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Late sodium current is a new therapeutic target to improve contractility and rhythm in failing heart

Albertas Undrovinas[*,1] and **Victor A. Maltsev**[2]

1*Dept. of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA*

2*Gerontology Research Center, National Institute on Aging, NIH, 5600 Nathan Shock Drive, Baltimore, Maryland 21224, USA*

Abstract

Most cardiac Na^+ channels open transiently within milliseconds upon membrane depolarization and are responsible for the excitation propagation. However, some channels remain active during hundreds of milliseconds, carrying the so-called persistent or late Na^+ current (I_{NaL}) throughout the action potential plateau. I_{NaL} is produced by special gating modes of the cardiac-specific Na^+ channel isoform. Experimental data accumulated over the past decade show the emerging importance of this late current component for the function of both normal and especially failing myocardium, where I_{NaL} is reportedly increased. Na^+ channels represent a multi-protein complex and its activity is determined not only by the pore-forming α subunit but also by its auxiliary β subunits, cytoskeleton, and by Ca^{2+} signaling and trafficking proteins. Remodeling of this protein complex and intracellular signaling pathways may lead to alterations of I_{NaL} in pathological conditions. Increased I_{NaL} and the corresponding Na^+ influx in failing myocardium contribute to abnormal repolarization and an increased cell Ca^{2+} load. Interventions designed to correct I_{NaL} rescue normal repolarization and improve Ca^{2+} handling and contractility of the failing cardiomyocytes. New therapeutic strategies to target both arrhythmias and deficient contractility in HF may not be limited to the selective inhibition of I_{NaL} but also include multiple indirect, modulatory (e.g. Ca^{2+}- or cytoskeleton-dependent) mechanisms of I_{NaL} function.

Keywords

Late sodium current; heart failure; calcium; action potential; numerical model; sodium-calcium exchanger

INTRODUCTION

Chronic HF is associated with profound abnormalities in both cardiac rhythm and contractile function. Despite recent progress in treatment of congestive HF, mortality remains high. Approximately 40% of these patients die suddenly due to the sudden cardiac death syndrome. Ventricular tachycardia and fibrillation have been documented in ~ 80% of patients with congestive HF in whom ECG Holter recordings were being obtained at the time of sudden death [1,2].

[*]***Address for correspondence***: Albertas Undrovinas, Ph.D., Henry Ford Hospital, Cardiovascular Research, Education & Research Bldg. Room 4015, 2799 West Grand Boulevard, Detroit, MI 48202-2689, Phone: (313)-916-1321, Fax: (313)-916-3001, E-mail: aundrov1@hfhs.org

Despite intensive research, the electrophysiological mechanisms leading to these arrhythmias are not completely clear. It is widely appreciated that perturbation in control of the action potential (AP) duration (APD) and its propagation, is the proximate cases of arrhythmia. Among numerous proteins involved in the cardiac cell remodeling in HF, the voltage-gated Na^+ channels (NaCh) deserve special consideration, as they seem to be critically involved in abnormal conduction, repolarization, and Ca^{2+} handling [3,4]. Most NaCh open only transiently and are quickly inactivated resulting in the peak transient current, I_{NaT}, which determines excitation and conduction. However, some NaCh remain active, carrying so-called persistent or late Na^+ current (I_{NaL}) throughout the AP plateau (reviews [5,6]).

A growing body of evidence shows that I_{NaL} provides a major contribution to the AP plateau duration in ventricular cardiomyocytes (VCs) in a variety of mammalian species including humans [7-11].

Since late openings of NaCh generate both electric current and Na^+ influx during the AP plateau, I_{NaL} is expected to contribute to at least two known HF cellular mechanisms: 1) electrophysiological remodeling and 2) altered cell Na^+ cycling. The latter mechanism is tightly integrated with Ca^{2+} cycling, as Na^+ modulates the Na^+/Ca^{2+} exchanger (NCX) operation [4]. These anticipated I_{NaL} contributions could be amplified at the state of chronic HF that reportedly increases the whole cell I_{NaL} [10,12,13].

The importance of I_{NaL} contribution into HF mechanisms has been demonstrated in experiments where "correction" of I_{NaL} in failing cardiomyocytes resulted in: 1) rescue of normal repolarization, 2) decrease beat-to-beat APD variability, 3) improvement of Ca^{2+} handling and contractility [10,13-15]. Accordingly I_{NaL} has emerged as a novel possible target for cardioprotection to treat the failing heart [6,16,17].

COMPLEX IONIC MECHANISMS OF IMPAIRED REPOLARIZATION IN CHRONIC HEART FAILURE

Studies with microelectrodes in ventricular myocardial fibers obtained from failing human hearts [18,19] and patch-clamped ventricular cardiomyocytes (VCs) isolated from failing hearts have demonstrated a prolongation of APD [10,11,20-22] indicating impaired repolarization in HF. The prolongation was less prominent at higher rates [18] and varied depending on the etiology of HF [22]. Experimental and clinical studies suggest that dispersion of repolarization and EADs are two major mechanisms underlying *torsade de pointes* [23, 24]. This type of arrhythmia is induced by a pause or bradycardia [25]. Indeed, the APD prolongation and dispersion of duration, as well as the incidence of EADs, were advanced at lower pacing rates in VCs of humans and dogs with chronic HF [10,11,14]. EADs, in turn, can be a substrate for triggered arrhythmias described in patients with HF [23,26].

