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Pathophysiology of the cardiac late Na Current and its potential as a drug target

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Abstract

A pathological increase in the late component of the cardiac Na^+ current, I_{NaL}, has been linked to disease manifestation in inherited and acquired cardiac diseases including the long QT variant 3 (LQT3) syndrome and heart failure. Disruption in I_{NaL} leads to action potential prolongation, disruption of normal cellular repolarization, development of arrhythmia triggers, and propensity to ventricular arrhythmia. Attempts to treat arrhythmogenic sequelae from inherited and acquired syndromes pharmacologically with common Na^+ channel blockers (e.g. flecainide, lidocaine, and amiodarone) have been largely unsuccessful. This is due to drug toxicity and the failure of most current drugs to discriminate between the peak current component, chiefly responsible for single cell excitability and propagation in coupled tissue, and the late component (I_{NaL}) of the Na^+ current. Although small in magnitude as compared to the peak Na^+ current (~1 – 3%), I_{NaL} alters action potential properties and increases Na^+ loading in cardiac cells. With the increasing recognition that multiple cardiac pathological conditions share phenotypic manifestations of I_{NaL} upregulation, there has been renewed interest in specific pharmacological inhibition of I_{Na}. The novel antianginal agent ranolazine, which shows a marked selectivity for late versus peak Na^+ current, may represent a novel drug archetype for targeted reduction of I_{NaL}. This article aims to review common pathophysiological mechanisms leading to enhanced I_{NaL} in LQT3 and heart failure as prototypical disease conditions. Also reviewed are promising therapeutic strategies tailored to alter the molecular mechanisms underlying I_{Na} mediated arrhythmia triggers.

INTRODUCTION

The cardiac action potential arises from a delicate balance of depolarization and repolarization orchestrated through precisely timed opening and closing of ion channels. Na^+ channel activation produces an influx of Na^+ that causes membrane depolarization. Membrane excitation then leads to rapid voltage dependent inactivation of Na^+ channels and nearly complete “turning off” of the current. A transient, or peak Na current (I_{NaT}) is observed and is chiefly responsible for the rapid action potential upstroke and, in coupled

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tissue, propagation of the action potential (AP). A second component of Na^+ current that persists throughout the duration of the action potential has also been identified, and because it occurs subsequent to the large transient peak current, is termed late I_{Na} (I_{NaL}). While I_{NaL} is miniscule compared to peak I_{NaT} (I_{NaL} < 1% of I_{NaT} [1]), it occurs throughout the low conductance phase of the action potential and thus contributes to action potential morphology, plateau potentials, and AP duration in human ventricular myocytes [2, 3] and Na^+ buildup in cardiac cells. Even though the magnitude of I_{NaL} is low, its persistence throughout the duration of the action potential results in net Na^+ loading comparable to that via I_{NaT} [1, 4].

It has recently been demonstrated that in some pathological settings I_{NaL} is upregulated, which may disrupt the repolarization phase of the action potential and lead to the development of arrhythmia triggers. Here, we review the latest findings on common pathophysiological mechanisms leading to an enhanced late I_{Na}, in the setting of congenital long QT3 syndrome and the acquired QT prolongation in heart failure. New strategies for therapeutic intervention directed at I_{NaL} will also be discussed. A historical perspective and other aspects related to the topic of the I_{NaL} have also recently been reviewed in [5, 6].

BRIEF REVIEW OF THE CARDIAC ACTION POTENTIAL WAVEFORM

Multiple distinct action potential morphologies exist, depending on myocardial location. Ventricular cells exhibit the “classical” action potential morphology with 5 discrete phases. Phase 0 is the rapid depolarizing phase that results when Na^+ channels activate and an influx of Na^+ causes the membrane potential to depolarize. Phase 1 corresponds to the “notch” marked by inactivation of Na^+ channels and outward movement of K^+ ions through transient outward current (I_{to}). In phase 2, a low conductance plateau phase, inward and outward ion movements are balanced mainly by L-type Ca^{2+} channels and delayed rectifier K^+ channels, respectively. Phase 3 marks the final repolarization phase of the action potential, which occurs due to inactivation of Ca^{2+} currents and continued K^+ efflux, allowing the cell to return to its resting potential (phase 4).

STRUCTURE AND FUNCTION OF THE VOLTAGE GATED CARDIAC SODIUM CHANNEL

The human cardiac voltage-gated sodium channel ($Na_V1.5$) is a macromolecular complex consisting of α and β subunits and accessory proteins [8, 9]. The α subunit, encoded by *SCN5A*, is composed of four heterologous domains (DI – DIV) each with six transmembrane segments (S1-S6) [8, 10]. Ion selectivity and permeation is controlled by the P loop between S5 – S6. Concerted movement of the positively charged S4 segments “activate” the channel in response to a transmembrane voltage depolarization [11, 12]. Channel inactivation occurs on three discrete timescales: fast inactivation within milliseconds, intermediate inactivation within 100 ms [13] and slow inactivation on the order of seconds [14]. Critical for fast inactivation is the hydrophobic isoleucine-phenylalanine-methionine (IFM) motif located on the intracellular linker between DIII and DIV [8, 11]. The COOH terminal has also been implicated in $Na_V1.5$ inactivation [2, 15, 16].

Gain of function mutations in *SCN5A* can result in variant 3 of the congenital long QT3 syndrome (LQT3) [8, 17, 18]. The long QT phenotype arising from LQT3 mutations generally results from a failure of inactivation of the Na^+ channel, which results in persistent inward Na^+ current (an increase in I_{NaL}) throughout the duration of the action potential. Increased I_{NaL} leads to prolongation of the action potential duration at the level of the cell, which manifests as QT-interval prolongation on the ECG.

In addition to the α subunit, the Na^+ channel is modulated by multiple accessory subunits. With respect to I_{NaL}, coexpression of the α with the β1 (but not β2) subunit slows I_{NaL} decay kinetics, dramatically increases I_{NaL} relative to the maximum peak current (2.3% vs 0.48%), and produces a rightward shift in the steady-state availability curve [19]. Additionally in the heart failure setting, $Na_V1.5$ is downregulated with no change in β1 expression, suggesting further β1 subunit enhanced I_{NaL} in heart failure [2, 20]. Recently, Mishra et al. has shown opposite effects of β1 and β2 in normal and heart failure models of canine hearts, with β1-siRNA post-transcriptional silencing reducing I_{NaL} density and accelerating decay, whereas β2-siRNA produces just the opposite [21].

The first β subunit (SCN4B – β4) mutation was described [22] in a 21-month old girl that had a QTc of 712 ms and intermittent 2:1 heart block. Coexpression with the α-subunit revealed a small (3.42 mV), but significant positive shift in the steady-state availability curve, leading to an increased window current (described in more detail below). At -60 mV, the expression of *SCN5A* with mutant β4 caused an 8-fold increase in I_{NaL} compared with *SCN5A* alone [22]. Mutations in all four β subunits have since been reported and causally linked to multiple arrhythmogenic phenotypes [23].

