Gene therapy to keep the QT rhythms “on the QT”

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Postoperative atrial fibrillation (POAF) is a major risk factor that can result in the death of the patient after cardiac surgery. The first 2 weeks after surgery are the most critical time when patients are at high risk for POAF. Improper neuromuscular stimulations, cellular stress in myocytes, fibrosis in the heart tissue, and inflammation are some of the many factors that have been found to cause POAF. Pre-clinical and clinical trials have identified several unique genes, including *SERCA2a* (the gene for sarcoplasmic reticulum calcium ion adenosine triphosphatase), *SDF1* (the gene for stem cell–derived factor-1), *AC6* (the gene for adenylyl cyclase type 6), *bARKct* (the gene for G protein–coupled receptor kinase-2 inhibitory peptide), and *CX43* (the gene for connexin43), as potentially therapeutic genes to control the rate and rhythm in POAF. The currently available treatment strategies are suboptimal, and a variety of factors can cause POAF. These limitations urge more investigations in the development of novel strategies to control POAF. Typical in situations in which the feasibility of targeting or modifying single-gene expression is studied, gene therapy with viral vectors offers a tremendous advantage and has been shown to be effective in treating many cardiac diseases, including tissue remodeling.¹⁻³

A promising approach taken by Dr Kevin Donahue's group, as reported by Liu and colleagues⁴ in this issue of the *Journal*, is to prolong the action potential to prevent POAF. In this approach, the epicardial expression of the mutant *KCNH2* (potassium voltage-gated channel subfamily H member 2) gene G628S (glycine to serine substitution at amino acid 628 in the protein product) is sufficient for the prevention of POAF, which voids the need for its transmural expression in the heart wall (Figure 1, A). This dominant negative mutation blocks the channel pore and primarily prevents the repolarizing rapidly activating delayed rectifier potassium channel (IKr) currents (Figure 1, B).^{5,6} Liu and colleagues⁴ describe preclinical evaluation in a Yorkshire

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Central Message

Gene therapy to prevent postoperative atrial fibrillation is a viable option.

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pig model of *KCNH2* G628S mutant gene therapy with adenoviral vectors. They have demonstrated safety, efficacy, and feasibility of this strategy in an impressive large animal model that is based on a burst pacing protocol to induce atrial fibrillation within 2 weeks. The findings provide a clinically feasible approach for potential clinical trials.

Although remarkable success was seen in this study, there are several important points that need to be considered. (1) Many known mutations in the *KCNH2* gene could either complement or confound the IKr-blocking effects of the expressed G628S mutant gene. For example, the K897T mutation (lysine substituted with threonine at amino acid 897 in the protein product) in the *KCNH2* gene is associated with atrial fibrillation, whereas the N629D mutation (asparagine substituted with aspartic acid at amino acid 629 in the protein product) can potentially ablate IKr currents. The N588K mutation (asparagine substituted with lysine at amino acid 588 in the protein product) in *KCNH2* was found to induce short QT syndrome and ventricular arrhythmia by increasing IKr in the ventricles. This variability necessitates profiling each subject for *KCNH2* gene mutation. (2) Drugs such as phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors prolong QT by inhibiting potassium ion currents and simultaneously increase late sodium ion current in cardiomyocytes, indicating that IKr blockers may also induce arrhythmia.⁷ (3) Exogenous serine proteases can selectively degrade *KCNH2*-regulated action potential; specifically, the protease XXIV was found to inhibit IKr currents selectively.⁸ (4) Several antibiotics, including moxifloxacin, erythromycin, sparfloxacin, and telithromycin, delay ventricular repolarization and may cause drug-induced long QT syndrome.⁹ (5) In patients after

FIGURE 1. Mutation of *KCNH2* gene that substitutes glycine (G) with serine (S) at the 628 amino acid region (G628S mutation). The larger serine blocks the pore channel and prevents the repolarizing potassium ion (K^{+}) currents across the membrane and prevents atrial fibrillation. A, In the absence of the G628S mutation, the influx and efflux of the potassium ion current across the pore channel were unaffected. B, The mutant serine residue (highlighted in red) prevents the potassium ion currents by blocking the pore channel. P, Pore helix domain with 20 residues in *KCNH2* protein; V, valine; N, asparagine; F, phenylalanine; T, threonine.

bypass surgery, labetalol, nebivolol, and propranolol are administered to induce relaxation in the arteries as a result of activation of calcium ion-activated potassium ion channels.¹⁰ This again emphasizes the need for personalized evaluation for the suitability of the proposed gene therapy.

CONCLUSIONS

No doubt a better treatment strategy for POAF is warranted. The findings from this POAF swine model would have direct implications extending into human trials. Indeed, the approach of epicardial viral painting to treat POAF opens a plethora of opportunities to advance

cardiovascular research. This model, which can successfully induce atrial fibrillation, not only can be used for gene therapy to prevent POAF but also has the potential to extend studies to understand membrane potential defects, to evaluate novel drug candidates, to identify drug interactions, and to improve cardiac operations.

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