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Antiarrhythmic gene therapy – will biologics replace catheters, drugs and devices?

Patrick Lugenbiel [a], Patrick A. Schweizer [a,b,c], Hugo A. Katus [a,b], Dierk Thomas [a,b,*]

[a] Department of Cardiology, Medical University Hospital, Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany
[b] DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany
[c] Heidelberg Research Center for Molecular Medicine (HRCMM), Im Neuenheimer Feld 350, D-69120 Heidelberg, Germany

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ABSTRACT

The clinical management of heart rhythm disorders still constitutes a major challenge. The development of alternatives to current approaches is of significant interest in order to establish more effective therapies that increase quality of life and reduce symptoms and hospitalizations. Over the past two decades the mechanistic understanding of pathophysiological pathways underlying cardiac arrhythmias has advanced profoundly, opening up novel avenues for mechanism-based therapeutic approaches. In particular, gene therapy offers greater selectivity than small molecule-based or interventional treatment. The gene of interest is packaged into viral or non-viral carriers and delivered to the target area via direct injection or using catheter-based techniques, providing the advantage of site-restricted action in contrast to systemic application of drugs. This work summarizes the current knowledge on mechanistic background, application strategies, and preclinical outcome of antiarrhythmic gene therapy for atrial fibrillation, ventricular tachycardia, and modulation of sinus node function.

Contents

Abbreviations: AERP, atrial effective refractory period; AF, atrial fibrillation; AP, action potential; APD, action potential duration; AV, atrioventricular; CHF, chronic heart failure; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERG, ether-a-go-go-related gene; HCN, hyperpolarization-activated, cyclic nucleotide-gated channel; LAD, left anterior descending artery; LBB, left bundle branch; MSC, mesenchymal stem cells; SCD, sudden cardiac death; SERCA, sarcoplasmic reticulum Ca^{2+} ATPase; SND, sinus node disease; SR, sinus rhythm; TBX18, embryonic transcription factor T-box 18; VERP, ventricular effective refractory period; VF, ventricular fibrillation; VT, ventricular tachycardia

* Corresponding author at: Department of Cardiology, University of Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany.
E-mail address: Dierk.Thomas@med.uni-heidelberg.de (D. Thomas).

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1. Gene therapy - an evolving treatment modality

Effective and safe management of cardiac arrhythmia represents an unmet need in cardiovascular medicine. In search for mechanism-based treatment, gene therapy has been suggested to provide incremental benefit by specifically targeting defective cellular signaling pathways. From the first report of DNA transfer from one organism to another in 1973 by Stanley Cohen, Herbert Boyer et al. (Cohen et al., 1973), a mere 17 years have elapsed before the first patient, Ashanti DeSilva, was successfully treated with retroviral gene therapy for ADA-SCID (adenosine deaminase deficiency- severe combined immunodeficiency) at the National Institutes of Health (USA) (Blaese et al., 1995). However, risks of gene transfer were drastically recalled when the first documented death occurred in a clinical gene therapy study program for OTC (ornithine transcarbamylase deficiency) at the University of Pennsylvania. Despite this setback, in subsequent years multiple gene therapeutic approaches were advanced to clinical application in studies. In 2012 the first gene therapy drug was approved by the European Commission (Ylä-Herttuala, 2012). Glybera® (alipogene tiparvovec) is an adeno-associated virus (AAV-1) engineered to express lipoprotein lipase in the muscle for the treatment of lipoprotein lipase deficiency, an orphan metabolic disease. The drug has been made available for application in clinical routine in 2014 and was joined in 2015 by Imlygic® (talimogene laherparepvec), an oncolytic herpes simplex virus 1 to treat melanoma. Gene therapy for heart rhythm disorders is currently being evaluated in preclinical stages. To date, no antiarrhythmic gene therapy drug is commercially available or has been investigated in clinical trials. The present work summarizes current approaches to gene therapeutic management of atrial and ventricular arrhythmias.

