[Frontiers in Bioscience, Scholar, 8, 143-159, January 1, 2016]

Physiological roles of the transient outward current I_{to} in normal and diseased hearts

Jonathan M.Cordeiro[1], Kirstine Calloe[2], Roozbeh Aschar-Sobbi[3], Kyoung-Han Kim[4], Adam Korogyi[3], Dona Occhipinti[1], Peter H. Backx[3], Brian K. Panama[1]

[1]Department of Experimental Cardiology, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, New York, 13501 USA, [2]Danish National Research Foundation Centre for Cardiac Arrhythmia, Department of Veterinary Clinical and Animal Sciences, University of Copenhagen, Dyrlægevej 100, 1870 Frederiksberg C, Denmark, [3]Departments of Physiology and Medicine, University Health Network, University of Toronto. 1 King's College Circle, Toronto, Ontario, M5S 1A8 Canada, [4]Program in Developmental & Stem Cell Biology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8 Canada

TABLE OF CONTENTS

1. ABSTRACT

The Ca^{2+}-independent transient outward K^+ current (I_{to}) plays a critical role in underlying phase 1 of repolarization of the cardiac action potential and, as a result, is central to modulating excitation-contraction coupling and propensity for arrhythmia. Additionally, I_{to} and its molecular constituents are consistently reduced in cardiac hypertrophy and heart failure. In this review, we discuss the physiological role of I_{to} as well as the molecular basis of this current in human and canine hearts, in which I_{to} has been thoroughly studied. In particular, we discuss the role of I_{to} in the action potential and the mechanisms by which I_{to} modulates excitation-contraction coupling. We also describe the effects of mutations in the subunits constituting the I_{to} channel as well as the role of I_{to} in the failing myocardium. Finally, we review pharmacological modulation of I_{to} and discuss the evidence supporting the hypothesis that restoration of I_{to} in the setting of heart failure may be therapeutically beneficial by enhancing excitation-contraction coupling and cardiac function.

2. INTRODUCTION

The Ca^{2+}-independent transient outward K^+ current (I_{to}), also referred to as A-type current in neuronal tissue, plays a critical role in shaping the action potential (AP). I_{to} is observed in atrial and ventricular myocytes as well as Purkinje fibers of mammals including human (1, 2), dog (3, 4), feline(5), ferret (6), rabbit (7), rat (8, 9) and mouse (10). In larger mammals,I_{to} underlies the early phase of repolarization of the cardiac action potential (AP), and growing evidence suggests that I_{to} plays a key role in excitation-contraction (EC) coupling(11, 12), as well as in arrhythmogenesis(13). In addition, I_{to} and its molecular constituents are consistently reduced in cardiac hypertrophy and heart failure (1, 14).This review will highlight the physiological role of I_{to} as well as the molecular basis of this current in human and canine hearts. We will also discuss the role of I_{to} in the normal and failing myocardium, as well as under various pathophysiological conditions, such as the Brugada syndrome. Finally, we will discuss pharmaceutical modulation of I_{to} and how restoration of I_{to} in the setting of heart failure may be therapeutically beneficial.

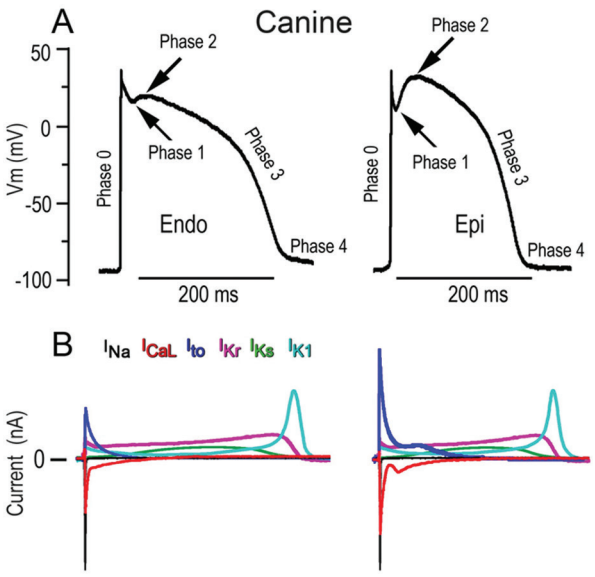

Figure 1. A cartoon depicting APs (Panel A) and underlying ionic currents (Panel B) from a canine left ventricular Endo and Epi cell. The time courses of ionic currents are partly based on recordings from previous publications (87,122-124).

3. THE ACTION POTENTIAL AND ROLE OF I_{TO}

The AP in cardiac muscle is critical for initiating and coordinating contraction of the working myocardium (15) while also minimizing arrhythmias via its relatively long refractory period (16, 17). The AP is generated by highly coordinate changes in different ionic conductances. In the human (or canine) heart, the AP is divided into five phases, 0 through 4 (Figure 1). In ventricular myocytes or Purkinje fibers, the initial depolarization (upstroke) to approximately +35 mV (Phase 0) is generated by Na^+ influx (I_{Na}), from coordinated opening of voltage-gated sodium channels(18) (Figure 1). The brief repolarization (Phase 1), or "notch," following the upstroke is due primarily to a Ca^{2+}-independent (fast) transient outward K^+ current (I_{to})(8, 19). I_{to} can be divided into two separate currents: $I_{to,f}$ (fast) and $I_{to,s}$ (slow), based upon their recovery times from inactivation. In addition, Ca^{2+}-activated Cl^- currents have also been thought to contribute to the Phase 1 repolarization (20, 21). The plateau (Phase 2) of the AP arises from a delicate balance between K^+ efflux through voltage-gated potassium channels and Ca^{2+} influx through voltage-gated calcium channels (I_{Ca}). In the late repolarization phase (Phase 3), the balance of ionic currents is shifted in favor of repolarization by the progressive increase in slow delayed rectifier potassium channels (I_{Ks}) due to slow activation as well as in the rapid delayed rectifier potassium channels (I_{Kr}) which has a unique rapid recovery from inactivation coupled with slow deactivation as the membrane potential becomes more negative. In the late phase 3, the K^+ conductance increases further due to the unblocking of inwardly rectifying potassium channels (I_{K1}), which are required to stabilize the resting membrane potential following full repolarization (Phase 4) (22). Marked differences in the shape and duration of the cardiac AP have been described in different regions of the mammalian heart, reflecting differences in the underlying ionic currents (7, 8, 23, 24). In humans and canines, the ventricular epicardium (Epi) tissue has a more prominent I_{to} compared to endocardial (Endo) tissue (7, 25, 26) (Figure 1). This transmural gradient of I_{to} results in the classical spike-and-dome morphology of Epi and midmyocardial (Mid) APs that is absent in Endo cells. In humans and canines, the Epi I_{to} is predominantly $I_{to,f}$ whereas $I_{to,s}$ is predominantly expressed in the Endo (1, 27). Besides transmural differences in phase 1 repolarization, there are marked differences in AP duration (APD), with long APs in Endo and Mid, whereas the APD is short in Epi (28).

4. PHYSIOLOGICAL ROLE OF I_{TO}

4.1. AP waveform and the initiation of Ca^{2+}-transients

Although much attention has focused on the electrical distinctions between the diverse ventricular cells types, it is clear the mechanical properties also vary across the ventricular wall (11, 12, 29). Coordinated contraction of the ventricle is necessary for the efficient ejection of blood to the body. For synchronization of ventricular contraction to occur one would anticipate that all areas of muscle are electrically excited at the same time (30, 31), however this is not the case. In dog, as in human, the electrical impulse distributed through the His-Purkinje system excites predominantly Endo. The wave of excitation must then traverse the ventricular muscle to excite the Mid and Epi layers. Although the Epi is the last region to be excited, it is the first region to repolarize. This observation is reflected by the positive T wave in the canine wedge model electrocardiogram (28). Studies have shown that the transmural conduction time is about 30-40 ms in the canine left ventricle (28). In spite of this difference in transmural conduction, all parts of the ventricle contract in unison. These observations suggest there are regional differences in cardiac excitation-contraction coupling must compensate for the inherent electrical time delays. Differences in AP waveform and duration, which are associated with variations in Ca^{2+} transient and Ca^{2+} homeostasis between Epi, Mid and Endo cells, are hypothesized to be important contributing factors for the appropriate synchronization of ventricular contraction (12) (Figure 2).

The Ca^{2+} transient is a dynamic process governed by Ca^{2+} influx and release as well as intracellular Ca^{2+} extrusion and re-uptake. Depolarization of the cardiac membrane results in influx of Ca^{2+} and subsequent release of Ca^{2+} from the SR, the process

© 1996-2016

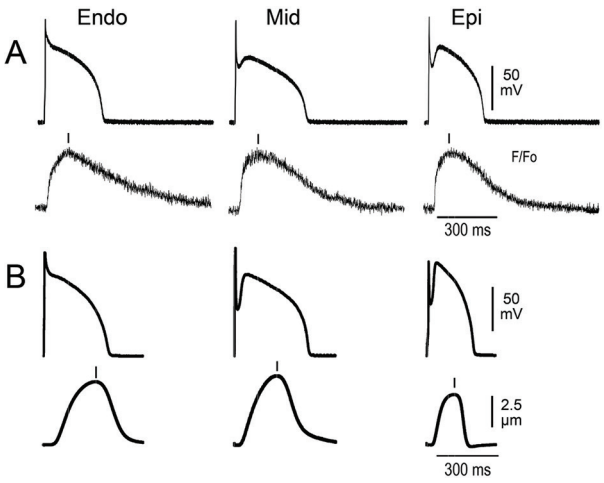

Figure 2. Panel A: Representative APs (top traces) and corresponding normalized Ca^{2+} transients (bottom traces) recorded from an Epi, Endo and Mid cell. Myocytes were paced at a cycle length of 2 s. The corresponding Ca^{2+} transients (lower trace) show that Endo cells have a slower time-to-peak as well as a slower decay of the Ca^{2+} transient. The tick marks on the Ca^{2+} transient traces denote the peak. Panel B: Representative APs (top) and corresponding unloaded cell shortening (bottom) recorded from and Epi, Endo and Mid cells. Myocytes were paced at a cycle length of 2 s. AP recorded from both Epi and Mid cells exhibit a rapid phase 1 repolarization and prominent spike and dome configuration compared to Endo cells. The latency to onset of contraction was relatively short in Epi and Mid cells and time-to-peak was longest in Endo cells. Modified with permission from (29).

of EC coupling. There are two sources of Ca^{2+} that contribute to this rise in intracellular Ca^{2+}: A) influx of Ca^{2+} across the sarcolemma via various pathways (32) and B) a release of Ca^{2+} from the sarcoplasmic reticulum (SR) (33-35). The classic model of excitation-contraction suggests that Ca^{2+} enters the cardiac cell via L-type Ca^{2+} channels and triggers a larger release of Ca^{2+} from the SR, a process referred to as "Ca^{2+}-induced Ca^{2+} release" (32, 36). Although the main source of trigger calcium is from L-type Ca^{2+} channels (37), activation of T-type Ca^{2+} current (38), and the Na^{+}-Ca^{2+} exchange operating in 'reverse-mode' (39, 40) are capable of initiating SR Ca^{2+} release to cause a contraction. The small, local increases in intracellular Ca^{2+} from ventricular cells (Ca^{2+} sparks; reviewed by (41)) are the result of brief, spontaneous openings from clusters of ryanodine receptors (RyRs) and are believed to be the elementary event underlying EC coupling in cardiac muscle. Ca^{2+} transients in cardiomyocytes represent the spatial and temporal summation of many Ca^{2+} sparks.

