Somatic gene and cell therapy strategies for the treatment of cardiac arrhythmias

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CARDIAC FUNCTION depends on the appropriate timing and synchronization of the mechanical contraction in various regions of the heart as well as on achieving the appropriate heart rate. These properties are ensured through the hierarchical organization and electrical specialization of the cardiac conduction system, which are governed by the differential expression of cardiac ion channels in each component (42). Cardiac electrical excitation originates in the sinoatrial (SA) node, propagates through the atria to the atrioventricular (AV) node, and then activates the ventricles through the specialized His-Purkinje system.

Cardiac arrhythmias are defined as any deviation from the normal pattern or rate of the cardiac electrical excitation. These rhythm disorders represent one of the more common causes of worldwide morbidity and mortality and create a major burden on the health care systems. For example, sudden cardiac death due to ventricular tachyarrhythmias claims approximately 300,000 lives per year in the United States (19), and atrial fibrillation, which affects more than 2 million Americans, is the single most important cause of ischemic strokes in the elderly population (33).

Traditionally, cardiac arrhythmias can be classified into rhythm disorders that result in abnormally low heart rate (bradyarrhythmias) usually requiring the implantation of a permanent electronic pacemaker or those that produce an abnormally fast and uncoordinated beating rate (tachyarrhythmias). The clinical consequences of the latter may range from simple palpitations to sudden cardiac death, rendering the diagnosis and clinical management of these rhythm disturbances an important and challenging aspect of modern cardiology.

Currently, antiarrhythmic strategies are aimed at modifying the abnormal electrophysiological substrate and can be broadly classified into three categories: pharmacotherapy, focal injury (surgery or catheter ablation), and implantable devices.

Pharmacotherapy has been the mainstay of antiarrhythmic therapy for decades. Traditionally, antiarrhythmic drugs have been classified based on their electrophysiological effects at the cellular level, namely, their ability to modify excitatory currents, action potential duration, or automaticity. Antiarrhythmic medications were shown to be capable of suppressing different types of cardiac arrhythmias. Yet, the utility of these pharmacological agents has been significantly hampered by their global cardiac action, relatively low efficacy, their often poorly tolerated systemic side effects, and, most importantly, by their significant proarrhythmic effects leading in some studies to a paradoxical increase in mortality (6).

Radiofrequency catheter ablation has revolutionized the field of clinical electrophysiology by providing cardiologists with a possible curative approach for a number of arrhythmias while abolishing the need for life-long pharmacological treatment. Consequentially, radiofrequency catheter ablation has become the treatment of choice for the majority of the supraventricular arrhythmias and some types of ventricular tachycardias (41). Nevertheless, this approach is still restricted to only a minority of the patients suffering from arrhythmias with the more common rhythm disorders (atrial fibrillation and ventricular tachycardia) being less amenable to this form of treatment.

Implantable devices such as pacemakers and defibrillators have become the treatment of choice for a number of cardiac arrhythmias. It is estimated that around 250,000 electronic pacemakers and 60,000 defibrillators are implanted annually in the United States. Pacemakers represent the current state-of-the-art treatment for bradyarrhythmias, whereas implantable cardiac defibrillators (ICDs) have now been successfully used for more than two decades for the palliative treatment of life-threatening ventricular arrhythmias. The benefit from this strategy for high-risk patients (namely, those with reduced left ventricular function, survivors of sudden death, etc.) was clearly demonstrated in a number of large randomized studies (1, 30). Yet, this strategy, despite being lifesaving, does not prevent the emergence of these arrhythmias. In addition, implantable cardiac defibrillators require a lifetime commitment to repeated surgical implantation procedures at a significant expense, may be associated with severe complications, and may not benefit low-risk patients such as those with relatively preserved left ventricular function.