DERANGED CHANNEL FUNCTION CAN CAUSE LATE I_{Na}

At least three distinct alterations in $Na_V1.5$ gating have been shown to increase in I_{NaL} including window currents, differential gating modalities, and nonequilibrium gating. These mechanisms are described below in the context of naturally occurring mutations, which generally led to their discovery. However, it is now clear that the gating properties of Na^+ channels can be altered by physiological modulators such as Ca^{2+}, calmodulin and phosphorylation, both in the context of normal physiology and in pathological conditions (discussed later and listed in Table 3).

Window currents and I_{NaL}

For cardiac Na^+ channels, there exists a voltage range where the steady state inactivation curve and activation curve overlap. Within this voltage regime, during repolarization of the cardiac AP, channels that have previously inactivated may reactive, or in the experimental setting, if the membrane is held at constant voltage, a steady-state equilibrium current ensues [6, 24, 25]. In the ventricular myocardium, voltages within the region of overlap between activation and inactivation occur subsequent to late repolarization (phase 3) and reactivation is not favorable. Conditions that slow repolarization, increase recovery from inactivation, or increase the width of the window can lead to enhanced reactivation of Na^+ channels and propensity to early afterdepolarizations and triggered activity [24]. Although window current is not appreciable in wild-type human [26] and guinea pig [27] ventricular myocytes, at least three LQT3 mutations, L619F, N1325S and R1644H have been shown to increase window current and, presumably, to cause the disease phenotype [28] [29]. See Figure 1.

Differential gating modes of $Na_V1.5$ produce I_{NaL}

In addition to window currents, burst mode gating of $Na_V1.5$ is another mechanism producing I_{NaL}. It was once thought that a “non-window” I_{NaL} was carried by a separate isoform of the cardiac Na^+ channel; however, it is now clear that I_{NaL} and I_{NaT} share molecular identity [30] since Maltsev and Undrovinas recorded I_{NaL} from heterologously expressed $Na_V1.5$ in the absence of other isoforms [1].

Using midmyocardial ventricular myocytes, Maltsev and Undrovinas separated the Na^+ current into three phases: early (transient), intermediate, and late, and recorded three distinct gating modalities: transients, bursts, and late scattered openings. The earliest phase of Na^+ current decay (<40 ms) involved all three modes of gating, while the intermediate phase (40

– 300 ms) only involved late scattered openings and bursts, with an inverse relationship between extent of depolarization and bursting. Finally an ultra late decay (>300 ms) involved only the late scattered mode. Of note, these recordings were made at room temperature [2].

Clancy et al. observed infrequent transitions from normally inactivating Na channels to bursting channels in recordings from heterologously expressed single $Na_V1.5$ sodium channels. These data were analyzed to determine "rates" into the burst mode of gating. The dwell time in the burst mode allowed an estimate of the rate of exit from the mode. A computational model based on these rates was then used to predict the magnitude of I_{NaL} expected from ensemble currents. These predictions were finally validated experimentally, suggesting that burst mode gating in $Na_V1.5$ underlies I_{NaL} [31].

Studies in canine ventricular myocytes have shown that the magnitude of the burst mode is pacing frequency dependent, with a decrease in I_{NaL} during rapid heart rates [32]. Rate dependence of I_{NaL} was also shown for human channels in heterologously expressed channels, where I_{NaL} was larger in magnitude at slow frequencies [31]. These data suggest a plausible explanation for bradycardia-linked arrhythmia events commonly observed in LQT3 [33].

The pharmacology of I_{NaL} is similar to $Na_V1.5$, with blockade by STX and TTX exhibiting a single site binding with affinities typical of $Na_V1.5$ [26, 34], and sensitivity to Cd^{2+} (typical for cardiac but not neuronal Na^+ channel isoforms) [2, 35]. Lastly, silencing by siRNA of *SCN5A* decreases I_{NaL} by 75%, significantly reducing APD and variability in canine heart failure models [36]. Thus, evidence suggests that $Na_V1.5$ is likely a major determinant of I_{NaL} in both normal and failing ventricular myocytes [2, 30].

Undrovinas and Maltsev [2] have summarized the major biophysical and pharmacological characteristics of *physiological* I_{NaL} as follows: 1) slow, voltage-independent inactivation and reactivation at room temperature (~0.5 s); 2) steady-state activation and inactivation similar to I_{NaT}; 3) low sensitivity to TTX and STX, comparable to $Na_V1.5$; and 4) the existence of an I_{NaL} with similar biophysical properties in dogs, guinea pigs, rabbits, and rats (see Table 2) [2]. Their results importantly suggest that the multi-modal composition of the I_{Na} current may allow for pharmacological targeting by gating mode specific modulation [1]

Importantly, I_{NaL} is *not* a background Na^+ current (I_{NaB}), which is TTX insensitive and shows no voltage dependence [37]. To date, I_{NaB} remains poorly characterized and has an unclear molecular identity [2].

Nonequilibrium gating produces I_{NaL}

An additional mechanism that can produce I_{NaL} during action potential repolarization was deemed "non-equilibrium" gating because I_{NaL} was not observed during experiments measuring steady-state or equilibrium current characteristics. As shown in Figure 1C, an LQT3 linked mutation I1768V did not alter I_{NaL} measured at the end of a prolonged depolarizing pulse compared to wild-type current amplitude. However, in response to a negative ramp current, a transient inward current twice the amplitude of wild-type current was observed. A computational analysis predicted that an increase in the rate of recovery from inactivation was a plausible explanation for the observed experimental results. The model predictions suggest that faster recovery from inactivation allowed sufficient I_{NaL} during a high resistance phase of action potential repolarization, at voltages favoring channel activation, so that the AP is prolonged, consistent with the phenotype. Thus, although

measurement of I_{NaL} is negligible under steady-state voltage conditions, protocols that simulate repolarization reveal I_{NaL} current amplitudes similar to other LQT3 mutations [38].

CELL TYPE SPECIFICITY OF I_{NaL}

Nearly all cardiac myocytes express a late component of I_{Na} (see Table 2). However, expression is not uniform; in studies of canine ventricular myocytes, I_{NaL} density was found to be 47% greater in M cells, as compared to endocardial and epicardial cells, with no difference in frequency dependence and recovery from inactivation [32]. However, this result may be species dependent; Noble et al. found just the opposite in guinea pig myocytes: the smallest I_{NaL} current density was observed in midmyocardial regions [27]. Other potential explanations for this discrepancy include M cells comprising only a small population of the midmyocardial layer, and the absence of M cells in particular species (e.g. guinea pig, rat, and pig) [4, 39-41]. Although I_{NaL} has been found in ventricular myocytes of humans [1, 26, 34], it will be especially important to determine the distribution of I_{NaL} density, since transmural heterogeneity of I_{NaL} current density is suggested as a plausible source of pathologic APD heterogeneity leading to ventricular tachyarrhythmias such as torsades de pointes [32, 42]. Rabbit atrial cells have I_{NaL} with similar current density to ventricular myocytes [43] but Purkinje fibers have increased I_{NaL} compared to ventricular cells [44, 45].