Consistent with the role of AP profile on Ca^{2+} release and contraction properties, regional differences in AP waveform and duration can dramatically affect the Ca^{2+} transient and mechanical shortening. The bulk of Ca^{2+} entry through I_{CaL} occurs during phase 1 and the plateau phase of the AP, where the membrane potential is in the optimal range for Ca^{2+} entry via I_{CaL} The magnitude of I_{CaL} is equivalent across the wall in the canine left ventricle when measured using a square wave voltage clamp pulse (Figure3A) (29, 42, 43). However, differences in AP morphology alter the size and kinetics I_{CaL} across the ventricular wall. Increasing the early rate of (phase 1) repolarization increases the driving force, which results in a large peak I_{CaL} amplitude, a faster time to peak of I_{CaL}, as well as greater total charge (Figure 3B) (11, 29, 44). These observations suggest that an AP waveform with a spike-and-dome morphology is a more efficient releaser of SR Ca^{2+} Conversely, an AP with a small phase 1 repolarization, such as in Endo, results in a smaller I_{CaL}, desynchronized SR Ca^{2+} release and reduced efficiency of EC coupling. This results in a slower velocity of cell shortening (Figure 3C). Nevertheless, variations in I_{to} and the size of the phase 1 repolarization across the ventricular wall contribute to differences in electrical and mechanical characteristics of the three cell types. The implications relative to the mechanical function of the heart under normal and diseased condition are numerous and will be described in the sections to follow.

4.2.The decline of Ca^{2+}transients

The duration of myocyte contraction is limited by the inactivation of I_{CaL} coupled with Ca^{2+} removal from the cytosol through several pathways, leading to a reduction in the cytosolic free Ca^{2+}, dissociation of Ca^{2+} from the contractile machinery and relaxation of the myocardium (45). The dominant pathway for removal of Ca^{2+} from the cytosol is through the activity of the SR Ca^{2+}-ATPase (SERCA), which derives the energy from ATP to actively pump Ca^{2+} into the lumen of the SR. The contribution of SERCA in the removal of Ca^{2+} from the cytosol varies between 70-92% depending on the species examined. The large contribution of SERCA to Ca^{2+} cycling ensures that the SR is replenished with Ca^{2+} and the cell is ready for the next round of EC coupling. In addition to SERCA, Ca^{2+} is also removed from the cytosol into the extracellular matrix through the activity of the Na^{+}-Ca^{2+} exchanger (NCX) which depending on the species, can contribute up to 30% to Ca^{2+} efflux (46). Evidently, the fraction of Ca^{2+} efflux by NCX is approximately equal to the amount of Ca^{2+} that enters the cell through the activity of I_{CaL} (47). In addition to playing a role in removal of Ca^{2+}, it has been suggested that Ca^{2+} influx through the reverse mode of the NCX may directly act as a trigger for Ca^{2+} release from the SR. The relative contribution of Ca^{2+} influx through NCX towards EC coupling remains to be determined.

When differences in the AP waveform and duration are eliminated by application of a square wave under voltage clamp conditions, some of these differences in cell shortening persists, suggesting there are intrinsic differences in E-C coupling between the three cell types. Therefore, factors other than AP morphology can contribute to the mechanical distinctions. These

© 1996-2016

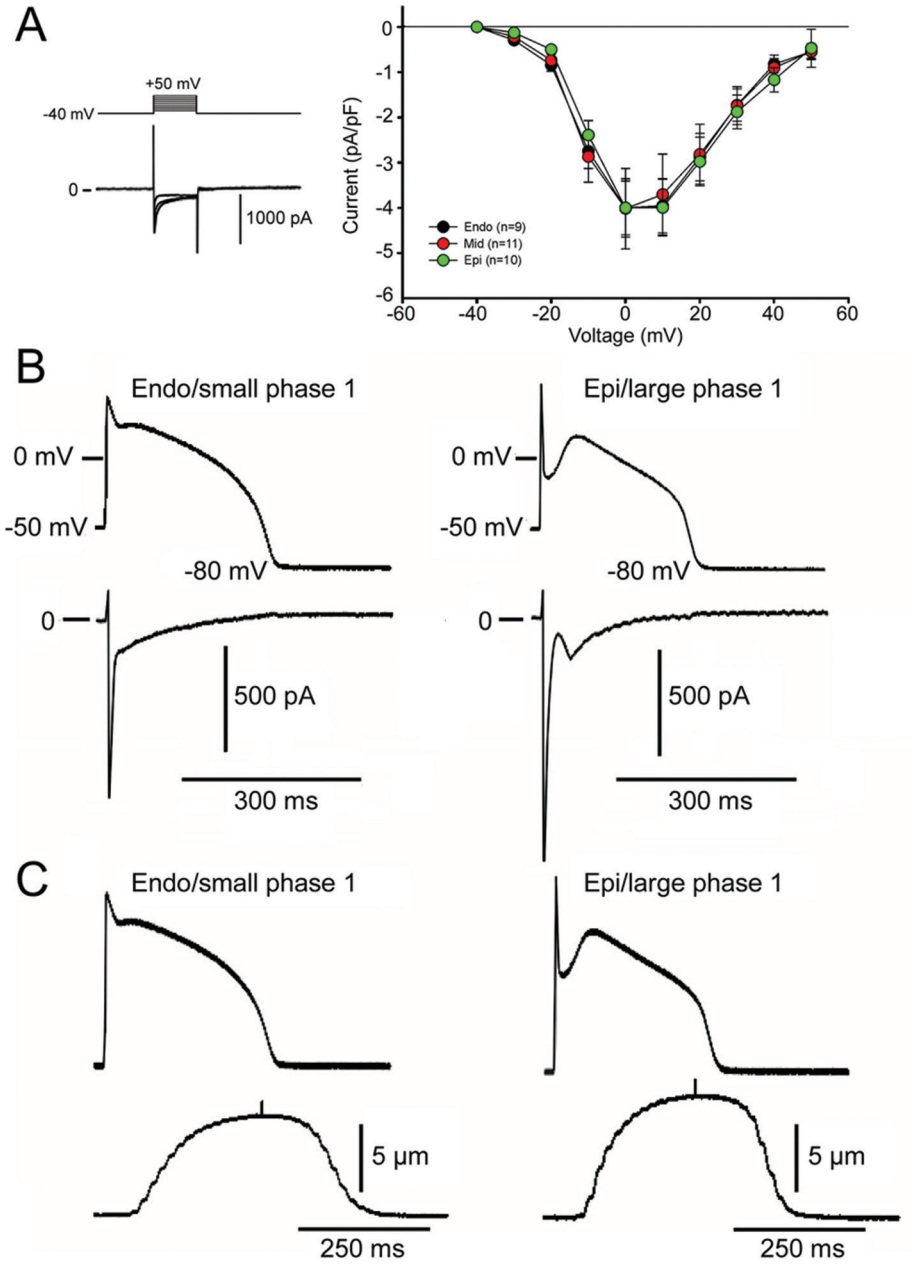

Figure 3. Panel A: Representative traces showing I_{Ca} recorded from a canine Mid ventricular myocyte. Ca^{2+} currents were recorded during a 300 ms step depolarization from –40 to +50 mV in 10 mV increments. Current-voltage relationship for I_{Ca} is shown on right side of Panel A. Panel B: Representative I_{CaL} current traces (defined as the nicardipine-sensitive difference current) recorded from a cell in response to an Endo (left side) or Epi (right side) AP waveform. To eliminate the effects of I_{Na}, the AP was modified so that -50 mV was the start of the waveform (top of figure). Application of the Epi- waveform produced a larger peak current and greater charge entry compared to the Endo- waveform. Panel C: Endo and Epi AP waveforms and corresponding cell shortening (bottom traces) recorded from a cell in response to endocardial and Epi AP waveforms (top). Five pre-pulses were applied to the cell to maintain uniform SR Ca^{2+} content. Application of the Epi waveform caused a faster time-to-peak and greater cell shortening. The tick marks on the cell shortening traces denote the peak. Modified with permission from (29).

variations may be due to differences in intracellular Ca^{2+} buffering or expression of Ca^{2+} handling proteins. In canine ventricular myocardium, it has been shown that the expression of SERCA is greater in the Epi versus Endo (Figure 4). The greater SERCA2a expression in Epi results in a faster decline of the Ca^{2+} transient (48).

5. MOLECULAR COMPONENTS AND REGULATION OF I_{TO}

5.1. Molecular composition of cardiac I_{to}

$I_{to,f}$ currents are generated by channels consisting of voltage-gated α-pore-forming Kv4

