Abnormal excitability of myocardial cells may give rise to ectopic beats and initiate re-entry around an anatomical or functional obstacle. As K\textsuperscript{+} currents control the repolarization process of the cardiac action potential (AP), the K\textsuperscript{+} channel function determines membrane potential and refractoriness of the myocardium. Both gain and loss of the K\textsuperscript{+} channel function can lead to arrhythmia. The former because abbreviation of the active potential duration (APD) shortens refractoriness and wave length, and thereby facilitates re-entry and the latter because excessive prolongation of APD may lead to torsades de pointes (TdP) arrhythmia and sudden cardiac death. The pro-arrhythmic consequences of malfunctioning K\textsuperscript{+} channels in ventricular and atrial tissue are discussed in the light of three pathophysiologically relevant aspects: genetic background, drug action, and disease-induced remodelling. In the ventricles, loss-of-function mutations in the genes encoding for K\textsuperscript{+} channels and many drugs (mainly hERG channel blockers) are related to hereditary and acquired long-QT syndrome, respectively, that put individuals at high risk for developing TdP arrhythmias and life-threatening ventricular fibrillation. Similarly, down-regulation of K\textsuperscript{+} channels in heart failure also increases the risk for sudden cardiac death. Mutations and polymorphisms in genes encoding for atrial K\textsuperscript{+} channels can be associated with gain-of-function and shortened, or with loss-of-function and prolonged APs. The block of atrial K\textsuperscript{+} channels becomes a particular therapeutic challenge when trying to ameliorate atrial fibrillation (AF). This arrhythmia has a strong tendency to cause electrical remodelling, which affects many K\textsuperscript{+} channels. Atrial-selective drugs for the treatment of AF without affecting the ventricles could target structures such as \(I_{Kur}\) or constitutively active \(I_{K,ACh}\) channels.

**Keywords**

Potassium channels; Ventricular fibrillation; Torsades de pointes; Atrial fibrillation; Genetic polymorphism; Drugs; Remodelling

**Introduction**

Regular excitation is generated in the sino-atrial node and spreads throughout the heart in an orderly manner, whereas disorganization of electrical activity is the basis of atrial or ventricular fibrillation. Arrhythmias are caused by the perturbation of physiological impulse formation, impaired impulse conduction, or disturbed electrical recovery. Abnormal excitability of myocardial cells may give rise to ectopic beats and initiate re-entry around an anatomical or functional obstacle (reviewed in Jalife\textsuperscript{1}).

The long-lasting action potential (AP) of the working myocardium maintains a refractory state for as long as the muscle contracts and thus ensures rhythmic pump function. Typical cardiac APs consist of five distinct phases (Figure 1). In phase 0, Na\textsuperscript{+} influx triggers a rapid depolarization followed by an early fast repolarization phase (phase 1) and a plateau phase (phase 2), in which repolarization is slowed due to the activation of inward Ca\textsuperscript{2+} current. During the final rapid repolarization phase (phase 3), membrane potential returns to the resting level (phase 4). The various potassium (K\textsuperscript{+}) currents are repolarizing outward currents. Their major contributions to the cardiac AP are control of stable resting membrane potential and termination of the AP.

**Potassium channels**

Ions traverse the lipid bilayer of the plasmalemma along their electrochemical gradient via hydrophilic ion channels. These ion channels open and close in a voltage- and time-dependent manner (activation, inactivation, or deactivation) and pass ions only in the open state. After-repolarization, some channels must recover from inactivation before they become available for re-opening, and during this time, the myocardial cells remain refractory for re-excitation.

Potassium channels form the largest family of ion channel proteins. Determining and depending on membrane
Potassium channels—differences between atrium and ventricle

Despite general similarity in the mechanisms of AP generation, APs exhibit distinct shapes in atrial and ventricular myocardium (Figure 1). The most striking differences are that (i) the plateau phase occurs at more negative potentials and (ii) overall APD is shorter in atrial when compared with ventricular cells. These differences are due to the non-uniform distribution of ion channels, including K⁺ channels. For instance, $I_{Kr}$ is detected only in atrial but not in ventricular myocytes, although the Kv1.5 protein is abundant in both chambers. Rapid activation of $I_{Kr}$ in the positive potential range following the AP upstroke may offset depolarizing $I_{Ca,L}$ and hence leads to the less positive plateau phase in atrial than ventricular cells. The acetylcholine-activated inward rectifying current $I_{K,ACH}$, too, is not detected in ventricle.

