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Late sodium current: A mechanism for angina, heart failure, and arrhythmia

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Abstract

The peak sodium current underlies excitability and conduction in heart muscle, but a late sodium current flowing after the peak contributes to maintaining and prolonging the action potential plateau, and also to intracellular sodium loading, which in turn increases intracellular calcium with consequent effects on arrhythmia and diastolic function. Late sodium current is pathologically increased in both genetic and acquired heart disease, making it an attractive target for therapy to treat arrhythmia, heart failure, and angina. This review provides an overview of the underlying bases for the clinical implications of late sodium current block.

Keywords

Sodium current; Long-QT syndrome; Antiarrhythmic drugs

Introduction

Late sodium current (I_{Na}) is the residual I_{Na} flowing after the large peak I_{Na} during an action potential (AP) or voltage clamp (Fig. 1). Although under "normal" conditions it is a small current (~0.5%) relative to peak I_{Na}, it is sufficiently large during the AP plateau to affect the duration, and the flow over hundreds of milliseconds during the AP contributes more to Na^+ loading than the brief transient of peak I_{Na} [1]. With the recognition that the mechanism of action for the antianginal drug ranolazine was through a relatively specific block of late I_{Na}, a role for late I_{Na} as a mechanism for pathogenesis of angina, heart failure, and arrhythmia has attracted much attention [2,3]. This article offers perspectives and observations on late I_{Na} and human cardiac disease with selective references focusing on late I_{Na}, its causes and regulation, an account of pathogenesis of cardiac disease through electrophysiology and altered Na–Ca homeostasis, and a consideration of clinically available drugs that block or increase late I_{Na}.

The role of late I_{Na} in angina, arrhythmia, and heart failure is speculative and subject to ongoing studies, and the reader is referred to key and recent comprehensive reviews of late I_{Na}

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and ranolazine that cover the wealth of experimental and clinical data [2–8] providing additional detail and supporting references.

Background

The recognition that late I_{Na} plays a role in cardiac physiology goes back to ~50 years, when it was shown that the selective Na^+ channel blocker tetrodotoxin shortened the AP plateau [9]. This late I_{Na} and its effect on the AP were subsequently studied as "window current" [10], "steady-state" current [11], "slow inactivation" current [12,13], "late current" [14], "slow current" [15], and "persistent current" [16]. As noted below, the characteristics and mechanisms for late I_{Na} are heterogeneous; therefore, the term "late I_{Na}" is preferred as the most general term not invoking particular mechanisms or characteristics. An important issue when reading the literature is to note how long after the depolarization late I_{Na} is measured. Because I_{Na} in cardiac tissue is subject to slow decay over tens of milliseconds, a measure of late I_{Na} at 10 ms will give a higher value than later measurement at 20 or 50 ms. Also note that for comparison purposes, late I_{Na} is often expressed as a percentage of the peak I_{Na} or normalized to cell size as measured by cell capacitance.

Several key features of late I_{Na} are important for understanding the clinical manifestations. An important biophysical distinction is the late I_{Na} produced by overlap of the voltage dependence of activation and inactivation to produce what is called "window current" that occurs over the voltage range of this overlap that affects AP duration. Window current is the consequence of the voltage dependence of more or less normal gating in the overall population of sodium channels and is regulated by the protein kinase C (PKC) pathway [17]. In contrast, increased late I_{Na} may involve a fundamental change or abnormality in the inactivation gate in a select population of channels. This abnormality may have diverse underlying causes and mechanisms. Another important feature of late I_{Na} addressed in more detail below is whether or not it is subject to "slow inactivation," which will lead to a frequency-dependent inactivation of the late I_{Na}. Finally, it is important to note that late I_{Na} is heterogeneous in amplitude by region in the heart [18]. Several comprehensive reviews [4,5] provide additional detail and references for these topics.

