, exercise-induced ventricular arrhythmias are considered to be the hallmark of CPVT [2].

CPVT is an inherited disease, and disease-causing mutations in ryanodine receptor (RyR2) or calsequestrin 2 genes (*CASQ2*) have been identified in 50–70% of affected patients [3]. The RyR2 mutations are responsible for the autosomal dominant form of CPVT, while *CASQ2* mutations are rare and account for the recessive form [4]. These mutations lead to diastolic calcium leakage producing calcium overload in the cardiac myocyte, which can result in triggered activity resulting from delayed after-depolarizations (DADs) [5].

For years beta-blockers were considered the mainstay therapy for CPVT. Recently, Wantabe et al. [6] demonstrated that flecainide has the ability to reduce Ca^{2+} release from the sarcoplasmic reticulum by inhibiting RyR2. Indeed, flecainide was found to reduce exercise-induced ventricular arrhythmias in patients with RyR2 and mutations [7]. Its exact mode of mechanism appeared to be a direct effect on RyR2. However, flecainide appeared to be effective also in non-genotyped patients [8] and in patients with *CASQ2* mutations [9]. Regardless of mode of action this drug appears to have a role in modulation of intracellular calcium [10].

However, not all patients respond to drug therapy. In those patients, or in patients after a life-threating arrhythmia, even an implantable cradioverter defibrillator (ICD) is needed [11]. Still, reducing the burden of ventricular arrhythmias in this disease is crucial even in patients with ICD as ICD shocks increase sympathetic tone leading to a vicious cycle of one shock begetting more arrhythmias begetting more shocks and so on.

In this issue of *IMAJ*, Marai and co-authors [12] describe three patients with CPVT2. All three had *CASQ2* mutations. They continued to experience ventricular events despite high dosages of beta-blockers and they underwent left sympathetic cardiac denervation (LSCD). Only patient 3 had life-threatening arrhythmias prior to the LSCD procedure. Thus, the indication for this procedure in the other two patients was not straightforward. In the HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes [11], LSCD is considered a IIb indication for those who continue to have significant arrhythmias on drug therapy or cannot tolerate medications. Most cases of LSCD reported to date involve patients with long QT syndrome (LQTS) and only a minority were CPVT patients. Only short-term follow-up is available, even in those reported in the consensus document [11].

In the report by Marai et al. [12] all three patients had recurrence of arrhythmias post-LSCD but only after long-term follow-up. Recurrence of arrhythmia occurred 6–18 months post-procedure. In two of the patients, adding felcainide to beta-blocker therapy was effective in suppressing arrhythmia, and in one of them increasing the beta-blocker dosage was enough. It is noteworthy that all of them had their first arrhythmic event post-LSCD only after reducing the beta-blocker dosage. Secondly, restoring high beta-blocker dosage prevented life-threatening events in two of the three patients.

What can one conclude from this study: that LSCD is not effective in CPVT2 patients, or that they behave differently from CPVT1 patients? I think not. First of all, the number of patients in this series is too small to reach conclusions (as acknowledged by the authors). Secondly, all had their first event after reducing the beta-blocker dosage. When restoring a full tolerated dosage only one experienced a syncope event. Lastly, it is of note that in the CPVT1 patients some also had fluctuations in response to surgery [13]. Still, the authors should be applauded for this report as it demonstrates clearly how complicated the management of CPVT patients is, leading to the inevitable conclusion that these patients should be followed and managed only at highly experienced centers.

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References

1. Francis J, Sankar V, Nair VK, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2005; 2: 550-4.
2. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in

catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2009; 119: 2426-34.

3. Laitinen PJ, Brown KM, Piippo K, et al. Mutations of the cardiac ryanodine receptor (ryr2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001; 103: 485-90.
4. Lahat H, Pras E, Eldar M. A missense mutation in CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Ann Med* 2004; 36 (Suppl 1): 87-91.
5. Liu N, Rizzi N, Boveri L, Priori SG. Ryanodine receptor and calsequestrin in arrhythmogenesis: What we have learnt from genetic diseases and transgenic mice. *J Molec Cell Cardiol* 2009; 46: 149-59.
6. Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nature Med* 2009; 15: 380-3.
7. van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol* 2011; 57: 2244-54.
8. Watanabe H, van der Werf C, Roses-Noguer F, et al. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2013; 10: 542-7.
9. Khoury A, Marai I, Suleiman M, et al. Flecainide therapy suppresses exercise-induced ventricular arrhythmias in patients with CASQ2-associated catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2013; 10: 1671-5.
10. Bannister ML, Thomas NL, Sikkel MB, et al. The mechanism of flecainide action in CPVT does not involve a direct effect on ryr2. *Circ Res* 2015; 116 (8): 1324-35.
11. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm* 2013; 10: 1932-63.
12. Marai I, Boulos M, Khoury A. Left cardiac sympathetic denervation in patients with *CASQ2*-associated catecholaminergic polymorphic ventricular tachycardia. *IMAJ* 2015; 17: 538-40.
13. Van der Werf C, Zwinderman AH, Wilde AA. Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: State of the art and future developments. *Europace* 2012; 14: 175-83.