The lack of optimal therapeutic options for several types of cardiac arrhythmias motivates the pursuit for alternative therapeutic paradigms. Recent advances in molecular and cell biology and in tissue engineering technologies have paved the way to the development of a new and exciting field in biomedicine. This approach seeks to devise new biological solutions to replace or modify the function of diseased, absent, or malfunctioning tissue. The heart represents an attractive candidate for this emerging field, and cell and gene therapies have already been proposed as novel strategies to improve myocardial perfusion and contractile properties for the treatment of chronic ischemic heart disease and congestive heart failure (14, 17, 37).

These same technologies could also theoretically be used to modify the electrophysiological properties of the heart, providing a new and exciting strategy for the treatment of cardiac arrhythmias. This may be achieved through manipulation of the expression of the different cardiac ion channels, modulators of ion channel function, or proteins involved in cell-to-cell interactions. Interestingly, this strategy has already been used extensively in the past mainly as a molecular genetic approach to alter cardiac excitability and thereby dissect the contribution of different elements to the electrophysiological phenotype of cardiac function.
the heart or for the creation of animal models of arrhythmias. This editorial will focus on the possible therapeutic applications of gene and cell therapies in the field of cardiac electrophysiology. These applications will be discussed in the context of the pioneering studies already performed in this field and through a description of the steps required to fully harness the research and clinical potential of this strategy.

**GENE THERAPY FOR THE TREATMENT OF BRADYARRHYTHMIAS**

The electrical impulses that trigger cardiac contraction originate in a group of pacemaking cells in the SA node. These cells possess specific ionic channel current combinations that enable them to spontaneously depolarize at a constant rate subject to neurohormonal influences (42). Disturbances in the pacemaker function or in the normal propagation of the electrical impulse through the cardiac conduction system may result in abnormally low heart rate, circulatory failure, and even death.

Implanted pacemakers have become the preferred treatment for sinus node dysfunction and high-grade AV block with excellent success and minimal morbidity (25). Nonetheless, the ideal therapy for these disorders may be the development of a biological solution allowing reconstitution of the physiological electrical activity of the cardiac conduction system with the same plasticity and adaptability to the human body and to the physiology of the cardiovascular system. The search for such a biological solution has centered on three different gene therapy strategies (Fig. 1).

**Enhancement of the chronotropic response of the native pacemaking cells.** This strategy proposes to regulate the normal pacemaking activity of the heart by local gene delivery. An elegant approach to achieve this goal was recently described by Edelberg et al. (7, 8). These investigators aimed to enhance the responsiveness of the native atrial pacemaking cells to adrenergic input through upregulation of the β2-adrenergic receptors. Using detailed ex vivo and in vivo studies, the authors were able to demonstrate a significant positive chronotropic effect following overexpression of the human β2-adrenergic receptor in atrial tissue. Although these studies clearly demonstrated the ability of local gene delivery to alter the chronotropic properties of the heart, it mainly focused on modifying the function of existing and abnormal pacemaking cells rather than actually creating a new biological pacemaker.

**Shifting the balance between excitatory and inhibitory currents.** A different approach for the creation of a biological pacemaker in vivo was recently described by Miake et al. (29). This elegant strategy is based on the production of dominant negative inhibition of the Kir2-encoded inward rectifier potassium channels (I_{Kir}) in ventricular myocytes (Kir2.1AAA). The I_{Kir} current, which is intensely expressed in atrial and ventricular myocytes but not in the pacemaking nodal cells, maintains the negative resting membrane potential of ventricular myocytes and thereby suppresses any spontaneous diastolic activity (24).

The investigators hypothesized that dominant negative inhibition of this current could restore the latent pacemaking activity in these cells and convert the quiescent ventricular myocytes into pacemaking cells. To test this hypothesis, adenoviral gene delivery of Kir2.1AAA into the left ventricular cavity of guinea pigs was performed. In some of the animals studied, electrocardiogram recordings demonstrated the emergence of a new ventricular source of impulse initiation. In vitro electrophysiological recordings from the transfected myocytes demonstrated, electrophysiological properties and spontaneous activity resembling those of genuine pacemaking cells.