Contribution of K⁺ channel function to arrhythmias

Because of their impact on membrane potential and refractoriness, K⁺ currents play a prominent role in arrhythmogenesis. An increase in K⁺ currents abbreviates APD and thereby facilitates re-entry. Conversely, impaired K⁺ current amplitudes prolong APD with contrasting outcome, whereas moderate prolongation maintains the myocardium in a refractory state and is actually considered an anti-arrhythmic mechanism (class III anti-arrhythmic action according to the classification of Vaughan Williams), excessive prolongation predisposes to early after-depolarizations that may trigger torsades de points arrhythmias (TdP). This form of arrhythmia may either resolve spontaneously or deteriorate into ventricular fibrillation causing sudden cardiac death.
Therefore, both gain and loss of K\(^+\) channel function can lead to arrhythmia. Malfunction of K\(^+\) channels may be due to diverse causes such as mutations in the encoding genes for any of the subunits, drug actions, or remodelling in adaptation to heart disease. These three factors will be discussed first for ventricular and, subsequently, for atrial arrhythmias.

**Ventricular arrhythmias**

**Arrhythmogenic potential of K\(^+\) channel mutations**

The number of mutations identified in K\(^+\) channel-encoding genes that have been related to arrhythmias is increasing rapidly. The consequences of missense mutations include faulty protein folding and disturbed co-assembly between subunits and therefore early degradation, disruption of trafficking or defects in plasmalemmal integration, altered voltage dependency, or impaired ion selectivity of the channel. These adverse effects reduce repolarizing K\(^+\) currents and thereby delay the repolarization process. The resulting long-cardiac APD or long-QT interval in the electrocardiogram predisposes a patient to TdP arrhythmias. Therefore, patients with the hereditary long-QT syndrome (LQTS) are at increased risk for sudden cardiac death. Mutations in the genes for KvLQT1 (\(i_{K}\)) and hERG (\(i_{Kr}\)) account for 80–90% of all hereditary LQTS, although mutations that cause LQTS were also discovered in other ion channels, in ion-handling, or associated proteins (for recent review, see Saenen and Vrints\(^3\)). As mentioned above, rare gain-of-function mutations in hERG and KvLQT1 shorten cardiac APs and also give rise to potentially lethal arrhythmias (short-QT syndrome).

**Arrhythmogenic potential of K\(^+\) channel blockers**

Many drugs used in cardiac and non-cardiac diseases prolong APs and give rise to acquired LQTS. Besides underlying heart disease, several factors predispose to drug-induced TdP. These include female gender, long-QT interval at baseline, bradycardia, low K\(^+\) and Mg\(^{2+}\) plasma levels, old age, and the increased incidence of heart disease. Similar to congenital LQTS, the actual incidence of drug-induced TdP is low and that of proven drug-associated syncope or sudden cardiac death is even lower.\(^4\) The absolute incidence of cardiotoxicity of any drug must be judged in relation to the severity of the treated disease: a high risk may be perfectly acceptable when treating a life-threatening condition, whereas even a very low incidence as reported for non-sedating antihistaminics is not acceptable as these drugs are widely prescribed for minor complaints. Nevertheless, the increasing number of drugs recognized to cause acquired LQTS has become a concern for patients, physicians, and safety regulation authorities.

Almost all drugs with reported QT-prolongation and TdP are blockers of potassium channels, particularly \(i_{Kr}\) channels.\(^5\) In fact, hERG channels are sensitive to block by a surprisingly large variety of agents, and block of hERG channels is so common that drug safety agencies require data on hERG channel block for new drugs when filed for registration. hERG screening tests are performed at very early stages in drug development and even promising new compounds are usually abandoned when testing positive. This is not always justified, because the block of \(i_{Kr}\) may in part be compensated by changes in opposing currents (increase in ‘repolarization reserve’).\(^6,7\)

Although there appears to be no strict concentration–response relationship for triggering TdP, drug plasma concentrations should not be allowed to rise above the therapeutic level and interference with drug metabolism or excretion should be avoided.