A delicate balance between inward and outward currents maintains the cardiac AP plateau, and repolarization occurs as activating outward currents prevail over inactivating inward currents. Accordingly, APD increase can be explained by reduction of hyperpolarizing outward currents and/or by an increase of depolarizing inward currents. The balance of ion currents is substantially altered in HF as a result of the remodeling of ion channels [3,27]. Decrease of the transient outward potassium current (I_{to}) has been reported by many investigators and is now accepted as a common feature of ischemia and HF (review [3]). However, some studies also showed that I_{to} in human VCs shows no dramatic differences between cells derived from failing and non-failing hearts [28]. Remodeling of other potassium currents (I_{Kr}, I_{Ks}, and I_{K1}) is also variable and seems to be related to the HF etiology (ischemic vs. non-ischemic)[27]. While numerous studies tested HF-related changes of L- type Ca^{2+} channel expression and function, the data remain controversial: I_{CaL} was found decreased, unchanged or increased in HF. In

addition, alterations in expression of the electrogenic Na^+/Ca^{2+} exchanger (NCX) [29] and Ca^{2+} cycling by sarcoplasmic reticulum (SR) [4] contribute to the complex AP remodeling. Numerous pharmacological approaches targeting different players/contributors of abnormal electrical heart function have been tested to treat arrhythmias in HF, however the problem is still far from being solved. A novel perspective target could be I_{NaL} because this inward current greatly contributes to AP duration, especially in human myocardium [11,13,16], and it is reportedly increased by chronic HF [10,12,13].

DEFINITION AND MAJOR CHARACTERISTICS OF THE LATE SODIUM CURRENT

Voltage clamp studies have identified several types of single NaCh activity and whole cell Na^+ currents that could contribute to APD in cardiomyocytes. The variety of NaCh activities identified until the present time was classified (see review [6]) in terms of the late (or persistent) Na^+ current i.e. I_{NaL} (or I_{pNa}), and background Na^+ currents. Our review is focused on properties and targeting I_{NaL} rather than background Na^+ currents. In contrast to I_{NaL}, background Na^+ currents have been poorly characterized to date and have no clear molecular identity.

Major biophysical and pharmacological characteristics of the whole-cell I_{NaL} have been studied in great detail in human VCs by our research group [11,13,16] (Fig. (**1**)) and can be summarized as follows: 1) slow potential-independent inactivation and re-activation (~0.5 s), 2) steady-state activation and inactivation similar to that for I_{NaT}, 3) low sensitivity to the specific toxins TTX and STX similar to the cardiac NaCh isoform $Na_v1.5$. A slowly inactivating I_{NaL} with aforementioned biophysical characteristics has been identified in VCs of dogs [10,13,15,30], guinea pigs [31-33], rabbits [34] and rats [35]. I_{NaL} is also produced by heterologously expressed cardiac NaCh isoform main α-subunit $Na_v1.5$ (Fig. (**1F**)).

It is important to note, however, that I_{NaL} is not a "window" current that was suggested long time ago as a theoretical mechanism to explain the persistent Na^+ current in cardiac cells [36,37]. According to the Hodgkin-Huxley formalism [38], the "window" current is a non-inactivating component of I_{NaT}, resulting from the crossover of its steady-state activation and inactivation curves. The overlap of steady-state activation and inactivation curves occurs within a relatively narrow region of voltages close to I_{NaT} activation threshold (Fig 1C). However, I_{NaL} exhibit time-dependent inactivation and is present even at positive voltages (Fig.**1B**, filled circles, Fig. (**3C**)) [11,31], where the calculated "window" current is negligible.

I_{NAL} IS INCREASED IN FAILING HUMAN AND CANINE VENTRICULAR MYOCARDIUM

The first evidence of I_{NaL} importance in electrophysiological remodeling of cardiomyocytes in HF was found in 1995 in an experimental dog model of chronic HF [39]. Further patch clamp studies in human and canine hearts have conclusively shown that chronic HF increases I_{NaL} density and significantly slows inactivation kinetics of I_{NaL} in VCs [10,13] (Fig. (**2A**)). Analysis of idealized I_{NaL} time course (Fig. (**2B**)) in canine normal and failing VCs shows that 1) absolute I_{NaL} difference between normal and failing canine VCs at 37°C (top panel in Fig. (**2B**), gray area) has a maximum at 90 ms after membrane depolarization, i.e. within the time of AP plateau duration; 2) the relative difference between normal and failing cells increases progressively with membrane depolarization, doubling after 330 ms (Fig. (**2B**), inset)); 3) The integral of I_{NaL} reflecting Na^+ influx transferred by I_{NaL}, is much greater in HF (bottom panel in Fig. (**2B**), gray area) [13]. Accordingly, I_{NaL} may disturb cell Na^+ balance and have different

dynamic impacts on the balance of the ionic currents at the different phases of AP plateau in failing heart. The importance of these phenomena is discussed below.