**Overexpression of the pacemaker-specific current.** Another interesting approach for the generation of a biological pae-
maker was recently introduced by Qu et al. (36). These investigators assessed the ability of localized overexpression of the hyperpolarization-activated, cyclic nucleotide-gated (HCN-2) isoform pacemaker current to generate stable pacemaking activity in vivo. Four days after the injection of adenoviral constructs of the mouse HCN2 into the canine left atrium, the authors noted the emergence of a new atrial pacemaking activity during vagal stimulation-induced sinus arrest. Electrophysiological mapping localized the source of this activity to the injection site at the left atrium. Whole cell electrophysiological recordings from transfected myocytes demonstrated the presence of a relatively high-magnitude pacemaker current.

GENE THERAPY FOR THE TREATMENT OF TACHYARRHYTHMIAS

The different mechanisms underlying various cardiac tachyarrhythmias (reentry, triggered activity, and abnormal automaticity) usually result from abnormalities in the myocardial electrophysiological or structural substrate. These abnormalities may be inherited (20, 26, 39) (e.g., the different monogenic ion channel mutations in the congenital long QT syndrome, Brugada syndrome, etc.) or acquired in a variety of clinical conditions (ischemic heart disease and heart failure leading to ventricular tachyarrhythmias or diseased atria leading to atrial fibrillation). The pathological substrate underlying these rhythm disorders may be anatomic or functional and may be localized to a specific area within the myocardium or affect the heart globally.

An understanding of the electrophysiological abnormalities leading to the development of the different rhythm disorders may be used to target specific genes that will either reverse the abnormal phenotype or modify the excitable properties of the myocardial substrate in a favorable way (Fig. 2). A possible attractive target for this type of somatic gene therapy may be to correct the abnormal global electrophysiological substrate in the inherited or acquired long QT syndromes (Fig. 2). This syndrome, which may be familial, inherited as either an autosomal recessive or dominant trait, or acquired in a variety of clinical conditions, is characterized by the prolongation of the QT interval in the electrocardiogram and by an increased risk for the development of ventricular arrhythmias and sudden cardiac death (20, 26).

Heart failure represents a prototype of an acquired long QT condition, which predisposes the patients to the development of ventricular arrhythmias (27). Experimental evidence suggest that this increased propensity for ventricular arrhythmias may stem, in part, from the downregulation of potassium currents (namely \(I_{Ks}\) and \(I_{K1}\)) in failing myocytes leading to significant prolongation of the action potential duration (APD) (2, 27). APD prolongation in failing myocytes may initially be an adaptive response because it increases the time available for excitation-contraction coupling thereby augmenting myocardial contractility. In the long term, however, this process may be maladaptive, predisposing the ventricle to early afterdepolarizations (EADs), inhomogeneous repolarization, and the development of lethal ventricular arrhythmias.

Gene therapy has been suggested as a possible way to reverse the electrophysiological changes associated with the acquired or congenital long QT syndromes. Proof-of-concept studies, either in isolated cultured cardiomyocytes (15, 18) or following short-term in vivo transfection in small animals (16), demonstrated that overexpression of the KV4.3 gene encoding...
the $I_{kr}$ can significantly shorten the APD in myocytes having a normal APD at baseline.

Nuss et al. (34) extended these observations by demonstrating that overexpression of a foreign potassium channel can also effectively abbreviate the prolonged APD in failing cardiomyocytes. In this study, adenoviral delivery of the inactivated-defective Drosophila shaker B potassium channel (ShK) to cultured ventricular myocytes isolated from the rapid-pacing heart failure canine model resulted in significant shortening of the prolonged APDs in these cells. A low level of ShK expression was sufficient to modify the action potential waveform of the failing myocytes to resemble that of normal ventricular myocytes. However, already in this early study, the importance of adequate control of the level of transgene expression became apparent because higher levels of ShK expression resulted in the generation of bizarre-shaped and overly shortened action potentials leading to significant impairment of the contractile properties of the transfected myocytes.