Sodium channel macromolecular complex

Cardiac I_{Na} flows through a channel formed by the α-subunit NaV1.5 encoded by the gene *SCN5A*. Although the α-subunit alone accounts for major features of I_{Na}, it is part of a macromolecular complex consisting of auxiliary subunits and associated channel interacting proteins or ChIPs. Identification of components of the macromolecular complex and how they regulate I_{Na} is a rapidly evolving field [19]. Although NaV1.5 underlies the majority of I_{Na}, other "non-cardiac" isoforms may make up an important part of cardiac I_{Na}. In particular, the nerve/brain isoforms NaV1.1 [20] and NaV1.8 [21] may underlie an important part of late I_{Na} in human heart. Other components of the complex that may play important roles in regulating late I_{Na} in human heart include α1-syntrophin (Snta1) [22], caveolin 3 (Cav3) [23], and calmodulin kinase 2(CaMKII) [24]. The β1 subunit [25,26] and β4 subunit [27] also play a role in late I_{Na}. The biophysical mechanisms by which α-subunit structure and interacting proteins in the complex affect late I_{Na} are not completely understood. Late

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I_{Na} is generally thought to be a modification of or failure in the inactivation process. A structure responsible for fast inactivation of I_{Na} resides in "IFM" residues on the DIII–DIV linker as a "ball" or "lid" and on the bottom of the S4–S5 linker as a receptor, but myriad mutations throughout the NaV1.5 topology cause long-QT syndrome type 3 (LQT3), so it seems that diverse perturbations in NaV1.5 structure are associated with late I_{Na}. A way to think of it is that the complex for inactivation is a fine-tuned precise machine, and there are many different ways to disrupt normal gating to make late I_{Na}. If this is true, a single final common structure–function pathway for the cell signaling and biophysical mechanisms for regulating and causing late I_{Na} may be elusive.

Causes of increased late I_{Na}

Increased late I_{Na} has been characterized under a wide variety of experimental conditions. Table 1 in a recent review [7] lists and references conditions, drugs, toxins, and diseases associated with increased late cardiac I_{Na}. Table 1 in this article lists causes most relevant to mechanisms and treatment of cardiac disease, along with possible mechanisms for their effect. It is important to note that these "causes" are not mutually exclusive but may be upstream or downstream elements in a regulatory or pathological pathway. For example, increased late I_{Na} in ischemia may be caused by acidosis and ischemic metabolites such as lysophosphatidylcholine (LPC), and late I_{Na} in LQT9 and LQT12 is caused by enhanced nitrosylation. Possible mechanisms (Table 1) at the cellular level (such as altered signaling pathways) for the increased late I_{Na} cardiac diseases are coming into focus, but as noted above, discovery of the mechanisms at the biophysical level appears less tractable.

Regulation of late I_{Na} by cell signaling and post-translational modification

Late I_{Na} is present physiologically and is regulated by multiple pathways, including nitrosylation via nNOS and by phosphorylation via a number of kinases (Table 1). Specificity of nitrosylation for the NaV1.5 channel can be achieved because the syntrophin/dystrophin complex interacts with the c-terminus of NaV1.5 through PDZ domains [28], and α1-syntrophin (Snta1) is a member of the family of dystrophin-associated proteins containing multiple protein interaction motifs that act as molecular scaffolds for nNOS, and plasma membrane Ca-ATPase (PMCA). Plasma membrane Ca-ATPase subtype 4b (PMCA4b) interacts with Snta1 between the PH2 and SU domains to inhibit nitric oxide (NO) production [29]. These three proteins Snta1, nNOS, and Pcma4b associate with the c-terminus of NaV1.5, and the mutation A390V in Snta1, discovered in a patient with long-QT syndrome, specifically disrupts binding of PCMA4b from the complex [22]. NO increases late I_{Na} [30], and thus this finding is consistent with the mutation increasing late I_{Na} through locally increased production of NO.