THE I_{NaL} FINE STRUCTURE AND RELATED SODIUM FLUXES: PARADOXES AND THEIR MECHANISMS

In cell-attached patches from heterologously expressed $Na_v1.5$ and native human cardiomyocytes, the late NaCh activity is arranged in two major gating modes: late scattered mode (LSM) and "burst" mode (BM) (Fig. (**3C**) inset)). A detailed analysis of the properties of these modes and its contributions to whole cell I_{NaL} lead to some unexpected, paradoxical conclusions [12, 40]. Paradox #1: The late scattered openings were previously reported in guinea pig and considered to represent "background" activity [41]; however, they actually possess ultra slow (hundreds of ms) inactivation, similar to that of whole-cell current decay in human and dog cardiomyocytes [13, 40]. Paradox #2: While inactivation of I_{NaT} is voltage-dependent, the inactivation time constant of LSM is potential-independent. Paradox #3: Bursts are often considered as a persistent activity, but they do inactivate and cease well within AP duration (Fig.3B). Paradox #4: While bursts represent abundant NaCh activity, a numerical evaluation of the contributions of BM and LSM to I_{NaL} based on the Markov model of single channel data unexpectedly pointed to LSM openings, but not the bursts, as a major contributor to whole cell I_{NaL}. Paradox #5: While I_{NaT} amplitude is about 3 orders of magnitude larger than that of I_{NaL} (50 nA in comparison to 50 pA), the total charge (reflecting Na^+ influx) transferred across the membrane by I_{NaT} and I_{NaL} is almost the same! In fact, I_{NaT} span is about 3 orders of magnitude shorter than that of I_{NaL} (2 ms in comparison to 2 s), resulting in an almost equal total charge transfer by these currents.

I_{NaL} transfers significantly more Na^+ into failing vs. normal VCs. The total charge transferred by I_{NaL} is predicted to be 28.5 and 45 pC for normal and failing VCs, respectively, or a ~58% increase. This model estimate is in line with a 53.6% HF-induced increase of Na^+ influx via I_{NaL} evaluated from whole cell patch clamp measurements in canine normal and failing VCs (gray area in Fig. (**2 B**) bottom panel; [13]). Taking into account that I_{NaT} is reduced by 30-40% in HF VCs [42-44], the role of I_{NaL} in Na^+ homeostasis should be even more substantial in the failing cells, in line with the recent finding that $[Na]_i$ is significantly increased in failing paced cardiomyocytes [45].

One possibility for the increased I_{NaL} in HF could be an additional, HF-specific NaCh activity. However, no qualitative changes in NaCh gating were found in failing human VCs in comparison to normal VCs and $Na_v1.5$ clone [40]; they exhibit early openings and the two modes of late gating (LSM and BM) with the same single NaCh conductance [40]. The inconspicuous differences turn out to be quantitative: 1) inactivation of LSM (Fig. (**3A**)) was significantly slower and 2) burst length was significantly larger in failing compared to normal myocytes or $Na_v1.5$ clone (Fig. **3B**)) [13].

MOLECULAR IDENTITY OF I_{NAL} IN NORMAL AND FAILING VENTRICULAR MYOCARDIUM

The problem of molecular identity of I_{NaL} has been approached in many different ways including methods of biophysics, pharmacology, and molecular biology. Late NaCh openings show similar gating modes and Na^+ conductance in normal human cardiomyocytes and in heterologously expressed $Na_v1.5$. Furthermore, the heterologously expressed $Na_v1.5$ produces the slowly inactivating whole cell I_{NaL} in tsA201 cells (Fig. (**1F**)) similar to that observed in human cardiomyocytes (Fig. (**1A-D**)). These data indicate the common molecular origin of the late channel openings i.e., they are produced by $Na_v1.5$ in human cardiomyocytes. Dose-

response curves for blockade of I_{NaL} by TTX and STX reveal only a single-site binding with the half-concentration that is to say typical for the $Na_v1.5$ in both dog and human failing hearts (IC_{50} was 1.2 *vs*. 1.53 μM for TTX and 62 *vs*. 98 nM for STX comparing dog vs. human cardiomyocytes) [11, 13]. Furthermore, I_{NaL} is sensitive to Cd^{2+} (IC_{50}=104 μM) [13], what is typical for cardiac but not neuronal Na^+ channel isoforms [46]. Silencing the SCN5A gene responsible for $Na_v1.5$ expression with siRNA decreases I_{NaL} by 75% in wide range of membrane potentials (including AP plateau), resulting in a significant reduction of AP duration and variability in dogs with chronic HF [47]. Thus, while contributions of other NaCh isoforms to I_{NaL} are still not excluded [17], $Na_v1.5$ likely provides a major contribution to I_{NaL} in both normal and failing canine and human VCs.

MECHANISMS FOR I_{NaL} ALTERATIONS IN PATHOLOGICAL CONDITIONS: POSSIBLE ROLE OF THE CHANNEL MICROENVIRONMENT

Since results of multiple studies (described above) indicate that HF alters I_{NaL} likely via modulation(s) of $Na_v1.5$ gating, the question of which specific modulatory mechanisms may underlie I_{NaL} alterations, deserve special consideration, because these might represent new indirect targets for I_{NaL}-related therapies.

NaCh and associated modulatory proteins

The function of the NaCh is not fully determined by its protein structure, but also depends on its environment. Na^+ channels represent a multi-protein complex comprising not only the main pore-forming α subunit and its auxiliary β subunits, but also components of cytoskeleton, Ca^{2+}-sensitive protein calmodulin, regulatory kinases and phosphatases, trafficking proteins, and extracellular matrix proteins embedded into lipid bilayer plasma membrane. A diagram of $Na_v1.5$ and its interacting proteins is shown in Fig. (**4 A**). For in-depth reviews on this matter see [48-50]. Here we highlight only the components that seem to modulate I_{NaL} in different pathological conditions, including hypoxia and HF. The III-IV linker (see Fig. (**4 B**)) is responsible for NaCh inactivation [51], and mutations in this region disrupt $Na_v1.5$ inactivation causing persistent Na^+ current linked to inherited LQT3 syndrome [52]. Recently, COOH terminal that has binding sites for abundant regulatory proteins has been implicated in $Na_v1.5$ inactivation [53, 54].