DISEASES AND CONDITIONS ASSOCIATED WITH I_{NaL}

As shown in Table 3, there are multiple mechanisms of action underlying enhanced pathologic I_{NaL}, which can be separated into congenital, acquired, and experimentally induced conditions that mimic physiological conditions. This review will focus on LQT3 as the prototypical congenital mutation, and heart failure and its antecedent processes as the prototypical acquired disease leading to enhanced I_{NaL}.

Congenital disorders

Of the congenital conditions associated with I_{NaL}, LQT3 syndrome has been most widely studied and characterized. The link between late Na^+ current and congenital arrhythmias began when Bennett et al. described the first LQT3 mutation, ΔKPQ [52], which results from a 3 amino acid deletion (lysine, proline, glutamine at positions 1505 - 1507) in the linker region between domains III and IV [52]. ΔKPQ causes a transient failure of fast inactivation of the Na^+ channel, which results in a small population of channels fluctuating between a normal “dispersed” mode, and a “burst” mode of gating [52, 53]. The persistent Na^+ current induced by the bursting mode causes an increase in the action potential duration that manifests as QT prolongation on the body surface ECG (see Figure 2A and 2B).

Importantly, not all LQT3 mutations produce I_{NaL} via noninactivating bursting channels; as discussed, I1768V [38] via non-equilibrium gating, the D1790G mutation by PKA induced bursting [54], increased window currents as seen with N1325S and R1644H [29], and S1103Y, a mutation implicated in sudden infant death syndrome (SIDS) which causes a pH-dependent increase in I_{NaL} [55]. The reader is referred to [8] for a detailed review of Na^+ channel mutations and arrhythmia.

Independent of mechanism, LQT3 mutations promote a delay in ventricular repolarization during plateau potentials. This can promote a substrate for triggered activity via early afterdepolarizations (EADs), which result from reactivation of L-type Ca^{2+} channels [56-58] (during phase 2 of the action potential). It is important to note that the enhanced late Na^+ current is not necessarily the charge carrier of the EAD, but merely sets up conditions favorable for a normally functioning L-type Ca^{2+} channel to reactivate. It has been

suggested that these EADs lead to triggered activity and propensity to polymorphic ventricular tachycardia and torsades de pointes [8], the primary arrhythmia mechanism and cause of sudden cardiac death in LQT3 carriers [10].

Other congenital clinical conditions associated with an enhanced I_{NaL} result from mutations in proteins that either interact with $Na_V1.5$ directly as part of a macromolecular complex [61], or are important for cellular localization. For example, sequence analysis of the gene encoding caveolin-3, a major scaffolding protein present in the caveolae of the heart, revealed 4 novel mutations in CAV3-encoded caveolin-3 from patients referred for LQTS genetic testing. In each of these mutations, expression of mutant caveolin-3 with $Na_V1.5$ resulted in a 2 – 3 fold increase in I_{NaL} compared with wild-type caveolin-3 [62]. This study also confirmed colocalization of $Na_V1.5$ with caveolin-3, suggesting that mutations in proteins within the macromolecular complex containing $Na_V1.5$ can disrupt normal Na^+ channel function and lead to a persistent I_{NaL}. Cronk et al. have also reported CAV3 mutations implicated in LQT associated SIDS [63].

Other studies have implicated mutations in SNTA1, the gene encoding α1-syntrophin, and associated with the SIDS disease entity, as a novel regulator of $Na_V1.5$ function. These mutations lead to release of neuronal nitric oxide synthase by the plasma membrane Ca-ATPase PMC4Ab, causing an increase in both peak and late Na current [64, 65].

Calcium signaling mediated increase in I_{NaL}

Ca^{2+} modulation of the Na^+ channel has also been demonstrated after direct binding sites for Ca^{2+} [66] and the Ca^{2+} binding protein calmodulin (CaM) [67] were found on the carboxy terminus of the Na^+ channel. These discoveries led to studies that revealed inactivation of I_{NaT} can be modulated by Ca^{2+}, CaM, and/or the Ca^{2+} / CaM / CaM-kinase signaling cascade [2]. While the Ca^{2+} / CaM / CaM-kinase signaling cascade and interaction with the Na^+ channel is complex, and not fully elucidated, a few studies, in particular with CaMKII have revealed interesting interactions with Na^+ channels [68, 69].

In studies examining the interaction of the Na^+ channel and I_{NaL} with CaMKII, it was found that CaMKII coimmunoprecipitates and phosphorylates Na^+ channels [68]. Overexpression of CaMKIIδ_C in rabbit myocytes (acute) and transgenic mice (chronic) led to (1) enhanced I_{NaL}, (2) slowed fast inactivation (but enhanced intermediate inactivation), (2) slowed recovery from inactivation, (3) shifted steady state availability in hyperpolarizing direction that was Ca^{2+}-dependent, and (4) a rise in intracellular Na [2, 68]; importantly, these results were reversible with CaMKII inhibition (acute only). Interestingly, Bers and Grandi [70] note the striking similarity of these CaMKII-induced changes with the LQT3- and Brugada-linked mutant 1795insD [71]. Maltsev and Undrovinas [69] found that in both normal and failing canine ventricular myocytes, that I_{NaL} was enhanced by direct Ca^{2+} binding, CaM interactions and by CaMKII signaling. All three mechanisms were shown to cause increased I_{NaL} and Na influx by slowing inactivation kinetics, observed as a positive shift in the steady state availability curve [2, 69]. Evidence of CaMKII upregulation has also been confirmed in other studies examining the effects of CaMKII in the heart failure setting [72-74]. These data point to the potential for novel therapeutic targeting of Ca^{2+}-dependent modulation of I_{NaL} to prevent calcium loading that likely underlies arrhythmia propensity in pathological remodeling.

Acquired disorders: A role for late Na current in arrhythmogenesis in heart failure

Late Na^+ current and increased intracellular Na^+ have been shown to play a crucial role in arrhythmias associated with acquired diseases such as heart failure and post MI remodeling, due to their impact on action potential duration and repolarization abnormalities.

Approximately 40% of chronic heart failure patients die due to sudden cardiac death, with ventricular tachycardia and fibrillation documented in 80% of patients with ECG Holter monitoring at the time of death [2, 95, 96].

