Two components of delayed rectifier K^+ current in heart: molecular basis, functional diversity, and contribution to repolarization[1]

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ABSTRACT

Delayed rectifier K^+ current (I_K) is the major outward current responsible for ventricular repolarization. Two components of I_K (I_{Kr} and I_{Ks}) have been identified in many mammalian species including humans. I_{Kr} plays a pivotal role in normal ventricular repolarization. A prolongation of action potential duration (APD) under a variety of conditions would favor the activation of I_{Ks} so that to prevent excessive repolarization delay causing early afterdepolarization. The pore-forming α subunits of I_{Kr} and I_{Ks} are composed of HERG (KCNH2) and KvLQT1 (KCNQ1), respectively. KvLQT1 is associated with a function-altering β subunit, minK to form I_{Ks}. HERG may be associated with minK (KCNE1) and/or minK-related protein (MiRP1) to form I_{Kr}, but the issue remains to be established. I_{Ks} is enhanced, whereas I_{Kr} is usually attenuated by β-adrenergic stimulation via cyclic adenosine 3',5'-monophosphate (cAMP)/protein kinase A-dependent pathways. There exist regional differences in the density of I_{Kr} and I_{Ks} transmurally (endo-epicardial) and along the apico-basal axis, contributing to the spatial heterogeneity of ventricular repolarization. A decrease of I_{Kr} or I_{Ks} by mutations in either HERG, KvLQT1, or KCNE family results in inherited long QT syndrome (LQTS) with high risk for Torsades de pointes (TdP)-type polymorphic ventricular tachycardia and ventricular fibrillation. As to the pharmacological treatment and prevention of ventricular tachyarrhythmias, selectively block of I_{Ks} is expected to be more beneficial than selectively block of I_{Kr} in terms of homogeneous prolongation of refractoriness at high heart rates especially in diseased hearts including myocardial ischemia.

INTRODUCTION

Delayed rectifier K^+ current (I_K) is the major outward current involved in ventricular repolarization. I_K in the heart has two major components with different biophysical properties and different drug sensitivities[1]. A rapidly activating component (I_{Kr}) rectifies inwardly at depolarized membrane potential due to C-type inactivation, whereas a slowly activating component (I_{Ks}) has almost linear current voltage-relationship. I_{Kr} is highly sensitive, but I_{Ks} is resistant to the blockade by methanesulfonalinide class III antiarrhythmic agents[1].

In most mammalian species, I_{Kr} plays a pivotal role in normal ventricular repolarization. A lengthening

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of cardiac action potential duration (APD) under a variety of conditions would favor I_{Ks} activation so that to prevent excessive APD prolongation and generation of early afterdepolarization (EAD)[2,3]. A decrease of I_{Kr} or I_{Ks} by mutations of their pore-forming α subunits (HERG and KvLQT1) or regulatory β subunits (KCNE family) underlies the inherited long QT syndrome (LQTS) with increased risk of Torsades de Pointes (TdP)-type polymorphic ventricular tachycardia and ventricular fibrillation (VF)[4].

The present review summarizes recent progress in our understanding on I_{Kr} and I_{Ks} in terms of molecular basis, biophysical and pharmacological properties, functional roles in ventricular repolarization of normal and diseased hearts.

I_K IN MAMMALIAN VENTRICULAR CELLS

Functional properties The existence of the two components of I_K (I_{Kr} and I_{Ks}) has been recognized in many mammalian species including human. There are substantial species differences in their functional properties. Activation and deactivation kinetics of I_{Kr} and I_{Ks} of ventricular myocytes from dogs, rabbits, and human (undiseased hearts) are compared (Tab 1)[2,5-8]. Compared with guinea pig[1], I_{Kr} deactivates more slowly and I_{Ks} deactivates more rapidly in other animal species and human. Lu *et al* compared the accumulation of I_{Ks} at high stimulation rates in guinea pig and rabbit ventricular myocytes[9]. After thirty 200-ms depolarization pulses to +30 mV applied at 3.0 Hz to mimic high frequency ventricular excitation, I_{Ks} tail in guinea pig was markedly augmented (from 2.3 pA/pF to 3.5 pA/pF), whereas the current amplitude in rabbit was little affected[9]. This can be explained by a longer time required for full deactivation of I_{Ks} during electrical diastole in guinea pig than in rabbit.