Modulation of I_{NaL} by β subunits

Mammalian voltage gated NaCh are associated with auxiliary β subunits. The β-subunit gene family has four members β_1(SCN1B), β_2 (SCN2B), β_3 (SCN3B) β_4 (SCN4B) (see for review [48,50]). All these β-subunits are expressed in rodent hearts and are differently localized to specific sub cellular domains and cell types. β_1 subunit is non-covalently attached to α subunit, and β_2 subunit is covalently linked to α subunit by a disulfide bond [55]. The protein of these β subunits contains an extracellular amino-terminus, a single transmembrane segment, and an intracellular COOH terminus (C-terminus) (Fig. (**4B**)). The extracellular N-terminus of all β subunits contain immunoglobulin domain found in cell adhesion molecules. Particularly, immunoglobulin domain for β_2 (and probably for β_4) is similar to contactin, whereas for β1 and its splice variant β_1A it is similar to myelin P_o. This unique property allows interactions with variety of signaling molecules and components of the extracellular matrix. With the regard to the intracellular domain, direct interactions of β_1 subunit C terminus and ankyrin B in rat brain membranes have been demonstrated, indicating a role of this subunit in main α subunit (Na_v) localization. Direct interaction between cytoplasmic C-terminus domain of $Na_v1.1$ with β_1 and β_3 has been recently demonstrated [56]. β subunits do not form an ion-conducting pore, but modulate NaCh function, NaCh protein expression at the plasma membrane (trafficking), and cell adhesion [48,50]. More specifically, β_1-subunit: 1) is involved in abnormal NaCh activity associated with the LQT3 mutation [57], 2) aggravates NaCh dysfunction in Brugada

syndrome [58], 3) modifies the blockade of NaCh by fatty acids [59] and lidocaine [60], 4) modulates the trafficking of $Na_v1.5$ [61], and 5) affects the burst mode of the heterologously expressed skeletal muscle NaCh isoform [62].

Very few reports are currently available about modulation by β subunits of late openings of the cardiac Na^+ channel. Heterologous co-expression of β_1 subunit with $Na_v1.5$ in HEK293 cells diminishes I_{bNa} [63], but increases I_{NaL} amplitude and significantly slows I_{NaL} decay in tsA201 cells [64]. At the same time, β_2 subunit does not affect I_{NaL} parameters [64]. The potency of β_1 subunit to modulate I_{NaL} has been confirmed in preliminary studies in native cell environment. In normal dog VCs, knocking down of SCN1B by antisense nucleotides significantly accelerated I_{NaL} decay [65]. In HF, $Na_v1.5$ protein level is down regulated, whereas β_1 remains unchanged, indicating a relatively higher membrane content of β_1 [43]. This suggests potential involvement of β_1 in the reported I_{NaL} alterations in HF.

Modulation of I_{NaL} by cytoskeleton

The cytoskeleton proteins form a framework within the cytoplasm with links to the membrane that include attachments to integral membrane proteins. This framework maintains cell shape, plasma membrane integrity, and localization of membrane proteins such as ion exchange carriers and ion channels (Fig 7, see for review [48-50,66]). Multiple experimental studies demonstrated that the sub-membrane cytoskeleton modulate I_{NaL} in cardiomyocytes.

Ankyrin-B—An adapter protein ankyrin-B, which is expressed in heart, links $Na_v1.5$ to the cytoskeleton. A knockout of ankyrin B in affects late Na^+ channel openings in mouse cardiomyocytes [67]. Furthermore, mutations in ankyrin B cause the LQT4 syndrome in one French family [68], indicating the importance of channel environment for the channel function. Accordingly, a disruption of any member of this multi-protein complex by pathological conditions may lead to alterations of I_{NaL}.

F-actin—Cytochalasin-D, an agent that interferes with F-actin polymerization as well as anti-actin antibody [69], slows inactivation of cardiac Na^+ channel by inducing bursts of openings. It also affects coupling of steady state activation and availability of Na^+ current [70,71].

Fodrin—Fodrin (spectrin)-based cytoskeleton, another element of the NaCh microenvironment in heart, is a dynamic structure, which is altered under a variety of pathological conditions (e.g. ischemia or heart failure [72-74]). The role of the fodrin-based cytoskeleton in I_{NaL} modulation has been suggested in experiments with the antisense oligonucleotides targeting mRNA's encoding α- and β-fodrin in dog VCs [75].

The fodrin breakdown that happens in some disease states featuring poor Ca^{2+} handling can be mediated by the Ca^{2+} - activated enzyme calpain and caspase [72,76,77]. Therefore, disturbances of the ankyrin and/or fodrin-based cytoskeleton may affect the Na^+ channel inactivation process. Cytoskeleton elements such as ankyrin may bind directly to α and β subunits (see above). The link to β subunits may thus modulate I_{NaL} indirectly.

Tubular cytoskeleton—also may be involved in NaCh gating regulation. For example, antitumor agent taxol, that stabilizes microtubules, shifts NaCh activation threshold towards more negative membrane potentials [78] and thus may increase the pool of NaCh that underlies I_{NaL}.