Even in asymptomatic patients, a genetic predisposition related to congenital LQTS may exacerbate drug action that turns the otherwise borderline QT interval into overt prolongation. Some polymorphisms, for instance, in the gene encoding for a common ancillary subunit (i.e. the KCNE2 gene) have normal function at baseline, but are susceptible to block by sulfamethoxazole that imposes no prolongation in healthy individuals.\(^8\)

Arrhythmogenic exacerbation frequently occurs due to pharmacokinetic interactions by co-administered drugs that interfere with biotransformation and excretion of a previously tolerated drug resulting in excessive plasma concentrations. If the parent compound is more effective than the metabolite in producing a pro-arrhythmic event, inhibition of drug metabolizing enzymes will enhance arrhythmogenicity. Conversely, if the metabolite is more effective, induction of enzymes is pro-arrhythmogenic. The antifungal agent, ketoconazole for instance, interferes with biotransformation of the non-sedating antihistaminic terfenadine into a metabolite that does not prolong the AP. Thus, co-medication of the two drugs results in a high plasma concentration of terfenadine leading to acquired LQTS. Such an interaction applies for many drugs that inhibit cytochrome P450 enzymes and even grapefruit juice may interfere (reviewed by Priori et al.\(^4\)).

Intuitively, cardiac drugs and, in particular, anti-arrhythmics that prolong APD (class III action according to the Vaughan Williams classification) are expected to produce an increased risk not only because of their mechanism of action but also because they are given to patients with diseased hearts that are per se at a high risk for rhythm disturbances. However, drugs for treating non-cardiac diseases such as antihistamines, antibiotics, antipsychotic, or prokinetic agents also may increase risk. Comprehensive lists of drugs with reported or suspected risk for TdP are available in the internet (for instance, http://www.qtdrugs.org/).

**Disease-induced remodelling**

Heart failure is associated with a plethora of ventricular ionic changes that predispose to arrhythmias (for recent review, see Nass et al.\(^9\)). These remodelling processes include electrophysiological changes that lead to APD prolongation, especially in the endocardial region. We and others have shown that \(i_{Kr}\) amplitude is down-regulated, but other K\(^+\) currents (\(i_{Ks}\), \(i_{Kr}\), and \(i_{K1}\)) are depressed as well.\(^10,11\) Reduced K\(^+\) currents increase the propensity for early after-depolarizations, dispersion of repolarization, and ventricular arrhythmias, thereby significantly increasing the risk of sudden cardiac death in heart failure patients. In contrast, delayed after-depolarizations occurring at high intra-cellular Ca\(^{2+}\) load may initiate triggered activity and induce ventricular tachycardia, particularly in non-ischaemic heart failure patients, and decreased \(i_{Kr}\) enhances the propensity for triggered activity.\(^12\) K\(^+\) channel down-regulation also contributes to enhanced sensitivity of failing myocardium to other triggering factors such as hypokalaemia, ischaemia, and anti-arrhythmic agents with
Arrhythmias. Recent evidence from a genome-wide association study identified three novel single nucleotide polymorphisms loss-of-function mutation, it was demonstrated that mice expressing the mutated channel in cell lines and verifying the association with AF exhibited—with one exception—gain-of-function, leading to abbreviation of the APD and facilitating re-entry. In the individual studies, gain-of-function was verified by expressing mutated channels in cell lines and measuring increased K⁺ current density when compared with wild-type channels (reviewed in Roberts15). For the loss-of-function mutation, it was demonstrated that mice expressing the mutated channels had long APs with early after-depolarizations and were more prone to stress-induced arrhythmias.16 Recent evidence from a genome-wide association study identified three novel single nucleotide polymorphisms that confer predisposition to AF.17 Moreover, a systematic candidate gene-based analysis of the gene encoding for hERG discovered a hitherto unknown variant, which strongly associated with AF.18

Arrhythmogenic potential of K⁺ channel mutations

In contrast to the vast majority of several hundreds of known K⁺ channel mutations being associated with LQTs, there are, but a few, mutations directly linked to familial AF (Table 1). Nevertheless, LQTs patients may also exhibit polymorphic atrial tachyarrhythmias.14 Although in the ventricles loss-of-function mutations predominantly predispose to chaotic electrical activity, the K⁺ channel mutations associated with AF exhibit—with one exception—gain-of-function, leading to abbreviation of the APD and facilitating re-entry. In the individual studies, gain-of-function was verified by expressing mutated channels in cell lines and measuring increased K⁺ current density when compared with wild-type channels (reviewed in Roberts15). For the loss-of-function mutation, it was demonstrated that mice expressing the mutated channels had long APs with early after-depolarizations and were more prone to stress-induced arrhythmias.16 Recent evidence from a genome-wide association study identified three novel single nucleotide polymorphisms that confer predisposition to AF.17 Moreover, a systematic candidate gene-based analysis of the gene encoding for hERG discovered a hitherto unknown variant, which strongly associated with AF.18