© 1996-2016

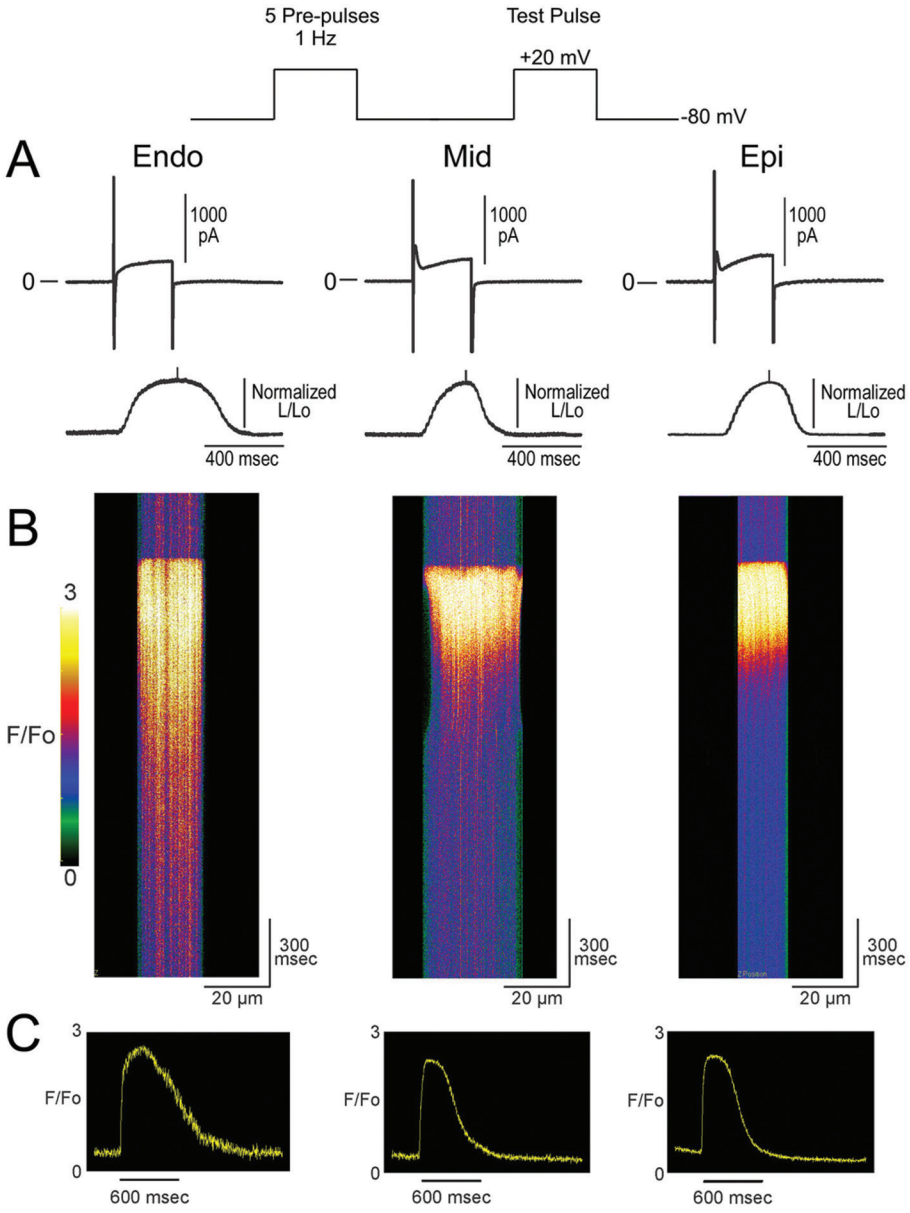

Figure 4. Representative recording of ionic currents (upper panel) and cell shortening (lower panel) from an Endo, Mid and Epi myocardial cell recorded under voltage clamp conditions. The voltage clamp protocol is shown at the top. Five pre-pulses were applied to maintain a constant SR load. Following application of a 300 ms test-pulse to +20 mV, a large I_{to} can be observed in the Epi and Mid cells (upper traces). The tick marks on the cell shortening traces denote the peak. Representative recording of corresponding confocal xt line scans (panel B) from an Endo, Mid and Epi cell recorded under voltage clamp. The voltage clamp protocol is shown at the top of the figure. Five pre-pulses were applied to the myocytes to maintain a constant SR load. Following application of a 300 ms test-pulse to +20 mV, a large I_{to} can be observed in the epi and mid cell (panel A). The corresponding line scan recordings (panel B) and time course of F/Fo (panel C) for Epi and Mid cells show similar kinetics. In contrast, the line scan recorded from the Endo cell has a much slower decay compared to the other two cell types. Modified with permission from (29, 125).

subunits. Assembly of four Kv α-subunits into a tetrameric structure forms functional $I_{to,f}$ channels (49). In human and canine hearts, the majority of studies have shown that Kv4.3 is the predominant α-subunit of $I_{to,f}$ (50, 51). Heterologous expression of Kv4 α subunits show rapidly activating, inactivating and recovering $I_{to,f}$-like outward K^+ currents (9), which are sensitive to heteropodatoxins (HpTx) (52), and phrixotoxin (PaTxs) similar to native $I_{to,f}$. Several transgenic mouse studies have provided further evidence regarding molecular identity of $I_{to,f}$. Heterologously expressed Kv4 channels do not recapitulate entirely the kinetics of native cardiac I_{to}, and Kv4 channels have been shown to assemble with various ancillary β-subunits in cardiac tissue (Figure 5). The most prominent, K^+ Channel Interaction

© 1996-2016

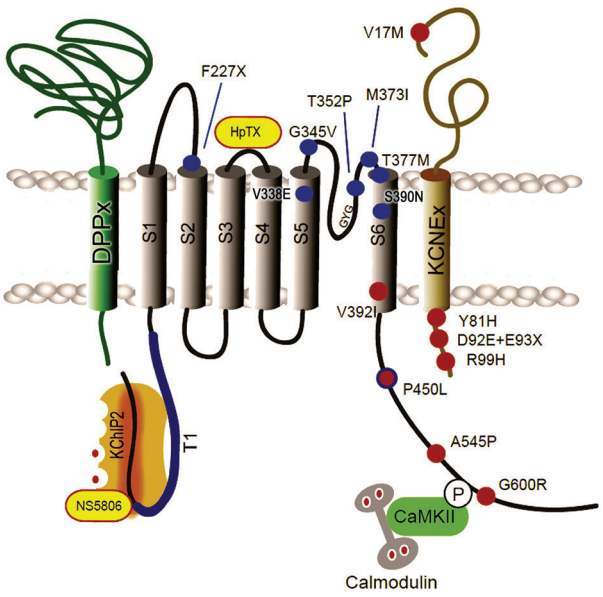

Figure 5. Disease causing mutations in Kv4 and interacting subunits as well as putative drug binding sites. Heteropoda venatoria toxins selectively inhibit Kv4 channels by stabilization of the closed state by binding to the S3B to S4 linker segment (108).NS5806 has been suggested to modulate the interaction between the hydrophobic groove on KChIP and Kv4 as well as to affect calcium sensitivity of KChIP (118). Loss-of-function mutations in Kv4 have been linked to spinocerebellar ataxia (SCA) (indicated by blue dots). SCA19 is associated with T352P, M373I and S390N (92). SCA22 is associated with an in-frame 3-nucleotide deletion F227del, V338E, G345V and T377M (126). Gain-of-function mutations (marked by reddots) have been linked to sudden unexpected death, V392I and G600R (86), the Brugada syndrome (BrS), L450F and G600R (85) and early onset atrial fibrillation, A545P (87). P450L (marked by red dot with blue outline) has been associated with both BrS and SCA (93). P450L results in a gain of function of Kv4.3.In the accessory subunit KCNE3, R99H resulting in increased Kv4 currents has been linked to BrS (90). Likewise, mutations in KCNE5, Y81H, D92E+E93X, resulting in increased Kv4 currents has been linked to BrS (73).

Protein 2 (KChIP2) is one of four KChIPs (KChIP1–4) that are members of the neuronal calcium sensor subfamily of Ca^{2+} binding proteins characterized by four Ca^{2+}-binding EF-hand motifs (53). It is believed that only KChIP2 is specifically expressed in the heart (54), and KChIP2 co-immunoprecipitates with both Kv4.2 and Kv4.3 (55).

KChIP2 increases Kv4.3 current density by facilitating trafficking, slowing inactivation and accelerating recovery kinetics (10, 56). Co-expressed with KChIP2, Kv4-encoded currents in heterologous systems are almost identical to native $I_{to,f}$ in rodent cardiomyocytes(57). Interestingly, mice lacking KChIP2 have no $I_{to,f}$, (10, 58)suggesting an additional role of KChIP2 in facilitating expression of Kv4 channels by stabilizing Kv4 proteins in their formation (59, 60). Several studies suggest that Kv4.3 mRNA levels are uniform throughout the canine left ventricle and the gradient in I_{to} expression is due to a gradient in KChIP2, as KChIP2 mRNA is more abundant in Epi- and Mid than in Endo (2, 27, 61, 62). Interestingly, the time constant (t) of decay was faster in Epi and Mid than in Endo (6, 63). As KChIP2 slows Kv4.3. current decay (64), this may suggest that Endo I_{to} is not merely Kv4.3. in absence of KChIP2 and indicates that other K^+ subunits contribute to Endo I_{to} in human and canine hearts.

Besides KChIP2, several other proteins expressed in ventricular tissue have been shown to interact with Kv4.3. Similar to KChIP2, dipeptidyl-peptidases (DPP6 and DPP10) can facilitate Kv4.3 trafficking and accelerate recovery from inactivation; however, in contrast to KChIP2, the DPPs accelerate Kv4.3 inactivation (65) and increase single channel conductance of Kv4.2 (66). DPP6 expression in the heart has been demonstrated both at mRNA and protein level (67). Whether DDP10 is expressed in cardiomyocytes is at the present unclear, though DPP10 mRNA has been detected in atrial tissue (68). Very little is known about the nature of the interaction between Kv4 and DPP, it has been suggested to involve the transmembrane regions of both proteins (69).

Several members of the KCNE β-subunit family have been demonstrated to modulate Kv4 density and kinetics. Loss of KCNE2 in mice leads to a reduction in ventricular $I_{to,f}$ (70).whereas KCNE3 inhibits Kv4 (71). A recent study demonstrated that KCNE4 expression is localized in the transverse tubules of murine cardiac myocytes, where it co-assembles with Kv4.2 regulating I_{to} in a "KChIP2-dependent manner" (72). KCNE5 modulates Kv4 channels in the heterologous system and a mutation in KCNE5 resulting in less inhibition of Kv4.3 current have been linked to the Brugada syndrome (BrS)(73). Interestingly, the KCNE5 expression is elevated in failing human hearts (74). Other subunits have been proposed to modulate $I_{to,f}$ but the physiological importance may be uncertain.

Several studies have demonstrated that I_{to} in human and canine is not simply mediated by Kv4.3 channel but that other α subunits may be involved. The presence of Kv1.4 and Kv1.5 has been noted in the ventricle of both human and canine ventricle (3, 14). These α-subunit are expressed at lower levels compared to Kv4.3 but their presence have been consistently measured by numerous investigators. Kv1.4 gives rise to a slowly recovering $I_{to,s}$ and is likely responsible for the slow phase of I_{to} recovery in dog ventricle (27). The presence of a TEA- sensitive I_{to} conducted through Kv3.4. was noted in dog ventricular and Purkinje tissue (75). The presence of Kv3.4 message was verified in human tissue by Gaborit *et al*. (51). In that same study, the authors noted the presence of Kv4.2 message, an α-subunit thought to only be present only in rodents (51). Interestingly, a more recent publication noted a rare genetic mutation of the *KCND2* gene in a patient with J-wave syndrome supporting a functional role for Kv4.2

© 1996-2016

in human ventricle (76). These observations suggest that $I_{to,}$ in human ventricle may also consist of Kv1.4, Kv1.5, Kv3.4 and Kv4.2, but the precise subunit composition remains to be elucidated.

5.2. Molecular regulation of I_{to}

I_{to} and its molecular constituents are highly regulated by multiple transcription factors, both constituently and in response to pro-hypertrophic stimulation, as well as stimulation of adrenergic pathways. With regards to constitutive regulation, Iroquois-class homeo-domain protein 5 (Irx5), which is expressed transmurally as a gradient from Endo-to-Epi (large to small), is a repressor of Kv4.2 expression in the mouse heart and Irx5 has been suggested to establish the $I_{to,f}$ Epi-to-Endo gradient in murine hearts (77). In addition, Jia *et al*. found that GATA and FOG2 transcription factors can drive expression of the Kv4.2. promoter (78). The same group also found that c-Jun NH(2)-terminal kinases play a role in mediating the α-adrenergic receptor-induced reduction in KChIP2, and the MEK-ERK pathway mediates the protein kinase C-mediated down-regulation. In mouse, I_{to} was found to negatively regulate by the calcineurin/nuclear factor activated T-cell system (NFAT) (79).This mechanism is intriguing since calcineurin/NFAT is activated in heart failure (HF) (80), which coincides with decreases in I_{to}. However, in rat neonatal cardiomyocytes calcineurin/NFAT increases I_{to} via up-regulation of Kv4.2 (81). Adding to this complexity, we found that ubiquitous transcription factor nuclear factor kappaB mediates α-adrenergic receptor-induced reductions in KChIP2 expression (82). Further studies are warranted to more fully understand the complicated transcriptional regulation of I_{to} subunits by adrenergic stimulation in the context of heart disease.

