HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Pharmacol Ther. 2017 August ; 176: 60–65. doi:10.1016/j.pharmthera.2017.06.005.

Current state of the art for cardiac arrhythmia gene therapy

J. Kevin Donahue, MD

University of Massachusetts Medical School, Division of Cardiology, 55 Lake Ave. North, Worcester, MA 01655. (774) 441-6649 donahuelab@gmail.com

Abstract

Cardiac arrhythmias are a leading cause of morbidity and mortality. Currently available therapeutic options lack sufficient efficacy and safety. Gene therapy has been proposed for treatment of cardiac arrhythmias. This review will discuss the current state of development for arrhythmia gene therapy. So far, all published studies are short-term, proof-of-concept animal studies. Potential replacement of cardiac pacemakers has been shown for combination gene therapy using the HCN2 gene and either the gene for adenylate cyclase, the skeletal muscle isoform of the sodium channel, or a dominant negative mutant of the potassium channel responsible for resting membrane potential. Atrial fibrillation has been prevented by gene transfer of either a dominant negative mutant of a repolarizing potassium channel, a gap junction, or an siRNA directed against caspase 3. Inherited arrhythmia syndromes have been corrected by replacement of the causative genes. Post-infarct ventricular tachycardia has been reduced by gene therapy with the skeletal muscle sodium channel and connexins and eliminated with the dominant negative mutant of the potassium channel responsible for resting membrane potential. These ideas show considerable promise. Long-term efficacy and safety studies are required to see if they can become viable therapies.

Keywords

arrhythmia; gene therapy; atrial fibrillation; sinus node dysfunction; ventricular tachycardia; gene transfer

1. Introduction

Heart rhythm disorders are responsible for considerable morbidity and mortality, particularly in developed nations. Cardiac arrest is the leading cause of death in developed countries. (Mozaffarian, Benjamin et al. 2015) Ventricular tachyarrhythmias are the most common cause of cardiac arrest, and ischemia, infarction or heart failure create a substrate conducive to the generation of ventricular arrhythmias.(Nuss, Kaab et al. 1999;Beuckelmann, Nabauer et al. 1995;Beuckelmann, Nabauer et al. 1993;Janse and Wit, 1989;de Bakker, van Capelle et

Conflict of interest statement: The author is an inventor on gene therapy intellectual property assigned to Johns Hopkins University. The author is a co-founder of Rithim Biologics, Inc., a gene therapy company with interests in post-operative atrial fibrillation.

al. 1988) Atrial fibrillation (AF) is the leading cause of stroke and a common contributor to overall morbidity and mortality.(Mozaffarian et al. 2015) Atrial fibrillation generally occurs in the setting of structural and electrical changes brought about by heart failure, hypertension, diabetes, pulmonary disease, age and other cardiac risk factors.(Benjamin, Chen et al. 2009) Sinus node dysfunction and bradyarrhythmias are often associated with advancing age, but risk factors associated with other cardiac disease can accelerate or amplify sinus or atrioventricular (AV) nodal disease.(Mozaffarian et al. 2015) All of these disease associations illustrate the point that effective treatment of cardiac arrhythmias must address the electrical aspects of the rhythm disorder but must also attempt to reverse or at least attenuate the underlying cardiac structural and functional abnormalities that create the arrhythmic substrate.

Currently available therapies to control heart rhythm are conventionally divided into 3 categories: (1) pharmacotherapy, (2) device-based therapy and (3) ablative therapy. All currently available therapies have limited efficacy and considerable toxicity. Antiarrhythmic drugs are effective at decreasing arrhythmia burden, but breakthrough arrhythmia episodes are common and toxicities include proarrhythmia (i.e. the drug causes rather than prevents the arrhythmia) in up to 5% of patients taking potassium channel blocking drugs in addition to numerous systemic side-effects for the other antiarrhythmic medications.(Hockings, George et al. 1987;Echt, Liebson et al. 1991;Coplen, Antmann et al. 1990;AFFIRM First Antiarrhythmic Drug Substudy Investigators, 2003;Pfizer, 2011;Bayer, 2011;Torp-Pedersen, Moller et al. 1999)

Device therapies include pacemakers and defibrillators. Pacemakers effectively prevent bradycardia, but their ability to reproduce normal physiologic heart rate responses to activity or stress remain limited.(Israel and Hohnloser, 2000) Defibrillators do not prevent arrhythmia onset; they terminate ventricular tachyarrhythmias by overdrive pacing or administration of an electrical shock. Cardiac devices are effective in these roles, but they do not cure the underlying disease. Cardiac devices also subject patients to a number of uncommon but potentially important risks either at implant (infection, bleeding, cardiac perforation, etc.) or in the long-term (infection, hardware failure).(Persson, Earley et al. 2014;Parsonnet and Cheema, 2003;Bernstein and Parsonnet, 2001)

Ablation is an invasive procedure where catheters are used to identify and then destroy the portions of the heart critical to the targeted arrhythmia. Ablation is curative for arrhythmias that exist in confined areas (e.g. focal atrial or ventricular tachycardias, AV node or accessory pathway-dependent rhythms, etc.), and ablation can decrease arrhythmia burden for more diffuse rhythms [AF, scar-related ventricular tachycardia(VT)]. (Kirchhof and Calkins, 2016;Calkins, Yong et al. 1999;Stevenson, Wilber et al. 2008) The fundamental limitation of all current ablation technologies is that destruction of heart tissue is an integral element of the therapy.

