

New Strategies for Arrhythmia Treatment

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ABSTRACT

Arrhythmias are an important class of cardiovascular disease, the most common of which are impulsive mechanisms (automatic,

triggering activities), impulsive conduction disorders (re-entry, blockade) or both. Arrhythmia may occur at any age and is characterised by a heartbeat that is either too slow (< 60 beats per min) or too fast (> 100 beats per min). Traditional arrhythmia treatment is divided into drug therapy and non-drug therapy. Non-pharmacological treatments include electric shock, heart rate adjustment, surgery and radiofrequency ablation. While these treatments can alleviate the symptoms of arrhythmia to some extent, the radical treatment cannot be achieved. This article briefly introduces several common arrhythmia diseases, and discusses the advantages and disadvantages of traditional arrhythmia treatment methods, focusing on new application strategies of gene therapy.

Key words: Arrhythmia; Cardiac conduction system; Traditional therapy; Gene therapy; Heart failure

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INTRODUCTION

Arrhythmia is the leading cause of morbidity and mortality in heart disease, and is the cause of death in up to 250,000 people a year in the United States alone^[1,2]. There are two situations in which human arrhythmias occur. First, in the early stages of life, arrhythmias may appear as a result of natural (congenital) and electrophysiological changes. Structural abnormalities can either be absent (e.g. long QT syndrome^[3-5]), minimal [e.g. Wolff-Parkinson-White syndrome (WPW) caused by paraneopathic pathways] or severe (e.g. endocardial pad defects with cardiac block). Secondly, arrhythmia may occur as a result of acquired disease (such as ventricular tachycardia after myocardial infarction) or aging [atrial fibrillation (AF)]^[6]. The most common arrhythmias include AF^[7] and ventricular arrhythmia^[8]. Among these, AF is most common in mitral stenosis and/or mitral regurgitation, and rarely occurs in aortic valve defects. Ventricular arrhythmia is associated with most valvular heart disease. Severe arrhythmias such as sick sinus syndrome^[9], rapid AF^[10], paroxysmal supraventricular tachycardia^[11] and persistent

ventricular tachycardia^[12] have clinical manifestations including heart palpitations, chest tightness, dizziness, low blood pressure and sweating, and severe cases may even result in syncope or even sudden death.

Defects in the heart conduction system are a leading cause of heart disease. Early studies using chicken^[13] and other animal models^[14] showed that the conduction system has a functional existence but is morphologically unrecognisable, and its different components have different functions. The sinoatrial node contains a pacemaker that functions to ensure that blood pressure and one-way blood flow can cause excitement from the atrial muscle to the atrioventricular (AV) node. Further conduction is interrupted by insulating fibres at the AV junction, and at another site, the specific AV bundle penetrates the AV connection through the central fibrous body. The AV node is located at the atrial side of the AV connection and can be regarded as the end of the atrial conduction axis. There is a short delay in the excitatory spread into the ventricle, which is generated by the AV node, allowing the ventricle to fill when the atrium contracts. These delays are necessary to maintain normal heart function (Figure 1)^[14].

In 2009, Christoffels *et al*^[15] published a study entitled ‘Development of the cardiac conduction system: why are some regions of the heart more arrhythmogenic than others?’, clarifying the relationship between the development of cardiac conduction system and various diseases of the heart. In 2014, van Duijvenboden *et al*^[16] stated that due to the pacemaker activity of the venous pole and the delay in the impulse in the AVC (atrio-ventricular canal), the slow contraction of the heart tube translates into a rapid continuous contraction pattern of the atria and ventricles, leading to arrhythmias^[17-20].

TRADITIONAL TREATMENT

Currently, treatment for arrhythmia mainly focuses on the physical and chemical treatment of restoring normal heart rhythm. The aim is to temporarily or continuously restore the normal fluctuation of the heart rhythm; however, it cannot be completely cured. Traditional arrhythmia treatment is divided into drug and non-drug treatment. Non-drug treatment includes electric shock, heart rate regulator, operation and radiofrequency ablation.