6. PATHOPHYSIOLOGICAL CONDITIONS AND THE ROLE OF I_{TO} AND ITS PHARMACOLOGY

The transient outward potassium current I_{to} has been linked to several pathophysiological conditions and inherited syndromes. In the cardiac field, I_{to} has been suggested to play a role in the BrS or J-wave syndromes, atrial fibrillation (AF) as well as in hypertrophy and HF. Since I_{to} is altered in multiple diseases, its potential as a pharmacological target is also highly relevant.

6.1. Inherited I_{to} linked channelopathies

The Brugada syndrome was first described as a new clinical entity in 1992(83) and is associated with nocturnal polymorphic ventricular tachycardia and sudden death, predominantly in young males. BrS is characterized by a ST-segment elevation in the right precordial leads, occurring in the absence of structural heart disease. The majority of BrS cases have been linked to loss-of function mutations in cardiac I_{Na} ((84) for a recent review); however, several gain-of-function mutations in Kv4.3. have been linked to BrS (L450F and G600R (85)) or sudden unexpected death (SUD, V392I and G600R (86). Kv4.3. gain of function has also been linked to atrial fibrillation (AF, A545P (87)). All these known gain-of-function mutations in Kv4.3. are located to the C-terminus of Kv4.3. (Figure 5). The C-terminus harbors several sites involved in post-translational modifications (reviewed by (88)), and may be involved in stabilizing the interaction between KChIP2 and Kv4 subunits (89). Furthermore, mutations in the accessory subunits KCNE3 (90) and KCNE5 (91) have been linked to BrS. Both KCNE3 and KCNE5 normally exert an inhibitory effect on Kv4.3. to suppress I_{to} (71, 90) and mutations in these subunits remove this inhibitory effect resulting in higher I_{to} densities.

It is important to note that not all BrS patients harboring mutations in Kv4.3. exhibit documented AF (85, 86), and conversely, a Kv4.3. AF patient did not show a BrS ECG phenotype when administered a flecanide challenge (87), suggesting that the expression and/or regulation of other cardiac currents may influence the phenotype. In addition, the Kv4.3. protein is expressed in many different tissue types including neuronal tissue. Loss-of-function mutation in the Kv4.3.α-subunit has been associated with inherited spinocerebellar ataxia (SCA), a progressive disease associated with atrophy of the cerebellum causing ataxia of gait and limbs as well as eye movement and speech impediments. SCA has been linked to loss-of-function and impaired trafficking mutations in Kv4.3 (92). Interestingly, P450L has been associated with both BrS and SCA (93). This puzzling observation has not been resolved, but electrophysiological studies revealed P450L results in a gain of function of Kv4.3. For the other loss-of-function mutations (Figure 5), no cardiac phenotype has been reported.

6.2. Alterations in heart failure

Besides the inherited syndromes due to mutations in I_{to} subunits, changes in I_{to} expression has repeatedly been linked to a number of cardiac pathologies, including hypertrophy and HF.

During the development of HF, a cascade of events occurs to cardiac tissue that ultimately results in a reduced cardiac output. These changes are multiple and complicated but include alterations in ion channel currents, Ca^{2+} cycling proteins and ultrastructure changes. The changes that occur, predispose the failing heart to ventricular tachyarrhythmias and sudden cardiac death triggered by early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). Typically, studies have focused on defects in intracellular Ca^{2+} cycling and the subsequent remodeling of these processes. Indeed, altered Ca^{2+} handling during heart failure has been linked to changes in Ca^{2+} handling proteins such as a decrease in I_{CaL} density (94) and increased NCX (95, 96).

© 1996-2016

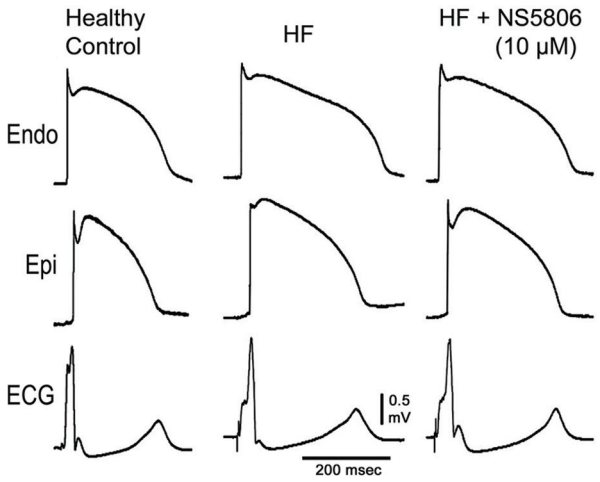

Figure 6. Ventricular tachypacing-induced heart failure-induced reduction in epicardial AP notch and ECG J wave is reversed by NS5806. Left Panel: Representative LV wedge isolated from a normal heart showing Epi and Endo AP as well as corresponding transmural ECG. A pronounced spike-and-dome AP is apparent in the Epi recording. Middle Panel: Representative LV wedge isolated from a 2-week HF heart showing a decrease in Phase 1 repolarization, loss of spike-and-dome morphology and J wave. Right panel: 10 μM NS5806 restores AP notch and J wave toward control. Basic cycle length = 2000 ms. Modified with permission from (120).

Down regulation of many repolarizing potassium currents during heart failure is well documented (for review see (97,98)). $I_{to,f}$ is reduced in both human and animal models of HF (1, 99-101), concomitant with a decrease in phase 1 repolarization and an increase in AP duration (102).The early repolarization phase of the ventricular AP determines the electrochemical driving force for Ca^{2+} influx through L type Ca^{2+} channels. Therefore, cell types with a large I_{to} and spike and dome morphology have a significantly larger peak I_{CaL} as well as greater total charge compared to a cell type where I_{to} is absent (29, 44). However, what happens under pathophysiological conditions when I_{to} is altered? How does this affect the magnitude and kinetics of I_{CaL}?

A smaller I_{to} results in a significant reduction in peak I_{CaL} as well as total charge when compared with a cell type where I_{to} is prominent (Figure 3B) (12, 29). The reduction in I_{CaL} will affect Ca^{2+} transients (12) and ultimately contraction (Figure 3C). These observations were verified in a study by Cooper *et al*., (103) who applied previously recorded failing human hearts APs to healthy ventricular rat myocytes using AP voltage clamp techniques. The results demonstrated that applying HF-like AP waveforms to healthy cardiomyocytes lead to a reduced I_{CaL} and a reduced Ca^{2+} transient compared to when a human non-failing AP waveform was applied to the same cell. The loss of $I_{to,f}$ also results in a loss of the transmural gradient in phase 1 repolarization resulting in Epi and Endo tissue having a similar AP morphology (Figure 6). As the early repolarization phase is important to synchronize Ca^{2+} transients and cell shortening across the ventricular wall, a loss of I_{to} will ultimately affect contraction and worsen energy expenditure in the failing heart. This indicates that restoration of the early repolarization may be beneficial to patients in heart failure. However, it is important to note that in the failing heart, changes in AP waveform and duration due to loss of I_{to} and other ionic currents should not be considered separately from changes in EC coupling.

6.3. Pharmacology

Kv4 currents are selectively inhibited by several spider toxins containing three disulfide bonds that form an “inhibitory cysteine knot,” including the Heteropoda venatoria toxins (104) HpTX2 (105) and HpTX3 (6), the Phrixotrichus auratus toxins PaTx1 and PaTx2 (106) and the Theraphosa leblondi toxins TLx1-3 (107).These toxins exert their function by binding to the extracellular linker region between transmembrane segments S3B and S4 (105, 108)and rather than occluding the channel pore, these toxins work by interfering with the channel’s gating mechanism and stabilizes the closed state of the channel protein(108,109). Recently, Kv4 channels have been shown to be blocked by the AmmTX3 of the α-KTX15 family of scorpion toxins, principally in the presence of the auxiliary subunits DPP6 and DPP10 (110).

Kv4.3/$I_{to,f}$ is blocked by 4-aminopyridine (4-AP) in millimolar range concentrations(111). However, 4-AP also blocks Kv1 channels/$I_{to,s}$ in micromolar concentrations, which limits the use of 4-AP to discriminate between $I_{to,f}$ and $I_{to,s}$. Interestingly the underlying mechanisms are different. $I_{to,s}$ 4-AP is blocked in the open-state whereas 4-AP binds to $I_{to,f}$ in the closed state (112), which results in complex recovery properties of I_{to}(112). $I_{to,f}$ is blocked by several sodium channel blockers, including flecainide(113) and quinidine(114) and several calcium channel blockers, including nifedipine (115). Since a large phase 1 repolarization and I_{to} is thought to play a central role in the BrS, I_{to} blockers could be of therapeutic value in BrS. In line with this, hydroquinidine could prevent VT/VF induction in a group of asymptomatic BrS patients with inducible arrhythmias (116) as well as reduced the occurrence of arrhythmias in BrS patients that had suffered several ICD shocks (117). However, quinidine is associated with frequent gastrointestinal side-effects (84) and the development of better I_{to} antagonists could be beneficial for treating BrS patients.

We have recently added an $I_{to,f}$ activator, NS5806, to this list of I_{to} affecting compounds. NS5806 increases $I_{to,f}$ peak currents and slows current decay (27). This resulted in enhanced phase 1 repolarization in canine ventricular wedge preparations(62). NS5806 has been suggested to modulate the interaction between the hydrophobic groove on KChIP2 and Kv4 as well as to

© 1996-2016

affect Ca^{2+} sensitivity of KChIP2(118); however, in the absence of KChIP2 there is still substantial effect of NS5806 on Kv4.3. currents(119) suggesting additional binding sites for NS5806 on the Kv4 subunits.

7. I_{TO} AS THERAPEUTIC TARGET FOR HEART FAILURE?

Several lines of evidence suggest that restoring I_{to} in the setting of heart failure could be beneficial: 1) Application of an $I_{to,f}$ activator will result in restoration of the spike-and-dome morphology (120) resulting in an immediate increase in Ca^{2+} influx into the cell during the course of an AP; 2) by restoring $I_{to,f}$, the transmural gradient in phase 1 repolarization would also be restored which would results in a better coordination of the calcium transients and transmural contraction. This could potentially decrease the energy expenditure and improve the contractile function of the heart, and 3) on the long term basis, enhancement of $I_{to,f}$ will maintain SR load since a greater amount of Ca^{2+} will enter the cell during each AP. We have recently demonstrated that application of the I_{to} activator NS5806, resulted in restoration in the spike and dome morphology of the AP in failing hearts (Figure 6). Despite the clear evidence for the potential benefit of modulation of $I_{to,f}$ in heart failure, these studies are still lacking in animal models with classical spike-dome AP morphology, which would be more applicable to humans. Novel $I_{to,f}$ agonists, such as NS5806, and the greater technological potential for viral gene transfer (121) will greatly enhance the prospects of exploring this hypothesis in the near future.