The impact of cardiac arrhythmias coupled with the limitations of currently available therapies is the driving force for investigation of new therapeutic options. This review discusses the current status of cardiac arrhythmia gene therapy development for sinus node dysfunction, AF and VT. Each of these therapies starts with a focus on the underlying

arrhythmia mechanism (Fig 1), and the therapy is generally developed to counteract that mechanism. The mechanistic approach is an established strategy for therapy development, but of course, it is only as good as the validity of the available mechanistic data. This problem has been especially relevant to arrhythmia research where differences between all animal models and human disease is a relevant concern, and in particular the considerable differences between mouse and human electrophysiology calls into question the translational potential of data derived from transgenic mouse models.

Sinus node dysfunction

Generation of a normal sinus heart rate depends on the reliability of action potential generation from the cells in the sinus node and the ability of that electrical signal to expand beyond the confines of the sinus node to electrical capture the broader tissue of the cardiac atria. To accomplish this feat, cells in the sinus node have automaticity (the mechanism of which is still debated) in which they progressively lose resting membrane potential and generate repetitive action potentials.(Maltsev and Lakatta, 2012;DiFrancesco and Noble, 2012;Lakatta and Maltsev, 2012) The sinus node also has limited connectivity with the atrial myocardium so this electrical signal can start in a single myocyte or a few cells and gradually increase in size until it is sufficient to capture the atrial myocardium.(Fedorov, Schuessler et al. 2009;Inada, Zhang et al. 2014)

The first attempt to genetically modify cardiac myocytes to achieve automaticity was reported by Miake et al. They introduced a dominant negative mutation of the I_{K1} channel (KCNJ2 GYG144-146AAA) into guinea pig ventricles.(Miake, Marban et al. 2002) The logic behind this approach was that automaticity would occur if the resting membrane potential was destabilized. Miake did indeed find evidence of automaticity, but the picture was complicated. The automatic rhythm was not stable, and the transgene also caused QT prolongation.(Miake, Marban et al. 2003)

Subsequent attempts to generate cardiac automaticity were based primarily on delivery of the HCN family of genes that encoded the I_f current, the putative pacemaker channel. Wild-type HCNs 1, 2 and 4 have been delivered to hearts of various animals by several investigators.(Plotnikov, Sosunov et al. 2004;Cai, Yi et al. 2007;Tse, Xue et al. 2006) Like the I_{K1}-reducing strategy above, transduction with HCN-family genes created nodes of automaticity, but the rhythm was unstable and the heart rate was considerably less than the normal rate for the animal. Attempts to modify function with use of various HCN1 and HCN2 mutations resulted in modulation of the heart rate (VT was produced), but the generated rate remained unstable, with abrupt termination of automaticity causing asystole.

Combination therapy with HCN2 and either the gene for adenylate cyclase (a component of the intracellular signaling cascade for adrenergic, purinergic, and cholinergic receptors), (Boink, Nearing et al. 2012) or the gene for the skeletal muscle isoform of the sodium channel (SkM1),(Boink, Duan et al. 2013) or the KCNJ2-AAA mutation appears to have generated stable pacing at reasonable rates.(Cingolani, Yee et al. 2012) An interesting and consistent finding between these reports is that automaticity is more stable when cells in the specialized conduction system are transduced rather than myocardial cells.

An entirely different approach to the problem was reported by Kapoor et al.(Kapoor, Liang et al. 2013) Rather than focus on addition of a limited number of ion channels, they transduced cardiac myocytes with the transcription factor TBX18. They reported a number of morphological and functional changes in the transduced myocytes. Affected cells had spontaneous firings and morphological changes including smaller size and less myofibrillar organization that the authors felt were consistent with a sinus node cell phenotype. Electrophysiological analysis of the cells showed decreased resting membrane potential, reduced I_{K1} density, increased I_f density, and regular release of calcium from the sarcoplasmic reticulum.

Attempts at recapitulation of sinus node function seem to be coalescing into 2 approaches. Ion channel modulation appears effective if a combination of channels are introduced, with one component being from the HCN-family of ion channels and the other component supplementing function by increasing overall responsiveness to adrenergic stimulation, increasing the activating current after phase 4 depolarization or destabilizing resting membrane potential. The second approach involves overall cell reprogramming from transcription factor introduction. Either approach will require demonstration of efficacy and safety that is sufficiently compelling to warrant competition with electronic pacemakers that for the most part have a long history of efficacy and safety. In particular, long-term gene expression and functional stability, achievement of physiologically-relevant pacing rates, and complete avoidance of inappropriate rates (either too fast or too slow) are issues that need to be convincingly demonstrated with either of the current gene therapy approaches.