Modulation of I_{NaL} by the metabolites of membrane phospholipids

Lysophosphatidylcholine (LPC) is the endogenous amphiphilic lipid metabolite that rapidly accumulates in myocardium during ischemia and represents a major factor causing the

electrophysiological alterations that contribute to cardiac arrhythmia [79,80]. Recently, a significant prolongation of QTc interval has been found during early transmural ischemia in patients undergoing balloon angioplasty [81]. Experimentally, LPC causes membrane depolarization, reduction of the maximal upstroke velocity of AP, sustained abnormal rhythmic activity in Purkinje fibers, and delayed afterpotentials (DADs) in isolated tissue [79,82]. The cellular mechanisms of the LPC effects include specific modifications of Na^+ current: significant decrease of I_{NaT} and an emergence of late NaCh openings that produce a sustained Na^+ current [35,83-86]. Interestingly, the late NaCh openings caused by LPC form clusters of the synchronized multiple channel openings [83,85]. One of the mechanisms underlying these LPC-induced modifications might be an integration of LPC into the lipid membrane, which would increase the membrane fluidity [87]. This, in turn, enhances motility and interaction of proteins within the membrane. On the other hand, LPC can activate neuromodulation signaling via PKA and PKC [88,89], affecting NaCh slow inactivation [90].

Recently emerged modulators

A novel protein partner of $Na_v1.5$ has been discovered using a yeast 2-hybrid screen [91]. This protein, called 14-3-3η, interacts with the cytoplasmic I inter-domain of NaCh (see Fig. (**4 B**)). Although its direct effect on I_{NaL} properties has not yet been studied, it was shown that this protein influences the inactivation process by delaying recovery from inactivation[91]. Additionally, Src family tyrosine kinase Fyn has the phosphorylation site on $Na_v1.5$A III-IV linker [92], which is known to be responsible for the inactivation. The most recently emerged modulator is a membrane micro domain protein Caveolin-3. This protein was previously linked to NaCh trafficking, [93] but now is implicated in LQT syndrome [94]. Implementation of these new players in I_{NaL} modulation in different pathological conditions awaits further studies.

Modulation of I_{NaL} by the Ca^{2+}signaling pathways

Structurally, the carboxyl terminus of NaCh has binding sites for Ca^{2+} itself [95] and for Ca^{2+}-binding protein calmodulin (CaM) that acts as a Ca^{2+} sensor translating changes in cytoplasmic Ca^{2+} into cellular responses [96] (Fig. (**7**)). Discovery of these sites inspired multiple studies in heterelogously expressed NaCh, including a brain, skeletal and cardiac muscle isoforms [97-101]. It was found that some inactivation states of I_{NaT} of heterologously expressed cardiac and skeletal NaCh isoforms may be modulated directly by Ca^{2+}, CaM and/or *via* Ca^{2+} /CaM/CaM-kinase signaling cascade. There are only a few studies to date performed in cardiomyocytes that addressed the question about I_{NaL} modulation by Ca^{2+} signaling specifically in NaCh native environment. It was shown that over expression of $CaMKII\delta_c$ enhances I_{NaL} and increases $[Na]_i$ [102]. Our recent detailed studies in normal and failing dog cardiomyocytes have demonstrated multiple, complex effects of Ca^{2+}, CaM, and CaMKII on I_{NaL} properties (summarized in Fig.7), including the fine structure of I_{NaL}, described by fast (originated from bursts) and slow (originated from LSM) exponentials. More specifically, I_{NaL} greatly enhances as $[Ca^{2+}]_i$ increase: its maximum density increases, decay of both exponentials describing I_{NaL} decay slows, and steady-state inactivation curve (SSI) shifts towards more positive potentials. The latter means that more available NaCh generate a larger I_{NaL}. Testing inhibition of CaMKII and CaM revealed similarities and differences of I_{NaL} modulation in failing vs. normal dog myocytes. Similarities were as follows: 1) CaMKII slows I_{NaL} decay and decreases the amplitude of fast exponential; 2) Ca^{2+} shifts SSI rightward. The following differences in failing vs. normal myocytes were found: 1) slowing I_{NaL} by CaMKII is greater; 2) CaM shifts SSI leftward; 3) Ca^{2+} increases the amplitude of slow exponential. These data suggest that Ca^{2+}/CaM/CaMKII signaling increases I_{NaL} and Na^+ influx in both normal and failing myocytes by slowing inactivation kinetics and shifting SSI. This Na^+ influx provides a novel Ca^{2+} positive feedback mechanism (via Na^+/Ca^{2+} exchanger), enhancing contractions at higher beating rates, but worsening cardiomyocytes contractile and

electrical performance in conditions of poor Ca^{2+} handling in heart failure (multiple I_{NaL}-mediated Na^+ - Ca^{2+} interactions in HF are discussed in detail below).