8. SUMMARY

Because of its prominent role in cardiac excitability, I_{to} is one of the most studied K^+ currents. I_{to} plays a role Brugada syndrome and is altered in a number of cardiomyopathies including heart failure. In addition, it is clear that the I_{to} mediated spike-and-dome morphology is essential for normal repolarization and can have important effects on EC coupling in canine and human hearts. The spike and dome-morphology results in a significant increase in peak I_{CaL} as well as total charge when compared to a cell type where I_{to} is reduced or absent. In the setting of heart failure, where I_{to} is known to be reduced, this reduction in I_{to} results in reduced Ca^{2+} influx into the cell via I_{CaL}. Augmentation of I_{to} in heart failure may have a beneficial effect on cardiac output since application of an I_{to} activator will result in restoration of the spike-and-dome morphology resulting in an immediate increase in Ca^{2+} influx into the cell during the course of an AP. Furthermore, enhancement of I_{to} may re-establish the transmural gradient of phase 1 repolarization and improve the synchronization of contraction which will minimize the metabolic stress of the failing heart. On a long term basis, increasing I_{to} may help maintain SR load since a greater amount of Ca^{2+} will enter the cell during each AP. Further studies are warranted to examine this hypothesis.

9. ACKNOWLEDGEMENTS

JM. Cordeiro, K. Calloe and R. Aschar-Sobbi contributed equally to this work. The authors are grateful to Judy Hefferon for assistance with Figure formatting. This study was supported by the Masons of New York State, Florida, Massachusetts and Connecticut, Danish National Research Foundation Centre for Cardiac Arrhythmia (KC) in addition to grants from Heart and Stroke Foundation (H&SF) of Ontario Canada (T6485) and Canadian Institutes for Health Research (MOP185773) to PHB. PHB is a Career Investigator with the H&SF of Ontario.

10. REFERENCES

1. S. Kaab, J. Dixon, J. Duc, D. Ashen, M. Nabauer, D. J. Beuckelmann, G. Steinbeck, D. McKinnon and G. F. Tomaselli: Molecular basis of transient outward potassium current downregulation in human heart failure: a decrease in Kv4.3. mRNA correlates with a reduction in current density. *Circulation*, 98(14), 1383-1393 (1998)
DOI: 10.1161/01.CIR.98.14.1383

2. B. Rosati, Z. Pan, S. Lypen, H. S. Wang, I. Cohen, J. E. Dixon and D. McKinnon: Regulation of KChIP2 potassium channel beta subunit gene expression underlies the gradient of transient outward current in canine and human ventricle. *J.Physiol*, 533(Pt 1), 119-125 (2001)
DOI: 10.1111/j.1469-7793.2001.0119b.x

3. E. J. Dixon, W. Shi, H.-S. Wang, C. McDonald, H. Yu, R. S. Wymore, I. S. Cohen and D. McKinnon: Role of the Kv4.3. K+ channel in ventricular muscle. A molecular correlate for the transient outward current. *Circ.Res.*, 79, 659-668 (1996)
DOI: 10.1161/01.RES.79.4.659

4. S. Zicha, L. Xiao, S. Stafford, T. J. Cha, W. Han, A. Varro and S. NatTel: Transmural expression of transient outward potassium current subunits in normal and failing canine and human hearts. *J.Physiol*, 561(3), 735-748 (2004)
DOI: 10.1113/jphysiol.2004.075861

5. T. Furukawa, R. J. Myerburg, N. Furukawa, A. L. Bassett and S. Kimura: Differences in transient outward currents of feline

© 1996-2016

endocardial and epicardial myocytes. *Circ. Res.*, 67, 1287-1291 (1990)
DOI: 10.1161/01.RES.67.5.1287

6. M. V. Brahmajothi, D. L. Campbell, R. L. Rasmusson, M. J. Morales, J. S. Trimmer, J. M. Nerbonne and H. C. Strauss: Distinct transient outward potassium current (Ito) phenotypes and distribution of fast-inactivating potassium channel alpha subunits in ferret left ventricular myocytes. *J.Gen.Physiol*, 113(4), 581-600 (1999)
DOI: 10.1085/jgp.113.4.581
7. D. Fedida and W. R. Giles: Regional variations in action potentials and transient outward current in myocytes isolated from rabbit left ventricle. *J Physiol*, 442, 191-209 (1991)
DOI: 10.1113/jphysiol.1991.sp018789
8. R. B. Clark, R. A. Bouchard, E. Salinas-Stefanon, J. Sanchez-Chapula and W. R. Giles: Heterogeneity of action potential waveforms and potassium currents in rat ventricle. *Cardiovasc.Res.*, 27, 1795-1799 (1993)
DOI: 10.1093/cvr/27.10.1795
9. A. D. Wickenden, R. G. Tsushima, V. A. Losito, R. Kaprielian and P. H. Backx: Effect of Cd^{2+} on $K_v4.2$. and $K_v1.4$. expressed in *Xenopus* oocytes and on the transient outward currents in rat and rabbit ventricular myocytes. *Cell Physiol Biochem.*, 9(1), 11-28 (1999)
DOI: 10.1159/000016299
10. H. C. Kuo, C. F. Cheng, R. B. Clark, J. J. Lin, J. L. Lin, M. Hoshijima, V. T. Nguyen-Tran, Y. Gu, Y. Ikeda, P. H. Chu, J. Ross, W. R. Giles and K. R. Chien: A defect in the K_v channel-interacting protein 2 (KChIP2) gene leads to a complete loss of I_{to} and confers susceptibility to ventricular tachycardia. *Cell*, 107(6), 801-813 (2001)
DOI: 10.1016/S0092-8674(01)00588-8
11. R. Sah, R. J. Ramirez and P. H. Backx: Modulation of Ca^{2+} release in cardiac myocytes by changes in repolarization rate: role of phase-1 action potential repolarization in excitation-contraction coupling. *Circ.Res.*, 90(2), 165-173 (2002)
DOI: 10.1161/hh0202.103315
12. R. Sah, R. J. Ramirez, G. Y. Oudit, D. Gidrewicz, M. G. Trivieri, C. Zobel and P. H. Backx: Regulation of cardiac excitation-contraction coupling by action potential repolarization: role of the transient outward potassium current (I(to)). *J Physiol*, 546(Pt 1), 5-18 (2003)
DOI: 10.1113/jphysiol.2002.026468
13. K. Calloe, J. M. Cordeiro, J. M. Di Diego, R. S. Hansen, M. Grunnet, S. P. Olesen and C. Antzelevitch: A transient outward potassium current activator recapitulates the electrocardiographic manifestations of Brugada syndrome. *Cardiovasc.Res.*, 81(4), 686-694 (2009)
DOI: 10.1093/cvr/cvn339
14. F. G. Akar, R. C. Wu, G. J. Juang, Y. Tian, M. Burysek, D. DiSilvestre, W. Xiong, A. A. Armoundas and G. F. Tomaselli: Molecular mechanisms underlying K^+ current downregulation in canine tachycardia-induced heart failure. *Am J Physiol Heart Circ.Physiol*, 288(6), H2887-H2896 (2005)
DOI: 10.1152/ajpheart.00320.2004
15. B. F. Hoffman and P. F. Cranefield: Electrophysiology of the heart. McGraw-Hill, New York (1960)
16. G. W. Mainwood and S. L. Lee: Rat heart papillary muscles: action potentials and mechanical response to paired stimuli. *Science*, 166(3903), 396-397 (1969)
DOI: 10.1126/science.166.3903.396
17. G. A. Langer, A. J. Brady, S. T. Tan and S. D. Serena: Correlation of the glucoside response, the force staircase, and the action potential configuration in the neonatal rat heart. *Circ. Res.*, 36, 744-752 (1975)
DOI: 10.1161/01.RES.36.6.744
18. A. L. Goldin: Resurgence of sodium channel research. *Annu.Rev.Physiol*, 63, 871-894 (2001)
DOI: 10.1146/annurev.physiol.63.1.871
19. K. K. Deal, S. K. England and M. M. Tamkun: Molecular physiology of cardiac potassium channels. *Physiol.Rev.*, 76, 49-67 (1996)
20. A. C. Zygmunt and W. R. Gibbons: Calcium-activated chloride current in rabbit ventricular myocytes. *Circ.Res.*, 68, 424-437 (1991)
DOI: 10.1161/01.RES.68.2.424
21. A. C. Zygmunt: Intracellular calcium activates chloride current in canine ventricular myocytes. *Am.J.Physiol.*, 267(5 Pt 2), H1984-H1995 (1994)
22. A. N. Lopatin and C. G. Nichols: Inward rectifiers in the heart: an update on I(K1).

© 1996-2016

J.Mol.Cell Cardiol., 33(4), 625-638 (2001)
DOI: 10.1006/jmcc.2001.1344

23. C. Antzelevitch, S. Sicouri, S. H. Litovsky, A. Lukas, S. C. Krishnan, J. M. Di Diego, G. A. Gintant and D. W. Liu: Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. *Circ.Res.*, 69(6), 1427-1449 (1991)
DOI: 10.1161/01.RES.69.6.1427

24. E. Wettwer, G. J. Amos, H. Posival and U. Ravens: Regional differences in transient outward current I_{to} in ventricular myocytes from subendocardium and subepicardium in human hearts. *Proceeding of IUPS (Glasgow)*, 13 (1993)

25. D. W. Liu, G. A. Gintant and C. Antzelevitch: Electrophysiologic characteristics of myocytes isolated from canine ventricular epicardium, midmyocardium and endocardium. *Proc First Annual Upstate NY Cardiac Electrophysiol. Soc.* (1991)

26. D. L. Campbell, R. L. Rasmusson, Y. H. Qu and H. C. Strauss: The calcium-independent transient outward potassium current in isolated ferret right ventricular myocytes. I. Basic characterization and kinetic analysis. *J.Gen.Physiol.*, 101, 571-601 (1993)
DOI: 10.1085/jgp.101.4.571
DOI: 10.1085/jgp.101.4.603

27. K. Calloe, E. Soltysinska, T. Jespersen, A. Lundby, C. Antzelevitch, S. P. Olesen and J. M. Cordeiro: Differential effects of the transient outward K^+ current activator NS5806 in the canine left ventricle. *J Mol Cell Cardiol*, 48(1), 191-200 (2010)
DOI: 10.1016/j.yjmcc.2009.07.017

28. G. X. Yan and C. Antzelevitch: Cellular basis for the electrocardiographic J wave. *Circulation*, 92(8), I-71 (1995)

29. J. M. Cordeiro, L. Greene, C. Heilmann, D. Antzelevitch and C. Antzelevitch: Transmural heterogeneity of calcium activity and mechanical function in the canine left ventricle. *Am J Physiol Heart Circ.Physiol*, 286, H1471-H1479 (2004)
DOI: 10.1152/ajpheart.00748.2003