Atrial Fibrillation

AF is a complex rhythm centered either within the atria or in the pulmonary veins that are electrically connected to the atria. Paroxysmal AF in many cases is a rhythm of the pulmonary veins, where the rapid beating pattern degenerates as it spreads to the atria causing a loss of organized conduction within the atrial tissues.(Haissaguerre, Jais et al. 1998;Jais, Haissaguerre et al. 1997) Persistent AF is generally a reentrant rhythm that exists diffusely throughout the atria.(de Groot, Houben et al. 2010;Eckstein, Zeemering et al. 2013;Hansen, Csepe et al. 2016) The exact arrhythmia mechanism for either paroxysmal or persistent AF is incompletely defined.

Efforts to disrupt AF have focused predominately on the reentrant nature of that arrhythmia and the reported electrical and structural remodeling caused by either AF or the comorbidities that increase susceptibility to AF. The initial report of AF elimination by gene therapy used a dominant negative mutation of the KCNH2 channel (KCNH2-G628S).(Amit, Kikuchi et al. 2010) KCNH2 plays a critical role in myocyte repolarization. The dominant negative mutant delayed repolarization, disrupted reentry and thereby terminated pacing-induced AF. A similar strategy using the canine variant of the channel (CERG-G627S) verified these AF-terminating results.(Soucek, Thomas et al. 2012)

Additional attempts to disrupt reentry have focused on improvement in improving conduction through the atria. Gap junction proteins connexin 40 and connexin 43 have both been shown to disrupt AF by attenuating the conduction slowing caused by AF.(Igarashi,

Finet et al. 2012;Bikou, Thomas et al. 2011) This strategy was motivated by observations that AF caused heterogeneities in and/or slowing of conduction through atrial tissues, in part by decreasing connexin 40 and/or connexin 43 amounts in the intercalated disk connections between adjacent myocytes. Bolstering the intercalated disk connexin content with either connexin 40 or connexin 43 prevented the reduction in conduction velocity and terminated AF. An observation with both of these gap junction proteins that has potentially reassuring safety implications is that it appears to be impossible to overdo the conduction effects. Normal tissue retains normal conduction, which might reduce the potential for proarrhythmia with this approach.

More recent efforts have focused on disrupting the structural remodeling process of atrial myocyte hypertrophy – apoptosis – inflammation – fibrosis caused by AF. Trappe et al. evaluated a strategy to prevent caspase 3 activation and apoptosis by transduction of atrial tissues with an siRNA targeting caspase 3.(Trappe, Thomas et al. 2013) They found that *in vivo* gene transfer with Ad-siRNA-Cas3 effectively reduced apoptosis, improved conduction velocity and delayed onset of AF, but it did not significantly alter myocardial fibrosis.

The available data suggest that therapies focused on disrupting reentry are capable of terminating AF, but long-term durability of this approach has not yet been tested. Supplemental therapies aimed at reversing the myocyte dysfunction and fibrosis have been minimally investigated. Unlike the sinus node strategies, combination therapies have not yet been reported for AF, but these are likely to be tested as the field progresses.

Ventricular tachyarrhythmias

Reports of therapies directed against ventricular tachyarrhythmias can be divided into 2 categories: those targeting congenital arrhythmia syndromes and those aimed at preventing arrhythmias associated with myocardial infarction. A principle difference between the 2 approaches is that congenital arrhythmia syndromes are caused by genetic mutations affecting all cardiac myocytes, so a global approach is likely needed for efficacy. Infarct-related arrhythmias generally come from the surviving myocytes in the infarcted territory,(de Bakker et al. 1988;Rothman, Hsia et al. 1997;Miller, Marchlinski et al. 1988;de Chillou, Lacroix et al. 2002) and a more regional approach has been shown effective.

Brunner et al. showed proof-of-principle correction of the QT interval in a mouse model of the long QT syndrome.(Brunner, Kodirov et al. 2003) The long QT syndrome is caused by defects in the myocyte repolarization process, which can lead to triggered arrhythmias from early afterdepolarizations occurring during the delay in repolarization and/or reentrant arrhythmias due to local heterogeneities in repolarization creating areas of temporary conduction block. Brunner’s work did not exactly reproduce the human situation because the mouse action potential differs drastically from the larger mammalian counterpart, but Brunner did provide critical proof-of-principle data on a method for countering some of the ion channel defects associated with the long QT syndrome. In Brunner’s model, expression of an N-terminal tag of the Kv1.1 channel caused dominant negative suppression of mouse ventricular myocyte repolarizing currents, prolongation of the mouse QT interval and ventricular arrhythmias. They found that gene transfer of a related but sufficiently different

ion channel Kv1.5 overcame this dominant negative effect, shortened action potential duration and QT interval. This work illustrated a strategy for overcoming effects of an endogenous mutation. A principle weakness of the work is that the targeted channels are more relevant to repolarization in rodents and they are not major effectors of repolarization in larger mammals.