EXPERIMENTAL EVIDENCE OF I_{NaL} IMPORTANCE FOR ABNORMAL REPOLARIZATION, Ca^{2+} HANDLING, AND CONTRACTILITY IN FAILING MYOCARDIUM

Inhibition of I_{NaL} normalizes AP duration and beat-to-beat variability and eliminates EADs in HF VCs

APD is extremely frequency dependent in failing VCs [10]. At low pacing rates of 0.2-0.5 Hz the mean APD is significantly larger in failing VCs (Fig. (**5 A**)), and failing cells eventually exhibit EADs (Fig. (**3 C**)) [10,11,13]. In addition to the prolongation, APD also exhibits significant beat-to-beat variability in failing VCs. Although AP prolongation is not evident at physiological frequencies (1Hz and higher), variability of APD in failing cells is substantially larger than in normal cells (compare APD distributions and their SD values in Fig. (**5 B**)) [10,13]. Increased and slowed I_{NaL} (Fig. (**2**)) greatly contributes to APD prolongation, variability, and EADs. Partial reduction in the magnitude of I_{NaL} caused by specific NaCh blockers (TTX, 1.5 μM, STX, 100 nM), a new antianginal drug ranolazine (that turned out to be a specific I_{NaL} blocker), or injection of external current opposite to I_{NaL} during the AP plateau significantly shorten the prolonged APD, decrease beat-to-beat variability of APD, and abolish EADs [10,11,13,15].

Blockade of I_{NaL} improves Ca^{2+} transient and contractility in HF

The contractile dysfunction in HF is related not only to ongoing loss of functional cardiac units, but also to abnormal function of cardiomyocytes. HF is characterized by systolic dysfunction as a result of depressed Ca^{2+} transients [4] and by abnormal relaxation of cardiac myocytes [103,104]. At low pacing rates, the prolonged relaxation is associated with the spike-dome configuration of contractile response of cardiomyocytes (Fig. (**6 A**)). The ratio between amplitudes of the spike and dome phases was suggested to be an index for the severity of HF [103]. Similar to the shape of abnormal contraction, abnormally prolonged Ca^{2+} transients have also been observed in both ventricular muscle strips [103] and cardiomyocytes isolated from failing hearts [14,105] (Fig. (**6 A**)). At the higher frequencies, these abnormalities account for the reversal of the force-frequency relationship in failing myocardium, leading to an increase in diastolic $[Ca^{2+}]_i$ and diastolic tension (Fig. (**6 B**) "Control") [15,106]. A partial blockade of I_{NaL} by STX, TTX or ranolazine greatly improves performance of failing VCs; it abolishes the dome phase of both contraction-relaxation cycle and Ca^{2+} transient at low pacing rates and prevents the rising diastolic tension and $[Ca^{2+}]_i$ at the higher pacing rates in failing VCs [14,15] (Fig.(**6**)).

INTEGRATION OF I_{NaL} INTO ELECTROPHYSIOLOGICAL AND Ca^{2+} MECHANISMS IN HF

Dramatic improvement of cardiomyocyte function by I_{NaL} inhibition described above provides an evidence for a substantial I_{NaL} contribution to the functional remodeling in the failing heart. However, the interpretation of these effects needs extreme care because electrophysiology, contraction, and Ca^{2+} dynamics in cardiomyocytes are interrelated via multiple feedback mechanisms. The extent of deterioration of cardiomyocyte function and these feedback mechanisms vary greatly with the progression of HF and etiology. Since late openings of NaCh generate both an electric current and a Na^+ influx, I_{NaL} is expected to contribute to at least two established HF mechanisms: 1) electrophysiological remodeling [3], and 2) altered cell Na^+ and Ca^{2+} cycling [4].

The role of I_{NaL} in AP prolongation and EADs

Given the high membrane resistance during the AP plateau, I_{NaL} provides a critical contribution to the altered delicate balance of ion currents and thus to the APD. The relative contribution of I_{NaL} to the AP plateau in failing VCs is amplified by the reduced K^+ currents in HF [3]. Since HF simultaneously increases and slows I_{NaL} it is expected to contribute directly to AP prolongation in HF, thus explaining APD normalization with I_{NaL} inhibition described above. Prolonged APD allows more time for I_{CaL} reactivation and thus facilitates EADs [107]. Since I_{NaL} contributes to AP prolongation, it thus indirectly contributes to EADs. Accordingly, I_{NaL} inhibition eliminates EADs likely as a result of APD shortening.

I_{NaL} and elevated $[Na^+]_i$ increase Ca^{2+} entry via NCX and limit depression of systolic function

A major problem in HF is systolic dysfunction, which is associated with smaller Ca^{2+} transient and sarcoplasmic reticulum (SR) Ca^{2+} content. The extent of deterioration of systolic function is limited by multiple compensatory mechanisms (listed below), which are indirectly linked to I_{NaL} and elevated Na^+.

1. NCX function depends on Na^+ and Ca^{2+} concentrations and membrane voltage. In HF VCs, increased Na^+ influx (including that via I_{NaL}) shifts the NCX operation from the predominant forward mode to the reverse mode i.e. from Ca^{2+} efflux to Ca^{2+} entry [108]. Elevated Na^+ in HF thus limits SR unloading and provides additional Ca^{2+} influx during the AP [4]. Interestingly, in addition to preserving SR Ca^{2+} load, this operational shift in failing human myocardium results in the direct activation of contraction during the terminal phases of the AP via the reverse mode NCX Ca^{2+} influx [109]. Thus, a larger cellular Na^+ load (contributed by I_{NaL}) may be also important to drive contractions via this HF-specific mechanism.
2. The vast majority of studies demonstrated that NCX is upregulated in HF [29], therefore the above effects could be amplified by the enhanced NCX function.
3. I_{NaL} contributes to APD prolongation and thus indirectly prolongs Ca^{2+} influxes via I_{CaL} and the reverse mode NCX.
4. I_{NaL} in HF is positively modulated by intracellular Ca^{2+} [110] (Fig.7), which could yield a new possible amplification mechanism of the Ca^{2+} entry. This creates a positive feedback loop from I_{NaL} via NCX to larger cell Ca^{2+} load, then from the larger Ca^{2+} load back to I_{NaL}.