Phosphorylation of NaV1.5 at specific residues S516 and T594 by calcium–calmodulin kinase (CaMK)-dependent mechanisms also increases late I_{Na} [24]. The Ca2+-sensing protein calmodulin (CaM) activates CaMKIIδ, the predominant isoform in heart, and regulates many aspects of excitation–contraction coupling [31]. CaM binds near the isoleucine and glutamine at residues 1908 and 1909 on the carboxy-terminus of NaV1.5 in a Ca^{2+}-dependent manner, where it slows inactivation of I_{Na} [32]. CaM also interacts with the

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DIII–DIV linker with similar functional effects [33]. CaMKIIδ was also shown to associate with and phosphorylate NaV1.5 and cause late I_{Na} [34]. Possible interactions or synergy between nitrosylation and this phosphorylation are not known.

PKC phosphorylation pathways are also involved in regulation of late I_{Na}. PKC-dependent phosphorylation of NaV1.5 at S1503 causes alterations in I_{Na} kinetics that open up a window current [35], and PKC inhibition blocked increased late I_{Na} that was caused by calcium loading the cell [36], suggesting the invovlement of PKC in CaM pathway causes of late I_{Na}.

The phosphoinositide 3-kinase (PI3K) signaling pathway including tyrosine kinase (TK) as an upstream activator and the protein kinase Akt as a downstream effector has been recently reviewed as a modulator of cardiac ion channels including I_{Na} [37]. TK inhibitors such as the anti-cancer drug nilotinib were found to increase the QT interval in patients, and the drugs were shown to increase late I_{Na} by inactivating PI3K [38]. The antiarrhythmic drugs dofetilide and sotalol as well as the drugs thioridazine and erythromycin were also found to increase late I_{Na} by inhibiting this pathway [39]. It is important to note that the full effect to increase late I_{Na} took up to 48 h. The detailed mechanism and the phosphorylation target(s) by which late I_{Na} is decreased by TK/PI3K/Akt is unclear, but it is important to note that unlike regulation by nNOS and CaMK, which increase late I_{Na}, the PI3K pathway suppresses late I_{Na}. This pathway affects many other ion currents, and so far it is not known if the machinery for this pathway is part of the NaV1.5 macromolecular complex to allow specificity for I_{Na}, in a way analogous to Cav3/Snta1 and nitrosylation, and to the CaM-dependent phosphorylation pathway.

Drugs that increase late I_{Na}

Drugs that increase late I_{Na} such as DPI 201-106 were studied as positive inotropes but did not reach clinical practice because of toxicity [40]. As noted above, PI3K inhibition by anti-cancer [38] and by antiarrhythmic and other drugs [39] increase late I_{Na} and prolong APD by this mechanism in addition to their effects to reduce potassium currents. This suggests that drug safety screening for long QT might need to include testing for effects on late I_{Na}.

Increased late I_{Na} in genetic cardiac disease—LQT3, 9, 10, and 12

Late I_{Na} causes QT prolongation and arrhythmia for mutations in NaV1.5, causing the LQT3 syndrome. Late I_{Na} may be increased by several biophysical mechanisms such as failure to inactivate completely and increased window current. Depending upon the underlying mutation, late I_{Na} undergoes a gradual voltage-dependent decay because of slow inactivation into a state from which recovery is slow, such as that for late I_{Na} in the LQT3 mutation KPQ [41], or it can be flat and persistent such as that for E1784K [42]. Slow inactivation of late I_{Na} accumulates with faster heart rates, causing a decrease in late I_{Na}, shortening of the AP plateau, and a correspondingly enhanced rate-adaptation of the QT interval on the surface ECG. About half of LQT3 mutations studied exhibit slow decay of late I_{Na}. Mutations in NaV1.5 implicated in SIDS did not have this decay [43] and perhaps this lack of decay leads to increased Na loading and underlies the greater lethality compared to LQT3. This possibly clinically important feature is not often characterized or noted in

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studies of late I_{Na}. This finding also suggests an underappreciated heterogeneity in the behavior of late I_{Na} that may be clinically important.