More recently, Denegri et al. evaluated gene transfer in mice with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).(Denegri, Avelino-Cruz et al. 2012) In CPVT, the normal control of calcium release from the sarcoplasmic reticulum is altered, allowing diastolic release of calcium to cause delayed afterdepolarizations and triggered arrhythmias. Calcium handling in mice is altered relative to larger mammals, but the basic elements of calcium uptake and release (either appropriate or inappropriate) from the sarcoplasmic reticulum are essentially the same. Denegri focused on a mouse model where CPVT is caused by a decrease in calsequestrin (a calcium buffering protein normally present at high levels in the sarcoplasmic reticulum). Gene transfer of wild-type calsequestrin normalized calcium handling, reduced susceptibility to delayed afterdepolarizations and ventricular arrhythmias. Efficacy of this strategy with the more common CPVT mutations affecting the sarcoplasmic reticulum calcium-release channel remain to be determined, but it does appear to be efficacious for the calsequestrin variant of CPVT.

Unlike the congenital arrhythmia syndromes, reentry is the dominant mechanism causing post-infarct ventricular arrhythmias. As such, strategies that delay myocyte repolarization or improve electrical conduction, similar to those discussed above for AF, have been shown effective for reducing or eliminating ventricular arrhythmias.

In the early phase of infarct healing, downregulation and dysfunction of connexins and sodium, calcium and potassium channels reduces cellular excitability, alters repolarization and reduces electrical conduction through tissues surviving the infarct. In order to overcome the cellular electrophysiological dysfunction in this early post-infarct phase, Lau et al. tested the hypothesis that myocardial conduction velocity would improve and reentrant arrhythmias would be disrupted by introduction of the SkM1 sodium channel.(Lau, Clausen et al. 2009) Unlike the cardiac isoform of the sodium channel, SkM1 remains active at the relatively depolarized membrane potentials found in damaged myocytes. Lau reasoned that myocytes expressing SkM1 would regain electrical excitability, thereby improving electrical conduction through the infarct region. They found that gene transfer with SkM1 did indeed improved overall conduction velocity and homogeneity, and that this effect significant reduced ventricular tachyarrhythmia susceptibility.(Lau et al. 2009;Coronel, Lau et al. 2010)

After the infarct has healed, the MI scar border generally consists of surviving myocytes interdigitated with fibrosis. The disruption in cell-to-cell communication caused by the fibrosis most likely accompanied by some residual dysfunction of the surviving myocytes is the ideal substrate for reentrant arrhythmias. Greener et al. and Sasano et al. hypothesized that reentry through the infarct borderzone could be disrupted by either extending myocyte repolarization time or improving cellular connectivity.(Sasano, McDonald et al. 2006;Greener, Sasano et al. 2012) They used the connexin 43 and KCNH2-G628S transgenes discussed above for AF. Greener found that infarct-targeted delivery of connexin

43 significantly improved but did not normalize conduction velocity, and that this effect was sufficient to reduce arrhythmia susceptibility. Sasano showed that KCNH2-G628S prolonged action potential duration in the infarct borderzone, and this completely eliminated ventricular arrhythmia inducibility.

Overall, approaches to VT gene therapy are arrhythmia mechanism-based and less focused on tissue structure. The targeted congenital syndromes exist with normal ventricular structure. Ischemia and infarction disrupt the endogenous structure, and the currently investigated therapies do not modify that process. Investigated therapies, so far, have focused on basic principles for triggered and reentrant arrhythmias and have succeeded by disrupting these mechanisms.

Summary

Arrhythmia gene therapy investigations have been limited to proof-of-concept short-term demonstrations of efficacy. Safety has not been a principle focus of these early studies, but no safety issues have been noted. Still, the lessons learned from antiarrhythmic drug studies need to be heeded. Proarrhythmic as well as other risks need to be investigated prior to institution of clinical trials.

Since the majority of arrhythmias are permanent problems, a permanent solution is required under most circumstances. Adeno-associated virus and lentivirus vectors have been shown to give permanent expression, so they remain available to address the longevity of expression issue. Adequate delivery to the target tissue remains a problem for many of the arrhythmia applications. Remaining elements of long-term cure include the interactions between a potentially one-time gene intervention and the long-term evolution of the arrhythmia substrate. Presumably, pressure from comorbidities and arrhythmia susceptibility factors would continue in the absence of intervention, and an initially successful intervention may lose efficacy as the substrate evolves over time. An integrated approach of addressing comorbidities, normalizing cardiac structure and function may be required for long-term control. Only long-term studies will address this issue and allow us to identify the needed components of these therapies.

Currently available data show promise for gene therapy to treat sinus node dysfunction, AF, certain inherited arrhythmia syndromes, and post-infarct VT. With long-term efficacy and safety studies, these novel interventions may represent the next generation of therapies for cardiac arrhythmias.