There are considerable species differences between the relative expression of I_{Kr} and I_{Ks} in ventricular myocytes. The relative current density of I_{Ks} to I_{Kr} in guinea pig is 11.4 (tail current measured at -40 mV after 7.5-s depolarization to +60 mV)[1]. In dogs, the ratio is about 5.0 (tail current measured at -40 mV after 3-s depolarization to +65 mV)[10]. In rabbits, we demonstrated that the ratio was about 3.0 at the basal and about 0.5 at the apical myocytes (tail current measured at -40 mV after 3-s depolarization to +40 mV)[3]. However, caution should be taken when these values are extrapolated to the intact heart. The relative contribution of I_{Ks} in ventricular repolarization (APD is less than several hundred milliseconds) must be much less than the above-described ratio of I_{Ks}/I_{Kr}.

Tab 1. Comparison of the activation and deactivation time constants of I_{Kr} and I_{Ks} in mammalian ventricular myocytes[2,5-8].

Species	Current	Activation/ms	Deactivation/ms
Rabbit	I_{Kr}	35±3	641±29
			6531±343
	I_{Ks}	888±48	57±4
Dog	I_{Kr}	53±5	360±26
			3310±280
	I_{Ks}	1045±103	86±12
Human	I_{Kr}	31±7	600±53
			6297±875
	I_{Ks}	903±101	122±11

Values are expressed as mean±SD. Activation time kinetics for I_{Kr} and I_{Ks} were measured as tail current at -40 mV after test pulses to +30 mV (+50 mV for human I_{Ks}) with gradually increasing durations. Deactivation kinetics of I_{Kr} and I_{Ks} were measured as tail current at -40 mV after a long test pulse to +30 mV (+50 mV for human I_{Ks}). The activation time constants of I_{Kr} and I_{Ks} and the deactivation time constants of I_{Ks} were approximated by a single-exponential function, while the deactivation time constants of I_{Kr} were approximated by a double-exponential function.

In mouse and rat, ventricular repolarization depends primarily on a large transient outward K^+ current (I_{to}), and the relative contribution of I_{Kr} and I_{Ks} is small. The contribution of I_{to} to ventricular repolarization in dog, rabbit and human is much less, and I_{to} is undetectable in guinea pig. These species differences should be taken into account in clinical implications of the experimental results.

Regional difference There exists a prominent transmural electrophysiological gradient in the mammalian ventricles[7,11-13]. In dog ventricles, I_{Ks} density was shown to be significantly less in the midmyocardial ventricular (M) cell compared with sub-epicardial and sub-endocardial cells (0.92 pA/pF *vs* 1.99 pA/pF and 1.83 pA/pF, respectively), whereas I_{Kr} density was comparable among the three layers[12]. The lower I_{Ks} density is supposed to contribute to the longer APD in M cells. In the rabbit ventricle, I_{Ks} density in sub-epicardial myocytes was shown to be greater than that in sub-endocardial myocytes (1.1 pA/pF *vs* 0.43 pA/pF), whereas their I_{Kr} densities were similar (0.31 pA/pF *vs*

0.36 pA/pF)[7]. In guinea pig, I_{Kr} and I_{Ks} densities in sub-endocardial myocytes are both smaller than those in mid-myocardial and sub-epicardial myocytes[13].

However, these observations obtained in voltage-clamp experiments in isolated ventricular myocytes can not be extrapolated directly to the intact heart. The transmural gradient of refractoriness observed in the animal hearts (including dogs) is moderate or minimal[14-16]. The apparent discrepancy between *in vivo* and *in vitro* experiments could be attributed to electrotonic cell-cell interactions, an influence of mechanical stress to the ventricular wall, or other neurohumoral factors.

