INTRODUCTION

Despite recent advances in the treatment of atherosclerosis and congestive heart failure, morbidity and mortality from cardiac disease continue to be a significant problem in the developed world. Cardiac rhythm disorders contribute substantially to this problem. In the United States, cardiac arrest accounts for at least 220,000 deaths per year, more than 10% of the total deaths for the entire country (1). Atrial fibrillation affects more than 2 million people in the United States, including 5–10% of people over the age of 65 and 10–35% of the 5 million patients with congestive heart failure (2). Furthermore, other types of arrhythmias account for thousands of emergency room visits and hospital admissions each year.

The lack of effective treatment options for common arrhythmias contributes to the continued prevalence of arrhythmic disease. Modern treatment of cardiac arrhythmias is limited to pharmacotherapy, radiofrequency ablation, and implantable devices. Although effective at reducing some arrhythmic events, antiarrhythmic medications often have adverse systemic effects, and their proarrhythmic tendencies may increase mortality in many situations (3). Radiofrequency ablation cures a limited number of arrhythmias and has become standard treatment for patients with atrioventricular (AV) node reentry tachycardia, accessory pathway-mediated tachycardia, and atrial flutter. Recent advances in technology have expanded the indications for ablation; however, the most problematic arrhythmias, atrial fibrillation and infarct-related ventricular tachycardia, are not effectively managed with ablation. Device-based therapies (pacemakers and defibrillators) correct bradyarrhythmias and can be lifesaving for patients with tachyarrhythmias; however, devices do not completely emulate normal sinus nodal function for patients with bradyarrhythmias, and they do not prevent tachyarrhythmias. In addition, devices are associated with a lifetime commitment to repeated procedures, significant expense, and potentially catastrophic complications such as infection, cardiac perforation, and lead failure.

Over the last several decades, tremendous advances have been made in understanding the pathophysiologic and genetic bases of cardiac arrhythmias. These advances, coupled with the inadequacies of current treatment options for cardiac arrhythmias, have prompted the search for genetic strategies to treat these common diseases. In this review, we will discuss the underlying pathophysiology of arrhythmias and the current status of gene therapy for the treatment of arrhythmias.

NORMAL CARDIAC ELECTROPHYSIOLOGY

The cellular basis for all cardiac electrical activity is the action potential (AP). The AP is usually divided into five phases (0–4) (Fig. 1). Each phase is defined by the cellular membrane potential and the activity of ion
channels that affect that potential. Phase 4 is the resting baseline. During this phase, the dominant ionic current is the inward rectifier potassium current, \( I_{K1} \). Phase 0 is the initial membrane depolarization initiated by activation of the sodium current, \( I_{NA} \). Phase 1 is a quick dip in the potential from the peak achieved at the end of phase 0. Activation of transient outward potassium (\( I_{to1} \)) and chloride (\( I_{to2} \)) currents and inactivation of the sodium current are responsible for phase 1 of the AP. During phase 2, the plateau period, the L-type calcium current (\( I_{CaL} \)) maintains the positive depolarization, and the rapid and slow components of the delayed rectifier potassium current (\( I_{Ks} \) and \( I_{Kr} \)) try to force repolarization. In phase 3, the potassium current ultimately dominates; the calcium current is inactivated; and the membrane potential returns to the baseline of phase 4. The membrane potential during each phase of the AP is an unstable equilibrium between positive and negative currents, and any slight perturbation of this balance can affect the shape of the AP and potentially cause an arrhythmia. The genes responsible for most of the currents participating in the AP have been identified (Fig. 2), and mutations of these genes cause several inherited arrhythmias.

In the later stages of phase 4, normal atrial and ventricular cells are quiescent but can generate an AP if stimulated by an adjacent cell. Specialized conducting tissue in the sinoatrial (SA) node, the AV node, and the His–Purkinje system has intrinsic automaticity; therefore, these cells gradually depolarize during phase 4 until they reach a membrane potential that activates \( I_{NA} \) at which point an AP is started. Because the cells in the SA node usually depolarize at a faster rate, the normal cardiac impulse radiates from the SA node. All cells are refractory to stimulation during phases 1–3 of the AP (Fig. 1).

In the later part of phase 3, a stronger than normal pulse can generate an AP, so this portion of the cardiac cycle is called the relative refractory period. Because cells are impervious to excitation during phases 1 and 2 and the early part of phase 3, this part of the cycle is called the absolute refractory period. The effective refractory period comprises the entire period during which the generation of an AP is impaired.

The AP is transmitted from one cell to the next via gap junctions. Within cardiac tissue, the direction of current flow is anisotropic (e.g., current flow in a longitudinal direction is faster than flow in a transverse direction) because of the distribution of gap junctions. Of the gap junction connections, about 20% are side-to-side, 33% are end-to-end, and the remaining 47% are end-to-side (4). The average myocyte is connected to about 10 neighboring myocytes.

**PATHOPHYSIOLOGY OF INHERITED ARRHYTHMIAS**

**The Long QT Syndrome**

The long QT syndrome was the first arrhythmic disorder characterized at the genetic level. In genetic studies of the long QT syndrome, several potassium channel subunits have been identified, and the interactions of components of the AP are now better understood. The syndrome has been associated with mutations of the sodium channel a-subunit gene and mutations of the genes for several potassium channel subunits (Table 1). The underlying