The first evidence for the potential role for I_{NaL} in arrhythmogenesis derived from experiments of rat ventricular myocytes in the absence and presence of hypoxia. I_{NaL} increased during hypoxia 2 – 4-fold (from 50-100 pA during normoxia to 180 – 205 pA during hypoxia), and was suggested to give rise to early afterdepolarizations (EADs) and arrhythmias during hypoxic states [4, 88, 97]. Later, the importance of I_{NaL} in heart failure was found through experiments that acted to normalize pathologic I_{NaL}; this "rescue" resulted in 1) normalization of repolarization; 2) decrease in beat-to-beat APD variability; and 3) improvement in Ca^{2+} handling and contractility [2, 48, 98, 99]. Because hypoxia, ischemia and overt heart failure represent a continuum of global oxygen deprivation and subsequent disease, the general mechanisms leading to these derangements will be discussed together.

Under various "oxygen deprivation" insults (hypoxia, ischemia, reactive oxygen species, and heart failure), intracellular Na^+ quickly rises due both to deranged ion homeostasis (both Na^+ and Ca^{2+}) as well as altered Na^+ channel gating [100], leading to an increased I_{NaL}.

Failure of ion homeostasis begins with an influx of Na^+ through the Na^+/H^+ exchanger (NHE) [101] in attempt to raise the acidified pH (through the extrusion of H^+) due to ischemia. For example, under conditions of hypoxia, NHE from rabbit ventricular myocytes stimulated at 1 Hz accounted for 39% of the total Na^+ influx (as compared to 5% during normoxia) [102]. Inhibition of the NHE during ischemic episodes attenuated the rise in intracellular Na^+ [103, 104].

Along with Na^+ influx via the NHE, a parallel decrease in energy production due to mitochondrial dysfunction and loss of ATP results in reduced Na^+ elimination through the Na^+/K^+ ATPase [105], which further augments intracellular Na^+.

A direct consequence of intracellular Na^+ overload is an increase in cytosolic Ca^{2+} accumulation. Intracellular Na^+ accumulation causes the Na^+/Ca^{2+} (NCX) exchanger to work in reverse-mode (3 Na^+ ions extruded for 1 Ca^{2+} influxed). Pharmacological and antisense inhibition of NCX greatly reduce the rise in Ca^{2+} [106, 107]. Entry of Ca^{2+} into the myocyte via the NCX (as well as the L-type Ca^{2+} channel) ultimately exceeds Ca^{2+} efflux and precipitates Ca^{2+} overload. Deranged Ca^{2+} homeostasis leads to spontaneous SR Ca^{2+} release, a pathological version of the Ca^{2+}-induced-Ca^{2+} release process [4, 108], resulting in beat-to-beat variability in repolarization with cellular repolarization abnormalities (e.g. EADs and delayed afterdepolarizations (DADs)) and triggered arrhythmias [105]. Propensity for triggered arrhythmias via APD prolongation, dispersion of repolarization, and EADs and DADs, have all been described in patients with heart failure [2, 109]. In addition to repolarization abnormalities and electrical instability from deranged accumulation and cycling of Ca^{2+}, the ventricular myocardium is predisposed to mechanical instability including impaired diastolic relaxation, contractile dysfunction, and microcirculatory resistance [100].

At the cellular level, failing (but not normal) canine ventricular myocytes that exhibited prolonged APs, Ca^{2+} transients and substantial diastolic Ca^{2+} accumulation leading to spontaneous Ca^{2+} release were rescued by addition of TTX and ranolazine (a selective I_{NaL} blocker) [110-112]. The improved function in canine ventricular myocytes [110] is further evidence linking I_{NaL} to the induction of deranged Ca^+ homeostasis at the cellular level. A subsequent study using human ventricular myocytes [26] similarly found a normalization of APD and abolishment of EADs with the addition of TTX.

Intrinsic gating abnormalities of the cardiac Na^+ channel, in addition to ion homeostatic dysfunction has also been linked to conditions of heart failure. Maltsev and Undrovinas first reported the existence of a novel, ultraslow inactivating Na current, I_{NaL}, in both normal and failing human hearts [26], and recently have shown that chronic heart failure leads an increased density and slower inactivation kinetics of I_{NaL} [34] as compared to normal hearts, with a 53.6% increase in total Na^+ influx in failing myocytes. Single channel analysis reveals that the two modes of gating comprising the late I_{Na}, late scattered mode and burst mode of gating, are significantly slower in failing human ventricular myocytes compared to normal ventricular myocytes and heterologously expressed $Na_V1.5$ [1]. Importantly, there were no differences in the unitary conductance of late Na^+ current between normal and failing human hearts, further suggesting that enhanced late current appears to be generated by a single population of channels that are upregulated in HF [113].

As shown in Figure 3, conditions and diseases that lead to an increased late I_{Na} exhibit electrical instability (due to afterdepolarizations, beat-to-beat variability in repolarization, ventricular arrhythmias), mechanical instability (impaired diastolic relaxation and ventricular wall tension, increased diastolic and decreased systolic force generation), as well as mitochondrial dysfunction [42]. This cascade leads to further ischemia and abnormal contraction, setting up a pathological feedback loop.

PHARMACOLOGY OF I_{NaL}

Pharmacological enhancement of late I_{Na}

There are various compounds that can increase late I_{Na} including veratridine [114], peptide toxins (e.g. ATX-II, AP-A, AP-Q, β-pompilidotoxin) [115], pyrethroids [116-118], and small molecules (BDF9148, DPI201106) [6, 83, 84, 117]. Zaza et al. notes that although these compounds serve as important experimental tools, interpretation of their results must be with caution as their varied mechanisms of action producing late I_{Na} will impact the severity of repolarization abnormality and proarrhythmic potential [6].

For example, there have been numerous recent studies using ATX-II as a pharmacological model of LQT3 syndrome [111, 119-122] to probe antiarrhythmic efficacy of ranolazine. As the mechanism of ATX-II on $Na_V1.5$ is thought primarily to destabilize inactivation [85], this model may only be useful for some LQT3 linked mutations, but not others (e.g. I1768V [38], D1790G [123]). Furthermore, mutations might alter the affinity of Na^+ channels for certain drugs (e.g. affinity of wild-type Na^+ channels with ATX-II for ranolazine ~6 μM [124] vs. ΔKPQ Na^+ channel ~ 12 μM [125] for ranolazine), making interpretation of pharmacokinetics (e.g. potency ratios between I_{NaL} and I_{Kr}) difficult.

