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The regulation of the small conductance calcium activated potassium current and the mechanisms of sex dimorphism in J wave syndrome

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Abstract

Apamin-sensitive small-conductance calcium-activated potassium (SK) current (I_{KAS}) plays an important role in cardiac repolarization under a variety of physiological and pathological conditions. The regulation of cardiac I_{KAS} relies on SK channel expression, intracellular Ca^{2+} and interaction between SK channel and intracellular Ca^{2+}. I_{KAS} activation participates in multiple types of arrhythmias, including atrial fibrillation, ventricular tachyarrhythmias and automaticity and conduction abnormality. Recently, sex dimorphisms in autonomic control have been noticed in I_{KAS} activation, resulting in sex differentiated action potential morphology and arrhythmogenesis. This review provides an update on the Ca^{2+}-dependent regulation of cardiac I_{KAS} and the role of I_{KAS} on arrhythmias, with a special focus on sex differences in I_{KAS} activation. We propose that sex dimorphism in autonomic control of I_{KAS} may play a role in J wave syndrome.

Keywords

sex difference; sex dimorphism; J wave syndrome; Brugada syndrome; early repolarization; ion channel; autonomic control

1. Introduction

K^+ currents, such as transient outward K^+ current (I_{to}), inward rectifier K^+ current (I_{K1}), ultrarapid delayed rectifier K^+ current (I_{Kur}) and slow component of the delayed rectifier

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6. Declarations

Conflicts of interest: none.

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K^+ current (I_{Ks}), seem to be significantly, although not necessarily directly, modulated by intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) [29]. The importance of Ca^{2+} in modulating neuronal and cardiac potassium currents have been intensively studied since at least the 1980s [34,23,46]. Kohler et al [45] first identified the small conductance Ca^{2+}-activated K^+ (SK) channel in the brain and found it to be responsible for afterhyperpolarization of the neurons. The same channel was later found to be important in cardiac repolarization in animal models and in humans [97]. Unlike voltage-gated and other ligand-gated K^+ channels, the SK channel is gated solely by changes in intracellular Ca^{2+} [1,96]. Hence, intracellular Ca^{2+} provides a direct and critical link between SK channel and the forming of functional SK current [1,96]. Study of SK channel is facilitated by the use of apamin, an active neurotoxin discovered more than 70 years ago [38]. Apamin is a highly specific SK channel inhibitor in both neuronal and cardiac tissues [38,104]. The 3 subtypes of SK channels (SK1, SK2 and SK3) exhibit differential sensitivity to apamin[45,30]. Among them, SK2 is most sensitive while SK1 is least sensitive and may not be blocked by up to 100 nM of apamin [38]. Because not all SK currents are sensitive to apamin, our laboratory generally used the term apamin-sensitive SK current (I_{KAS}) to describe the current we were studying. All 3 isoforms of SK channels are expressed in animal and human hearts, and are capable of forming homomeric or heteromeric channels [45,84,62,91,98]. Other agents, including I_{kas} blocker and positive and negative modulators, are also widely adopted to investigate the effects of I_{KAS} inhibition or activation on cardiac electrophysiology and arrhythmias.

2. Regulation of cardiac I_{KAS}

The regulation of cardiac I_{KAS} relies on (1) SK protein expression, (2) intracellular Ca^{2+} concentration and (3) interaction between Ca^{2+} and SK channel. This review attempts to provide an overview of the literature on the 3 aspects of cardiac I_{KAS} regulation and the role of I_{KAS} in arrhythmogenesis. In addition, we focus on the sex differences of I_{KAS} activation in multiple experimental conditions.

2.1 SK channel expression regulates I_{KAS}

The SK channels are not uniformly distributed throughout the hearts, with higher mRNA and protein expression levels in atria than ventricles in both animals and humans [91,98]. One exception is equal mRNA levels were reported between chambers in horses [33]. Both patch clamp at cellular level and optical mapping in whole hearts found prominent blocking effects of apamin in atria which were functionally dormant in normal ventricles, indicating more pronounced I_{KAS} in atria than ventricles [91,98,10,13]. In addition, SK channel expression and corresponding I_{KAS} are abundant in cells with automaticity, such as sinoatrial node [11,87], atrioventricular node [111], Purkinje networks [72,93] and pulmonary veins [70,11,68]. The abundant expression of SK channel in Purkinje cells may mediate the increased intracellular Ca^{2+}-membrane potential coupling gain in Purkinje cells [59,72]. In accordance with low expression of SK channels in ventricles of normal hearts, I_{KAS} is minimally activated at baseline condition that apamin prolongs APD by less than 5% [10,13]. However, ventricular I_{KAS} can still be activated at slow heart rate and by pharmacologic interventions, including I_{KAS} or $I_{Ca,L}$ activators and β-adrenergic

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stimulation, suggesting the capability of SK channel forming functional I_{KAS} in ventricles of normal hearts [6,10,9]. Of note, our previous study found higher SK2 protein expressions in ventricles of female than male rabbits [10]. Whether or not sex differentiated expressions of SK channels are present in other species remain unclear.

Multiple pathological conditions, such as atrial fibrillation (AF) and heart failure (HF), might alter the expression of SK channels, contributing to the regulation of I_{KAS}. In a rabbit model of short-term atrial burst pacing, SK2 mRNA, protein and corresponding I_{KAS} were increased in the pulmonary veins, involving in the early electrical remodeling [68]. In contrast, mRNA and proteins of SK channels were downregulated in patients with chronic AF, suggesting an opposite regulatory direction in the chronic remodeling process [51,108,81,27]. In streptozotocin-induced Type 1 diabetic mice, the expression of both SK2 and SK3 were reduced in atrium [101]. However, SK2 expression in atria was downregulated whereas SK3 was upregulated in a Type 2 diabetic mice model [53]. While the downregulation of SK channels led to decreased I_{KAS} in most AF studies [51,81,108], intriguingly increase of I_{KAS} could be possible via the enhanced Ca^{2+} and Ca^{2+}-SK interaction [27]. On the other hand, upregulation of SK channels expression was commonly observed in HF. In patients with end-stage HF, SK2 protein expression was upregulated in ventricles and SK3 protein also exhibited an increasing tendency [7,3]. In canine HF ventricles, SK3 channel was significantly upregulated while SK2 channel showed a tendency towards increased expression, albeit not significantly [3]. In a rat HF model, mRNA and protein expressions of SK1 and SK3 channels were upregulated while SK2 expressions remained similar with normal controls [65]. In contrast, SK2 mRNA levels were similar between failing and normal rabbit ventricles [13].