Drug therapies

Drugs can restore the heartbeat to normal, or reduce the frequency of an irregular heartbeat, but this can only be controlled and the effects are limited^[21]. Drug therapy is the main treatment method for arrhythmia; however, due to the complexity of arrhythmias, the manner and approach of drug action also differs. Drug administration is generally oral, but for acute attacks drugs may be taken intravenously or via an aerosol. In principle, treatment of slow arrhythmias generally uses drugs that enhance myocardial self-discipline and/or accelerates conduction, such as sympathomimetic drugs (e.g. isoproterenol^[22,23]), vagus nerve inhibitors (e.g. atropine^[24]) or alkalinizing agents (e.g. sodium lactylate^[25,26] or sodium bicarbonate^[27,28]). Treatment of tachyarrhythmia uses drugs that slow down conduction and prolong the refractory period, such as vagus nerve stimulants (e.g. neostigmine^[29]), digitalis preparation^[30,31], sympathetic nerve agents indirectly exciting the vagus nerve (e.g. methoxyl, benzodiazepine^[32-34]) or antiarrhythmic drugs. Antiarrhythmic medication aims to destroy the pathological tissue causing the arrhythmia and make pathological changes to the myocardial cells and change the electrical physiology. However, long-term use has various adverse side effects, which

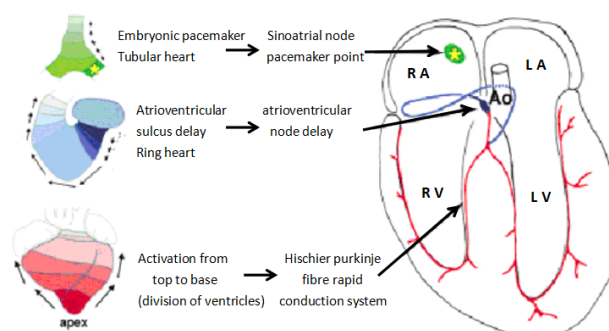


Figure 1 Model of the developing cardiac conduction system^[14]. The yellow star indicates the activation position of the pacemaker. The direction and rate of action potential propagation are marked with small arrows at different stages of cardiac development. AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

can cause ventricular arrhythmia or heart block, and may cause death. Therefore, it is necessary to strictly control the indications in clinical application and understand the effects of the commonly used antiarrhythmic drugs, including half-life, absorption, decomposition, excretion, active metabolites, dosage and side effects.

An increase in interest in traditional Chinese medicine has led to a better understanding of the role of this therapy in the treatment of diseases. The significant efficacy and fewer side effects has meant their use has been increasingly recognised in clinical practice^[35]. Clinical studies have shown that Chinese medicine has a significant effect on the treatment of cardiovascular diseases, with mild side effects and few sequelae. For example, in 2016, Chuang *et al*^[36] reported the risk of stroke in Chinese medicine for patients with arrhythmia. They identified arrhythmia groups in one million groups of the National Health Insurance Research Database in Taiwan, including 2029 patients who received traditional Chinese medicine treatment between 2000 and 2004, and identified stroke events during the end of 2010. Their results showed that during the follow-up period, the incidence of new stroke in patients with arrhythmia treated by Chinese medicine (11.4/1000) was lower than that in patients not treated using Chinese medicine (17.7/1000), and the relationship between Chinese medicine treatment and the reduction of new stroke was significant in both men and women. These results indicate that in patients with arrhythmia, Chinese medicine treatment is associated with a lower risk of stroke. Herbal remedies, acupuncture and yoga have also been studied and have been reported to have anti-arrhythmia effects.

Electroconvulsive therapy

During arrhythmia, a defibrillator (a medical electric shock device) may be used to treat a decrease in cardiac blood transfusion. This provides a shock or quasi-shock to the patient's chest to restore the normal heart rate^[37].

Pacemaker therapy

Electronic pacemakers have saved many lives since they were introduced into the clinic^[38-40]. They work by placing an electrode wire on the surface of the heart or inside the RV. When the heartbeat is slowed to a certain degree or stops, the sensor emits a wave. This stimulates the heart to beat, and is specifically used to treat heart block. Another type of regulator is used for tachycardia, and it acts like an external shock. The batteries of the pacemaker are usually placed under the subcutaneous tissue of the chest collarbone or abdomen. The battery life is more than 10 years, but can be replaced

by surgery if it runs out. Patients with pacemakers should avoid high voltages and electromagnetic waves, or bringing mobile phones close to the battery, so as not to affect the function of the pacemaker.

