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Advancements in the use of gene therapy for cardiac arrhythmia

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by adrenergically mediated ventricular tachycardia in the absence of structural heart disease. CPVT typically presents in young individuals, between the ages of 7 and 12, as syncope during times of physical or emotional stress.^{1,2} Unfortunately, in many cases, sudden cardiac death may be the presenting symptom.² While the exact prevalence of CPVT is unclear because of underdiagnosis,³ it is estimated to be ~1 in 10,000 individuals.⁴ In the absence of treatment, ~80% of patients with CPVT will experience syncopal episodes and ~30% will suffer a cardiac arrest.⁵ By some reports, mortality of untreated CPVT may reach ~50% by 20 years of age.¹

Currently, only a small cadre of genes is known to contribute to CPVT. Variants in cardiac ryanodine receptor (*RYR2*) and calsequestrin 2 (*CASQ2*) are most common, contributing to ~60% and 5% of CPVT cases, respectively.⁶ Additional genes, including Calmodulin 1 (*CALM1*) and Triadin (*TRDN*), are also associated with CPVT.⁶ At the molecular level, CPVT is commonly associated with aberrant sarcoplasmic reticulum calcium release through RyR2.⁶ Incomplete penetrance, diverse inheritance patterns, and phenocopy of other cardiac arrhythmia syndromes complicate the genetic understanding of disease. Notably, in about one-third of CPVT cases, no causative pathogenic variant has been identified.⁴

Despite the heavy disease burden of CPVT, specific therapies are not yet available. The current treatment includes exercise reduction, avoidance of stressful situations, and prescription of β -blockers.^{7,8} However, approximately one-third of patients with CPVT experience recurrent arrhythmia with exercise, despite conventional β -blocker therapy.⁷ For these patients and those who do not tolerate β -blocker therapy, implanted cardiac defibrillator placement was, until recently, the only viable treatment option.⁹ However, recent experimental and clinical data support a reduction in arrhythmic events with flecainide treatment in patients refractory to β -blocker therapy.^{9–11} A prospective randomized crossover clinical trial has recently been completed, but results are not yet available (<https://clinicaltrials.gov/ct2/show/NCT01117454>). While there has been

suggestion of flecainide as a monotherapy for patients with CPVT who cannot tolerate β -blockers, further clinical investigation of this treatment regimen is necessary.¹² Despite these advancements in CPVT treatment, the current regimen is nonspecific and fraught with risk of incomplete treatment and side effects that limit adherence and increase risk of sudden cardiac death. Thus, there is an urgent need for improved specific therapies to treat CPVT.

A recent avenue of investigation into new treatments of CPVT focuses on gene therapy to correct the underlying genetic defect. The use of adeno-associated virus (AAV) for gene therapy in cardiac conditions is particularly promising. AAV gene administration has been shown to produce myocardial gene transfer lasting at least 2 years¹³ and had been shown to be safe in patients with compromised cardiac function.^{14,15} However, there are limitations to this treatment strategy, including risk of immune response and off-target effects.^{15,16} Furthermore, between 35% and 70% of the human population produce AAV-specific neutralizing antibodies that may impede the treatment of a significant proportion of patients with CPVT.¹⁵

In this issue of **HeartRhythm**, Kurtzwald-Josefson et al¹⁷ provide further support for the potential of gene therapy for treating CPVT. Their new work uses virally delivered gene therapy to alleviate arrhythmia burden in a model of CPVT.¹⁷ This work builds on prior studies conducted by Priori and colleagues,^{13,18} where the CPVT phenotype was prevented by treating newborn *Casq2* p.R33Q or *Casq2* null mice with *CASQ2* delivered via AAV9. In the new work, the authors treated adult mice from 2 mouse models of *Casq2*-mediated CPVT with an adeno-associated viral vector (AAV9) carrying wild-type (WT) *CASQ2* through intracardiac or intraperitoneal injection. Mice treated with virus demonstrated increased expression of WT *CASQ2* protein and those with >33% WT *CASQ2* expression experienced significant reductions in arrhythmia burden. These findings are particularly relevant to treatment of human disease, as arrhythmia burden was reduced with a relatively low rate of infection. While this new work provides additional support for this technique, as with all studies, there are important limitations. The efficacy of treatment over time is unclear, as murine models of AAV9 treatment are able to confirm only expression for 2 years postinfection and clinical trials using AAV1-mediated treatment have confirmed only vector presence for 3 years posttreatment.^{15,16} Furthermore, the modulation of the calcium handling in cardiomyocytes may have unintended and undesired effects including cardiac remodeling. However, these proof-of-principle studies offer the potential for not only CPVT but also more common forms of both congenital and even acquired forms of arrhythmia. In summary, the new work presents an intriguing method for the treatment of CPVT caused by *CASQ2* loss-of-function variants. This may lead to more effective and less onerous treatment, dramatically improving quality of life for patients living with this devastating disease.

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