Abbreviations

AF	atrial fibrillation
AV	atrioventricular
CPVT	catecholaminergic polymorphic ventricular tachycardia
VT	ventricular tachycardia

References

AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. J. Am. Coll. Cardiol. 2003; 42:20–29. [PubMed: 12849654]

Amit G, Kikuchi K, Greener ID, Yang L, Novack V, Donahue JK. Selective molecular potassium channel blockade prevents atrial fibrillation. Circulation. 2010; 121:2263–2270. [PubMed: 20479154]

Bayer. Betapace AF (sotalol HCl) [package insert]. Bayer HealthCare Pharmaceuticals; Wayne, NJ: 2011.

Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A, Calkins H, Connolly SJ, Curtis AB, Darbar D, Ellinor PT, Go AS, Goldschlager NF, Heckbert SR, Jalife J, Kerr CR, Levy D, Lloyd-Jones DM, Massie BM, Nattel S, Olgin JE, Packer DL, Po SS, Tsang TS, Van Wagoner DR, Waldo AL, Wyse DG. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation. 2009; 119:606–618. [PubMed: 19188521]

Bernstein A, Parsonnet V. Survey of cardiac pacing and implanted defibrillator practice patterns in the United States in 1997. Pacing Clin Electrophysiol. 2001; 24:842–855. [PubMed: 11388104]

Beuckelmann DJ, Nabauer M, Kruger C, Erdmann E. Altered diastolic [Ca2+]i handling in human ventricular myocytes from patients with terminal heart failure. Am Heart J. 1995; 129:684–689. [PubMed: 7900618]

Beuckelmann D, Nabauer M, Erdmann E. Alterations of K^+ currents in isolated human ventricular myocytes from patients with terminal heart failure. Circ Res. 1993; 73:379–385. [PubMed: 8330380]

Bikou O, Thomas D, Trappe K, Lugenbiel P, Kelemen K, Koch M, Soucek R, Voss F, Becker R, Katus HA, Bauer A. Connexin 43 gene therapy prevents persistent atrial fibrillation in a porcine model. Cardiovasc Res. 2011; 92:218–225. [PubMed: 21799069]

Boink GJ, Duan L, Nearing BD, Shlapakova IN, Sosunov EA, Anyukhovsky EP, Bobkov E, Kryukova Y, Ozgen N, Danilo P Jr, Cohen IS, Verrier RL, Robinson RB, Rosen MR. HCN2/SkM1 gene transfer into canine left bundle branch induces stable, autonomically responsive biological pacing at physiological heart rates. J. Am. Coll. Cardiol. 2013; 61:1192–1201. [PubMed: 23395072]

Boink GJ, Nearing BD, Shlapakova IN, Duan L, Kryukova Y, Bobkov Y, Tan HL, Cohen IS, Danilo P Jr, Robinson RB, Verrier RL, Rosen MR. Ca(2+)-stimulated adenylyl cyclase AC1 generates efficient biological pacing as single gene therapy and in combination with HCN2. Circulation. 2012; 126:528–536. [PubMed: 22753192]

Brunner M, Kodirov S, Mitchell G, Buckett P, Shibata K, Folco E, Baker L, Salama G, Chan D, Zhou J, Koren G. In vivo gene transfer of Kv1.5 normalizes action potential duration and shortens QT interval in mice with long QT phenotype. Am J Physiol. 2003; 285:H194–H203.

Cai J, Yi FF, Li YH, Yang XC, Song J, Jiang XJ, Jiang H, Lin GS, Wang W. Adenoviral gene transfer of HCN4 creates a genetic pacemaker in pigs with complete atrioventricular block. Life Sci. 2007; 80:1746–1753. [PubMed: 17382969]

Calkins H, Yong P, Miller J, Olshansky B, Carlson M, Saul J, Huang S, Liem L, Klein L, Moser S, Bloch D, Gillette P, Prystowsky E. Atakr Multicenter Investigators Group. Catheter ablation of accessory pathways, atrioventricular nocal reentrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. Circulation. 1999; 99:262–270. [PubMed: 9892593]

Cingolani E, Yee K, Shehata M, Chugh SS, Marban E, Cho HC. Biological pacemaker created by percutaneous gene delivery via venous catheters in a porcine model of complete heart block. Heart Rhythm. 2012; 9:1310–1318. [PubMed: 22521937]

Coplen S, Antmann E, Berlin J, Hewitt P, Chalmers T. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized controlled trials. Circulation. 1990; 82:1106–1116. [PubMed: 2144796]