A substantial electrophysiological gradient was also recognized along the apico-basal axis of ventricles in some animal species[16,17]. In the isolated Langendorff-perfused rabbit heart, the QT interval of ventricular surface electrograms was shown to be significantly longer in the apex than in the base, and the regional difference was enhanced by the application of methanesulfonalinide Class III antiarrhythmic drugs[17]. In the intact canine heart *in vivo*, the effective refractory period (ERP) was shown to be longer in the apex than in the base, and application of dofetilide enhanced the gradient through a greater ERP prolongation in the apex than in the base[16].

In rabbit ventricular myocytes, Cheng *et al* demonstrated significant differences in I_K density between the base and the apex; the total I_K density was higher in the base than in the apex (2.09 pA/pF *vs* 1.56 pA/pF), and the I_{Ks} density was also higher in the base than in the apex (1.43 pA/pF *vs* 0.40 pA/pF), whereas the I_{Kr} density was lower in the base than in the apex (0.66 pA/pF *vs* 1.15 pA/pF)[3]. In concordance with this observa-tion, Brahmajothi *et al* reported that the expression of ERG transcript (mRNA) and protein in ferret ventricles was more abundant in the apex than in the base[18]. Recently, interventricular differences of I_K were demonstrated in dog hearts; I_{Ks} density was significantly higher (approximately double) in the right ventricle (RV) than in the left ventricle (LV), whereas I_{Kr} density was comparable in the two ventricles[19].

MOLECULAR BASIS OF I_K AND LONG QT SYNDROME

Molecular basis of I_{Kr} and I_{Ks} The K^+-selective channel encoded by HERG (KCNH2) shows currents similar to native I_{Kr} in terms of the characteristic inward rectification and high sensitivity to La^{3+}[20,21]. HERG is also sensitive to methanesulfonanilide drugs. However, there are some differences between native I_{Kr} and the first HERG clone studied (HERG1): the HERG current expressed in Xenopus oocytes or mammalian cell lines has 4-10 times slower activation and deactivation kinetics than native I_{Kr} in guinea pig ventricular myocytes[1,20]. Additional channel subunits, minK (KCNE1) or MinK-related peptide 1 (MiRP1 or KCNE2) have been identified, which may act as a function-altering β subunit and associate with the pore-forming α subunit, HERG[22-24]. The mixed complexes were shown to form channels quite similar to native I_{Kr} in terms of gating kinetics, unitary conductance, regulation by potassium, and distinctive biphasic inhibition by methanesulfonalinide drugs[23].

Weerapura *et al* compared the biophysical and pharmacological properties of HERG channels expressed in Chinese hamster ovary (CHO) cells with and without MiRP1[25]. The results have revealed that MiRP1 coexpression significantly accelerates inward I_{HERG} deactivation, but does not affect more physiologically relevant outward I_{HERG} deactivation. Native I_{Kr} is activated at more positive potential range than I_{HERG}, but MiRP1 coexpression resulted in a hyperpolarizing shift of I_{HERG} activation. Moreover, the methanesulfonanilide sensitivity of IHERG is indistinguishable from that of native I_{Kr}, and the sensitivity is unaffected by MiRP1 coexpression. These observations seem to be unfavorable for the functional significance of MiRP1. The subunits underlying I_{Kr} and their interaction are, therefore, still under controversy, and remain to be settled.

Two N-terminal splice variants of HERG have been described[26,27]. An ERG isoform (MERG1b), which is expressed specifically in the heart, has a very short and divergent N-terminal domain, and has more rapid deactivation kinetics than HERG[26]. When MERG1b is coassembled with another isoform (MERG1a) having a long N-terminal domain in Xenopus oocytes, the channel showed a further acceleration of deactivation kinetics that is almost identical to native I_{Kr}[26]. An alternatively processed isoform of MERG (MERG B) expressed selectively in the heart has a unique 36-amino acid N-terminal domain, and its current characteristics closely resemble cardiac I_{Kr}[27]. HERG B, the human homologue of MERG B, has also been isolated with analogous current properties[27]. A C-terminal splice variant of HERG (HERGUSO) cloned by Kupershmidt *et al* is non-functional when expressed by itself, but modifies and reduces HERG1 current (the original clone

obtained from hippocampal cDNA library) when they are coexpressed[28].