In addition to the change of total expression, SK channel expression may develop heightened heterogeneity, thus predisposing transmural and regional differentiated regulation of I_{KAS}. In failing human ventricles, I_{KAS} exhibited higher density in epicardium and endocardium compared with midmyocardium, with some hearts exhibiting M-cell islands [7,106]. The transmural gradient of I_{KAS} was attributed, at least in part, to heterogeneous SK channel expression. The regional differences of SK channel expression were also reported. In chronically paced but not failing rabbit hearts, mRNA levels of SK2 and SK3 channel were significantly higher at the distal compared to the proximal pacing sites [102]. In normal rabbit ventricles, the CyPPA-induced activation of I_{KAS} exhibited more pronounced heterogeneity in right than left ventricles, suggesting a more subtle regional differentiated expression [9]. In contrast, the mRNA and protein expressions of 3 subtypes of SK channels did not alter in animal models of acute or chronic myocardial infarction, suggesting the contributions of SK channel expressions on I_{KAS} upregulation are limited [31]. Other factors, such as Ca^{2+} and Ca^{2+}-SK interaction, might be important.

SK channels were not only expressed in the plasma membrane, but also were recently discovered in the inner mitochondrial membrane of cardiomyocytes [83,41]. The activation of mitochondrial SK channels attenuated Ca^{2+}-dependent arrhythmia in hypertrophic hearts by reducing the mito-ROS-dependent oxidation of RyR2 channels [41]. Therefore, by contributing to intracellular Ca^{2+} homeostasis, mitochondrial SK channels might affect I_{KAS} activation on the plasma membrane indirectly. Nevertheless, only channels expressing on

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the membrane surface of cardiomyocytes were capable to form I_{KAS} directly, consequently shaping action potential and affecting arrhythmogenesis. In rabbit pulmonary vein, 3-hour intermittent burst pacing, which mimicking ectopic pulmonary vein foci, induced SK2 channel trafficking from perinucleus to the membrane, leading to increased I_{KAS} [68]. The trafficking of SK channel to membrane was regulated by multiple factors, in a Ca^{2+}-dependent or independent ways. Filamin A, α-actinin2 and junctophilin type 2 (JP2) were necessary for the Ca^{2+}-dependent trafficking of SK2 channels in atrial myocytes [114,26,71], whereas vesicle-associated membrane protein type 2 (VAMP2)-mediated membranization of SK2 channel was Ca^{2+} independent [50]. While the binding with wildtype calmodulin (CaM) showed normal trafficking process, SK3 channel binding with CaM^{N541}, a catecholaminergic polymorphic ventricular tachycardia associated variant, showed increased retention in the intracellular compartments, thus leading to decreased I_{KAS} [74]. In addition, SK membrane localization might be modulated by its crosstalk with L-type calcium channel (LTCC). Ablation of $Ca_v1.3$ channels resulted in increased membrane localization of SK2 channels [54].

In rat, rabbit, dog and human, ventricular myocytes from failing hearts showed transmurally heterogeneously upregulation of I_{KAS} densities compared with ventricular myocytes from normal hearts [3,13,7,65]. Similar I_{kas} upregulation was demonstrated in infarcted ventricles of human and animal model [7,31,48] and protect the heart against ischemia-reperfusion injury [83]. Ventricular pacing results in Ca^{2+} elevation in late activation sites [39], which in turn upregulates I_{kas} to shorten the action potential duration (APD). This sequence of events predisposes to the development of the short-term cardiac memory in paced ventricles [5]. I_{KAS} upregulation was also observed in chronically paced rabbit ventricles, contributing to the formation of long-term cardiac memory [102].

2.2 Intracellular Ca^{2+} regulates I_{kas}

SK channels were gated solely by changes in intracellular Ca^{2+}, hence, intracellular Ca^{2+} provided a direct link between SK channel and the forming of functional I_{KAS} [1,96]. During the Ca^{2+} induced Ca^{2+} release (CICR) process, the Ca^{2+} influx through LTCCs raises the local concentration from 0.1 to 10 μM, and subsequent Ca^{2+} release through RyR2 further increased the cleft Ca^{2+} concentration to ~100 μM, even though the global intracellular Ca^{2+} concentration only reached ~1 μM. SK channels were very sensitive to local subsarcolemmal Ca^{2+} and were activated by submicromolar concentrations of intracellular Ca^{2+} with apparent Kd of ~0.5 μM. Therefore, the sequential activation of LTCC and RyR2 regulated the activation of I_{KAS}. Cardiac SK2 channels coupled with LTCC through a physical bridge, α-actinin2 [55]. The activation of I_{KAS} were critically dependent on the normal expression of LTCC in atrial myocytes, that null deletion of $Ca_v1.3$ channel resulted in reduced I_{KAS}, leading to APD prolongation and atrial arrhythmias [55]. BayK 8644, which increased influx of Ca^{2+} through LTCC, activated dormant I_{KAS} in normal ventricles [10]. On the other hand, the necessity and sufficiency of RyR2-mediated SR Ca^{2+} release in I_{KAS} activation has been established in SK2-overexpressed rat ventricular myocytes [86]. Inhibition or knockdown of RyR2 or depletion of SR Ca^{2+} store significantly reduced I_{KAS} in mouse atrial myocytes [63]. Further studies suggest both LTCC and RyR2 were critical in I_{KAS} activation. β-adrenergic receptor stimulation by

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isoproterenol, which increased both $I_{Ca,L}$ and RyR2-mediated Ca^{2+} releases, prominently activated I_{KAS} in normal ventricles [10]. The super-resolution imaging revealed the physical distances of LTCCs and RyR2 from SK2 channels were within hundreds of nanometers in cardiomyocytes [112]. The spatial proximity of the 3 molecules enabled the optimal I_{KAS} activation by precise control of the SK channel gating on the beat-to-beat basis by integrating the local Ca^{2+} signaling. Other $[Ca^{2+}]_i$ regulator, such as sodium-calcium exchanger (NCX), SR Ca^{2+}-ATPase, sarcolemmal Ca^{2+}-ATPase and mitochondrial Ca^{2+} uniporter, may also exert effects on I_{KAS} indirectly. For instance, NCX knockout mice, a model of cellular Ca^{2+} overload, exhibited higher I_{KAS} than wildtype mice in sinoatrial (SA) node [87].