As noted above, LQT3 mutations are scattered throughout NaV1.5 and not localized in specific domains, making it difficult to propose a detailed biophysical mechanism for how the mutations cause late I_{Na}, although some LQT3 mutations may mimic phosphorylation [44]. Mutations in sodium channel complex proteins other than NaV1.5 also result in late I_{Na}. LQT10 was associated with a mutation in the β4 subunit, but the mechanism for increased late I_{Na} is not known. On the other hand, increased late I_{Na} associated with mutations in Cav3 (LQT9) and Snta1 (LQT12) are associated with enhanced direct nitrosylation of NaV1.5 [22,23]. Late I_{Na} has also been noted in both dilated cardiomyopathy and hypertrophic cardiomyopathy that are or can be genetic diseases, but it is unclear if the cause of late I_{Na} is specific to the mutation, or if it should be considered acquired as a non-specific consequence of the hypertrophy or failure.

Direct electrophysiological effect of late I_{Na} and arrhythmia

Increased late I_{Na} is often called a "gain of function," and decreased peak I_{Na} is called a "loss of function." In heart failure, peak I_{Na} is decreased but late I_{Na} is increased, posing an apparent contradiction that heart failure causes both a gain in function as well as a loss of function. The contradiction is resolved by recognizing the timing of these effects and that they are not mutually exclusive. Increased late I_{Na} is a persistent depolarizing force during the plateau, which opposes repolarizing currents and lengthens the AP, corresponding to a prolonged QT on the surface ECG (Fig. 1). Loss of function as a decrease in peak and early I_{Na} is arrhythmogenic through mechanisms diagramed (Fig. 2), whereas increased late I_{Na} is arrhythmogenic through AP duration prolongation and long-QT arrhythmia, which has both elements of triggered activity (early afterdepolarizations or EADs) and effects on re-entry as diagramed (Fig. 2).

Indirect effect of late I_{Na} on Na–Ca homeostasis on arrhythmia, heart failure, and angina

Na^+ enters the cell through I_{Na}, Na–Ca exchange, and Na–H exchange, and this "Na^+ loading" under normal circumstances is balanced by Na^+ leaving the cell through Na–K ATPase. Na^+ loading by I_{Na} depends upon the amplitude and duration of I_{Na} during each phase of the AP [1]. Under normal conditions the majority of Na^+ loading from I_{Na} occurs during phase 2, followed by phase 1, phase 0, phase 3, and phase 4. Even though I_{Na} amplitude is the highest during phase 0, the duration is short so that Na^+ loading is low. I_{Na} amplitude is low during phase 2, usually <0.5% of peak, but the duration is much longer, making phase 2 dominant in Na^+ loading. An increase in late I_{Na} amplitude as found in pathological states [45] increases Na^+ loading sufficiently to raise intracellular Na^+. An increase in late I_{Na} amplitude also prolongs phase 2 duration, further increasing Na^+ loading by sustaining the driving force for a longer time. Increased intracellular Na^+ will cause increased intracellular Ca^{2+} because less energy is available in the Na^+ gradient to extrude Ca^{2+} through Na–Ca exchange (Fig. 3), and if intracellular Na^+ is sufficiently increased then Na–Ca exchange may operate in reverse mode with Ca^{2+} actually entering the cell [46],

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although it is important to point out that Ca^{2+} loading would tend to increase with any decrease in extrusion and without an actual reversal of Na–Ca exchange.

Increased intracellular Ca^{2+} can contribute to arrhythmia by the mechanism of delayed afterdepolarizations and could have effects on re-entrant mechanisms. More direct effects occur through effects on contractility where decreased Ca^{2+} can cause decreased systolic function, and increased Ca^{2+} can cause impaired relaxation or decreased diastolic function (Fig. 3). Increased late I_{Na} in ischemia and the subsequent calcium loading can elevate left ventricular end-diastolic pressure, causing a “vicious feedback” on both limbs of the supply–demand mismatch worsening angina (Fig. 4). Block of late I_{Na} can interrupt this feedback and is the proposed mechanism for the proven effectiveness and clinical indication for ranolazine treatment of effort angina. It is interesting to note that amiodarone, a potent late I_{Na} blocker (Table 2), was initially developed as an antianginal drug before its antiarrhythmic properties came to the forefront.