These observations may provide intriguing insights into the molecular basis for the interspecies and regional differences of I_{Kr}. It is possible that the native I_{Kr} could result from a mixture of N-terminal or C-terminal splice variants with HERG1 to form homomultimers or heteromultimers. Different expression of N-terminal truncated isoform would alter the kinetics of the endogenous I_{Kr}, while different expression ratio of HERGUSO *vs* HERG1 would alter the I_{Kr} density.

A voltage-dependent K^+ channel underlying I_{Ks} is composed of a pore-forming α subunit, KvLQT1 (KCNQ1), and a function-altering β subunit, minK (KCNE1)[29,30]. An N-terminal truncated isoform of the KvLQT1 gene product (isoform 2) has been identified in the human adult ventricle (with an amount of 28 % of total KvLQT1 expression)[31]. The isoform 2 exerts a pronounced dominant negative effect on the original isoform of KvLQT1 (isoform 1) when they are co-expressed in Xenopus oocytes. Péréon *et al* demonstrated that the overall expression of KvLQT1 (isoform 1, isoform 2) and minK genes in the ventricle was similar among the epicardial, midmyocadial and endocardial tissues from explanted human hearts, but the gene expression of isoform 2 was most abundant in the midmyocardial tissue[32]. This observation is in a good agreement with the least I_{Ks} density in the midmyocardial layer, and may provide a molecular basis for the longest APD in this region[12,33].

Dysfunction of I_K in inherited cardiac arrhythmias Long QT syndrome (LQTS) is a cardiac disorder characterized by prolonged ventricular repolarization and a high risk for the polymorphic ventricular tachycardia known as "Torsades de Pointes (TdP)", which often leads to sudden cardiac death as the first manifestation of the disease. Mutations in genes encoding ion channels are the main cause of the heritable (congenital) LQTS. The inheritance pattern is most frequently autosomal-dominant: alterations of a single allele are sufficient to produce the arrhythmogenic phenotype (Romano-Ward syndrome). Genetic linkage analysis has identified 6 forms of the autosomal-dominant congenital LQTS[4]. Either Na^+ channel gene SCN5A or one of the four genes underlying I_{Kr} and I_{Ks} can be affected (the existence of other LQT genes is suggested, but their identity is not yet known). Chromosome 11-linked LQT1 is associated with a mutation in KvLQT1 (KCNQ1). Chromosome 7-linked LQT2 is associated with a mutation in HERG (KCNH2). Chromosome 21-linked LQT5 and LQT6 are caused by mutations in minK (KCNE1) and MiRP1 (KCNE2), respectively. Mutations in KvLQT1 (KCNQ1) and minK (KCNE1) have also been identified in the autosomal-recessive congenital LQTS associated with deafness (Jervell-Lange-Neilsen syndrome)[4]. The LQT-associated mutations in the K^+ channels decrease K^+ outward current through I_{Kr} or I_{Ks} by loss-of-function or dominant-negative mechanisms[34]. This has been studied extensively in heterologous expression systems.

The penetrance of genetic effects of LQT1 is relatively lower than other forms of LQT. Priori *et al* reported that only about 25 % of patients with genetic defects for I_{Ks} channels actually had abnormally long QT intervals[35]. This observation suggests that I_{Ks} may play a less important role in human ventricular repolarization than I_{Kr}. However, the individuals with KvLQT1 (KCNQ1) mutations but with no or only marginal QT prolongation still have a high susceptibility to arrhythmias induced by drugs or adrenergic factors (physical and emotional stress) compared with other channel mutations[36].

β-ADRENERGIC MODULATION OF I_K

The onset of polymorphic ventricular tachycardia (TdP) in patients with LQTS is often triggered by adrenergic stress, suggesting the physiological importance of β-adrenergic regulation of ion channels responsible for ventricular repolarization. The K^+ current through I_{Ks} is enhanced by β-adrenergic stimulation, that causes an elevation of intracellular cAMP and an activation of protein kinase A (PKA)[3,37,38]. An elevation of cytosolic cAMP is shown to increase the I_{Ks} current amplitude, slow down the deactivation kinetics and shift the activation curve to more negative potential range[38].