Adverse effects of increased $[Ca^{2+}]_i$ in HF. Role of I_{NaL} and NCX in diastolic dysfunction

While the increased I_{NaL} boosts a cell Ca^{2+} load and thereby limits the depression of systolic function in HF, it also leads to diastolic dysfunction, especially at high rates as described above. Relaxation of cardiac myocytes occurs when $[Ca^{2+}]_i$ declines, allowing Ca^{2+} dissociation from the myofilaments. Ca^{2+} is removed from cytosol, mainly via SERCA, which takes Ca^{2+} back into the SR, and, by NCX operating in the forward mode during diastole [111]. It is believed that the diastolic dysfunction in HF is mainly due to a reduced SERCA function in HF. At the same time, increased expression and function of NCX in HF tends to offset the deficiency of Ca^{2+} removal by SERCA (review [4]). The contribution of the increased I_{NaL} to the Ca^{2+} removal could be twofold. First, as discussed above, I_{NaL} and related increase of $[Na^+]_i$ facilitate Ca^{2+} influx. Secondly, higher $[Na^+]_i$ during diastole partially offsets the function of the forward mode NCX and thus worsens the problems of Ca^{2+} removal from the cytosol and diastolic dysfunction. The improvement of diastolic function by the inhibition of I_{NaL} (Fig. 10B) can be attributed both to a decrease in Ca^{2+} load during the AP plateau and to improve removal of Ca^{2+} by forward mode NCX during diastole. Indeed partial blockade of the NCX improves EC coupling in HF [112] and reduces both EADs and DADs [113,114].

Ca^{2+} overload and increased diastolic Na^+: potential importance of I_{NaL} for DADs

DADs occur as a result of spontaneous Ca^{2+} releases during diastole via the activation of the forward mode of NCX. I_{NaL} does not occur at low diastolic potentials in humans and dogs (see Fig. **2B**, filled circles), so it cannot have a direct contribution to DADs. However, as discussed above, in HF VCs a larger Na^+ influx via I_{NaL} increases Ca^{2+} influx via NCX during AP leading to SR Ca^{2+} overload, which, in turn, is critical for initiation of spontaneous Ca^{2+} release (such as Ca^{2+} waves) during diastole. I_{NaL} involvement in DADs is thus limited to the contribution of the I_{NaL} to the Ca^{2+} overload. On the other hand, high diastolic $[Na^+]_i$ in HF [45] decreases the forward mode NCX current and, hence, attenuates the amplitude of DADs. This positive factor of I_{NaL} can be counterbalanced by down regulation of I_{K1} in HF [115], facilitating membrane excitations.

Role of I_{NaL} in dispersion of repolarization: a feedback from abnormal Ca^{2+} cycling?

The mechanisms of dispersion of repolarization in HF remain unclear. A possible mechanism involves beat-to-beat alternations and/or fluctuations in intracellular Ca^{2+} cycling transduced to abnormal repolarization by electrogenic feedback mechanisms (review [116]). As discussed above, there are at least three possible indirect contributions of I_{NaL} to the beat-to-beat variability problem.

1. The I_{NaL} contribution to the abnormal Ca^{2+} cycling.
2. The I_{NaL} dependence on Ca^{2+}/CaM/CaMKII. Thus I_{NaL} can serve as one of the electrogenic Ca^{2+} feedback mechanisms along with other Ca^{2+} -dependent ion currents, such as I_{CaL} inactivation, I_{Ks}, I_{to}, Ca^{2+}-activated Cl^--current, and NCX.
3. The synchronicity of Ca^{2+} release depends on the state of phosphorylation of Ca^{2+} cycling proteins [117] and on the AP shape [118] (including the AP shape of failing VCs, [119]). Thus I_{NaL} contributes to the fluctuations of Ca^{2+} transients to the extent to which I_{NaL} contributes to the AP shape. More specifically, the contribution of I_{NaL} could be important for the abnormal early repolarization phase in HF via its increased burst mode [12] (Fig. (**3 B**)), especially when I_{to} is decreased [3]. Further, the activity of LSM of NaCh also increased in human HF VCs [12] (Fig. (**3 A**)); they persist on the AP plateau (Fig. (**3 C**)) and, hence, tend to prevent further repolarization.

Summary of I_{NaL} role in failing myocardium: friend or foe?

I_{NaL} and its Na^+ influx can directly and indirectly contribute to several important HF mechanisms related to electrophysiological remodeling and ion homeostasis. These contributions could either improve or worsen performance of HF myocardium, i.e. being "friend" or "foe", respectively (Fig.1). I_{NaL} is "friend" as it contributes to 1) APD prolongation as an adaptive and an anti-arrhythmic (anti-re-entry) response [3], and 2) Ca^{2+} entry to limit depression of systolic function. The latter mechanism is an intrinsic, adaptive, digitalis-like effect with all corresponding risks and benefits. Interestingly, a large slow component of the Na^+ current decay (burst mode) has been identified in post-myocardial infarction-remodeled myocytes [120], i.e. in the transitional period from an infarction to HF. The increased I_{NaL} may indeed serve as an initial mechanism of adaptation to match an increased contractility demand for the survived VCs.