Pharmacology of late I_{Na}

Because of the role for increased late I_{Na} in the pathogenesis of arrhythmia, diastolic heart failure, and ischemia, it is an attractive target for treatment in these conditions. It is an especially attractive target because it exists as a larger target under the pathological conditions where it is increased, thus reducing the chances of on-target toxic effects. Moreover, block of late I_{Na} in normal hearts has been shown to have no deleterious effects on contractility or conduction [47]. A wealth of experimental data with ranolazine, a relatively specific blocker of late I_{Na}, in cellular and animal models of arrhythmia support a role for late I_{Na} in the treatment of arrhythmia [2] and raises the question of whether block of late I_{Na} may be a mechanism for the effectiveness of clinically available antiarrhythmic drugs (Table 2). It is important to note, however, that none of the drugs in the table are specific blocker of I_{Na}, and all have effects on other ion channels, receptors, and other targets at therapeutic concentrations.

No drug known is completely specific for late I_{Na} over peak I_{Na}, probably because they produce both types of block by binding to the same site on NaV1.5 [48]; a key question is the relative selectivity of the drug to block late I_{Na} versus peak I_{Na}. The mechanisms for relative selectivity to block late I_{Na} probably arise from state dependence of the block (open and inactivated states) and the on- and off-rate kinetics of the drug, which varies from drug to drug, and which varies with study conditions. A simple way to portray selectivity is to take a ratio of the inhibitory concentration at 50% block (IC_{50}) for late I_{Na} compared to peak I_{Na}. Table 2 lists clinically available drugs that have been shown to block late I_{Na} in order of their selectivity for late I_{Na}. All of these drugs have other targets for their action; how much of the therapeutic effect is block of late I_{Na}? Table 2 also shows the IC_{50} for block of late I_{Na} and the therapeutic concentration range to address this question. It is important to note that the IC_{50} for late I_{Na} block is obtained under much different conditions than would apply in humans treated with these drugs. Often they are determined with NaV1.5 expressed in heterologous cell expression systems, and under tonic and not use-dependent protocols. In many cases, the IC_{50} may be higher than it is *in vivo* so that the block of late I_{Na} may be greater than suggested. Overall, based on the correspondence of the IC_{50} with the

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therapeutic range of the drug, it seems likely that block of late I_{Na} may be clinically important for the action of ranolazine, amiodarone, mexiletine, flecainide, and quinidine (Table 2). Drugs in development such as Gilead's GS-6615 that even more specifically target late I_{Na} [7] may tell us more about late I_{Na} as therapeutic target.

As noted above in discussing PI3K regulation of late I_{Na}, clinically available drugs including anti-cancer agents such as nilotinib [38] and antiarrhythmic agents dofetilide and other drugs [39] increase late I_{Na} by blocking the PI3K pathway. This increased late I_{Na} has the potential to underlie long-QT arrhythmia and other deleterious effects of increased late I_{Na}. Increased late I_{Na} may take its place with potassium channel block as an off-target cardiac safety issue.

Summary

Late I_{Na} is a physiological phenomenon where I_{Na} continues to flow through the cardiac sodium channel complex during the AP plateau. It is subject to regulatory pathways including phosphorylation and nitrosylation, and it is increased with many genetic and acquired cardiac diseases. Increased late I_{Na} in the heart can lead to arrhythmia by direct electrophysiological action to prolong the AP duration and by indirect action to cause calcium overload. The calcium overload can also lead to diastolic dysfunction contributing to heart failure, and increased wall stress in ischemia leading to angina. Block of late I_{Na} to treat these conditions is supported by data from many experimental models as well as an expanding list of clinical data, and it is likely to be at least part of the mechanism of action of some clinically used drugs to treat arrhythmia, angina, and arrhythmia. Increased late I_{Na} has many underlying causes and diverse behavior; the mechanisms for increased late I_{Na} are multiple and complex and remain under investigation. Understanding these mechanisms may lead to improved and more selective therapy.