The cAMP regulation of recombinant KvLQT1 (KCNQ1)/minK (KCNE1) complex requires PKA anchoring by A-kinase anchoring proteins (AKAP). The PKA-mediated response of native cardiac I_{Ks} may, therefore, depend on the coexpression of AKAP in the cell membrane together with the channel subunits (KvLQT1 and minK)[39]. Marx *et al* have recently demonstrated that the β-adrenoceptor modulation of hKCNQ1 is mediated by both PKA and protein phosphatase 1 via the targeting protein, yotiao[40]. Thus, the precise molecular mechanisms of signal transduction for the β-adrenergic modulation of I_{Ks} are still under investigation.

Previous studies reported that β-adrenergic stimulation by isoproterenol had no substantial effects on I_{Kr} in guinea pig and rabbit ventricular myocytes[3,37]. However, HERG contains a cyclic nucleotide binding domain in the C-terminal[41], and several recent studies have provided evidences of cAMP/PKA-dependent modulation of I_{Kr}. In guinea pig ventricular myocytes, I_{Kr} is shown to be inhibited by β_1-adrenoceptor activation through cAMP/PKA pathway[42]. In HERG channels, Cui *et al* showed that an activation of cAMP-dependent PKA results in HERG phosphorylation accompanied by a rapid reduction of the current amplitude, acceleration of deactivation, and depolarizing shift of the activation curve[43]. cAMP may also directly bind to the HERG protein with a hyperpolarizing shift of the activation curve, and this stimulatory effect of cAMP on HERG is enhanced by coexpression of accessory proteins (MiRP1 or minK)[43].

CONTRIBUTION OF I_K TO REPOLARIZATION AND ITS MODULATION BY I_K BLOCKERS

Contribution of I_{Kr} and I_{Ks} to action potential repolarization The relative contributions of I_{Kr} and I_{Ks} to repolarization have been studied in cardiac myocytes of different species by using a rectangular test pulse (about 200 ms) or an artificial action-potential like test pulse. In guinea pig ventricular myocytes, the two components have similar amplitude at membrane potentials corresponding to the plateau phase of action potential (-20 mV to +20 mV), suggesting their roughly equal contribution to repolarization[1]. In isolated guinea pig hearts, pharmacological block of either I_{Kr} or I_{Ks} resulted in a similar moderate prolongation of ventricular repolarization, whereas concomitant block of both I_{Kr} and I_{Ks} resulted in a much greater prolongation of repolarization[44]. In the rabbit ventricle, the tail current amplitude of I_{Kr} measured after a 200-ms depolarization to +40 mV is 3-fold as large as I_{Ks} in the myocytes from apex, but their amplitudes are similar in the myocytes from base. The overall contribution of IKr to ventricular repolarization in rabbits is, therefore, much greater than that in guinea pigs[3].

In dog ventricular myocytes, the relative amplitude of I_{Kr} was shown to be larger than I_{Ks} when they were measured with test pulses corresponding to normal APD (a 200-ms rectangular pulse to +30 mV or a 250-ms action potential like pulse), suggesting a greater contribution of I_{Kr}[2]. However, when the currents were measured at a longer test pulse (500 ms), I_{Ks} had a larger amplitude than I_{Kr}. The greater contribution of I_{Ks} to the repolarization of long action potentials in dog ventricular muscle was confirmed in experiments using selective I_{Ks} blockers (L-735,821 and chromanol 293B)[2].

In dog and rabbit (and perhaps in human) hearts under the normal condition, I_{Kr} may provide the major source of outward current responsible for ventricular repolarization, whereas I_{Ks} may play a minimal role. However, when the repolarization is delayed by certain factors, the prolonged APD would favor I_{Ks} activation to limit a further APD prolongation. This may act as a repolarization reserve to prevent excessive APD prolongation, which will lead to EAD and TdP-type polymorphic ventricular tachycardia.

Modulation of repolarization by selective I_{Kr} and I_{Ks} blockers I_{Kr} is the primary target of most class III antiarrhythmic drugs currently available. They are supposed to exert antiarrhythmic actions by preventing or terminating the reentrant excitation through a prolongation of APD and the refractory period. These drugs possess a common unfavorable feature; the drug-induced APD prolongation is enhanced at lower stimulation frequencies, but diminished at higher frequencies. This "reverse" frequency-dependence limits their antiarrhythmic potential at higher heart rates, and favors a proarrhythmic propensity through an excessive repolarization delay at lower heart rates[45,46].