Pharmacological suppression of late I_{Na}

In the late 1980's, after decades of research into Class I Na^+ channel blockers, the Cardiac Arrhythmia Suppression Trial (CAST), a randomized placebo controlled study to assess the efficacy of Na^+ channel blockade, commenced. CAST compared three common antiarrhythmics, flecainide, encainide, and moricizine, for antiarrhythmic efficacy after myocardial infarction. The trial was abruptly and prematurely terminated when it was found that flecainide and encainide paradoxically increased mortality by 2 – 3x (relative risk 3.6) as compared to placebo [126, 127]. Because of this stunning failure, Na^+ channel blockade had fallen out of favor therapeutically, in part, because of the inability of current drugs to selectively discriminate between the peak and late components of I_{Na}. Revival of Na^+ channel targeting has been a result of a new understanding of the emergent effects of Na^+ channel drug blockade, diseases and conditions with selective increase in I_{NaL} (such as LQT3 and heart failure), as well as newer drugs that selectively target I_{NaL}, as discussed next.

Nonselective Na channel blockers—As I_{NaL} is presumably the same channel as I_{NaT} [2, 26, 34-36, 113, 128], classical Na^+ channel blockers (flecainide, lidocaine, quinidine, mexilitine, TTX, STX, Cd^{2+} etc.), as well as those with off-target Na^+ channel blocking effects (e.g. amiodarone) are effective at suppressing I_{NaL} [6]. To date, selective blockade of the late component of the Na^+ current, without concomitant blockade of the peak Na^+ current (responsible for maintaining cellular upstroke velocity and propagation in coupled tissue) has been elusive (see Table 4). For example, flecainide, a prototypical Class IC Na^+ channel blocker only displays 2.9 – 5-fold I_{NaL}/I_{NaT} selectivity, with potential toxicity owing to potent I_{NaT} blockade, which can set up conditions of conduction block and reentrant ventricular tachyarrhythmias [127, 129]; this was likely a major determinant of the arrhythmias observed during the CAST trial.

Amiodarone, a mixed ion channel blocker, was shown to have a 13-fold of selectivity of I_{NaL}/I_{NaT} (6.7μM vs 87 μM), with virtually no effect on I_{NaT} in the therapeutic range in studies of midmyocardial ventricular myocytes from failing human hearts. Amiodarone shifted steady-state inactivation curve and accelerated the decay time constant in a dose dependent manner, suggesting preferential blockade of inactivated and activated states [128]. While these data suggest a promising therapeutic strategy for patients with heart failure, chronic amiodarone therapy carries an extensive adverse effect profile including pulmonary fibrosis, hepatotoxicity, thyrotoxicity, marked QT prolongation and bradycardia, among the most serious [130].

Finally, both flecainide and amiodarone exhibit potent off-target effects, and in particular show virtually no selectivity between I_{NaL} and I_{Kr}, a key repolarizing current, that if blocked, could further increase action potential prolongation and destabilize repolarization.

Because of these limitations, current research is aimed at developing selective I_{NaL} inhibitors with minimal off target and toxic side effects.

Selective Late Na^+ channel blockers—It was first reported in the 1970's that I_{NaL} was more sensitive to TTX than I_{NaT}, demonstrating selective targeting of each component of the Na^+ current [136, 137]. More recently, it was shown that a partial inhibition of I_{NaL} (~50%) with TTX acted to normalize APD and abolish arrhythmogenic EADs in ventricular myocytes from failing hearts [26, 34]. There has also been considerable recent interest in a novel antianginal agent, ranolazine, with distinct efficacy against I_{NaL}.

Ranolazine: The first selective I_{NaL} Na^+ channel blocker

Ranolazine is a piperazine derivative, structurally similar to lidocaine, that exhibits minimal effects on hemodynamics such as heart rate and blood pressure [17]. Approved in 2006 by the FDA for the treatment of chronic angina pectoris, it is the only FDA-approved drug that specifically blocks the late component of the Na^+ current. While the precise mechanism of ranolazine is unknown, it has been an effective antianginal and anti-ischemic agent ostensibly by reducing Ca^{2+} overload through inhibition of I_{NaL} [138], inhibiting reverse mode of the Na^+/Ca^{2+} exchanger [42].

Mutational analysis suggests that ranolazine shares the common local anesthetic binding site, with mutation of F1760A in ΔKPQ mutant Na^+ channels reducing potencies of both ranolazine and lidocaine [125]. Ranolazine is also more potent than lidocaine for ΔKPQ; taken together, this implies a common receptor, but differential state-dependent binding affinity between ranolazine and lidocaine [6, 125].

In addition to potent, selective I_{NaL} inhibition (6 μM vs 294 μM peak I_{Na}) [98, 124] ranolazine blocks multiple ion channels, but importantly blocks the repolarizing hERG

current I_{Kr} with therapeutic concentrations (1 – 10 μM) [139]. The result is a mild concentration dependent QTc prolongation seen in patients with chronic stable angina [140]. Of note, ranolazine showed no increased proarrhythmic potential, and may even reduce the incidence of ischemia related arrhythmias [138]. Lastly, ranolazine is a very weak inhibitor of the L-type Ca^{2+} channel (IC_{50} = 296 μM) and the NCX (IC_{50} = 91 μM) [124], indicating that within the therapeutic regime, ranolazine primarily acts on I_{NaL} and I_{Kr}, with minimal to no effects on I_{CaL}, $I_{Na/Ca}$ or the NHE, important contributors to Na^+ and Ca^{2+} homeostasis [42].

Ranolazine for the treatment of ischemia, hypoxia, and heart failure—Many large clinical trials have already proven the utility of ranolazine for the treatment of cardiac ischemia, hypoxia, and heart failure [141, 142]. As discussed, these conditions share the commonalities of an increased I_{NaL}, and deranged ion homeostasis with Na^+ overload preceding Ca^{2+} overload. Selective blockade of I_{NaL} by ranolazine thus diminishes I_{NaL} and the consequent Ca^{2+} overload induced by reverse mode NCX. Clinically, this decreases diastolic wall tension, and extravascular compression allowing enhanced perfusion to ischemic myocardium [138]. Importantly, the cardioprotective effects of ranolazine occur at a concentration that has minimal effects on heart rate, coronary blood flow and systemic arterial blood pressure [143, 144], making ranolazine unique among other antianginal agents currently in use. Reduction of APD variability has also been elegantly shown in a study of canine heart failure treated with ranolazine [98]. See Figure 4.

Ranolazine for the treatment of LQT3—Although the QT prolongation observed with therapeutic ranolazine has resulted in a contraindication for patients on other QT prolonging drugs and those with preexisting QT prolongation [145], ranolazine's strong selectivity for I_{NaL} might prove beneficial in specific patient populations, such as those with LQT3. Numerous *in vitro* [120, 121, 124, 125, 146] and *in vivo* [146-148] studies suggest that through preferential reduction of I_{NaL} (9 – 38x) [124], ranolazine, appears effective in attenuating action potential duration (APD) prolongation and suppressing the development of EADs. See Figure 4.