Coronel R, Lau DH, Sosunov EA, Janse MJ, Danilo P Jr, Anyukhovsky EP, Wilms-Schopman FJ, Opthof T, Shlapakova IN, Ozgen N, Prestia K, Kryukova Y, Cohen IS, Robinson RB, Rosen MR. Cardiac expression of skeletal muscle sodium channels increases longitudinal conduction velocity

in the canine 1-week myocardial infarction. Heart Rhythm. 2010; 7:1104–1110. [PubMed: 20385252]

de Bakker J, van Capelle F, Janse M, Wilde A, Coronel R, Becker A, Dingemans K, van Hemel N, Hauer R. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. Circulation. 1988; 77:589–606. [PubMed: 3342490]

de Chillou C, Lacroix D, Klug D, Magnin-Poull I, Marquie C, Messier M, Andronache M, Kouakam C, Sadoul N, Chen J, Aliot E, Kacet S. Isthmus characteristics of reentrant ventricular tachycardia after myocardial infarction. Circulation. 2002; 105:726–731. [PubMed: 11839629]

de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allessie MA. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circulation. 2010; 122:1674–1682. [PubMed: 20937979]

Denegri M, Avelino-Cruz JE, Boncompagni S, De Simone SA, Auricchio A, Villani L, Volpe P, Protasi F, Napolitano C, Priori SG. Viral gene transfer rescues arrhythmogenic phenotype and ultrastructural abnormalities in adult calsequestrin-null mice with inherited arrhythmias. Circ. Res. 2012; 110:663–668. [PubMed: 22298808]

DiFrancesco D, Noble D. The funny current has a major pacemaking role in the sinus node. Heart Rhythm. 2012; 9:299–301. [PubMed: 21925134]

Echt D, Liebson P, Mitchell L, Peters R, Obias-Manno D, Barker A, Arensberg D, Baker A, Friedman L, Greene H. Cardiac Arrhythmia Suppression Trial Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. N Engl J Med. 1991; 324:781–788. [PubMed: 1900101]

Eckstein J, Zeemering S, Linz D, Maesen B, Verheule S, van HA, Crijns H, Allessie MA, Schotten U. Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: evidence from simultaneous endoepicardial high-density activation mapping. Circ. Arrhythm. Electrophysiol. 2013; 6:334–341. [PubMed: 23512204]

Fedorov VV, Schuessler RB, Hemphill M, Ambrosi CM, Chang R, Voloshina AS, Brown K, Hucker WJ, Efimov IR. Structural and functional evidence for discrete exit pathways that connect the canine sinoatrial node and atria. Circ. Res. 2009; 104:915–923. [PubMed: 19246679]

Greener ID, Sasano T, Wan X, Igarashi T, Strom M, Rosenbaum DS, Donahue JK. Connexin43 gene transfer reduces ventricular tachycardia susceptibility after myocardial infarction. J Am Coll Cardiol. 2012; 60:1103–1110. [PubMed: 22883636]

Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le MA, Le MP, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998; 339:659–666. [PubMed: 9725923]

Hansen BJ, Csepe TA, Zhao J, Ignozzi AJ, Hummel JD, Fedorov VV. Maintenance of Atrial Fibrillation: Are Reentrant Drivers With Spatial Stability the Key? Circ. Arrhythm. Electrophysiol. 2016; 9

Hockings BE, George T, Mahrous F, Taylor RR, Hajar HA. Effectiveness of amiodarone on ventricular arrhythmias during and after acute myocardial infarction. Am J Cardiol. 1987; 60:967–970. [PubMed: 3673913]

Igarashi T, Finet JE, Takeuchi A, Fujino Y, Strom M, Greener ID, Rosenbaum DS, Donahue JK. Connexin gene transfer preserves conduction velocity and prevents atrial fibrillation. Circulation. 2012; 125:216–225. [PubMed: 22158756]

Inada S, Zhang H, Tellez JO, Shibata N, Nakazawa K, Kamiya K, Kodama I, Mitsui K, Dobrzynski H, Boyett MR, Honjo H. Importance of gradients in membrane properties and electrical coupling in sinoatrial node pacing. PLoS. One. 2014; 9:e94565. [PubMed: 24759974]

Israel CW, Hohnloser SH. Current status of dual-sensor pacemaker systems for correction of chronotropic incompetence. Am J Cardiol. 2000; 86:86K–94K. [PubMed: 10867099]

Jais P, Haissaguerre M, Shah D, Chouairi S, Gencel L, Hocini M, Clementy J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation. 1997; 95:572–576. [PubMed: 9024141]

Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol Rev. 1989; 69:1049–1169. [PubMed: 2678165]

Kapoor N, Liang W, Marban E, Cho HC. Direct conversion of quiescent cardiomyocytes to pacemaker cells by expression of Tbx18. Nat. Biotechnol. 2013; 31:54–62. [PubMed: 23242162]

Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. Eur. Heart J. 2016

Lakatta EG, Maltsev VA. Rebuttal: what I(f) the shoe doesn't fit? "The funny current has a major pacemaking role in the sinus node". Heart Rhythm. 2012; 9:459–460. [PubMed: 21925131]

Lau DH, Clausen C, Sosunov EA, Shlapakova IN, Anyukhovsky EP, Danilo P Jr, Rosen TS, Kelly C, Duffy HS, Szabolcs MJ, Chen M, Robinson RB, Lu J, Kumari S, Cohen IS, Rosen MR. Epicardial border zone overexpression of skeletal muscle sodium channel SkM1 normalizes activation, preserves conduction, and suppresses ventricular arrhythmia: an in silico, in vivo, in vitro study. Circulation. 2009; 119:19–27. [PubMed: 19103989]

Maltsev VA, Lakatta EG. The funny current in the context of the coupled-clock pacemaker cell system. Heart Rhythm. 2012; 9:302–307. [PubMed: 21925132]

Miake J, Marban E, Nuss H. Biological pacemaker created by gene transfer. Nature. 2002; 419:132–133.