The remodeling of LTCC properties may contribute to altered dynamics of I_{KAS} under pathological conditions. During AF, the expression of LTCCs and current density of $I_{Ca,L}$ were reduced [16]. AF was also associated with increased RyR2 diastolic leak, increased sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase function and t-tubule loss [16]. Such Ca^{2+} dynamics, together with SK channel downregulation, led to reduced peak I_{KAS} density during atrial repolarization, but activation during late repolarization phases and diastolic afterdepolarization. On the other hand, T-tubule loss, LTCC dislocation and the impaired communication between LTCC and RyR2 were found in HF. However, constitutive phosphorylation of LTCCs by cytoplasmic CaMKII led to an increased LTCC open probability, predisposing spontaneous secondary $[Ca^{2+}]_i$ rising during repolarization phases of AP [6,75]. Under such circumstances, I_{kas} might be amplified by elevated microdomain $[Ca^{2+}]_i$ and during the secondary $[Ca^{2+}]_i$ rising [6]. Together with upregulated SK channel expression and increased sensitivity to $[Ca^{2+}]_i$, those three factors contributed to the augmented I_{KAS} in ventricles during HF [7,13]. Other conditions causing $[Ca^{2+}]_i$ overload also elicited I_{KAS} activation, such as hypokalemia and slow ventricular rate [5]. The effects of apamin on APD prolongation and Ca_iTD-APD shortening were more prominent at slow ventricular rate in both normal and failing ventricles[5,106,6], suggesting a more profound activation of I_{KAS} as longer diastolic intervals allowing persistent Ca^{2+} inflow. Similarly, ventricular I_{KAS} was prominently activated at sites remote from the pacing site where abundant cytosolic Ca^{2+} accumulation, which attenuated APD prolongation and maintained repolarization reserve [5].

The assemble of SK channels might also affect its binding to LTCC, which consequently affects I_{KAS}. A previous study proposed that homomeric SK channels did not contribute to the I_{KAS} activation because the homomeric SK channels were not within a suitable microdomain containing LTCC [32]. Only SK2-SK3 heteromultimers were activated, which was likely the result of the colocalization of LTCC and heteromeric SK channels within microdomains [90,55]. SK channels preferentially co-assembled to form heteromeric channels and heteromeric channels might predominate in cells expressing multiple SK channel subunits [14].

On the other hand, the effects of I_{kas} activation on action potential provided a feedback mechanism in driving Ca^{2+} transient, leading to negative coupling between Ca^{2+} and membrane potentials [112]. For instance, $I_{Ca,L}$ and subsequent CICR process were amplified during isoproterenol infusion, which activated I_{KAS} at early repolarization phases where Ca_i

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was more abundant [10]. I_{KAS} activation reversely shortened APD more prominently at the beats with large Ca_i transient and at phase 2 repolarization, leading to AP triangulation and negative Ca_i-V_m coupling [10]. Such I_{KAS} mediated negative coupling were also observed during hypothermia [9]. Low body temperature decreased peak $I_{Ca,L}$, reduced Ca^{2+}-dependent $I_{Ca,L}$ inactivation and prolonged Ca_i transient, which in turn increased sarcoplasmic Ca^{2+} stores and release. The differentiated I_{KAS} activation between larger and small Ca transients and between proximal and distal sites from pacing site led to spatially and electromechanically discordant alternans [9]. I_{KAS} as a negative coupler between intracellular Ca^{2+} to membrane voltage was further verified by *in silico* modeling [40].

2.3 Sensitivity of SK channel to Ca^{2+} regulates I_{kas}

The sensitivity of SK channel to Ca^{2+} also contributed to I_{KAS} modulation. During heart failure, in addition to upregulation of SK channel expression, the sensitivity of I_{KAS} to intracellular Ca^{2+} was also increased, leading to increased I_{KAS} [13,65]. In contrast, the steady-state Ca^{2+} response of I_{KAS} was shifted rightwards in failing myocytes treated with β-blocker compared with nontreated myocytes, contributing to downregulated I_{KAS} [65].

The affinity of SK channels to Ca^{2+} was modulated by multiple cofactors. SK channels were activated exclusively by Ca^{2+}-bound calmodulin (CaM). Arrhythmogenic CaM variants causing LQTS and CPVT, including CaM^{N54I}, CaM^{D96V}, CaM^{D130G}, and CaM^{F142L}, significantly down-regulated I_{KAS} mediated by SK3 [74]. Phosphorylation of CaM, when complexed with the channel, casein kinase 2 (CK2) inhibited SK channels, while protein phosphatase 2A (PP2A) reversed the effect of CK2 [110]. During heart failure, the interaction between casein kinase 2 (CK2) and SK channel was decreased in HF while protein phosphatase 2A (PP2A) was increased, upregulating the sensitivity of I_{KAS} to intracellular Ca^{2+} [99]. The sex-specific I_{KAS} response to isoproterenol was also partially attributed to different CK2/SK2 ratio between females and males [10]. I_{KAS} was increased via the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)-dependent pathway in hypertrophic ventricles in rats [61]. Similarly in AF patients, CaMKII activation by autophosphorylation at Thr287 increased calcium sensitivity of I_{KAS} and consequently induced increased I_{KAS} [27].