Surgical therapy

Surgical treatment of arrhythmia^[41] may involve electrocautery surgery through cardiac catheterisation after electrophysiological examination. This is used to burn the source of arrhythmia or inborn abnormal nerve to achieve the purpose of radical treatment. WPW syndrome^[42-44] and paroxysmal ventricular tachycardia^[45-47] can often be treated with this method, with a success rate of up to 95%.

Radiofrequency catheter ablation therapy

Treatment of arrhythmia is a complex process involving both pharmacological and non-pharmacological methods. The mainstay of non-drug arrhythmia treatment is radiofrequency ablation of the transcatheter arterial catheter^[48]. A physiological electrical examination is used to identify a path with abnormal radio wave conduction, and a high-frequency current is used to instantaneously burn tissue that conducts abnormal electric waves, eliminating abnormal physiological electric conduction.

Currently available drugs for the treatment of arrhythmia or non-drug therapy aim to restore sinus rhythm or control the ventricular response rate. The current treatment options are not ideal and have spurred research into more effective and innovative treatments. Gene therapy has the potential to treat a variety of human diseases, including arrhythmias. With the improvement of transduction efficiency and biosafety, gene transfer vectors have been developed and tested for the treatment of cardiovascular diseases^[49]. In recent years, gene therapy has become a popular candidate for clinical research and treatment of cardiovascular diseases. Next, we present a review of the progress of gene therapy for arrhythmia.

NEW STRATEGIES

We have briefly introduced the close relationship between the development of cardiac conduction system and arrhythmia. Development of the conduction system is regulated by multiple transcription factors. Some transcription factors, including homologous domain protein and t-box protein, are crucial to the morphogenesis of the cardiac conduction system and the activation or inhibition of key regulatory genes. Some transcription factors modify expression of genes that encode ion-channel proteins that contribute to the electrophysiological properties of the conduction system and control the contraction of the surrounding myocardium. Loss of transcriptional regulatory function is often detrimental to heart development and may lead to arrhythmia^[50-54]. For example,

Hatcher *et al*^[55] described a subset of transcription factors involved in the development of cardiac conduction systems, including Nkx2.5, Shox2, Hop, Irx4, Irx5, Tbx2, Tbx3, Tbx18, Tbx5 and Id2 that are key transcription factors that significantly contribute to the specification, pattern, maturation and function of the cardiac conduction system (Figure 2). Further analysis of the molecular mechanisms involved in this process and the introduction of gene therapy protocols will help to improve the diagnosis and treatment of arrhythmias caused by defects in the conduction system.

Gene therapy refers to the introduction of a foreign normal gene into a target cell to correct or compensate for diseases caused by genetic defects and abnormalities to achieve therapeutic purposes. It also describes the application of technologies such as transgenic technology, which involves inserting exogenous genes into the appropriate receptor cells of patients through gene transfer technology, in order to use the products of the exogenous genes to treat certain diseases. Nowadays, with the rapid development of science and technology, many genes related to arrhythmia have been identified. If we can identify which genes have been mutated in patients with arrhythmia, we can select the appropriate gene therapy. There are currently five basic gene therapy strategies: gene complementation, gene inactivation, immunotherapy, gene repair and gene replacement (Table 1).