2. Gene therapy for rhythm control in atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and accounts for significant morbidity and mortality. The arrhythmia has a prevalence of 1–2% in the general population and is age-dependent with 16% of women and 24% of men >85 years being affected (Krijthe et al., 2013). The significance of AF is further illustrated by a predicted 2-fold increase of AF prevalence in the European Union by the year 2060 (Krijthe et al., 2013). Despite its high epidemiological and clinical relevance, effective and safe management of AF requires further optimizing efforts (Dobrev et al., 2012). Medical therapy represents the initial standard treatment for most AF patients, but pharmacotherapy is limited by low efficacy, side effects, and safety concerns in a significant number of patients. In addition, non-pharmacological therapy is improving rapidly. However, only 8% of AF patients are currently treated by catheter ablation (Lip et al., 2014). The efficacy of an antiarrhythmic intervention to eliminate AF depends on its capacity to suppress the underlying mechanisms. Basic research has revealed insights into fundamental mechanisms contributing to the arrhythmia that may be exploited in future therapeutic approaches: AF results from a variety of pathophysiological processes, leading to electrical and structural remodeling. The generation of substrates that support slow conduction, shortening of atrial refractory periods, and electrical reentry appears to be particularly relevant as it provides the basis for maintenance of AF in a significant number of patients. Alterations are observed as early as 24–48 h after the onset of AF (Wijffels et al., 1995). Increasing evidence emerges that multifactorial etiology and pathogenesis of AF requires multimodal treatment of the disease, tailored to patient-specific mechanisms. Targeted biological modification of atrial electrophysiology and structure by gene transfer has been explored for rhythm control in AF through direct modification of disease-associated pathways (Farraha et al., 2016).

2.1. Genetic suppression of reentry for rhythm control in AF

At the mechanistic level, shortening of atrial refractory periods (AERP) promotes electrical reentry and provides the “classical” basis for maintenance of AF (Schmidt et al., 2011; Schotten et al., 2011). Rhythm control in this subgroup of AF patients may be achieved by impairing electrical reentry. Class III antiarrhythmic drugs suppress AF through K^+ channel block, resulting in prolongation of action potential duration (APD) and in prevention of reentry. However, currently available pharmacological approaches to treat AF show limited effectiveness, and proarrhythmia is a rare but major risk that may increase mortality and reverse beneficial effects of antiarrhythmic drugs. Atrial repolarization is primarily carried by the delayed rectifier potassium current, which consists of rapidly (I_{Kr}) and slowly activating (I_{Ks}) components. Shortening of AERP and action potentials (AP) in AF may be attenuated or reversed by suppression of repolarizing outward potassium currents. In two independent, large animal proof-of-concept studies, targeted atrial suppression of I_{Kr} current was achieved through gene transfer of dominant-negative mutants of the underlying ether-a-go-go-related gene (ERG; Kv11.1) potassium ion channel (Table 1). The vector was applied either to the epicardial atrial surface within a trypsin-containing gel (“gene painting”; Amit et al., 2010) or via direct atrial injection (Soucek et al., 2012). Inactivation of ERG channels induced AP and AERP prolongation and successfully suppressed AF in pigs, demonstrating antiarrhythmic efficacy of the therapeutic concept.

In addition to enhanced repolarization, electrical reentry and AF are facilitated by slowing of electrical conduction within the atria. Gap junctions serve as regulators of conduction velocity in the heart and are formed by connexin (Cx) proteins. AF is associated with reduced expression of connexins 40 and 43. Connexin downregulation is expected to result in slowed and heterogeneous atrial conduction. To further explore conduction as target in antiarrhythmic gene therapy for rhythm control, atrial connexin 40 or 43 gene transfer was applied in pigs (Table 1). Genetic correction of AF-associated connexin remodeling resulted in acceleration of atrial conduction velocity and reduced AF in two preclinical studies (Bikou et al., 2011; Igarashi et al., 2012).

2.2. Rhythm control achieved through prevention of structural remodeling

Electrical remodeling directly affects electrical properties of atrial tissue. By contrast, structural alterations generate substrates that indirectly determine conduction heterogeneity and promote