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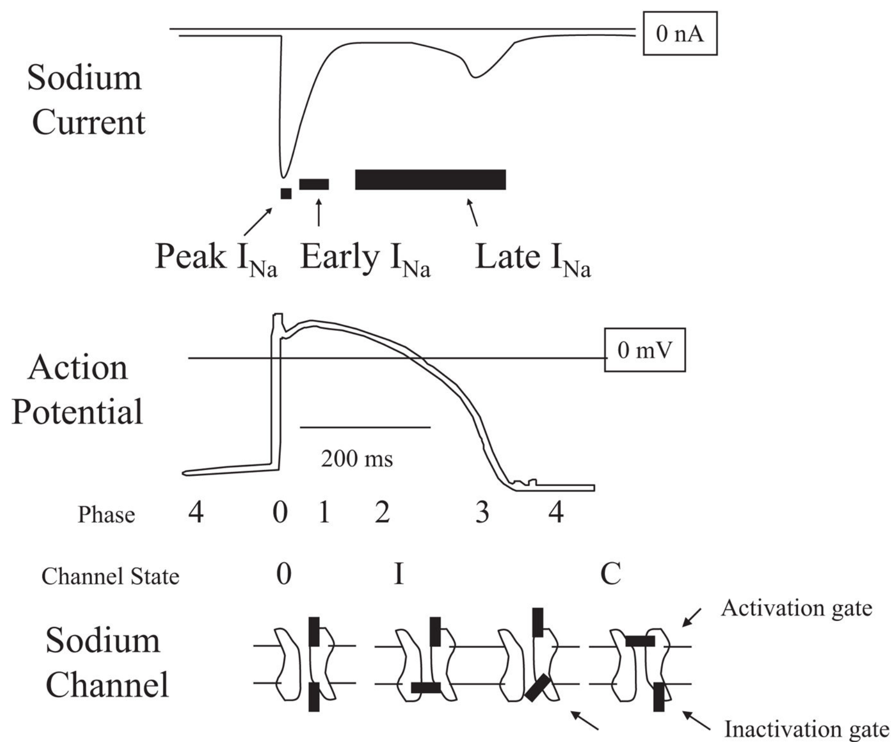

Fig. 1.

Peak, early, and late I_{Na}. Diagrams of cardiac sodium current (I_{Na}) action potential (AP), and sodium channel cartoon, lined up with time on the horizontal. Peak I_{Na} occurs in less than a millisecond and underlies the rapid upstroke or phase 0 of the AP. At this time, the activation gate and the inactivation gate on the channel are both open. Then over several milliseconds the current begins to decay, contributing to a notch in the AP called phase 1. At this time, some of the channels are inactivated (shown as "I" with the inactivation gate closed). There is no commonly accepted name for this phase of I_{Na} but here it is labeled "early I_{Na}." After several milliseconds I_{Na} normally decays to $<1\%$ of peak I_{Na}, but a residual current flows as late I_{Na} and this depolarizing current along with calcium currents supports phase 2 or the plateau of the AP. The mechanisms for late I_{Na} at the sodium channel level are multiple but can generally be thought of as incomplete inactivation. Eventually, activating potassium currents repolarize the membrane (phase 3 of the AP) and when the voltage decreases below the sodium channel threshold, the activation gate closes.

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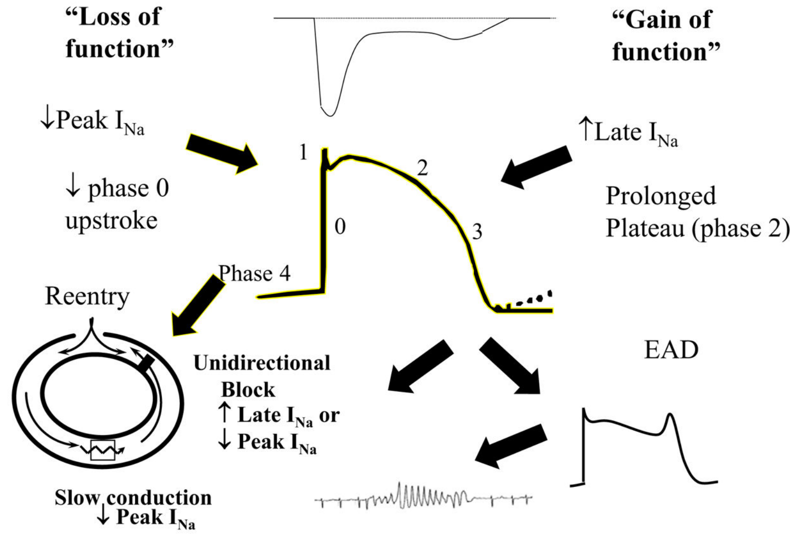

Fig. 2.

