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 Ca2+ 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-threatening arrhythmia, even an implantable cardioverter 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 flecainide to beta-blocker therapy was effective in suppressing arrhythmias, 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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**Capsule**

**The way to a broken heart**

Mice lacking cardiac myosin binding protein C (MYBC) develop defective hearts that are twice the normal size. MYBC is a component of contractile thick filaments in the cardiac muscle. Jiang and collaborators found that the heart cells in mice lacking MYBC divided one extra time shortly after birth – when normal mouse heart cells would have stopped dividing. This caused the mice to have more myocytes with single nuclei, which compromise heart function. This unanticipated role of a structural protein in regulating how muscle cells divide may be important in different types of cardiomyopathy in human patients. *Proc Natl Acad Sci USA* 2015; 112: 9046

Eitan Israeli

**Capsule**

**Hydrogels cozy up to inflamed tissues**

Inflammation drives many chronic conditions. Directing potent drugs to the site of inflammation is highly desirable for improving treatment. Zhang et al. designed a hydrogel that self-assembles and delivers hydrophobic anti-inflammatory drugs directly to inflamed colon cells. Dexamethasone-loaded hydrogel enemas administered to a genetic mouse model of ulcerative colitis – a type of inflammatory bowel disease – relieved inflammation more effectively than free dexamethasone. In tissue samples from these patients, as well as in a chemically induced mouse model of colitis, hydrogel microfibers preferentially attached to inflamed tissue. *Sci Transl Med* 2015; 7: 300ra128

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**Capsule**

**TH17 cells promote microbial killing and innate immune sensing of DNA via interleukin 26**

Interleukin 17-producing helper T cells (TH17 cells) play a major role in protecting against infections and in mediating autoimmune diseases, yet the mechanisms involved are incompletely understood. Meller and co-researchers found that interleukin 26 (IL-26), a human TH17 cell-derived cytokine, is a cationic amphipathic protein that kills extracellular bacteria via membrane-pore formation. Furthermore, TH17 cell-derived IL-26 formed complexes with bacterial DNA and self-DNA released by dying bacteria and host cells. The resulting IL-26-DNA complexes triggered the production of type I interferon by plasmacytoid dendritic cells via activation of Toll-like receptor 9, but independently of the IL-26 receptor. These findings provide insights into the potent antimicrobial and pro-inflammatory function of TH17 cells by showing that IL-26 is a natural human antimicrobial that promotes immune sensing of bacterial and host cell death. *Nature Immunol* 2015; 16: 970

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