30. V. S. Markhasin, O. Solovyova, L. B. Katsnelson, Y. Protsenko, P. Kohl and D. Noble: Mechano-electric interactions in heterogeneous myocardium: development of fundamental experimental and theoretical models. *Prog.Biophys.Mol.Biol.*, 82(1-3), 207-220 (2003)
DOI: 10.1016/S0079-6107(03)00017-8

31. R. C. Kerckhoffs, P. H. Bovendeerd, J. C. Kotte, F. W. Prinzen, K. Smits and T. Arts: Homogeneity of cardiac contraction despite physiological asynchrony of depolarization: a model study. *Ann.Biomed.Eng*, 31(5), 536-547 (2003)
DOI: 10.1114/1.1566447

32. M. B. Cannell, J. R. Berlin and W. J. Lederer: Effect of membrane potential changes on the calcium transient in single rat cardiac muscle cells. *Science*, 238, 1419-1423 (1987)
DOI: 10.1126/science.2446391

33. A. Fabiato: Rapid ionic modifications during the aequorin-detected calcium transient in a skinned canine cardiac Purkinje cell. *J Gen. Physiol*, 85(2), 189-246 (1985)
DOI: 10.1085/jgp.85.2.189

34. A. Fabiato: Simulated calcium current can both cause calcium loading in and trigger calcium release from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J Gen. Physiol*, 85(2), 291-320 (1985)
DOI: 10.1085/jgp.85.2.291
DOI: 10.1085/jgp.85.2.247

35. A. Fabiato: Time and calcium dependence of activation and inactivation of calcium-induced release of calcium from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J Gen.Physiol*, 85(2), 247-289 (1985)
DOI: 10.1085/jgp.85.2.291
DOI: 10.1085/jgp.85.2.247

36. M. Nabauer, G. Callewaert, L. Cleemann and M. Morad: Regulation of calcium release is gated by calcium current, not gating charge, in cardiac myocytes. *Science*, 244, 800-803 (1989)
DOI: 10.1126/science.2543067

37. K. R. Sipido: Efficiency of L-type Ca2+ current compared to reverse mode Na/Ca exchange or T-type Ca2+ current as trigger for Ca2+ release from the sarcoplasmic reticulum. *Ann.N.Y.Acad.Sci.*, 853, 357-360 (1998)
DOI: 10.1111/j.1749-6632.1998.tb08299.x

38. Z. Zhou and C. T. January: Both T- and L-type Ca2+ channels can contribute to excitation- contraction coupling in

© 1996-2016

cardiac Purkinje cells. *Biophys.J*, 74(4), 1830-1839 (1998)
DOI: 10.1016/S0006-3495(98)77893-2

39. S. Litwin, O. Kohmoto, A. J. Levi, K. W. Spitzer and J. H. Bridge: Evidence that reverse Na-Ca exchange can trigger SR calcium release. *Ann.N.Y.Acad.Sci*, 779, 451-463 (1996)
DOI: 10.1111/j.1749-6632.1996.tb44820.x

40. A. M. Vites and J. A. Wasserstrom: Ca2+ influx via Na-Ca exchange and ICa can both trigger transient contractions in cat ventricular myocytes. *Ann.N.Y.Acad.Sci*, 779, 521-524 (1996)
DOI: 10.1111/j.1749-6632.1996.tb44826.x

41. H. Cheng, M. R. Lederer, R. P. Xiao, A. M. Gomez, Y. Y. Zhou, B. Ziman, H. Spurgeon, E. G. Lakatta and W. J. Lederer: Excitation-contraction coupling in heart: new insights from Ca2+ sparks. *Cell Calcium*, 20(2), 129-140 (1996)
DOI: 10.1016/S0143-4160(96)90102-5

42. D. Li, P. Melnyk, J. Feng, Z. Wang, K. Petrecca, A. Shrier and S. NatTel: Effects of experimental heart failure on atrial cellular and ionic electrophysiology. *Circulation*, 101(22), 2631-2638 (2000)
DOI: 10.1161/01.CIR.101.22.2631

43. T. Banyasz, L. Fulop, J. Magyar, N. Szentandrassy, A. Varro and P. P. Nanasi: Endocardial versus epicardial differences in L-type calcium current in canine ventricular myocytes studied by action potential voltage clamp. *Cardiovasc.Res.*, 58(1), 66-75 (2003)
DOI: 10.1016/S0008-6363(02)00853-2

44. T. J. Hund and Y. Rudy: Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. *Circulation*, 110(20), 3168-3174 (2004)
DOI: 10.1161/01.CIR.0000147231.69595.D3

45. D. A. Eisner, A. W. Trafford, M. E. Diaz, C. L. Overend and S. C. O'Neill: The control of Ca release from the cardiac sarcoplasmic reticulum: regulation versus autoregulation. *Cardiovasc Res*, 38(3), 589-604 (1998)
DOI: 10.1016/S0008-6363(98)00062-5

46. C. R. Weber, V. Piacentino, III, K. S. Ginsburg, S. R. Houser and D. M. Bers: Na^+-Ca^{2+} exchange current and submembrane (Ca^{2+}) during the cardiac action potential. *Circ.Res.*, 90(2), 182-189 (2002)
DOI: 10.1161/hh0202.103940

47. J. H. Bridge, J. R. Smolley and K. W. Spitzer: The relationship between charge movements associated with ICa and INa-Ca in cardiac myocytes. *Science*, 248, 376-378 (1990)
DOI: 10.1126/science.2158147

48. K. R. Laurita, R. Katra, B. Wible, X. Wan and M. H. Koo: Transmural heterogeneity of calcium handling in canine. *Circ.Res.*, 92(6), 668-675 (2003)
DOI: 10.1161/01.RES.0000062468.25308.27

49. L. Y. Jan and Y. N. Jan: Structural elements involved in specific K^+ channel functions. *Annu.Rev.Physiol.*, 54, 537-555 (1992)
DOI: 10.1146/annurev.ph.54.030192.002541

50. F. G. Akar, R. C. Wu, I. Deschênes, A. A. Armoundas, V. Piacentino, III, S. R. Houser and G. F. Tomaselli: Phenotypic differences in transient outward K^+ current of human and canine ventricular myocytes: insights into molecular composition of ventricular I_{to}. *Am J Physiol Heart Circ.Physiol*, 286(2), H602-H609 (2004)
DOI: 10.1152/ajpheart.00673.2003

51. N. Gaborit, B. S. Le, V. Szuts, A. Varro, D. Escande, S. Nattel and S. Demolombe: Regional and tissue specific transcript signatures of ion channel genes in the non-diseased human heart. *J Physiol*, 582(Pt 2), 675-693 (2007)
DOI: 10.1113/jphysiol.2006.126714

52. H. Xu, W. Guo and J. M. Nerbonne: Four kinetically distinct depolarization-activated K+ currents in adult mouse ventricular myocytes. *J Gen.Physiol*, 113(5), 661-678 (1999)
DOI: 10.1085/jgp.113.5.661

53. M. Ikura: Calcium binding and conformational response in EF-hand proteins. *Trends Biochem Sci*, 21(1), 14-17 (1996)
DOI: 10.1016/S0968-0004(06)80021-6

54. W. F. An, M. R. Bowlby, M. Betty, J. Cao, H. P. Ling, G. Mendoza, J. W. Hinson, K. I. Mattsson, B. W. Strassle, J. S. Trimmer and K. J. Rhodes: Modulation of A-type potassium channels by a family of calcium sensors. *Nature*, 403(6769), 553-556 (2000)
DOI: 10.1038/35000592

55. W. Guo, H. Li, F. Aimond, D. C. Johns, K. J. Rhodes, J. S. Trimmer and J. M. Nerbonne: Role of heteromultimers in the generation of myocardial transient outward K+ currents.

© 1996-2016

Circ Res, 90(5), 586-593 (2002)
DOI: 10.1161/01.RES.0000012664.05949.E0

56. J. Barghaan, M. Tozakidou, H. Ehmke and R. Bahring: Role of N-terminal domain and accessory subunits in controlling deactivation-inactivation coupling of Kv4.2. channels. *Biophys J*, 94(4), 1276-1294 (2008)
DOI: 10.1529/biophysj.107.111344

57. E. Bou-Abboud and J. M. Nerbonne: Molecular correlates of the calcium-independent, depolarization-activated K+ currents in rat atrial myocytes. *J Physiol*, 517 (Pt 2), 407-420 (1999)
DOI: 10.1111/j.1469-7793.1999.0407t.x

58. S. Grubb, K. Calloe and M. B. Thomsen: Impact of KChIP2 on Cardiac Electrophysiology and the Progression of Heart Failure. *Front Physiol*, 3, 118 (2012)
DOI: 10.3389/fphys.2012.00118

59. N. C. Foeger, A. J. Norris, L. M. Wren and J. M. Nerbonne: Augmentation of Kv4.2.-encoded Currents by Accessory Dipeptidyl Peptidase 6 and 10 Subunits Reflects Selective Cell Surface Kv4.2. Protein Stabilization. *J Biol Chem.*, 287(12), 9640-9650 (2012)
DOI: 10.1074/jbc.M111.324574

60. N. C. Foeger, W. Wang, R. L. Mellor and J. M. Nerbonne: Stabilization of Kv4 Protein by the accessory K+ Channel Interacting Protein 2 (KChIP2) subunit is required for the generation of native myocardial fast transient outward K+ currents. *J Physiol*, 591(Pt 17), 4149-4166 (2013)
DOI: 10.1113/jphysiol.2013.255836

61. B. Rosati, F. Grau, S. Rodriguez, H. Li, J. M. Nerbonne and D. McKinnon: Concordant expression of KChIP2 mRNA, protein and transient outward current throughout the canine ventricle. *J Physiol*, 548(Pt 3), 815-822 (2003)
DOI: 10.1113/jphysiol.2002.033704

62. K. Calloe, E. Nof, T. Jespersen, S. P. Olesen, J. M. Di Diego, N. Chlus, S. P. Olesen, C. Antzelevitch and J. M. Cordeiro: Comparison of the effects of the transient outward potassium channel activator NS5806 on canine atrial and ventricular cardiomyocytes. *J Cardiovasc Electrophysiol*, 22(9), 1057-1066 (2011)
DOI: 10.1111/j.1540-8167.2011.02053.x

63. E. Wettwer, G. J. Amos, H. Posival and U. Ravens: Transient outward current in human ventricular myocytes of subepicardial and subendocardial origin. *Circ.Res.*, 75(3), 473-482 (1994)
DOI: 10.1161/01.RES.75.3.473

64. I. Deschenes, D. DiSilvestre, G. J. Juang, R. C. Wu, W. F. An and G. F. Tomaselli: Regulation of Kv4.3. current by KChIP2 splice variants: a component of native cardiac I_{to}? *Circulation*, 106(4), 423-429 (2002)
DOI: 10.1161/01.CIR.0000025417.65658.B6

65. M. S. Nadal, A. Ozaita, Y. Amarillo, M. E. Vega-Saenz de, Y. Ma, W. Mo, E. M. Goldberg, Y. Misumi, Y. Ikehara, T. A. Neubert and B. Rudy: The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K+ channels. *Neuron*, 37(3), 449-461 (2003)
DOI: 10.1016/S0896-6273(02)01185-6