Many studies assessing ranolazine for the treatment of LQT3 syndrome have utilized pharmacological models of LQT3 via the addition of ATXII to induce a persistent Na^+ current [111, 119-121]. Because the affinity of ΔKPQ mutant Na^+ channels for ranolazine is 2-fold lower than WT Na^+ channels (12 μM vs. 6 μM) [124, 125], and is equivalent to the I_{Kr} affinity (12 μM) [124, 139], these studies must be interpreted with caution, as these similar affinities might render ranolazine proarrhythmic in this specific patient population.

Clinical assessment of ranolazine has been carried out in one study of 5 carriers of the LQT3-ΔKPQ mutation, where Moss et al. found a modest reduction of QTc (~4%) with ~5 μM peak ranolazine infusion [146]. Importantly, ranolazine had minimal effects on upstroke velocity (phase 0) of the action potential [146, 149, 150]. However, there was a nonsignificant, but unexplained rebound increase in repolarization parameters (QT, QTc, QTpeak, Tpeak – Tend, and Tduration) 16 hours after ranolazine infusion. While this, in addition to the small sample size of this study and intravenous administration of the drug necessitates further clinical validation, this study highlights the proof-of-principle that selective targeting of pathologically induced late I_{Na} represents a tractable therapeutic target for this, and other disease linked mutations arising from enhanced I_{NaL}.

Although promising, ranolazine is marred by its potent inhibition of I_{Kr}, a key repolarizing current, and its consequent potential to prolong QT interval. In terms of treatment of syndromes arising from overabundance of late Na^+ current, it has yet to be conclusively demonstrated which effect will predominate – therapeutic block of late Na^+ current, or

pathological suppression of I_{Kr}. The answer may lie in consideration of combined effects of ranolazine and its many metabolites. Clinical pharmacokinetic studies of ranolazine suggests extensive metabolism via CYP3A mediated pathways of biotransformation [151]. Four predominant metabolites were identified at plasma concentrations 30 – 40% of the parent compound, all of which produce a substantially weaker inhibition of I_{Kr} (40 – 50% inhibition at 50 μM). IC_{50} values for an additional 7 metabolites tested were all >50 μM [138]. Importantly, all 11 metabolites potently inhibited I_{NaL} by 12 – 57% at 10 μM [138].

Thus, a higher I_{NaL}/I_{Kr} selectivity may explain ranolazine's safety and efficacy. Nonetheless, future work should focus on ranolazine analogues with greater selective targeting of I_{NaL}; this could prove most beneficial in diseases such as the LQT3 syndrome. Additional studies should also address the safety and efficacy in this specific patient population; although the study by Moss et al. [146] showed moderate benefit with ranolazine and LQT3-ΔKPQ carriers, this study was small (5 patients), and of limited duration (~24 hours). Future studies should also address whether ranolazine is merely effective at normalizing surrogate markers of arrhythmia (e.g. normalization of the QTc interval), or is actually effective at *preventing* LQT associated rhythm sequences, such as short-long-short sequences, and pause-induced arrhythmia [152].

CONCLUSIONS AND FUTURE DIRECTIONS

A wealth of experimental evidence suggests that a number of clinical conditions may result from the common pathway of deranged *late* Na^+ current. This realization has led to renewed interest in pharmacological targeting of Na^+ current as a therapeutic strategy. The ideal therapeutic is one that specifically targets late current, without affecting peak current, since attenuation of the latter is chiefly responsible for proarrhythmia associated with Na^+ channel blocking drugs [4, 129].

To date, ranolazine is the only FDA-approved drug that specifically blocks I_{NaL}, with 9 – 38 fold selectivity over I_{NaT}. It has been safe and effective in reducing myocardial ischemia, and symptomatic angina [138]. The MERLIN study [153] also demonstrated a reduction in both tachy- and bradyarrhythmias within the first week of treatment.

With respect to acquired conditions such as heart failure, this review focused on pharmacological targeting of the Na^+ channel, but other ion channels (e.g. Ca^{2+} channels), pumps, and exchangers represent equally plausible drug targets to reduce intracellular Na^+, Ca^{2+} overload, and cardiac dysfunction [42].

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LIST OF ABBREVIATIONS

ATX-II	Anemonia sulcata toxin
AP-A,Q	Anthopleurin A, Q
hERG	Human Ether-a-go-go Related Gene, $K_V11.1$
I_{NaT}	Transient (T) Na^+ current
I_{NaL}	Late (L) Na^+ current
LQT(3)	Long QT syndrome (variant 3)
STX	Saxitoxin
TTX	Tetrodotoxin

Highlights

- I_{NaL} can disrupt cellular repolarization and increase propensity to ventricular arrhythmia.
- Although small compared to peak Na^+ current, I_{NaL} increases Na^+ loading in cardiac cells.
- Multiple cardiac pathological conditions share phenotypic manifestations of I_{NaL} upregulation.
- Specific pharmacological inhibition of I_{Na} is desired