3. I_{kas} and cardiac arrhythmias

3.1 I_{kas} and atrial fibrillation

The importance of SK channels in atrial arrhythmogenesis has been supported by genome-wide association studies in humans. The Caucasian patients with lone atrial fibrillation (AF) have identified genomic regions associated with AF on chromosomes 1q21 (rs13376333), which is intronic to *KCNN3* (SK3) [25,24]. The association between the single nucleotide polymorphism (SNP) rs13376333 and AF was replicated in Asian cohorts[57,8], and was further linked to structural AF [100,8]. Therefore, SNP rs13376333 was considered as one of the top AF-susceptibility SNPs. SNP rs13376333 has been incorporated into a risk assessment model to identify subjects at the highest risk of developing AF [64]. However, it failed to predict AF recurrence after catheter ablation [12]. Another synonymous *KCNN3* SNP rs1131820 was detected in association with lone AF [66]. In addition, variants of

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KCNN2 (SK2, rs13184658 and rs337711) also showed relevance with AF [105,36]. These results suggested *KCNN* variants are associated with AF. SK channels also participate in the atrial electrical remodeling. While mRNA and proteins of SK channels were downregulated in patients with chronic AF, inconsistent results appeared regarding I_{KAS} regulation [51,108,81,27]. I_{KAS} may decrease due to the low channel protein expressions [81,108], or intriguingly increase via the enhanced activation of CaMKII[27].

The SK channel-associated atrial electrical remodeling was also observed in animal models, such as diabetic mice [101,53,52]. However, discrepancies were noticed among studies. In streptozotocin-induced Type 1 diabetic mice, the expression of both SK2 and SK3 were reduced in atrium, which promoted the atrial arrhythmogenesis [101]. However, in a Type 2 diabetic mice model, SK2 expression was downregulated whereas SK3 was upregulated [53].

The mechanisms of SK channel in atrial arrhythmogenesis has been investigated in multiple animal studies. However, the results varied among different experimental models and study protocols, as summarized in Table 1. Of note, a recent study reported that I_{KAS} inhibitors NS8593 and UCL1684 prevented AF via I_{Na} inhibition with little effect on I_{KAS} [4].

3.2 I_{kas} and ventricular arrhythmias

In the past decade, the importance of SK channels in ventricular electrophysiology and arrhythmogenesis has been demonstrated in both human and experimental models. Association between *KCNN2* variants (rs13184658 and rs10076582) and ventricular tachycardia has been found in patients with aborted sudden cardiac death or unexplained syncope [105]. The p.F503L *KCNN2* variant facilitated the development of drug-induced long QT syndrome in human [44]. In explanted human hearts with non-ischemic dilated cardiomyopathy, reduced mRNA and protein expressions of SK2 channels were identified in subjects with than without VT [69]. Conversely, abundant SK2 protein were found in the intercalated discs of ventricular myocytes from explanted failing hearts [106]. In addition to SK2, upregulation of *KCNN3* gene was detected in patients with dilated cardiomyopathy and sustained monomorphic ventricular tachycardia [67]. Consistent with the human data, overexpression of *KCNN3* in mice resulted in high incidence of sudden cardiac death [58].

The mechanisms of SK channel in ventricular arrhythmogenesis has been investigated in multiple animal models, as summarized in Table 2.

3.3 I_{KAS} and arrhythmias from cardiac conduction systems

The expression of SK2 channel in AV node has been verified by multiple techniques[111]. The functional roles of I_{KAS} in AV node were investigated taking advantage of genetically altered mouse models with SK2 overexpression or null mutation. Overexpression of SK2 channels led to increased automaticity and shortened APD in AV node cells. In contrast, SK2 null mutant mice manifested with decreased spontaneous firing rate and prolonged APD in AV node [111].

In addition, SK channel was found more abundantly expressed in sinoatrial node, pulmonary veins and Purkinje cells than cardiomyocytes [11,87,72,93,70]. Consequently, I_{KAS} played

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important roles in automaticity and its associated arrhythmogenesis [11,87,72,93,70]. Histological studies in failing human hearts showed that I_{KAS} is abundantly expressed in the intercalated discs. I_{KAS} blockade by apamin significantly reduced the transmural conduction velocity [105]. The functional roles of I_{KAS} in cardiac conduction systems were summarized in Table 3.

3.4 Autonomic remodeling of neuronal SK channel and cardiac arrhythmias

Cardiac rhythmicity was regulated by autonomic nervous systems. Recently, several methods of neuromodulation were adopted to reduce atrial and ventricular arrhythmic burdens. As SK channel abundantly expressed in neuronal systems, the regulation of neuronal I_{KAS} might modulate cardiac arrhythmias. Low-level vagus nerve stimulation (LL-VNS) reduced stellate ganglion nerve activity and consequently ameliorated atrial arrhythmias [77]. Follow-up study showed that the LL-VNS induced neuronal remodeling was mediated by the increased SK2 proteins expression and membranization in the left stellate ganglion [76]. Therefore, modulating I_{KAS} activity in the stellate ganglion may serve as an upstream pathway to regulate cardiac arrhythmogenesis, and potentially serve as a therapeutic target. Subsequent studies, as summarized in Table 4, reported similar findings that, by stimulating right tragus and spinal cord, SK2 channels were upregulated in stellate ganglion and atrial ganglionated plexi, thus reduce cardiac arrhythmias [76,115,107,94]. The neuronal SK channel upregulation may rely on the increased intracellular Ca^{2+} induced by rapid electrical stimulation of the nerves, which in turn reduces neuronal discharges by inducing neuron cell death and hyperpolarizing the cell membrane [35].

4. Sex differences in I_{KAS}

Sex dimorphisms exert striking effects in almost all aspects of human cardiac arrhythmias, including the prevalence, symptoms, diagnosis, risk stratification, treatment, drug sensitivity and outcomes [22]. The most notable examples are long QT syndrome (LQTS) and Brugada syndrome, where prominent sex disparities in clinical expressivity exist. Women are at higher risk than men of Torsade de Pointes with LQTS type 1 and type 2 [73]. Conversely, male is predominant over female in the prevalence and arrhythmic events in J wave syndrome, including both Brugada syndrome and early repolarization syndrome [60,2]. The cellular basis of these sex-related distinctions in human cardiac arrhythmogenesis is not completely resolved due to the limited availability to human cardiac tissues. However, the importance of cardiac ion currents in sex differences of cardiac electrophysiology and dysrhythmia susceptibility have been demonstrated by animal experiments and reproduced by computer simulations. The densities of $I_{ca,L}$ and $I_{K,ATP}$ are higher, while I_{to}, I_{Kr} and I_{Kur} are lower in female than male [92]. Other currents, including I_{Na}, I_{Ks}, I_{K1} and I_{NCX} are equal between sexes [92]. These sex differences in ion current densities conjunctionally contributed to the longer action potential (AP) duration (APD) in cardiomyocytes of female compared with male under physiological conditions. In conjunction with other factors such as transmural and regional heterogeneities, heterotypic cell-cell coupling and abnormal intracellular calcium handling, the dysregulation of ion current densities led to altered automaticity, triggered activities and reentrant, thus predisposing cardiac arrhythmias.