Vagal nerve stimulation induces AF because of shortening of the refractory period due to acetylcholine release and subsequent activation of I_{K,ACh}. In analogy, drugs that shorten APD by activating K⁺ currents are expected to predispose to AF. However, much less is known about the actual incidence of drug-induced AF than of TdP in the case of LQTs. As outlined above, prolongation of atrial APD by the block of K⁺ channels, as, for instance, with cesium, may also induce AF;19 however, unlike ventricular fibrillation, this arrhythmias is not immediately life threatening.

Disease-induced remodelling

Arrhythmogenic potential of K⁺ channel mutations

Atrial fibrillation (AF) is initiated when a suitable trigger meets an appropriate substrate. The underlying pathophysiological mechanisms include ectopic electrical activity and single or multiple re-entry circuits. Re-entry often develops in large fibrotic atria associated with valvular disease or heart failure, whereas in seemingly healthy hearts, rapid local ectopic activity initiating in the pulmonary veins can give rise to re-entry circuits.

Table 1

<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>Current</th>
<th>Mutation</th>
<th>Amino acid change</th>
<th>Change</th>
<th>Origin</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNA5 (Kv1.5)</td>
<td>I_{Kur}</td>
<td>1123G→T</td>
<td>E375X</td>
<td>Loss-of-function</td>
<td>Mostly Caucasian</td>
<td>Olson et al.16</td>
</tr>
<tr>
<td>KCNH2 (Kv11.1)</td>
<td>I_{K}</td>
<td>1764C→G</td>
<td>N588K</td>
<td>Gain-of-function</td>
<td>—</td>
<td>Hong et al.29</td>
</tr>
<tr>
<td>KCNQ1 (Kv7.1)</td>
<td>I_{Ks}</td>
<td>418A→G</td>
<td>S140G</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Chen et al.30</td>
</tr>
<tr>
<td>KCNQ1 (Kv7.1)</td>
<td>I_{Ks}</td>
<td>491C→A</td>
<td>V141M</td>
<td>Gain-of-function</td>
<td>Caucasian</td>
<td>Hong et al.31</td>
</tr>
<tr>
<td>KCNQ1 (Kv7.1)</td>
<td>I_{Ks}</td>
<td>40C→T</td>
<td>R144</td>
<td>Gain-of-function (stretch)</td>
<td>—</td>
<td>Otway et al.32</td>
</tr>
<tr>
<td>KCE2</td>
<td>I_{Ks}</td>
<td>79C→T</td>
<td>R27C</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Yang et al.33</td>
</tr>
<tr>
<td>KCNJ2 (Kir2.1)</td>
<td>I_{K1}</td>
<td>277G→A</td>
<td>V93I</td>
<td>Gain-of-function</td>
<td>Chinese</td>
<td>Xia et al.34</td>
</tr>
</tbody>
</table>
with the actually measured changes in the current amplitude, indicating that AF-induced channel dysregulation must have occurred. Although ancillary subunits of K\(^+\) channels profoundly affect their expression and biophysical properties, little is presently known about AF-induced remodelling in these regulatory proteins.

The K\(^+\) currents, \(I_{\text{Kur}}\) and \(I_{\text{K,ACH}}\), have recently attracted special attention because they are confined to atrial myocardium and hence their blockade is not expected to cause pro-arrhythmic effects in the ventricles. In the past decade, several new compounds were developed for the prolongation of effective refractory period by the block of \(I_{\text{Kur}}\) however, the efficacy of most of these new drugs in converting AF back to SR has been rather disappointing, possibly due to low \(I_{\text{Kur}}\) amplitude in AF. With regard to \(I_{\text{K,ACH}}\) channels, we have recently reported that these channels develop constitutive activity during human AF, i.e. these channels become activated, despite the absence of stimulating acetylcholine.\(^\text{25}\) Constitutively active \(I_{\text{K,ACH}}\) can hyperpolarize the membrane and hence contribute to persistence of AF by stabilization of rotors. Therefore, selectively targeting constitutively active \(I_{\text{K,ACH}}\) channels only may preserve physiological stimulation by vagal nerves and could serve as a promising remodelling-related drug target.

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