The role of late I_{Na} in arrhythmia. An increase in late I_{Na} (gain of function) provides a depolarizing current during the plateau, prolonging the AP, and at the cellular level produces an early afterdepolarization (EAD), which at the tissue/organ level triggers Torsades des Pointes arrhythmia. It is important to point out that late I_{Na} might also contribute to re-entrant arrhythmia by prolonging refractoriness and producing unidirectional block. For completeness and contrast, “loss of function” generally refers to a loss of peak I_{Na} and can contribute to the substrate for re-entry as shown, or to a loss of early I_{Na} that might lead to early repolarization and phase 2 re-entry (not shown) thought to underlie Brugada syndrome arrhythmia. An increase in late I_{Na} is often called a “gain of function” especially when referring to mutations that increase late I_{Na} as in LQT3. Generally, the increase in late I_{Na} is out of proportion to the gain, if any, in peak I_{Na}.

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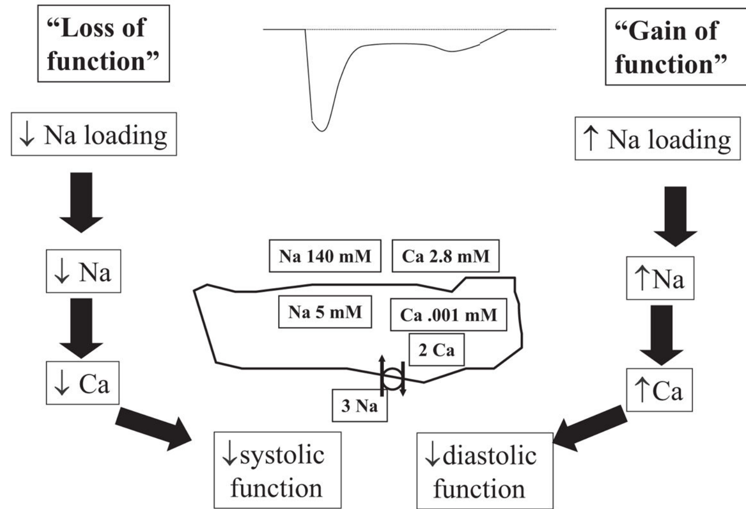

Fig. 3.

The role of late I_{Na} in contractility—sodium–calcium exchange (pictured as the circle with two arrows in the diagram of the cell at center) uses the energy stored in the sodium gradient to drive calcium out of the cell against its gradient, and thus it balances the calcium that enters the cell through calcium channels during each AP. With a "loss of function," internal Na will decrease, increasing the Na gradient and driving force for Ca extrusion through Na–Ca exchange, with a subsequent decrease in systolic function. On the other hand, increased late I_{Na} or "gain of function" will increase Na, decrease the driving force for Ca extrusion, and cause increased internal Ca and subsequent effects on diastolic relaxation.