66. Y. A. Kaulin, J. A. De Santiago-Castillo, C. A. Rocha, M. S. Nadal, B. Rudy and M. Covarrubias: The dipeptidyl-peptidase-like protein DPP6 determines the unitary conductance of neuronal Kv4.2. channels. *J Neurosci*, 29(10), 3242-3251 (2009)
DOI: 10.1523/JNEUROSCI.4767-08.2009

67. S. Radicke, D. Cotella, E. M. Graf, U. Ravens and E. Wettwer: Expression and function of dipeptidyl-aminopeptidase-like protein 6 as a putative □-subunit of human cardiac transient outward current encoded by Kv4.3. *J Physiol*, 565(Pt 3), 751-756 (2005)
DOI: 10.1113/jphysiol.2005.087312

68. D. Cotella, S. Radicke, A. Bortoluzzi, U. Ravens, E. Wettwer, C. Santoro and D. Sblattero: Impaired glycosylation blocks DPP10 cell surface expression and alters the electrophysiology of Ito channel complex. *Pflugers Arch.*, 460(1), 87-97 (2010)
DOI: 10.1007/s00424-010-0824-2

69. X. Ren, Y. Hayashi, N. Yoshimura and K. Takimoto: Transmembrane interaction mediates complex formation between peptidase homologues and Kv4 channels. *Mol Cell Neurosci*, 29(2), 320-332 (2005)
DOI: 10.1016/j.mcn.2005.02.003

70. T. K. Roepke, A. Kontogeorgis, C. Ovanez, X. Xu, J. B. Young, K. Purtell, P. A. Goldstein, D. J. Christini, N. S. Peters, F. G. Akar, D. E. Gutstein, D. J. Lerner and G. W. Abbott: Targeted deletion of *kcne2* impairs ventricular

© 1996-2016

repolarization *via* disruption of $I_{K,slow1}$ and $I_{to,f}$. *FASEB J* (2008)
DOI: 10.1096/fj.08-110171

71. A. Lundby and S. P. Olesen: KCNE3 is an inhibitory subunit of the Kv4.3. potassium channel. *Biochem.Biophys.Res.Commun.*, 346(3), 958-967 (2006)
DOI: 10.1016/j.bbrc.2006.06.004

72. D. I. Levy, E. Cepaitis, S. Wanderling, P. T. Toth, S. L. Archer and S. A. Goldstein: The membrane protein MiRP3 regulates Kv4.2. channels in a KChIP-dependent manner. *J Physiol*, 588(Pt 14), 2657-2668 (2010)
DOI: 10.1113/jphysiol.2010.191395

73. S. Ohno, D. P. Zankov, W. G. Ding, H. Itoh, T. Makiyama, T. Doi, S. Shizuta, T. Hattori, A. Miyamoto, N. Naiki, J. C. Hancox, H. Matsuura and M. Horie: KCNE5 (KCNE1L) variants are novel modulators of Brugada syndrome and idiopathic ventricular fibrillation. *Circ Arrhythm.Electrophysiol*, 4(3), 352-361 (2011)
DOI: 10.1161/CIRCEP.110.959619

74. A. L. Lundquist, C. L. Turner, L. Y. Ballester and A. L. George, Jr.: Expression and transcriptional control of human KCNE genes. *Genomics*, 87(1), 119-128 (2006)
DOI: 10.1016/j.ygeno.2005.09.004

75. W. Han, W. Bao, Z. Wang and S. NatTel: Comparison of ion-channel subunit expression in canine cardiac Purkinje fibers and ventricular muscle. *Circ.Res.*, 91(9), 790-797 (2002)
DOI: 10.1161/01.RES.0000039534.18114.D9

76. M. J. Perrin, A. Adler, S. Green, F. Al-Zoughool, P. Doroshenko, N. Orr, S. Uppal, J. S. Healey, D. Birnie, S. Sanatani, M. Gardner, J. Champagne, C. Simpson, K. Ahmad, M. P. van Den Berg, V. Chauhan, P. H. Backx, J. P. Van Tintelen, A. D. Krahn and M. H. Gollob: Evaluation of genes encoding for the transient outward current (Ito) identifies the *KCND2* gene as a cause of J wave syndrome associated with sudden cardiac death. *Circ Cardiovasc Genet* (2014)
DOI: 10.1161/CIRCGENETICS.114.000623

77. D. L. Costantini, E. P. Arruda, P. Agarwal, K. H. Kim, Y. Zhu, W. Zhu, M. Lebel, C. W. Cheng, C. Y. Park, S. A. Pierce, A. Guerchicoff, G. D. Pollevick, T. Y. Chan, M. G. Kabir, S. H. Cheng, M. Husain, C. Antzelevitch, D. Srivastava, G. J. Gross, C. C. Hui, P. H. Backx and B. G. Bruneau: The homeodomain transcription factor Irx5 establishes the mouse cardiac ventricular repolarization gradient. *Cell*, 123(2), 347-358 (2005)
DOI: 10.1016/j.cell.2005.08.004

78. Y. Jia and K. Takimoto: GATA and FOG2 transcription factors differentially regulate the promoter for Kv4.2. K(+) channel gene in cardiac myocytes and PC12 cells. *Cardiovasc Res*, 60(2), 278-287 (2003)
DOI: 10.1016/S0008-6363(03)00528-5

79. C. F. Rossow, E. Minami, E. G. Chase, C. E. Murry and L. F. Santana: NFATc3-induced reductions in voltage-gated K+ currents after myocardial infarction. *Circ.Res.*, 94(10), 1340-1350 (2004)
DOI: 10.1161/01.RES.0000128406.08418.34

80. B. J. Wilkins, Y. S. Dai, O. F. Bueno, S. A. Parsons, J. Xu, D. M. Plank, F. Jones, T. R. Kimball and J. D. Molkentin: Calcineurin/NFAT coupling participates in pathological, but not physiological, cardiac hypertrophy. *Circ Res*, 94(1), 110-118 (2004)
DOI: 10.1161/01.RES.0000109415.17511.18

81. N. Gong, I. Bodi, C. Zobel, A. Schwartz, J. D. Molkentin and P. H. Backx: Calcineurin increases cardiac transient outward K+ currents via transcriptional up-regulation of Kv4.2. channel subunits. *J Biol Chem.*, 281(50), 38498-38506 (2006)
DOI: 10.1074/jbc.M607774200

82. B. K. Panama, D. Latour-Villamil, G. P. Farman, D. Zhao, S. S. Bolz, L. A. Kirshenbaum and P. H. Backx: Nuclear factor kappaB downregulates the transient outward potassium current I(to,f) through control of KChIP2 expression. *Circ Res*, 108(5), 537-543 (2011)
DOI: 10.1161/CIRCRESAHA.110.229112

83. P. Brugada and J. Brugada: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J.Am.Coll.Cardiol.*, 20(6), 1391-1396 (1992)
DOI: 10.1016/0735-1097(92)90253-J

84. M. W. Nielsen, A. G. Holst, S. P. Olesen and M. S. Olesen: The genetic component of Brugada syndrome. *Front Physiol*, 4, 179 (2013)
DOI: 10.3389/fphys.2013.00179

85. J. R. Giudicessi, D. Ye, D. J. Tester, L.

© 1996-2016

Crotti, A. Mugione, V. V. Nesterenko, R. M. Albertson, C. Antzelevitch, P. J. Schwartz and M. J. Ackerman: Transient outward current (Ito) gain-of-function mutations in the KCND3-encoded Kv4.3. potassium channel and Brugada syndrome. *Heart Rhythm*, 8(7), 1024-1032 (2011)
DOI: 10.1016/j.hrthm.2011.02.021

86. J. R. Giudicessi, D. Ye, C. J. Kritzberger, V. V. Nesterenko, D. J. Tester, C. Antzelevitch and M. J. Ackerman: Novel mutations in the KCND3-encoded Kv4.3. K+ channel associated with autopsy-negative sudden unexplained death. *Hum Mutat.*, 33(6), 989-997 (2012)
DOI: 10.1002/humu.22058

87. M. S. Olesen, L. Refsgaard, A. G. Holst, A. P. Larsen, S. Grubb, S. Haunso, J. H. Svendsen, S. P. Olesen, N. Schmitt and K. Calloe: A novel KCND3 gain-of-function mutation associated with early-onset of persistent lone atrial fibrillation. *Cardiovasc Res*, 98(3), 488-495 (2013)
DOI: 10.1093/cvr/cvt028

88. N. Niwa and J. M. Nerbonne: Molecular determinants of cardiac transient outward potassium current (Ito) expression and regulation. *J Mol Cell Cardiol*, 48(1), 12-25 (2010)
DOI: 10.1016/j.yjmcc.2009.07.013

89. B. Callsen, D. Isbrandt, K. Sauter, L. S. Hartmann, O. Pongs and R. Bahring: Contribution of N- and C-terminal Kv4.2. channel domains to KChIP interaction (corrected). *J Physiol*, 568(Pt 2), 397-412 (2005)
DOI: 10.1113/jphysiol.2005.094359

90. E. Delpón, J. M. Cordeiro, L. Núñez, P. E. B. Thomsen, A. Guerchicoff, G. D. Pollevick, Y. Wu, J. K. Kanters, C. T. Larsen, A. Burashnikov, M. Christiansen and C. Antzelevitch: Functional effects of *KCNE3* mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol*, 1(3), 209-218 (2008)
DOI: 10.1161/CIRCEP.107.748103

91. S. Ohno, F. Toyoda, D. P. Zankov, H. Yoshida, T. Makiyama, K. Tsuji, T. Honda, K. Obayashi, H. Ueyama, W. Shimizu, Y. Miyamoto, S. Kamakura, H. Matsuura, T. Kita and M. Horie: Novel KCNE3 mutation reduces repolarizing potassium current and associated with long QT syndrome. *Hum.Mutat.*, 30(4), 557-563 (2009)
DOI: 10.1002/humu.20834

92. A. Duarri, J. Jezierska, M. Fokkens, M. Meijer, H. J. Schelhaas, W. F. den Dunnen, D. F. van, C. Verschuuren-Bemelmans, G. Hageman, d. van, V, B. Kusters, B. P. van de Warrenburg, B. Kremer, C. Wijmenga, R. J. Sinke, M. A. Swertz, H. H. Kampinga, E. Boddeke and D. S. Verbeek: Mutations in potassium channel kcnd3 cause spinocerebellar ataxia type 19. *Ann Neurol.*, 72(6), 870-880 (2012)
DOI: 10.1002/ana.23700

93. A. Duarri, E. Nibbeling, M. R. Fokkens, M. Meijer, E. Boddeke, E. Lagrange, G. Stevanin, A. Brice, A. Durr and D. S. Verbeek: The L450P mutation in KCND3 brings spinocerebellar ataxia and Brugada syndrome closer together. *Neurogenetics.* (2013)
DOI: 10.1007/s10048-013-0370-0