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However, the sex differences of SK channel and I_{KAS} have not been investigated until recently. In Table 1–4, we listed a total of 36 studies regarding I_{KAS} and cardiac arrhythmias. Among them, 14 studies did not mention the sexes of the animals, 10 studies only used male animals and 7 studies only used female animals. Only 5 studies were conducted in both sexes.

In normal rabbit ventricles, β-adrenergic stimulation by isoproterenol activated ventricular I_{KAS} in females to a much greater extent than in males, suggesting a sex specific activation of I_{KAS} [10]. The more prominent I_{KAS} activation in ventricles of female rabbits was attributed to more abundant expression of SK2 channel, larger $I_{Ca,L}$ and lower CK2/SK2 ratio in females. I_{KAS} activation in females induced negative Ca^{2+} -voltage coupling, promoted electromechanically discordant phase 2 repolarization alternans and facilitated ventricular fibrillation, which were not observed in males [10]. In addition, I_{KAS} was abundantly activated increased in female but not in male ventricles with drug-induced long QT syndrome. Increased I_{KAS} helped to preserve the repolarization reserve in female ventricles treated with I_{Ks} and I_{Kr} blockers or I_{NaL} activators [95]. However, a subsequent study found that concomitant I_{KAS} activation and I_{Na} inhibition by cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (CyPPA) recapitulated J wave syndrome in rabbits and exhibited more prominent effects in males than females [9]. In this CyPPA model, males had significantly higher J wave amplitude and more episodes of spontaneous ventricular fibrillation than females. Electrical storm only developed in males. β-adrenergic stimulation mainly activated SK2 rather than SK3 [10]. As CyPPA was a subtype-selective potentiator of SK3 channels, the effects of CyPPA were mainly attributed to SK3 rather SK2 activation[9]. While isoproterenol activates I_{KAS} in female more than male ventricles, acetylcholine activates I_{KAS} more in male than in female ventricles [28]. Activation by acetylcholine with concomitant I_{Na} inhibition by ajmaline also induced J-wave elevation and facilitated the induction of ventricular arrhythmias more in male than female ventricles [28]. Despite binding to M2 receptor reduces protein kinase A activity, acetylcholine binding to M1 receptor may gate Ca^{2+} release from intracellular stores and facilitate voltage-dependent refilling of Ca^{2+} stores, thereby maintaining the SK-mediated fidelity of inhibitory cholinergic signaling in pyramidal neurons [15]. As M2 receptor is dominant in the heart, the mechanism of acetylcholine activate I_{KAS} is not fully understood. However, as only low level of acetylcholine-sensitive K^+ current ($I_{K\cdot Ach}$) is present in the ventricles, the electrophysiological effects of acetylcholine in ventricles may largely rely on the activation of I_{KAS}. Taken together, these findings suggest that during the day time, sympathetic tone activates I_{KAS} in females but that outward current was counterbalanced by the increased inward current ($I_{Ca,L}$). Therefore, in spite of I_{KAS} activation, females do not exhibit J point elevation during the day. Males are less liable to J wave syndrome during daytime because of absence of I_{KAS} activation by the high sympathetic tone. However, at night, I_{KAS} in males is activated by the heightened parasympathetic tone without concomitant activation of $I_{Ca,L}$, leading to J point elevation, ventricular arrhythmia and sudden cardiac death. The absence of I_{KAS} activation by acetylcholine in females protects them against the ventricular arrhythmias at night. Therefore, sex differences in I_{KAS} may be used the explain the nocturnal occurrences of sudden death in males but not females. The

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schematic (Figure 1) shows the sex differentiated activation of I_{KAS} in arrhythmogenesis of J wave syndrome.

We do not yet have data to compare the relative importance of I_{KAS} and I_{to} in the generation of J wave syndrome. However, a major consequence of I_{to} activation is to increase Ca^{2+} entry through the already opened LTCC during phase 1 of the action potential. Colocalization of I_{KAS} channels with LTCC in the subsarcolemmal or junctional space may result in a spiky I_{KAS}, which can promote the development of J wave syndrome and ventricular arrhythmias in computer simulation studies [47]. Therefore, it is possible that a collaboration between I_{to}, LTCC and I_{KAS} is needed to generate the J wave syndrome.

5. Clinical perspectives

As I_{KAS} participated in cardiac arrhythmias, I_{KAS} has been considered as a new target of antiarrhythmic therapy in both experimental and clinical settings. E4031 and chromanol 293B were historically considered as specific blocker of I_{Kr} (IC_{50} 10–30 μM) and I_{Ks} (IC_{50} 400 nM), respectively. However, E4031 at 500 nM and chromanol 293B at 100 mM inhibited 37% and 38% I_{KAS}, respectively [89]. Therefore, it should be noticed that the effects of E4031 and chromanol 293B on cardiac electrophysiology may combine the effects of I_{Kr} or I_{Ks} blockade and I_{KAS} inhibition.

Several I_{KAS} specific blockers, such as apamin, are neurotoxins and cannot be used for antiarrhythmic therapy [38]. Although not specific blockers, several clinically used antiarrhythmic drugs might also target I_{kas}. A previous study suggested that dofetilide and propafenone inhibited I_{KAS} with no subtype selectivity [78]. Their inhibition may have minimal clinical importance for antiarrhythmic effect due to much higher IC_{50} values than the effective free therapeutic plasma concentration of the drugs when used for AF treatment [78]. Amiodarone, disopyramide, dronedarone, flecainide, ibutilide, quinidine, sotalol and vernakalant had no effect on the I_{KAS} conducted by SK3 [78]. However, other studies suggested that amiodarone and dronedarone inhibited I_{KAS} and dronedarone provided a greater degree of I_{KAS} inhibition than amiodarone in atrial myocytes from chronic atrial fibrillation [89,109].