Another candidate current that can be used to shorten the APD is the human ether-a-go-go (HERG) encoding the $I_{kr}$ rapid component of the delayed rectifier potassium current. $I_{kr}$ is believed to play an important role in normal repolarization (45), and both naturally occurring mutations as well as pharmacological blockade of this current may result in QT prolongation and induction of ventricular arrhythmias in predisposed individuals (20). Adenoviral delivery of the HERG gene to cultured rabbit myocytes (which usually develop APD prolongation and increased incidence of EADs after a few days in culture) resulted in significant APD abbreviation, a significant increase in the relative refractory period, and a more than fourfold decrease in the incidence of EADs (35).

An alternative strategy to $I_{ox}$ or $I_{kr}$ was recently suggested by Mazhari et al. (28). These investigators proposed to overexpress the accessory subunit KCNE3 (E3, encoding MiRP2), a well-known positive regulator of the KCNQ1 (Q1, encoding KvLQT1) channel in different cell types (43) that is not normally expressed in the heart. Ectopic expression of the KCNE3 subunit in ventricular myocytes both ex vivo and in vivo leads to an increase in $I_{Ks}$ and to a significant increase in the slowly activating delayed rectifier potassium ($I_{ks}$) current. This in turn resulted in significant shortening of APD at the cellular level and of the QT interval when delivered in vivo.

Because heart failure is characterized by both depressed contractility and delayed repolarization, the unopposed action of the latter by the strategies described above may further aggravate the already depressed mechanical properties. To overcome this potential limitation, Ennis et al. (9) designed a novel dual gene strategy aiming to offset the loss of contractility due to the potassium current-induced APD shortening with the overexpression of the calcium ATPase sarco(endo)plasmic reticulum Ca$^{2+}$-ATPase (SERCA). Using a bicistronic adenoviral vector allowing a single promoter to drive the expression of two genes, the authors coexpressed in guinea pig hearts the Kir2.1 cardiac inward rectifier potassium channel together with SERCA1. Myocytes isolated from these hearts demonstrated shortened APDs when compared with controls but also displayed larger calcium transients. In vivo, this dual gene therapy approach resulted in abbreviation of the QT interval with preservation of contractility.

The rational for using SERCA in the dual gene therapy strategy, described above, originates from previous studies showing the ability of SERCA overexpression to augment cardiac contractility by increasing sarcoplasmic reticulum calcium loading (14). Interestingly, overexpression of SERCA alone (4, 44) also resulted in a favorable electrophysiological effect manifested by shortening of APD and a significant reduction in the incidence of aftercontractions in the transfected myocytes.

Localized versus global treatment. Somatic gene therapy, as shown in the proof-of-concept studies described above, provides a conceptually attractive strategy for modifying the global cardiac electrophysiological substrate in disease states such as the inherited and acquired long QT syndromes. However, a number of important obstacles related to the inability to achieve widespread delivery and long-term activity may limit this approach in the near future. Perhaps more appealing targets in the short term may be arrhythmias in which localized manipulation of the electrophysiological substrate may be sufficient to allow effective treatment.

The generation of a biological pacemaker represents one possible application for local gene delivery. Other potential targets include treatment of focal tachyarrhythmias or reentrant arrhythmias with relatively narrow isthmuses. In a recent study, Burton et al. (3) investigated the effect of overexpression of the cardiac potassium channel missense mutation Q9E-hMiRP1. This gene mutation is one of the known causes of the long QT syndrome and results in diminished potassium currents following clarithromycin administration. In vitro transfection of the Q9E-hMiRP1 gene resulted in a clarithromycin-induced reduction of the potassium outward current in the transfected cells when compared to wild-type hMiRP1 overexpression. With the utilization of a novel gene delivery technique, both plasmids were injected locally into the pig’s atrial myocardium with 15% of the atrial cells being transfected. The authors (3) conclude that overexpression of this mutated channel gene may have an inducible localized class III-like antiarrhythmic effect on the atrial tissue that may be used in the future for the treatment of reentrant atrial arrhythmias.