Miake J, Marban E, Nuss H. Functional role of inward rectifier current in heart probed by Kir2.1 overexpression and dominant-negative suppression. J Clin Invest. 2003; 111:1529–1536. [PubMed: 12750402]

Miller J, Marchlinski F, Buxton A, Josephson M. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. Circulation. 1988; 77:759–766. [PubMed: 3349580]

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de FS, Despres J, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. Circulation. 2015; 131:e29–e322. [PubMed: 25520374]

Nuss HB, Kaab S, Kass DA, Tomaselli GF, Marban E. Cellular basis of ventricular arrhythmias and abnormal automaticity in heart failure. Am J Physiol. 1999; 277:H80–H91. [PubMed: 10409185]

Parsonnet V, Cheema A. The nature and frequency of postimplant surgical interventions: a realistic appraisal. Pacing Clin Electrophysiol. 2003; 26:2308–2312. [PubMed: 14675017]

Persson R, Earley A, Garlitski AC, Balk EM, Uhlig K. Adverse events following implantable cardioverter defibrillator implantation: a systematic review. J Interv. Card Electrophysiol. 2014; 40:191–205. [PubMed: 24948126]

Pfizer. Tikosyn (dofetilide) [package insert]. Pfizer, Inc.; New York, NY: 2011.

Plotnikov A, Sosunov E, Qu J, Shlapakova I, Anyukhovsky E, Liu L, Janse M, Brink P, Cohen I, Robinson R, Danilo PJ, Rosen M. Biological pacemaker implanted in canine left bundle branch provides ventricular escape rhythms that have physiologically acceptable rates. Circulation. 2004; 109:506–512. [PubMed: 14734518]

Rothman S, Hsia H, Cossu S, Chmielewski I, Buxton A, Miller J. Radiofrequency catheter ablation of postinfarction ventricular tachycardia: long-term success and the significance of inducible nonclinical arrhythmias. Circulation. 1997; 96:3499–3508. [PubMed: 9396447]

Sasano T, McDonald AD, Kikuchi K, Donahue JK. Molecular ablation of ventricular tachycardia after myocardial infarction. Nat Med. 2006; 12:1256–1258. [PubMed: 17072309]

Soucek R, Thomas D, Kelemen K, Bikou O, Seyler C, Voss F, Becker R, Koenen M, Katus HA, Bauer A. Genetic suppression of atrial fibrillation using a dominant-negative ether-a-go-go-related gene mutant. Heart Rhythm. 2012; 9:265–272. [PubMed: 21907172]

Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation. 2008; 118:2773–2782. [PubMed: 19064682]

Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, Agner E, Carlsen J, Videbaek J, Marchant B, Camm AJ. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N. Engl. J. Med. 1999; 341:857–865. [PubMed: 10486417]

Trappe K, Thomas D, Bikou O, Kelemen K, Lugenbiel P, Voss F, Becker R, Katus HA, Bauer A. Suppression of persistent atrial fibrillation by genetic knockdown of caspase 3: a pre-clinical pilot study. Eur. Heart J. 2013; 34:147–157. [PubMed: 21785105]

Tse H, Xue T, Lau C, Siu C, Wang K, Zhang Q, Tomaselli G, Akar F, Li R. Bioartificial sinus node constructed via in vivo gene transfer of an engineered pacemaker HCN channel reduces the dependence on electronic paemaker in a sicksinus syndrome model. Circulation. 2006; 114:1000–1011. [PubMed: 16923751]