Non-antiarrhythmic drugs may also have potential antiarrhythmic effects by targeting I_{KAS}. Ondansetron, a 5-HT3 receptor antagonist, blocked I_{KAS}, while did not inhibit I_{Ks} or I_{Kr} at therapeutic concentrations [44,103]. As I_{KAS} activation recapitulated J wave syndrome phenotype in the experimental model, i_{KAS} blockade by ondansetron may have the potential to prevent ventricular arrhythmias in Brugada or early repolarization syndromes [9]. Additionally, as I_{KAS} activation relied on intracellular Ca^{2+}, drugs targeting Ca^{2+} and Ca^{2+}- I_{KAS} interaction, such as LTCC, RyR2 and calmodulin, may have indirect effects on I_{KAS}, subsequently contributed to their antiarrhythmic or proarrhythmic mechanisms. On the translational level, the discovery and use of I_{KAS} blockers in the treatment of atrial fibrillation and ventricular tachyarrhythmias require further investigations, with specific consideration on sex differences.

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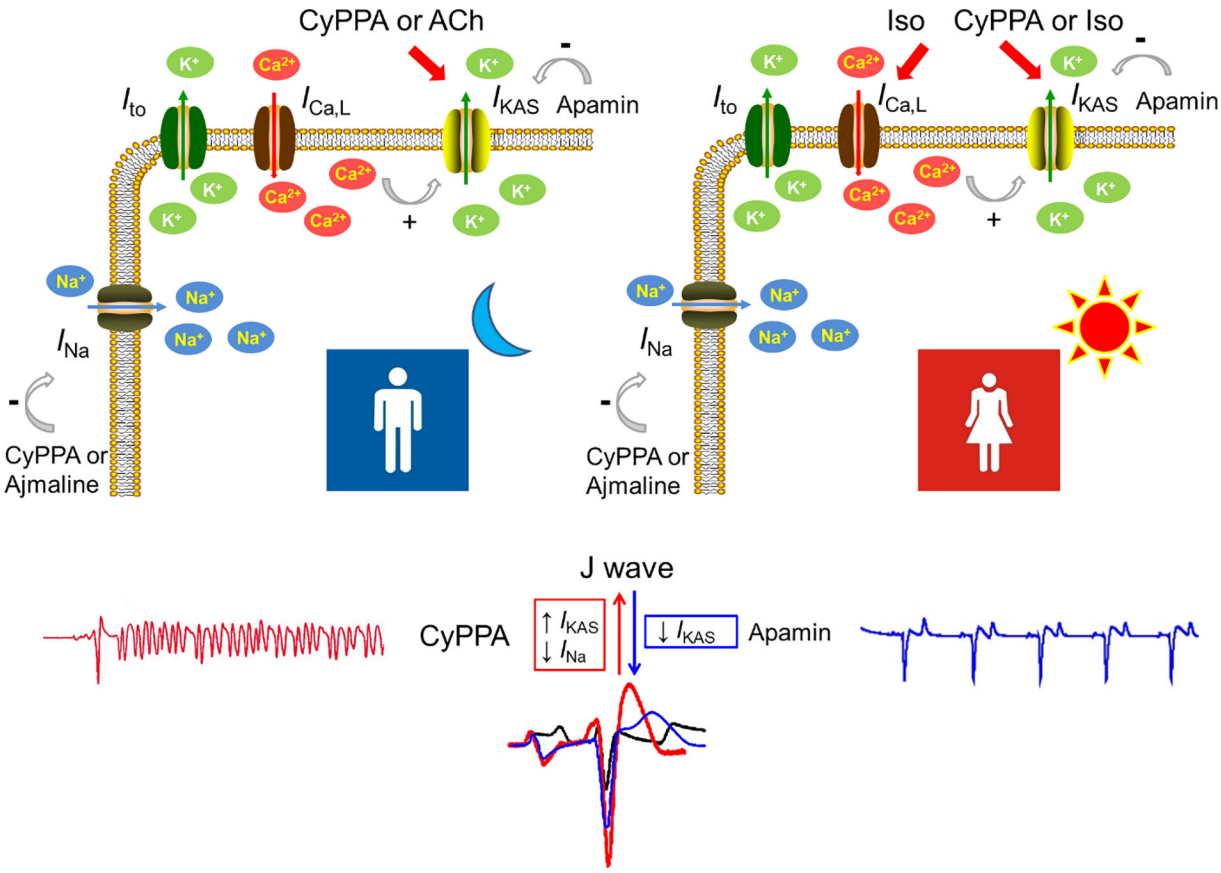

Figure 1.

I_{KAS} activation and J wave syndrome. Concomitant I_{KAS} activation (by CyPPA or acetylcholine) and I_{Na} inhibition (by CyPPA or ajmaline) lead to J point elevation and facilitate ventricular arrhythmias. J point elevation and ventricular arrhythmias are attenuated by I_{KAS} inhibition (by apamin). Acetylcholine activates I_{KAS} more prominently in men while isoproterenol activates I_{KAS} more prominently in women. We propose that I_{KAS} activation by sympathetic tone during the daytime is counterbalanced by the increased inward current ($I_{Ca,L}$) in females. Therefore, in spite of I_{KAS} activation, females do not exhibit J point elevation during the daytime. At night, I_{KAS} in males is activated by the heightened parasympathetic tone without concomitant activation of $I_{Ca,L}$, leading to J point elevation, ventricular arrhythmia and sudden cardiac death. The sex differences in I_{KAS} may explain the mechanisms of J wave syndrome, including both the Brugada syndrome and the early repolarization syndrome. Ach, acetylcholine; CyPPA, cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine; Iso, isoproterenol.

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Table 1.