Gene therapy for electrocardiogram dysfunction is an attractive strategy as there are limited ways to treat the most severe arrhythmias, such as ventricular tachycardia, ventricular fibrillation and arrhythmia. A growing understanding of disease-related molecular

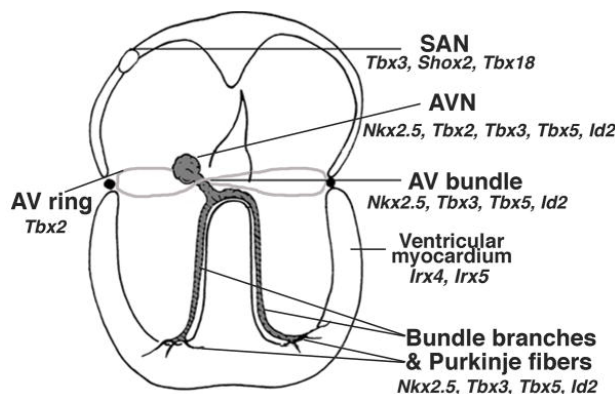


Figure 2 Transcription factors required for development of the cardiac conduction system^[55]. A schematic representation of the components of the mammalian cardiac conduction system is shown, including the position of the primitive embryonic AV ring (grey ellipse). The transcription factors known to regulate specification, patterning, maturation and function of these components are indicated in italics, and include Nkx2.5, Shox2, Hop, Irx4, Irx5, Tbx2, Tbx3, Tbx18, Tbx5 and Id2.

Table 1 Overview of the molecular strategies for gene therapy.

Gene therapy strategy	Principle
Gene complementation	Introducing the target gene into diseased cells or tissues so the gene product can strengthen or correct the function of the defective cells. This approach is mainly aimed at diseases caused by recessive genes, such as albinism and haemophilia.
Gene inactivation	The use of RNA interference, dominant negative mutations, ribozymes, antisense RNA, etc. to inhibit the expression of certain genes, mainly oncogenes and AIDS genes.
Immunotherapy	Introducing an antigen-antibody or cytokine gene into a patient, to change the immune status and prevent or treat a disease. For example, the principle of the recent hot CAR-T technology is to splice the extracellular specific tumour antigen recognition region, hinge, transmembrane region and intracellular signal transduction domain by genetic engineering technology, then using a retrovirus or lentiviral vector, transfer a transposon or transposase system or direct transfection into effector cells and express antigen-specific effector cells, followed by in vitro expansion to reach a therapeutic dose that is then infused into a patient's cellular immunotherapy strategy.
Gene repair	Gene editing technology that fixes the abnormal part of the gene using editing techniques such as CRISPR. It is currently in the clinical trial stage and may be put into clinical use in the future.
Gene replacement	Use of the normal gene to replace the pathogenic gene in situ so that the DNA in the cell completely restored to normal. This method is feasible in theory, but has not yet been achieved in experimentally or clinically.

mechanisms has provided researchers with sufficient tools to target specific genes and pathways associated with arrhythmia. Data from preclinical studies suggest that gene therapy can successfully ameliorate the symptoms of arrhythmias and prevent life-threatening arrhythmias^[56,57]. Myocardial gene transfer has shown great potential in studying the pathophysiology and potential therapeutic approaches of heart disease. There is a huge demand for new treatment options for arrhythmias^[58-60]. Next, we briefly introduce several methods for the treatment of arrhythmia using gene therapy.

AF gene therapy

As early as 2002, Marban *et al*^[61] used a pig model of acute AF to transfer recombinant adenovirus containing genes for inhibitive G protein (*Gai2*) subunit to the AV nodal artery. This transgene overexpressed *Gai2*, inhibiting basal adenylate cyclase activity, thereby indirectly inhibiting channel activity in calcium AV nodes. The results showed that in the AF model, the heart rate of the experimental group was reduced by 20% compared with the control group, indicating the feasibility of gene therapy in the AF model. In 2011, Bikou *et al*^[62] used pig models to develop and evaluate strategies to inhibit persistent AF using gene therapy. AF was induced in pigs by atrial burst pacing, resulting in a 62.4% reduction in atrial Cx43 protein. Adenovirus encoding Cx43 (AdCx43) or green fluorescent protein (GFP) was injected into the two atria, respectively, and then transfected by epicardial electroporation to enhance transgene expression. Direct injection of adenovirus combined with electrical perforation led to GFP reporter gene expression in ~50% atrial cells. The atrial Cx43 protein content of the adcx43-treated animals increased 2.5-fold, and no persistent AF occurred during the 14-day observation period. These results highlight the contribution of Cx43 to the pathophysiology of AF and demonstrate the feasibility of gene suppression techniques to prevent atrial arrhythmias in gene therapy. Over the years, research into the treatment of AF using gene therapy has made rapid progress. Many genes related to AF have been identified, and gene therapy for symptoms of AF using target genes in animal models has achieved good results^[63-66]. These findings suggest that targeted gene therapy is a promising alternative to pharmacological treatment or ablation of AF.