Another particular attractive target for local gene therapy may be to selectively modify the conduction properties of the AV node. This may bring a unique value to the treatment of atrial fibrillation. Atrial fibrillation is the most common sustained rhythm disorder and is responsible for considerable morbidity, mortality, and medical costs (33). Although multiple mechanisms may be involved in the genesis of atrial fibrillation, the end result is characterized by the rapid and irregular activation of the atrium (400–600 pulses per minute). Many of these impulses may travel to the ventricle via the AV node resulting in a rapid and irregular ventricular rate. Ventricular rate control, therefore, represents one of the most important objectives in the clinical management of atrial fibrillation patients, and therapies aiming to achieve this goal include pharmacotherapy or AV nodal ablation and ventricular pacing. The latter strategy is highly effective but results in lifelong pacemaker dependency.

The feasibility of using gene therapy for AV nodal modification in an attempt to control the ventricular rate during atrial fibrillation was recently demonstrated by Donahue et al. (5). Using adenoviral gene delivery selectively to the AV nodal
region via the coronary circulation, these investigators demonstrated that the AV nodal conduction properties could be modified by overexpression of an inhibitory G protein (Go_i2). Go_i2 overexpression in the AV nodal cells suppressed baseline atrioventricular conduction and slowed the ventricular rate during atrial fibrillation without producing complete heart block, thus mimicking the effects of β-adrenergic antagonists.

Advantages and shortcomings of the gene therapy approach. The key to success in gene therapy is primarily dependent on the selection of a number of essential elements; an “ideal vector” that can be used to deliver the desired transgene to the relevant tissue. The objective is that the transgene will be expressed in the appropriate quantity, location, and for long enough to exert its beneficial effects. To a large extent, the choice of the specific vector will determine the above properties. It is important to note that only a few vectors, namely recombinant adenoviruses, adeno-associated viruses, and perhaps lentiviral vectors can achieve efficient, high-level transgene expression in postmitotic cells such as cardiomyocytes (38).

After deciding about the specific vector and transgene, the next step involves choosing the appropriate route of delivery. In recent years, the feasibility of a number of methods for in vivo cardiac gene transfer was established. These approaches include intracoronary artery catheter delivery, retroinfusion through the coronary veins, direct injection into the myocardium using an epicardial or endocardial catheter approach, intrapericardial release, and intracavitary catheter delivery during transient cross-clamping of the aorta (14).

The pioneering studies described in the previous sections established the feasibility of gene delivery to modify the excitable properties of the myocardial tissue but also raised several issues that may limit the clinical utility of this approach. These limitations include those that are inherent to other gene therapy strategies such as the possible expression of the transgene in nontarget organs, the potential to trigger autoimmunity, potential toxic effect of the vector or transgene, and host immune response. Besides these pitfalls, the use of gene therapy for the treatment of cardiac arrhythmias may be hampered by a number of specific limitations. First, the limited knowledge of the molecular mechanisms underlying many of the cardiac arrhythmias and the spatial and temporal complexity of ion channel expression in various regions of the hearts may preclude the utilization of a single ion channel transgene. Second, in contrast to other cardiac gene therapy strategies, successful antiarrhythmic treatment would require, in most cases, sustained long-term expression of the transgene (for months and years). Such long-term expression is not feasible with current vector technologies. A third major hurdle relates to the inability to adequately control several other key parameters such as the level of transgene expression within the cells, the number of transfected myocytes, their transmural distribution, and their regional distribution within the heart. Consequently, in vivo myocardial expression using currently avail-

Fig. 3. High-resolution electrophysiological mapping of the human embryonic stem cell-derived cardiac tissue. A: beating tissue plated on a microelectrode array plate. B: electrograms recorded simultaneously from all 60 electrodes. C: local activation times determined at all electrodes color coded and used to generate high-resolution activation maps demonstrating the development of stable pacemaking activity (red area in the map) and a functional conducting tissue.
able viral vectors is not predictable, is relatively short-lived, is inhomogeneous, may lead to increased dispersion of different electrophysiological properties, and may actually facilitate the generation of arrhythmias. In that respect, the degree of coupling between the myocytes may have an important effect on this arrhythmogenic risk because the electrotonic currents generated between the cells would tend to reduce the inhomogeneities of repolarization generated by the heterogenous gene expression between neighboring cells.