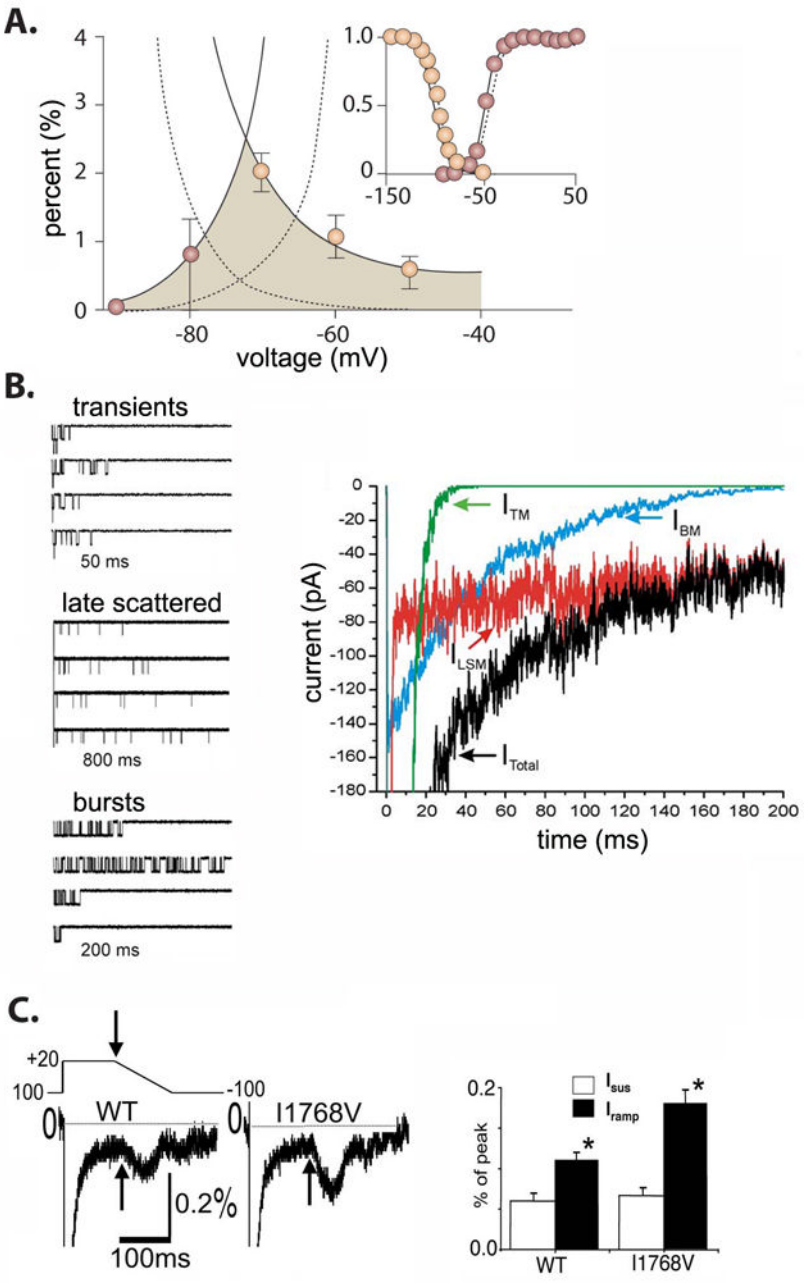

Figure 1. Mechanisms of late I_{Na}

A) Schematic of an increased window current (shaded region) in the LQT3 linked N1325S. The dotted lines represent the wild-type. Note the minimal overlap between steady-state inactivation and the activation curve normally exists outside the voltage range of repolarization. Adapted from [8]. B) Modal gating of I_{NaL}. A simulation demonstrating three modes (left panels) of gating, transients, late scattered, and bursts comprise the total I_{Na} current (right panel) (simulation time course is shown). Adapted from [1]. C) Non-equilibrium gating of I1768V. A schematic of a negative ramp protocol. Persistent current was measured at the end of a 100ms depolarizing pulse (arrow) and was not significantly different between wild-type and the I1768V mutation. Ramp currents were measured as the

peak inward current during the negative ramp protocol and were significantly larger in the mutant Na^+ channel (summary data in bar graph on right). Adapted from [38].

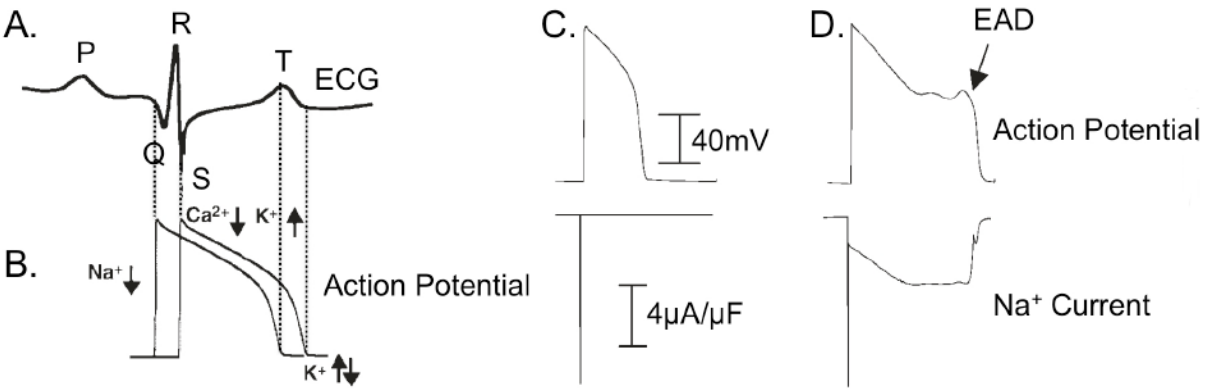

Figure 2. Electrical gradients within the myocardium detected on the ECG, and action potential prolongation via mutation induced late I_{Na}

A. and B. Schematic representation of the relationship between an action potential and the ECG detected as spatial and temporal gradients for one cardiac cycle. The P wave represents atrial depolarization, the QRS complex represents ventricular activation, and the T wave represents the gradient of ventricular repolarization. Dotted lines indicate the link between deflections on the ECG and underlying cellular level electrical events. B. Schematic of the cellular electrical activity underlying the ECG. C and D: Simulated action potential (top) and I_{Na} (bottom) for wild-type (C) and ΔKPQ (D). In the wild-type, Na^+ channels activate, followed quickly by inactivation; ΔKPQ mutant channels fail to inactivate and cause a small, persistent (<5% peak) Na^+ current (panel D, bottom) that prolongs the action potential and can lead to arrhythmogenic early afterdepolarizations (EADs) shown in the top panel of D. Note, in both C and D bottom panels, peak I_{Na} is off scale. Figure adapted from [59, 60].

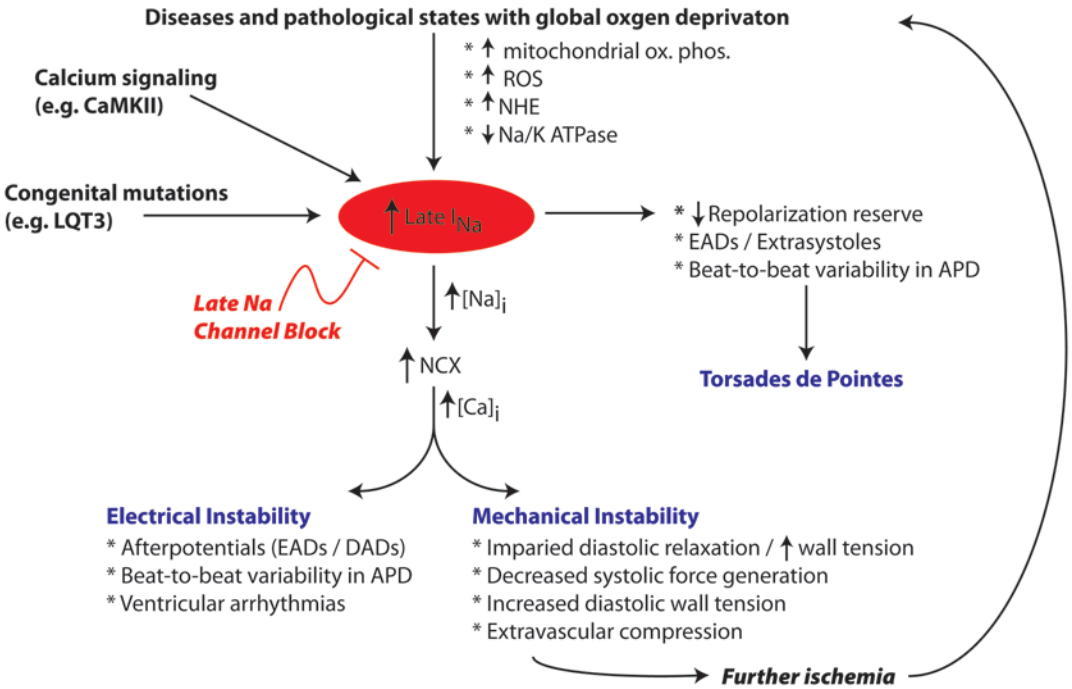

Figure 3. Cascade of I_{NaL} induced dysfunction

Congenital and acquired conditions exhbit an increased late Na^+ current, which can both cause electrical and mechanical instability. Blocking I_{NaL}, may effectively blunt the cascade of I_{NaL} induced cardiac dysfunction. See text for details. Figure adapted from [42, 105].