Ventricular arrhythmia gene therapy

As early as 2009, Lau *et al*^[67] used dogs model overexpressing SkM1 in the skeletal muscle sodium channel in the epicardial border region to activate myocardial activation, maintain conduction and inhibit ventricular arrhythmia. SkM1 increases V(max) in depolarised myocardium, reducing the incidence of induced persistent ventricular tachyarrhythmia/fibrillation. Gene therapy that normalises activation by increasing V(max) at the depolarising potential may be a promising antiarrhythmic strategy. In the same year, Sasano *et al*^[68] established a pig model of induced ventricular tachycardia, and, after verifying the model, evaluated a gene transfer technique that focused on local modification of boundary tissue. We found that gene transfer of the dominant negative KCNH2-G628S mutation in the anteroseptal infarct border caused localised prolongation of effective refractory period in the target region and eliminated all ventricular arrhythmia inducibility. In 2011, Lyon *et al*^[69] studied the effect of SERCA2a gene supplementation on ventricular arrhythmia in rats with chronic heart failure. The use of SERCA2a gene therapy to improve the mechanism of heart failure is currently at the clinical trials stage. Electrocardiographic monitoring studies have shown that SERCA2a gene therapy can reduce both spontaneous arrhythmias

and catecholamine-induced arrhythmias *in vivo*, with significant antiarrhythmic effects. At the same time, SERCA2a gene therapy also reduced the sensitivity to re-entry arrhythmias in *in vitro* programmed electrical stimulation studies. Recent in-depth molecular biology studies have identified more and more genes regulating ventricular arrhythmia; however, it is unclear whether these genes can be clinically applied to patients for gene therapy. Nevertheless, we believe that the continuous innovation and improvement of gene therapy technology to treat these diseases will evolve and may be put to clinical use in the future.

Biological pacemaker therapy

Heart diseases can be debilitating and even fatal. Electronic pacemakers are standard therapies for treating symptoms associated with bradycardia, but they also have disadvantages. Electronic pacemakers are very effective in the treatment of sinus and AV node dysfunction; however, they also have some limitations, ranging from a lack of basic autonomic regulation to severe complications. In the past 15 years, experimental evidence has shown that gene and cell therapy could be used to create biological pacemakers that could complement or replace electronic pacemakers^[70-72]. Biological pacing can be achieved by gene transfer to regulate ion currents or by injecting engineered pacemaker cells into a normally resting myocardium. Currently, researchers are working to use a stable and reliable biological product as an alternative to electronic pacemakers^[73].

In 2002, Miake *et al*^[74] reported the use of viral gene transfer to convert resting cardiomyocytes into pacemaker cells, with successful spontaneous production in the ventricles of the heart, producing rhythmic electrical activity. These results show that genetically engineered pacemakers can be used as a possible alternative to implanted electronic devices. In 2008, Piron *et al*^[75] injected a chimeric plasmid encoding HCN2 and ADRB2 into the left ventricular free wall (HCN2-ADRB2 mice). Non-viral gene delivery of hyperpolarisation-activated HCN2 channels combined with the beta-2 adrenergic receptor produced a functional pacemaker in a complete atrioventricular conduction block (CAVB) mouse model induced by radiofrequency ablation. The results showed that non-viral gene transfer could produce a functional cardiac biological pacemaker regulated by sympathetic input, thus improving the life expectancy of the CAVB mouse model. In 2014, Rosen *et al*^[76] published an article entitled 'Gene therapy and biological pacing', which stated that TBX18 is a transcription factor that plays a key role in the expression of sinoatrial node during normal development. The study used a porcine heart arrest model and injected a vector carrying TBX18 to induce pacemaker activity for 11 days. Research into biological pacemakers has developed rapidly in recent years, and many genes have been shown to play the role of biological pacemakers, laying a solid foundation for clinical practice in the future^[77-83].