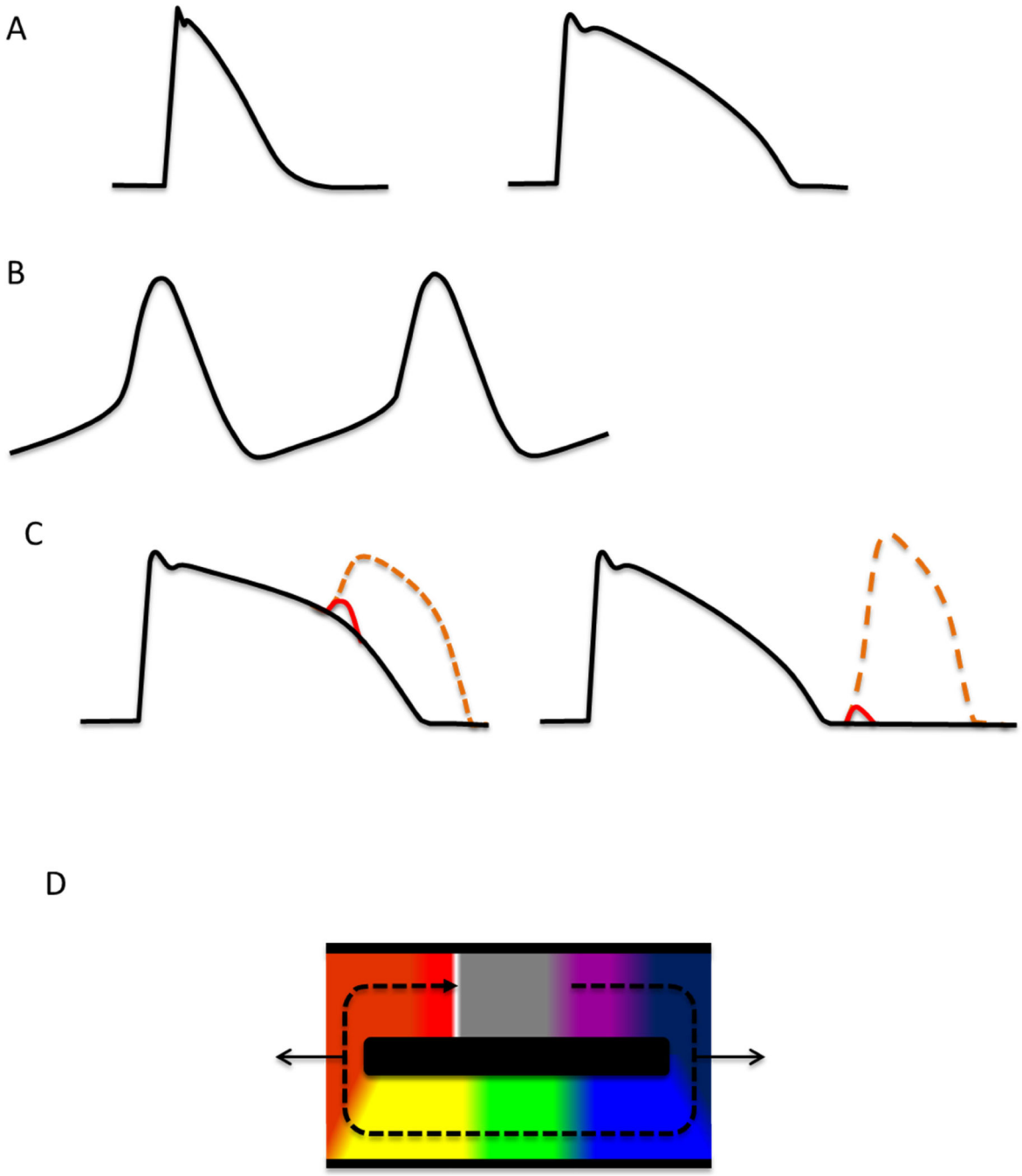

Figure 1.

Arrhythmia mechanisms (A) the normal morphologies of atrial (left) and ventricular (right) action potentials are shown. Normally, cardiac myocytes outside the specialized conduction system are quiescent and the cell maintains a polarized state with a stable negative resting membrane potential (baseline). (B) Unlike the stable baseline of normal myocytes, cells with automaticity (either cells from the specialized conduction system, cells modified to develop automaticity, or injured myocytes) have an unstable baseline with gradual depolarization. The slow rate of depolarization generally inactivated the sodium current that is responsible

for the rapid depolarization noted for atrial and ventricular myocytes in panel A. A calcium current is generally responsible for activation in automatic cells. The slower kinetics of the calcium current account for the less sharp depolarization in comparison to normal atrial and ventricular myocytes. (C) Triggered arrhythmias are generated from secondary electrical activation of the cardiac myocyte, either in the later stages of the initial action potential (early afterdepolarization, depicted on the left) or after completion of the prior action potential (delayed afterdepolarization, right panel). Activations can either be small shifts in membrane potential (red line) or full secondary action potentials (orange dotted line). Afterdepolarizations are generally triggered by abnormal behavior of the cellular ionic currents and/or intracellular calcium handling processes. (D) Unlike the automaticity and triggered activity that are largely cellular processes, reentry is a tissue level process. Fixed or functional barriers (black bars) allow progressive activation of the loop of tissue inside the barrier. In the schematic, the active electrical wavefront is the white bar. The progression of red-orange-yellow-green-blue-violet represents the tissue in various stages of electrical recovery from the prior action potential, and the gray region is myocardial tissue that has recovered from the prior action potential and is capable of generating a new action potential when activated. The dotted arrow shows progression of the activation wavefront around the reentrant circuit, and the solid arrows show escape of the electrical activation to surrounding tissues. A heart beat is generated for each revolution of the circuit. Reentry can be disrupted when the activation wavefront meets refractory tissue (i.e. no gray region. This occurs either with increased speed of conduction around the circuit or with a delay in electrical recovery of cells within the circuit.