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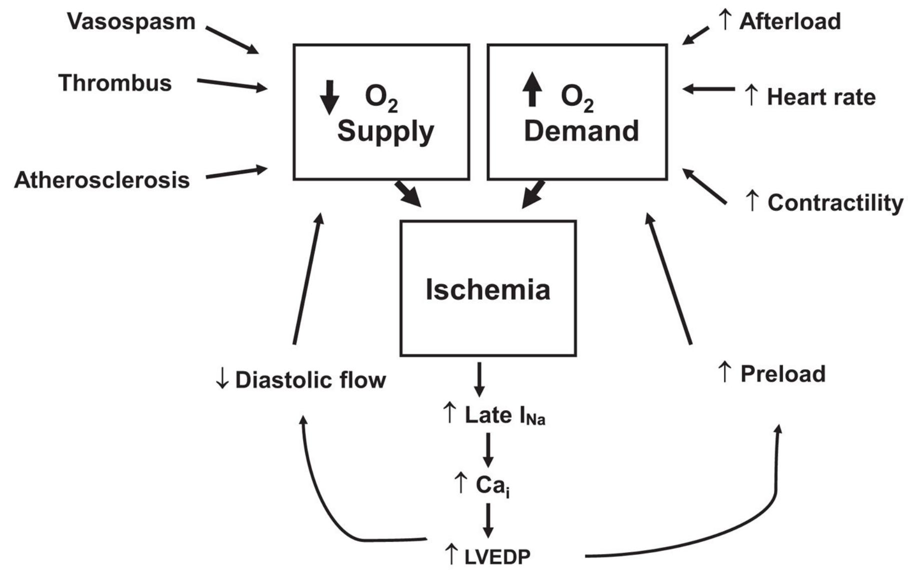

Fig. 4.

The role of late I_{Na} in ischemia/angina—ischemia is represented as the classic paradigm of supply–demand, which can be caused by any number of external factors. Once started, ischemia causes an increased late I_{Na}, which by mechanisms noted earlier, causes internal Ca loading and increase in left ventricular end-diastolic pressure (LVEDP). Increased LVEDP operates to exacerbate ischemia by actions on both limbs of the supply–demand mismatch. Increased LVEDP further decreases O_2 supply by decreasing the pressure gradient in coronary arteries for diastolic flow. It increases demand by augmenting preload.

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Table 1

Clinically relevant “causes” of late I_{Na} and possible mechanisms.

Genetic	
LQT3	Direct biophysical
LQT9	Enhanced nitrosylation
LQT10	?
LQT12	Enhanced nitrosylation
Acquired	
Hypertrophy	Stretch, altered signaling, and remodeling
Heart failure	Stretch, altered signaling, and remodeling
Ischemia	Acidosis and metabolites (LPC)
Diabetes	Cardiomyopathy and altered signaling
Molecules	
Carbon monoxide	?
Acidosis	?
LPC (ischemic metabolite)	PKC?
ROS (H_2O_2)	CaMK?
Drugs	
Dofetilide	PI3K inhibition
Sotalol	PI3K inhibition
Erythromycin	PI3K inhibition
Thioridazine	PI3K inhibition
Nilotinib	PI3K inhibition
Cell signaling	
nNOS nitrosylation	Direct on NaV1.5
CaMK phosphorylation	Direct on NaV1.5
PI3K–Akt pathway inhibition	?
PKC phosphorylation	Direct on NaV1.5

Remodeling means alteration of the Na channel complex in a way that favors late I_{Na} by, for example, the disappearance of subunits [49].

References for these clinically relevant and many other experimentally relevant causes of late I_{Na} have been recently reviewed [7].

A lone “?” indicates unknown, the “?” after PKC and CaMK indicates suggestive data to support.

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Table 2

Clinically available drugs that affect late I_{Na}.

Drug	Ratio late:peak IC_{50}	Late I_{Na} IC_{50} (μM)	Therapeutic concentration range (μM)
Block of late I_{Na}			
Ranolazine	38–61	7	0.4–6.1
Amiodarone	13–60	3–6.7	0.8–3.9
Mexiletine	9–51	3–5	3.4–9.5
Lidocaine	3–12	25	0.8–4.2
Propranolol	7	3	–0.4
Flecainide	3–7	1.4	0.5–2.4
Vernakalant	3–5	30	7.2–14.3
Quinidine	1	12	9.3–24.7
Increased late I_{Na}			
Dofetilide		0.103	0.005–0.023
Nilotinib		1.0	1.7–62

The blockers are in order of selectivity for late I_{Na} with concentrations for half block IC_{50} [6] and therapeutic concentrations [50]. For IC_{50} for drugs that increase late I_{Na}, we report the concentration for half-maximal increase from control for dofetilide [39] and the concentration to double late I_{Na} for nilotinib [38].