The effects of I_{KAS} blockade/activation on atrial arrhythmogenesis in animal models

AF model	Species	Sex	Agents	Experimental settings	Ca^{2+} (mmol/L)*	K^+ (mmol/L)*	Effects of I_{KAS} blockade on atrial electrophysiology	Effects of I_{KAS} blockade on atrial arrhythmogenesis	Effects on ventricular electrophysiology	Reference
Acutely induced AF	Rat	Male	Apamin, NS8593, UCL1684 or ICA	In vivo, isolated heart, cardiomyocytes	1.8	4.0	Prolong aERP, aAPD, slow conduction velocity	Antiarrhythmic: shorten AF duration	NA	[80,82,79]
Induced AF in hypertension-related remodeled atria	Aging, spontaneously hypertensive rats	Male	NS8593 or UCL1684	In vivo	Normal	Normal	Prolong aERP	Antiarrhythmic: shorten AF duration	NA	[19]
Acutely induced AF	Guinea pig, rabbit, rat	Female: guinea pig, rabbit Male: rat	NS8593, UCL1684 or ICA	In vivo, isolated heart	Normal	Normal	Prolong aERP	Antiarrhythmic: prevent and terminate AF	No effect on QT interval	[21]
Acutely induced AF	Guinea pig	Female	ICA, combined with ranolazine, flecainide or lidocaine	Isolated heart	2.5	4.0	** Prolong aERP	** Antiarrhythmic: shorten AF duration	**No effect on QT interval, no AP triangulation	[43]
Acutely induced AF	Guinea pig	NA	ICA, combined with dofetilide or amiodarone	Isolated heart	2.5	4.0	**Prolong aERP without significance	**Antiarrhythmic: shorten AF duration	**No effect on QT interval, no AP triangulation	[42]
Acutely induced AF	Homozygous Dct knockout mouse	Female, male	Apamin	Isolated heart	1.3	4.5	Prolong aAPD	Antiarrhythmic: reduce AF inducibility	NA	[88]
Acutely induced AF	Horse	Female and gelding male	NS8593	In vivo	Normal	Normal	Prolong aERP	Antiarrhythmic: shorten AF duration, reduce AF vulnerability score	No effect on QT interval	[33]
Induced AF in remodeled atria by 7-day tachypacing	Dog	NA	NS8593	In vivo, cardiomyocytes	Normal	Normal	Prolong aAPD and aERP	Antiarrhythmic: shorten AF duration	No effect on vERP	[70]
Sustained vernakalant-resistant AF by chronic atrial tachypacing	Pig	NA	AP14145	In vivo	Normal	Normal	Prolong aERP	Antiarrhythmic: prevent and terminate AF	No effect on vERP	[20]

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AF model	Species	Sex	Agents	Experimental settings	Ca^{2+} (mmol/L)*	K^{+} (mmol/L)*	Effects of I_{KAS} blockade on atrial electrophysiology	Effects of I_{KAS} blockade on atrial arrhythmogenesis	Effects on ventricular electrophysiology	Reference
Sustained vernakalant-resistant AF by chronic atrial tachypacing	Pig	Female	AP30663	In vivo	Normal	Normal	Prolong aERP	Antiarrhythmic: prevent and terminate AF	No effect on QT interval	[18]
Acutely induced AF	Dog	Male	Apamin or UCL1684	Isolated heart	1.8	4.5	Prolong aAPD with increased heterogeneity	Proarrhythmic: increase AF inducibility	NA	[37]
Acutely induced AF	SK2 null mutant mouse	NA	-	In vivo, cardiomyocytes	Normal	Normal	Prolong aAPD	Proarrhythmic: increase AF inducibility	NA	[49]
Acutely induced AF	SK3 overexpression mouse	NA	-	In vivo, cardiomyocytes	Normal	Normal	Shorten aAPD	Proarrhythmic: increase AF inducibility	No effect on QT interval	[113]

*Ion concentration in the Tyrode's solution used in the ex vivo whole heart experiments.

**Combined effects of I_{KAS} blockade and other antiarrhythmic drugs, compared with baseline.

aAPD, atrial action potential duration; aERP, atrial effective refractory period; AF, atrial fibrillation; vERP: ventricular effective refractory period; ICA: N-(23yridine-2-yl)-4-(23yridine-2-yl)thiazol-2-amine; Dct, dopachrome tautomerase

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Table 2

The role of I_{KAS} blockade on ventricular arrhythmogenesis in animal models

Model	Baseline rhythm at EPS	Ventricular arrhythmia	agents	Species	Sex	experimental settings	Ca^{2+} (mmol/L)*	K^{+} (mmol/L)*	Effects of I_{KAS} blockade on ventricular electrophysiology	Effects of I_{KAS} blockade on ventricular arrhythmogenesis	Reference
Normal heart with hypokalemia	AV block and ventricular pacing	Induced VF	Apamin	Rabbit	NA	Isolated heart, cardiomyocytes	1.8	2.4	Prolong APD	Proarrhythmic: increase VF inducibility	[5]
Heart with chronic ventricular pacing, no HF	AV block and ventricular pacing	Induced VF	Apamin	Rabbit	Female	Isolated heart	1.8	4.5	Prolong APD, prominent at distal sites from pacing site	Proarrhythmic: increase VF inducibility and duration	[102]
Heart hypertrophy by TAB, with isoproterenol and NS309 or CyPPA	Sinus rhythm	PVC, Spontaneous VT or VF	Apamin	Rat	Male	Isolated heart, cardiomyocytes	1.0	5.0	Prolong APD	Proarrhythmic: VT/VF induced by β-adrenergic stimulation	[41]
HF by tachypacing	AV block	PVC, TdP	Apamin	Rabbit	NA	Isolated heart	1.8	4.5	Prolong QTc and APD	Proarrhythmic: Increased EADs, PVC and TdP	[6]
Acute MI, with reperfusion	Sinus rhythm	PVC, spontaneous VT or VF	NS8593 or AP14145	Pig	Female	In vivo	Normal	Normal	No effect on QTc	Neutral: no effects on the frequency of PVC, VT, or VF	[56]
Normal heart with hypercalcemia	Atrial pacing	Induced VF	ICA, NS8593	Guinea pig	Female	Isolated heart	2.5	4.0	Prolong APD and ERP	Antiarrhythmic: prevent and terminate VF	[17]
Normal heart with isoproterenol	Sinus rhythm	Induced VF	Apamin	Rabbit	Female, male	Isolated heart, cardiomyocytes	1.8	4.7	Prolong APD in females	Antiarrhythmic: reduce VF inducibility	[10]
Normal heart with CyPPA	Sinus rhythm	Spontaneous VF	Apamin	Rabbit	Female, male	Isolated heart	1.8	4.7	Prolong APD heterogeneously	Antiarrhythmic: Prevent spontaneous VF	[9]
Normal heart with hypothermia	Sinus rhythm	Spontaneous VF	Apamin	Rabbit	Female, male	Isolated heart	1.8	4.7	Prolong APD heterogeneously	Antiarrhythmic: Prevent spontaneous VF	[9]
Heart hypertrophy with global hypoxia	Ventricular pacing	Spontaneous VF	Apamin, or UCL1684	Spontaneous hypertensive rats	Male	Isolated heart	1.8	5.4	Prolong APD	Antiarrhythmic: prevent VF	[85]