CELL THERAPY FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

An alternative approach that can overcome some of the aforementioned shortcomings of gene therapy may be the use of genetically modified cell grafts that can be initially transfected ex vivo with excellent long-term efficiency and then transplanted to the in vivo heart. Conceptually, cell therapy can be applied for the treatment of cardiac arrhythmias at three different levels: 1) to replace absent or malfunctioning cells of the conduction system, 2) to modify the myocardial electrophysiological substrate by using cell grafts genetically engineered to express specific ionic channels, which can couple and modify the electrophysiological properties of host tissue through electrotonic interactions, and 3) to modify the myocardial environment by local secretion of specific recombinant proteins.

Processes of tissue loss or dysfunction that occur at critical sites in the conduction system may lead to inefficient electrical impulse initiation or conduction. This may ultimately result in severe bradycardia requiring the implantation of a permanent electronic pacemaker. A possible novel therapeutic approach for this situation may be the establishment of a biological pacemaker using the gene therapy strategies described above. An alternative strategy may be to restore the normal function of the conduction system by transplantation of the appropriate cardiac cell populations (pacemaker cells, specialized conduction system cells, etc.). This futuristic strategy would require the following steps: 1) establish the proper cell sources for transplantation, 2) in vitro assessment of the phenotypic structural and functional properties of the cell grafts, 3) establish transplantation strategies to deliver the cells to the desired locations, and 4) achieve the desired in vivo effect by assuring the survival of the cell grafts, their integration and interactions with host tissue, and their proper function.

A major hurdle for the development of such cell replacement strategies is the paucity of cell sources for human cardiomyocytes. One solution to this cell-sourcing problem may be the use of the recently described human embryonic stem cell lines (13). These unique cell lines have the capability to be propagated in vitro in the undifferentiated state in large quantities and to be coaxed to differentiate to a plurality of cell lineages, including cardiomyocytes (23). More recently, we demon-

Fig. 4. Modulation of the electrophysiological substrate of cardiac cultures by fibroblasts, transfected to express a voltage-sensitive potassium channel Kv1.3. A: distribution of the transfected fibroblast clusters (white clusters) within the coculture. B: activation map of the cardiomyocyte culture before fibroblast seeding showing homogeneous conduction. C: activation map a number of days following fibroblast seeding showing the development of conduction block with the activation wave (white arrow) propagating around the conduction block generated by the fibroblast. D: resumption of uniform conduction following the application of the Kv1.3 blocker charibdotoxin. Adapted from Feld et al. (11).
strated that this differentiating system is not limited to the generation of isolated cardiac cells, but rather a functional cardiac syncytium is generated (Fig. 3) with a stable pacemaker activity and electrical propagation (22) that can also respond to adrenergic and cholinergic stimuli. The ability to generate, ex vivo, different subtypes of human cardiomyocytes (with pacemaking-, atrial-, ventricular-, or Purkinje-like phenotypes) (32) that could lend themselves to genetic manipulation may be of great value for future cell therapy strategies aiming to regenerate or to modify the conduction system.

A major prerequisite for the successful application of the above-mentioned approach is the ability of the grafted cells (pacemaker cells or conductive tissue) to integrate structurally and functionally with host tissue. To this end, it is interesting to note that in our preliminary studies, the human ES cell-derived cardiomyocytes were able to integrate ex vivo both structurally and functionally with preexisting cardiac tissue and to generate a single functional syncytium (21).