Gene therapies for arrhythmias in heart failure

Heart failure is mostly caused by organic cardiovascular diseases, and some arrhythmias may also induce heart failure, such as rapid supraventricular arrhythmia (AF, atrial flutter, paroxysmal supraventricular tachycardia), resulting in decreased ventricular filling and decreased cardiac output, resulting in heart failure. When heart failure occurs, it is often accompanied by sinus tachycardia and other arrhythmias. Therefore, heart failure and arrhythmia are very closely related. Heart failure is always associated with life-threatening ventricular arrhythmias, and ventricular arrhythmias

are also most likely to cause heart failure. In 2014, Akar *et al*^[84] published an article entitled ‘Gene therapies for arrhythmias in heart failure’, which reviewed recent advances in the understanding of arrhythmia mechanisms of heart failure, and focused on the changes in repolarisation, conduction and intracellular calcium circulation, which are important for the vast majority of clinical arrhythmias in heart failure. The article highlighted recent approaches to gene-based arrhythmias for ion channels, gap junctions and calcium cycle proteins. In the same year, Sikkil *et al*^[85] reported that SERCA2a protein levels and function were reduced in chronic heart failure by viral transfection. The SERCA2a gene successfully targets cardiac tissue, increases cardiac contractility and reduces mortality in several preclinical models of heart failure. SERCA2a gene therapy is used in a variety of preclinical models, including acute ischemia/reperfusion, chronic stress overload and chronic myocardial infarction, and ultimately leads to a reduction in ventricular arrhythmias. This demonstrates how the study of heart failure has led to the use gene therapy to treat arrhythmia.

CONCLUSION

In summary, arrhythmia can cause palpitations, chest tightness, dizziness, low blood pressure, sweating, severe syncope and even sudden death. Currently, the treatment of arrhythmia mainly includes drug treatment and non-drug treatment, both of which can alleviate the symptoms of the patients to some extent; however, these treatments are limited and are associated with side effects, some of which may even lead to death.

The use of gene therapy to treat patients with arrhythmias may avoid the side effects and sequelae of drug therapy and non-drug therapy^[86-90]. In recent decades, the rapid development of molecular biology has led to the identification of more and more genes related to arrhythmia. In particular, in 2016, Li *et al*^[91] described the PITX2 gene as the main indicator of AF. Regulatory factors influence the occurrence of AF. Therefore, PITX2, as the master regulatory gene, must regulate multiple downstream genes and ultimately control the occurrence and development of AF. This approach of downstream gene regulation influencing the occurrence and development of AF may help to clarify the molecular mechanism of PITX2. Thus, gene therapy may be used to completely resolve the symptoms of patients with AF.

On the other hand, research using targeted gene therapy for arrhythmia in patients with heart disease syndrome is increasing. In 2003, Burton *et al*^[92] explored the potential use of the myocardial potassium channel missense mutation Q9E-hMiRP1 as a potential arrhythmia gene therapy target. This genetic abnormality is one of the many mutations that causes long QT syndrome, a hereditary arrhythmia associated with sudden death. The results indicated that even in patients with heart syndrome, gene therapy may be used to prescribe the right medicine.

In addition, arrhythmias and conduction disorders are main causes of morbidity and mortality worldwide; however, the aetiology in many patients is unclear. It has been reported in the literature that autoimmune reactions may be involved in the development of arrhythmias and cardiac arrest. Accurate identification of autoantibody-mediated mechanisms opens up new possibilities for the treatment and prevention of arrhythmias, including the use of immunosuppressive agents to remove autoantibodies. This also represents a new prospect for the treatment of diseases such as arrhythmia in the future^[93].

It is well known that gene therapy methods are currently being

studied widely, using animal models such as pigs, rats and mice. While these animal models have high homology with human genomes, there are some differences. Therefore, gene therapy in animal models can cure and ameliorate some arrhythmia symptoms, indicating that these gene treatments do have positive effects; however, further studies are required to achieve clinical application.

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