In guinea pig ventricular myocytes, I_{Ks} deactivates slowly, and it will accumulate at fast stimulation rates[9]. Based on this behavior, selective block of I_{Ks} has been expected to cause a greater APD prolongation at higher stimulation frequencies. However, this is not always the case because of the species difference of I_{Ks} deactivation kinetics and frequency-dependent changes of other ionic currents during the repolarization phase.

The APD prolongation by selective I_{Ks} blockers (chromanol 293B, *L*-735,821) has been studied in multicellular tissue preparations or intact hearts. In dog papillary muscles and Purkinje fibers, chromanol 293B (10 μmol/L) or *L*-735,821 (100 nmol/L) caused only a slight (<7 %) but uniform APD prolongation over a wide range of pacing cycle length (300-5000 ms), whereas *d*-sotalol (30 μmol/L) or E-4031 (1 μmol/L) caused a prominent APD prolongation (by 20 %-80 %) with typical "reverse" frequency-dependence[2]. In support of this observation, *in vivo* application of these I_{Ks} blockers to anesthetized dogs resulted in minimal QTc prolongation[2]. Similar results were reported by Lengyel *et al* in

experiments using rabbits; chromanol 293B (10 μmol/L) and *L*-735 821 (100 nmol/L) caused a minimal prolongation of APD (<7 %) in papillary muscles in a frequency-independent manner, but no significant QT prolongation in Langendorff-perfused hearts[8].

Selective block of I_{Ks} causes much more prominent prolongation of cardiac APD under β-adrenergic stimulation[38,47]. In dog Purkinje fibers and guinea pig papillary muscles pretreated with isoproterenol (100 nmol/L), additional application of chromanol 293B (10 or 50 μmol/L) resulted in a marked APD prolongation (around 25 %) often associated with early afterdepolarization (EAD) or delayed afterdepolarization (DAD)[38,47]). In the presence of β-adrenergic stimulation, which is known to enhance L-type Ca^{2+} current ($I_{Ca,L}$), the role of I_{Ks} in the regulation of repolarization may be much greater than that in the resting state. In arterially perfused wedge preparations of the dog left ventricle, selective block of I_{Ks} by chromanol 293B was shown to cause a pronounced transmural dispersion of repolarization sufficient to induce TdP only when the drug treatment was accompanied by β-adrenergic stimulation[48].

In anesthetized dogs with recent myocardial infarction or acute myocardial ischemia, intravenous application of *L*-768 673 was quite effective in the prevention of ventricular tachycardia and fibrillation despite of a modest prolongation of ventricular refractory period (3 %-10 %) and QTc interval (4 %-6 %) by the drug treatment[49]. It was also demonstrated in dogs with recent myocardial infarction that concomitant application of *L*-768 673 and timolol at low doses had a potent protective action against malignant ventricular tachyarrhythmias, although a prolongation of QTc and paced QT intervals by the treatment was minimal (4.5 %-5.5 %)[50]. These observations suggest that selective block of I_{Ks} may be a potentially useful intervention to prevent ischemic ventricular tachyarrhythmias.

MODULATION OF I_K UNDER PATHOLOGICAL CONDITIONS

I_{Kr} and I_{Ks} in cardiomyocytes are modulated under a variety of pathological conditions including ventricular hypertrophy, myocardial infarction, and congestive heart failure. In a rabbit model of left ventricular hypertrophy produced by renal artery clipping, Xu *et al* reported a significant reduction of I_{Ks} density in both subepicardial and subendocardial ventricular myocytes by similar extents (about 40 %) with no significant changes in I_{Kr} density[7]. Application of dofetilide (a specific I_{Kr} blocker) to the hypertrophied myocytes resulted in a greater prolongation of APD (by 31 %-53 %) than control myocytes (18 %-32 %)[7]. In a dog model of myocardial infarction, ventricular myocytes in a border zone 5 d after the coronary occlusion showed significantly less densities of both I_{Kr} and I_{Ks}, and the electrophysiological changes were accompanied by reductions of transcripts (mRNA) of dERG and dminK (by 52 % and 76 %, respectively)[51].