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Model	Baseline rhythm at EPS	Ventricular arrhythmia	agents	Species	Sex	experimental settings	Ca^{2+} (mmol/L)*	K^{+} (mmol/L)*	Effects of I_{KAS} blockade on ventricular electrophysiology	Effects of I_{KAS} blockade on ventricular arrhythmogenesis	Reference
HF by tachypacing	Sinus rhythm	Spontaneous VF	Apamin	Rabbit	NA	Isolated heart	1.8	4.5	Prolong APD, prevent postshock APD shortening	Antiarrhythmic: Prevent spontaneous VF	[13]
Acute MI	Sinus rhythm	Spontaneous VF, induced VT	Apamin or UCL1684	Rat	Male	In vivo	Normal	Normal	Prolonged ERP, prolonged APD in MI area	Antiarrhythmic: Prevent spontaneous VF/VT, reduce VT inducibility	[31]
Chronic (5 weeks) MI	Sinus rhythm	NA	Apamin	Rabbit	Female	Isolated heart, cardiomyocytes	1.8	4.5	Prevented postpacing APD shortening	Antiarrhythmic	[48]

* Ion concentration in the Tyrode's solution used in the ex vivo whole heart experiments.

APD, action potential duration; CV, conduction velocity; CyPPA, cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine; EPS, electrophysiological study; ERP, effective refractory period; HF, heart failure; MI, myocardial infarction; NA, not available; PVC, premature ventricular complexes; TAB, thoracic aortic banding; TdP, Torsades de pointes; VF: ventricular fibrillation; VT, ventricular tachycardia;

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Table 3

The role of I_{KAS} blockade on pulmonary vein and cardiac conduction systems

Region	Model	Agents	Species	Sex	experimental settings	Ca^{2+} (mmol/L)*	K^+ (mmol/L)*	Effects of I_{KAS} blockade on automaticity	Effects of I_{KAS} on MDP	Effects of I_{KAS} on AP amplitude	Effects of I_{KAS} blockade on APD	Reference
PV	Remodeled atria by 7-day atrial tachypacing	NS8593	Dog	NA	In vivo, single cells	Normal	Normal	NA	No effect	No effect	Prolong APD	[70]
PV	Normal atria with intermittent burst pacing	Apamin	Rabbit	Male	Tissue, single cells	0.9	4.0	NA			Prolong APD	[68]
Non-denudated PV	Normal atria	Apamin	Rabbit	NA	Tissue, single cells	2.7	4.0	Increase automaticity	No effect	No effect	No effect	[11]
Denudated PV	Normal atria	Apamin	Rabbit	NA	Tissue, single cells	2.7	4.0	Decrease automaticity	No effect	No effect	Prolong APD	[11]
SA node	Normal atria	Apamin	Rabbit	NA	Tissue, single cells	2.7	4.0	Decrease automaticity	No effect	No effect	Prolong APD	[11]
SA node	atria	Apamin	Wildtype mouse	Female, male	Tissue, single cells	1.8	5.4	Decrease automaticity	Decrease MDP	NA	Prolong APD	[87]
SA node	atria	Apamin	NCX knockout mouse	Female, male	Tissue, single cells	1.8	5.4	No effect on firing rate, but increase firing regularity	NA	NA	Prolong APD	[87]
Purkinje fiber	Normal ventricle with AV block	Apamin	Rabbit	Female, male	Isolated heart and pseudotendon	1.8	4.0	Increase automaticity	No effect on MDP, but lower the threshold potential for phase 0 depolarization	No effect	Prolong APD	[72,93]

AV, atrioventricular block; APD, action potential duration; PV, pulmonary vein; MDP, maximal diastolic potential; NCX, sodium-calcium exchanger; SA, sinoatrial

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Table 4

The role SK channels in neuromodulation of cardiac arrhythmias

Intervention	Anatomical target of stimulation	Protocol of intervention	Animal model	Species	Sex	Cardiac effects	*Intervention related SK channel regulation		Disease of interest	reference
							Region	SK2 expression		
Vagal nerve stimulation	Left cervical vagal nerve	1 week, low level	Normal heart	Dog	Male	NA	LSG	Upregulation and redistribution to the cell membrane	Arrhythmia	[76]
Vagal nerve stimulation	Right tragus	3 hours	Normal heart	Dog	NA	Decrease LF and LF/HF ratio; attenuate sympathetically induced sinus rate acceleration	RSG	Upregulation	Inappropriate sinus tachycardia	[115]
Vagal nerve stimulation	Right tragus	2 months, intermittent, low-level	Post-MI	Dog	NA	Reduce ventricular arrhythmia inducibility	LSG	Upregulation	Post-MI ventricular arrhythmias	[107]
Spinal cord stimulation	T1-T5 level	6 hours	rapid atrial pacing-induced AF	Dog	NA	Reduce AF inducibility	LSG, ARGP	Upregulation,	AF	[94]

*Compared with non-intervention group of the same model

AF, atrial fibrillation; ARGP, anterior right ganglionated plexus; HF, high frequency component of heart rate variability; LF, low frequency component of heart rate variability; LSG, left stellate ganglion; MI, myocardial infarction; RSG, right stellate ganglion

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