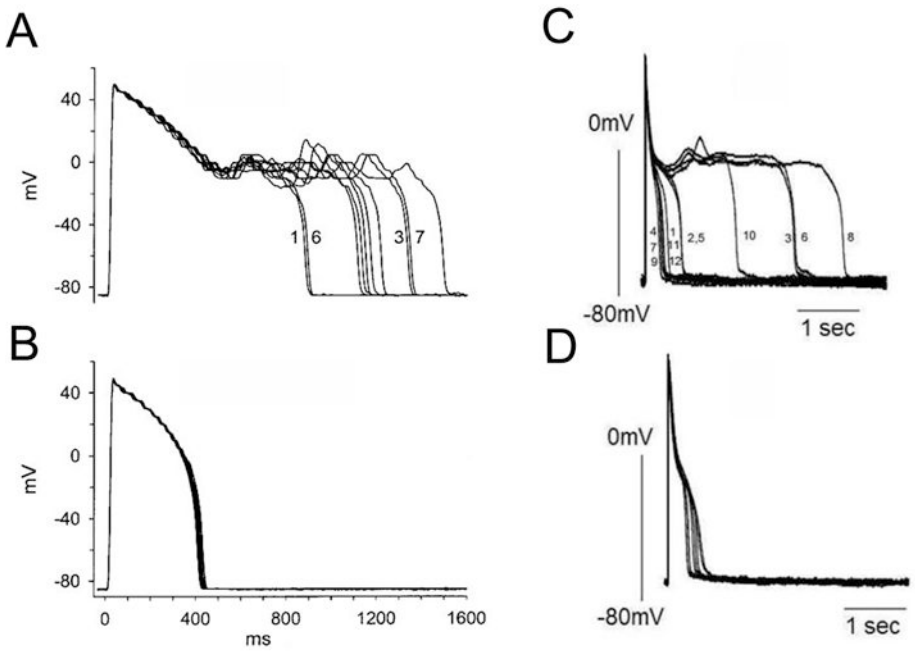

Figure 4. Pharmacological targeting of I_{NaL} normalizes APs in a pharmacological model of LQT3 and in heart failure

(A) Superimposed recordings of 10 consecutive action potentials from a guinea pig myocyte in the presence of 10nM ATX-II, and (B) in the presence of 10nM ATX-II and 10 μM ranolazine. Modified from [121]. (C) Ranolazine (RAN) reduces APD variability in left ventricular myocytes isolated from canine failing hearts. (A) Twelve consecutive APs recorded at a pacing rate of 0.25 Hz are superimposed. (B) APs recorded in the presence of 10 μM ranolazine. From [98].

Table 1

Major membrane currents underlying a typical ventricular action potential (adapted from [7])

Membrane Currents	Description	Gene (α-subunit)	Contribution to action potential
Inward ionic currents			
I_{Na}	Na^+ current	SCN5A ($Na_V1.5$)	Initial depolarization of the action potential
$I_{Ca,L}$	L-type Ca^{2+} current	CACNA1C ($Ca_V1.2$), CACNA1D ($Ca_V1.3$)	Maintains plateau phase of action potential
Outward ionic currents			
I_{to}	Ca^{2+}-independent transient outward K^+ current	KCND2 ($K_V4.2$), KCND3 ($K_V4.3$), KCNA4 ($K_V1.4$)	Responsible for early repolarization
I_{Kr}, I_{Ks}	Rapid and slow delayed K^+ rectifier currents	KCNH2 ($K_V11.1$), KCNQ1 ($K_V7.1$)	Aids repolarization during plateau
I_{SS}, $I_{Ks,Low}$	Slow inactivating K^+ currents	KCN1B ($K_V2.1$), KCNA5 ($K_V1.5$)	Aids late repolarization
I_{K1}	Inward rectifier K^+ current	KCNJ2 (Kir2.1), KCNJ12 (Kir2.2)	Late repolarization, helps establish V_{rest}
Other ionic currents			
I_{NaCa}	Na^+ - Ca^{2+} exchanger	SLC8A1 (NCX1), SLC8A2 (NCX2)	Late depolarization
I_{NaK}	Na^+ - K^+ pump	ATP1A1, 2, 3	Late repolarization

Table 2

Cardiac cell types physiologically expressing I_{NaL} (reproduced from [6])

Cardiac Cell Type	Reference
Atrial myocytes (rabbit, man)	[43, 46]
Ventricular Myocytes (human, dog, guinea pig)	[27, 34, 47, 48]
Purkinje fibers and M-cells (dog, rabbit)	[32, 34, 48, 49]
Fetal ventricular myocytes (rat)	[50]
Neonatal sinoatrial node myocytes (rabbit)	[51]

Table 3

Pathological and experimental conditions associated with an enhanced I_{NaL} (reproduced from [6])

Congenital clinical conditions	
LQT3 syndrome (Na+ channel mutations)	[52]
LQT-CAV3 (caveolin-3 mutations)	[62]
LQT-SCN4B (β4-subunit mutations)	[22]
Acquired clinical conditions	
Heart failure	[26, 48, 76]
Post-MI myocardial remodeling	[77]
Experimental conditions	
Second messengers (CaM and CaMKIIδ)	[68, 78]
Oxygen free radicals	[79-82]
I_{NaL} enhancing agents	[83-87]
Acute hypoxia	[88-90]
Ischemic metabolites	[82, 91-94]

Table 4

Comparison of block potency ratios for common Na^+ channel blockers (adapted from [6])

Agent	I_{NaL} / I_{NaT}	I_{NaL}/ I_{Kr}	Reference
Amiodarone	13	≤1.5	[128, 131]
Flecainide	2.9 – 5	<0.1 – 2	[132-135]
Ranolazine	9 – 38	1.5 – 2	[98, 125]
Lidocaine	2.7*	-	[98]

I_{NaL} / I_{Kr} ratios are approximate, because complete concentration-response curves are not available for all agents and within the same experimental setting.

* Reference to unpublished data in [98]