Whereas it is not surprising that cardiomyocyte cell grafts can form intercellular connections with host cells (17), recent studies have demonstrated that other cell types such as fibroblasts (10, 12, 40) are also capable of forming gap junctions with host cardiomyocytes and that specific electrotonic interactions can be generated between these cells. Based on the above concepts, we have recently examined the feasibility of using genetically engineered fibroblasts, transfected to express the voltage-gated potassium channel Kv1.3, to modify the electrophysiological properties of cardiomyocyte cultures (11). In this study, a high-resolution multielectrode array mapping technique was used to assess the electrophysiological and structural properties of primary neonatal rat ventricular cultures. The transfected fibroblasts were demonstrated to significantly alter the electrophysiological properties of the cardiomyocyte cultures. These changes were manifested by a significant reduction in the local extracellular signal amplitude and by the appearance of multiple local conduction blocks (Fig. 4). The location of all conduction blocks correlated with the spatial distribution of the transfected fibroblasts as assessed by vital staining and all of the electrophysiological changes were reversed following the application of a specific Kv1.3 blocker.

The possible utilization of cell grafts (fibroblasts, different stem cell derivatives, or other cell sources) that can be genetically manipulated ex vivo to display specific electrophysiological characteristics and then grafted to the in vivo heart may posses a number of theoretical advantages over direct gene therapy. These advantages may be related to a better efficiency and control of the transfection process ex vivo, the ability to screen the phenotypic properties of the cells before transplantation, and the possible achievement of long-term effect because cardiac cell grafts were demonstrated to survive for prolonged periods following transplantation (31). Yet, determining the optimal way for the delivery of the cells, controlling their survival following transplantation, assuring appropriate integration of the cells with host tissue, and developing means to control the required electrophysiological effect are all important obstacles for the future use of this approach as a therapeutic strategy.

**Indirect antiarrhythmic potential of gene and cell therapy strategies.** A number of myocardial pathologies such as ischemic heart disease, heart failure, and local myocardial autonomic denervation have been implicated in the pathogenesis of the different cardiac arrhythmias. Somatic gene and cell therapies have been suggested as novel treatment modalities for the aforementioned disorders by targeting the abnormal cardiac structure (promoting angiogenesis, sympathetic reinnervation, or preventing restenosis) or function (increasing contractility) as discussed below.

Ischemic heart disease represents one of the most important conditions predisposing to arrhythmias. A variety of preclinical and clinical studies have demonstrated the potential utility of gene therapy in the management of chronic ischemic patients through the local secretion of angiogenic growth factors such as vascular endothelium growth factor (VEGF) and fibroblast growth factor (17). Cell therapy strategies may similarly play a dual role in promoting angiogenesis. First, cells transplanted ex vivo may be used for sustained local release of recombinant proteins with angiogenic properties following in vivo grafting. Second, transplantation of specific cell types such as endothelial progenitor cells may contribute directly to the neovascularization process.

Similarly, somatic gene and cell therapies may also play an important role in the future treatment of heart failure. The improved understanding of the molecular pathways involved in the development of heart failure allow definition of several molecular targets for gene therapy to improve systolic and diastolic properties of failing myocytes (14, 17). These strategies focus on modulating calcium homeostasis, manipulating the β-adrenergic receptor signaling pathways, and improving cardiomyocyte resistance to apoptosis. Similarly, cellular cardiomyoplasty and tissue engineering approaches to regenerate functional myocardium also represent a novel approach for the treatment of heart failure (37).

Successful application of the above-mentioned strategies for the treatment of ischemic heart disease, heart failure, and other myocardial pathologies may also result in a secondary favorable effect on the myocardial electrophysiological substrate. This in turn may lead to a decreased tendency to the development of the typical arrhythmias commonly observed during the clinical course of these disease states.

In summary, cardiac arrhythmias represent a major cause of world-wide morbidity and mortality. Although marked progress has been achieved in several of the pharmacological and nonpharmacological therapeutic modalities for these rhythm disorders in recent years, there is still a need for the development of new therapeutic paradigms that are more targeted and associated with fewer side effects. Improvement in the understanding of the mechanisms underlying many of these arrhythmias and the development of molecular and cellular tools suggest a future role for gene and cell therapies for the treatment of these different rhythm disorders. Nevertheless, bridging the gap between the proof-of-concept and the clinical application will require important methodological developments as well as extensive animal experimentation.

**GRANTS**

This research was supported in part by the Nahum Guzik research fund.

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