In a rabbit model of pacing-induced heart failure, Tsuji *et al* observed significant reductions of both I_{Kr} and I_{Ks} densities in ventricular myocytes (by about 50 %) in association with a significant prolongation of APD (by 15 %-18 %) at physiological cycle lengths (333 ms and 1000 ms)[52]. In a dog model of pacing-induced heart failure, Li *et al* demonstrated a significant reduction of I_{Ks} density (by about 30 %) in atrial myocytes[53]. In atrial muscle sampled from patients with persistent atrial fibrillation, transcripts (mRNA) of HERG (KCNH2) and KvLQT1 (KCNQ1) were shown to be decreased significantly, whereas that of mink (KCNE1) was increased[54].

The dog with chronic atrioventricular block (AVB) has been described as an animal model of acquired QT prolongation and TdP[55]. In the model, the bradycardia-induced volume overload causes biventricular hypertrophy and heterogeneous prolongation of the ventricular APD[56-58]. Significant reduction of I_{Ks} in both ventricles (by about 50 %) and that of I_{Kr} only in the right ventricle (by 45 %) were demonstrated[58]. TdP was easily induced in the dog model by class III antiarrhythmic drugs (*d*-sotalol and almokalant) and programmed stimulation, but documented spontaneous TdP episodes and the incidence of sudden cardiac death were relatively rare. Recently, Tsuji *et al* reported a chronic AVB model in the rabbit[59]. The rabbit model showed a prominent (52 %-120 %) QT prolongation and a high incidence (71 %) of spontaneous TdP and sudden cardiac death. Ventricular myocytes isolated from the AVB rabbits were characterized by significant APD prolongation (by 20 %-60 %) and reductions of both I_{Kr} and I_{Ks} densities (by 50 %-55 %).

The reduction of I_{Kr} and/or I_{Ks} under these pathological conditions, that is most likely the result of a down regulation of the channel subunits (HERG, KvLQT1, mink, and MiRP1), may contribute to the arrhythmogenic substrate in the diseased hearts through spatially

inhomogeneous prolongation of APD and the refractory period.

CONCLUSION

I_{Kr} is the main outward K^+ current contributing to the ventricular repolarization in most mammalian species. I_{Ks} may have relatively small contribution in normal action potential repolarization, but it may act as an important "repolarization reserve" when APD is abnormally lengthened by pharmacological treatments or under a variety of pathological conditions (eg, hypokalemia, bradycardia, and genetic disorders of ion channels). Selective block of I_{Ks} produces minimal to moderate, but relatively frequency-independent prolongation of ventricular repolarization and refractoriness, that would be therapeutically relevant to reduce proarrhythmic propensity in ischemic hearts. I_{Ks} blockers are, therefore, expected to be more beneficial than I_{Kr} blockers (eg, *d*-sotalol, dofetilide, and E-4031) as class III antiarrhythmic agents.

Many drugs block K^+ channels unintentionally, and I_{Kr} is a common target. Apart from antiarrhythmic drugs, a growing number of non-cardiovascular drugs (eg, antihistamines, antipsychotics, and antibiotics) are included in this category[60]. This is probably due to a unique structural feature of the HERG (KCNH2) inner vestibule that renders it rather non-selective binding of small organic molecules[61]. Drug-induced long QT syndrome occurs more frequently in women than in men. The basis for this gender differences remains to be clarified. It is not known why relatively a small percentage of recipients are more prone to drug-induced LQTS. The repolarization process of cardiac cells has a substantial "reserve" built-in by the redundancy of K^+ channels. Certain mutations or polymorphisms of K^+ channels, which are otherwise innocent, could reduce such a repolarization reserve and increase the susceptibility for the acquired LQTS and TdP[62]. Remodeling of ion channels in diseased hearts (eg, down regulation of I_{Kr} and I_{Ks} in hypertrophied or failing ventricles) can also reduce the repolarization reserve and contribute to their proarrhythmic propensity. Further experimental and clinical studies will be required to unravel these issues.

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