94. K. R. Sipido, T. Stankovicova, J. Vanhaecke, W. Flameng and F. Verdonck: A critical role for L-type Ca^{2+} current in the regulation of Ca^{2+} release from the sarcoplasmic reticulum in human ventricular myocytes from dilated cardiomyopathy. *Ann.N.Y.Acad.Sci.*, 853, 353-356 (1998)
DOI: 10.1111/j.1749-6632.1998.tb08298.x

95. I. A. Hobai and B. O'Rourke: Enhanced Ca^{2+}-activated Na^{+}-Ca^{2+} exchange activity in canine pacing-induced heart failure. *Circ. Res.*, 87(8), 690-698 (2000)
DOI: 10.1161/01.RES.87.8.690

96. W. Xiong, Y. Tian, D. DiSilvestre and G. F. Tomaselli: Transmural Heterogeneity of Na+-Ca2+ Exchange: Evidence for Differential Expression in Normal and Failing Hearts. *Circulation Research*, 97(3), 207-209 (2005)
DOI: 10.1161/01.RES.0000175935.08283.27

97. G. F. Tomaselli and D. P. Zipes: What causes sudden death in heart failure? *Circ.Res*, 95(8), 754-763 (2004)
DOI: 10.1161/01.RES.0000145047.14691.db

98. F. G. Akar and G. F. Tomaselli: Ion channels as novel therapeutic targets in heart failure. *Ann.Med.*, 37(1), 44-54 (2005)
DOI: 10.1080/07853890510007214

99. A. D. Wickenden, R. Kaprielian, Z. Kassiri, J. N. Tsoporis, R. Tsushima, G. I. Fishman

© 1996-2016

and P. H. Backx: The role of action potential prolongation and altered intracellular calcium handling in the pathogenesis of heart failure. *Cardiovasc.Res.*, 37, 312-323 (1998)
DOI: 10.1016/S0008-6363(97)00256-3

100. T. Speerschneider, S. Grubb, A. Metoska, S. P. Olesen, K. Calloe and M. B. Thomsen: Development of Heart Failure is Independent of KChIP2 Expression. *J Physiol* (2013)
DOI: 10.1113/jphysiol.2013.263483

101. R. Kaprielian, R. Sah, T. Nguyen, A. D. Wickenden and P. H. Backx: Myocardial infarction in rat eliminates regional heterogeneity of AP profiles, I_{to} K^+ currents, and $(Ca^{2+})_i$ transients. *Am J Physiol Heart Circ.Physiol*, 283(3), H1157-H1168 (2002)
DOI: 10.1152/ajpheart.00518.2001

102. D. J. Beuckelmann, M. Nabauer and E. Erdmann: Alterations of K^+ currents in isolated human ventricular myocytes from patients with terminal heart failure. *Circ.Res.*, 73, 379-385 (1993)
DOI: 10.1161/01.RES.73.2.379

103. P. J. Cooper, C. Soeller and M. B. Cannell: Excitation-contraction coupling in human heart failure examined by action potential clamp in rat cardiac myocytes. *J Mol Cell Cardiol*, 49(6), 911-917 (2010)
DOI: 10.1016/j.yjmcc.2010.04.012

104. M. C. Sanguinetti, J. H. Johnson, L. G. Hammerland, P. R. Kelbaugh, R. A. Volkmann, N. A. Saccomano and A. L. Mueller: Heteropodatoxins: peptides isolated from spider venom that block Kv4.2. potassium channels. *Mol Pharmacol.*, 51(3), 491-498 (1997)

105. V. V. Zarayskiy, G. Balasubramanian, V. E. Bondarenko and M. J. Morales: Heteropoda toxin 2 is a gating modifier toxin specific for voltage-gated K+ channels of the Kv4 family. *Toxicon*, 45(4), 431-442 (2005)
DOI: 10.1016/j.toxicon.2004.11.015

106. S. Diochot, M. D. Drici, D. Moinier, M. Fink and M. Lazdunski: Effects of phrixotoxins on the Kv4 family of potassium channels and implications for the role of Ito1 in cardiac electrogenesis. *Br.J Pharmacol.*, 126(1), 251-263 (1999)
DOI: 10.1038/sj.bjp.0702283

107. J. Ebbinghaus, C. Legros, A. Nolting, C. Guette, M. L. Celerier, O. Pongs and R. Bahring: Modulation of Kv4.2. channels by a peptide isolated from the venom of the giant bird-eating tarantula Theraphosa leblondi. *Toxicon*, 43(8), 923-932 (2004)
DOI: 10.1016/j.toxicon.2003.12.012

108. C. V. Desimone, Y. Lu, V. E. Bondarenko and M. J. Morales: S3b amino acid substitutions and ancillary subunits alter the affinity of Heteropoda venatoria toxin 2 for Kv4.3. *Mol Pharmacol.*, 76(1), 125-133 (2009)
DOI: 10.1124/mol.109.055657

109. C. V. Desimone, V. V. Zarayskiy, V. E. Bondarenko and M. J. Morales: Heteropoda toxin 2 interaction with Kv4.3. and Kv4.1. reveals differences in gating modification. *Mol Pharmacol.*, 80(2), 345-355 (2011)
DOI: 10.1124/mol.111.072405

110. J. K. Maffie, E. Dvoretskova, P. E. Bougis, M. F. Martin-Eauclaire and B. Rudy: Dipeptidyl-peptidase-like-proteins confer high sensitivity to the scorpion toxin AmmTX3 to Kv4-mediated A-type K+ channels. *J Physiol*, 591(Pt 10), 2419-2427 (2013)
DOI: 10.1113/jphysiol.2012.248831

111. Z. G. Wang, B. Fermini and S. NatTel: Effects of flecainide, quinidine, and 4-aminopyridine on transient and sustained outward currents in human atrial myocytes. *J Pharmacol Exp. Ther.*, 272(1), 184-196 (1996)

112. S. P. Patel and D. L. Campbell: Transient outward potassium current, 'Ito', phenotypes in the mammalian left ventricle: underlying molecular, cellular and biophysical mechanisms. *J Physiol*, 569(Pt 1), 7-39 (2005)
DOI: 10.1113/jphysiol.2005.086223

113. S. Radicke, M. Vaquero, R. Caballero, R. Gomez, L. Nunez, J. Tamargo, U. Ravens, E. Wettwer and E. Delpon: Effects of MiRP1 and DPP6 beta-subunits on the blockade induced by flecainide of Kv4.3./KChIP2 channels. *Br.J Pharmacol.*, 154(4), 774-786 (2008)
DOI: 10.1038/bjp.2008.134

114. Y. Imaizumi and W. R. Giles: Quinidine-induced inhibition of transient outward current in cardiac muscle. *Am.J.Physiol.*, 253, H704-H708 (1987)

115. G. C. Bett, M. J. Morales, H. C. Strauss and R. L. Rasmusson: KChIP2b modulates the affinity and use-dependent block of Kv4.3. by

© 1996-2016

nifedipine. *Biochem Biophys Res Commun.*, 340(4), 1167-1177 (2006)
DOI: 10.1016/j.bbrc.2005.12.135

116. J. S. Hermida, I. Denjoy, J. Clerc, F. Extramiana, G. Jarry, P. Milliez, P. Guicheney, S. Di Fusco, J. L. Rey, B. Cauchemez and A. Leenhardt: Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol*, 43(10), 1853-1860 (2004)
DOI: 10.1016/j.jacc.2003.12.046

117. B. Belhassen and S. Viskin: Pharmacologic approach to therapy of Brugada syndrome: quinidine as an alternative to ICD therapy? In: *The Brugada Syndrome: From Bench to Bedside.* Ed C. Antzelevitch, P. Brugada, J. Brugada&R. Brugada. Blackwell Futura, Oxford (2004)

118. W. Gonzalez and J. Miksovska. *Biophysical Journal*, 104, 102a (2013)
DOI: 10.1016/j.bpj.2012.11.602

119. A. Lundby, T. Jespersen, N. Schmitt, M. Grunnet, S. P. Olesen, J. M. Cordeiro and K. Calloe: Effect of the I(to) activator NS5806 on cloned K(V)4 channels depends on the accessory protein KChIP2. *Br.J Pharmacol.*, 160(8), 2028-2044 (2010)
DOI: 10.1111/j.1476-5381.2010.00859.x

120. J. M. Cordeiro, K. Calloe, N. S. Moise, B. Kornreich, D. Giannandrea, J. M. Di Diego, S. P. Olesen and C. Antzelevitch: Physiological consequences of transient outward K+ current activation during heart failure in the canine left ventricle. *J Mol Cell Cardiol*, 52(6), 1291-1298 (2012)
DOI: 10.1016/j.yjmcc.2012.03.001

121. U. C. Hoppe, D. C. Johns, E. Marban and B. O'Rourke: Manipulation of cellular excitability by cell fusion: effects of rapid introduction of transient outward K^+ current on the guinea pig action potential. *Circ.Res.*, 84(8), 964-972 (1999)
DOI: 10.1161/01.res.84.8.964

122. K. Calloe, N. Schmitt, S. Grubb, R. Pfeiffer, J. P. David, R. Kanter, J. M. Cordeiro and C. Antzelevitch: Multiple arrhythmic syndromes in a newborn, owing to a novel mutation in SCN5A. *Can.J Physiol Pharmacol.*, 89(10), 723-736 (2011)
DOI: 10.1139/y11-070

123. J. M. Cordeiro, R. Brugada, K. Hong, C. Antzelevitch and R. Dumaine: Short QT syndrome mutation in HERG abolishes inactivation. *Biophysical Journal*, 86, 134a (2004)

124. J. M. Cordeiro, R. Brugada, Y. S. Wu, K. Hong and R. Dumaine: Modulation of I_{Kr} inactivation by mutation N588K in KCNH2: a link to arrhythmogenesis in short QT syndrome. *Cardiovascular Research*, 67(3), 498-509 (2005)
DOI: 10.1016/j.cardiores.2005.02.018

125. J. M. Cordeiro, J. E. Malone, J. M. Di Diego, F. S. Scornik, G. L. Aistrup, C. Antzelevitch and J. A. Wasserstrom: Cellular and subcellular alternans in the canine left ventricle. *Am J Physiol Heart Circ.Physiol*, 293:, H3506-H3516 (2007)
DOI: 10.1152/ajpheart.00757.2007

126. Y. C. Lee, A. Durr, K. Majczenko, Y. H. Huang, Y. C. Liu, C. C. Lien, P. C. Tsai, Y. Ichikawa, J. Goto, M. L. Monin, J. Z. Li, M. Y. Chung, E. Mundwiller, V. Shakkottai, T. T. Liu, C. Tesson, Y. C. Lu, A. Brice, S. Tsuji, M. Burmeister, G. Stevanin and B. W. Soong: Mutations in KCND3 cause spinocerebellar ataxia type 22. *Ann Neurol.*, 72(6), 859-869 (2012)
DOI: 10.1002/ana.23701

Key Words: Arrhythmia, Calcium, Heart Failure, Potassium Channel, Review

Send correspondence to: Brian K. Panama, Department of Experimental Cardiology, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, New York, 13501 USA, Tel: 315-735-2217, Fax: 315-735-5648, E-mail: panamab@mmrl.edu

© 1996-2016