Although APD prolongation can be beneficial in HF, the temporal and spatial dispersion of repolarization that accompanies AP prolongation is critical for arrhythmia and sudden cardiac death [3]. Additionally, DADs and EADs have critical importance for non-reentrant arrhythmia or triggered activity (recent review [4]). Accordingly, I_{NaL} is "foe" as it contributes to EADs, DADs, dispersion of repolarization, and diastolic dysfunction.

I_{NaL} IS A NOVEL TARGET FOR CARDIOPROTECTION

Na^+ channel: To block or not to block?

After negative outcomes of Cardiac Arrhythmia Suppression Trial (CAST) [121,122] Class I antiarrhythmic drugs [123] targeting NaCh became close to a "taboo". The trial tested whether the suppression of ventricular arrhythmias by encainide, flecainide, moricizine after myocardial infarction improves survival. The conclusion was that the "treatment strategies designed solely to suppress these arrhythmias should no longer be followed" [122]. However, the discoveries of inherited mutations in SCN5A gene that lead to an increased I_{NaL} (LQT3 syndrome, see for review [124]) and of increased and slowed I_{NaL} in acquired, chronic HF (discussed in this review) give rise to a revival of NaCh as a therapeutic target. However, these studies suggest that not all NaCh must be equally targeted. The emerging paradigm for Na^+ channels in HF is that I_{NaT} is decreased [42-44] but simultaneously I_{NaL} is increased (see above). Blockers of I_{NaT} are proarrhythmic in HF because they slow conduction, thus worsening conduction problems (review [124]) and facilitating development of re-entry. Accordingly, new strategies for treatment must be considered: the new type of "smart" drugs should preferentially block I_{NaL} over I_{NaT}. This requirement calls for a new classification of Class 1 drugs in the future.

As discussed above increased I_{NaL} likely contributes to both electrical and contractile abnormalities of failing VCs, the potential benefits of a preferential I_{NaL} blockade in HF could be both an antiarrhythmic effect and an improvement of diastolic function. A preferential blockade of I_{NaL} over I_{NaT} in failing human VCs was reported for amiodarone [16], suggesting an explanation of why amiodarone, classified as Class III anti-arrhythmic drug, shows a remarkable efficiency among K^+-channel blockers. Accordingly a new index of "smart drug" has been recently suggested as a ratio of the drug potencies to block I_{NaL} over of I_{NaT} (i.e. ($IC_{50\_INaT}/IC_{50\_INaL}$)) [15]. Based on this new index three different drugs were compared and fell in the following sequence: ranolazine (37.8) > amiodarone (12.9) > lidocaine (2.7), suggesting that the most promising drug is a new antianginal drug ranolazine [15].

The potential great benefits (preventing arrhythmias and Ca^{2+} overload) of the preferential I_{NaL} blockade can be expected not only in HF but also in other cardiac diseases, such as hypoxia and ischemia, in which I_{NaL} increase and Na^+-Ca^{2+} overload are major features. A hypothesis that Na^+ initiates Ca^{2+} overload in hypoxia, ischemia and reperfusion was based on the experimental finding that Na^+ accumulation precedes the Ca^{2+} overload [125-127]. NaCh are critically involved in this process because NaCh blockers or activators reduce or increase Ca^{2+} overload in these pathological conditions, respectively [128-130]. In ischemia, targeting I_{NaL} is especially encouraged because LPC dramatically increases I_{NaL} [84,85]. Indeed, in recent clinical trial ranolazine has been effective to reduce the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome [131]. On the other hand, the therapeutic strategy of a preferential I_{NaL} blockade should be exercised with care. The balanced and effective therapy targeting I_{NaL} should take into account that I_{NaL} might be involved in adaptive response at different states of cardiac disease, making the question whether I_{NaL} is "friend" or "foe" vitally important.

Alternative targets delineated by multiple mechanisms of I_{NaL} modulation

Figure **8** summarizes discussed above NaCh modulatory mechanisms, which could be involved in the I_{NaL} increase in HF. Thus, I_{NaL} increase in HF can be prevented, at least in part, in different ways: i. Stabilizing membrane phospholipid composition by preventing LPC accumulation, ii. Normalizing β-subunits membrane content, iii. Stabilizing subsarcolemmal cytoskeleton, iv. Normalizing Ca^{2+} homeostasis.

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List of abbreviations

AP, action potential
APD, action potential duration
CaM, calmodulin
CaMKII, Ca^{2+}-calmodulin activated protein kinase II
BM, burst mode of NaCh gating
DADs, delayed afterdeplarizations
DHP, dihydropiridine
EADs, early afterdepolarizations
HF, heart failure
I-V, current-voltage relationship
I_{NaT}, fast transient sodium current
I_{NaL}, late sodium current
LPC, lysophosphatilylcholine, the membrane phosholipid metabolite
LSM, late scattered mode of NaCh gating
NaCh, voltage sensitive sodium channels
NCX, Na^+/Ca^{2+} exchanger
PKA, protein kinase A
PKC, protein kinase C
SR, sarcoplasmic reticulum
TTX, tetrodotoxin, a specific blocker of NaCh
STX, saxitoxin, a specific blocker of NaCh
VCs, left ventricular cardiomyocytes
$(dV/dt)_{max}$, maximal AP upstroke velocity

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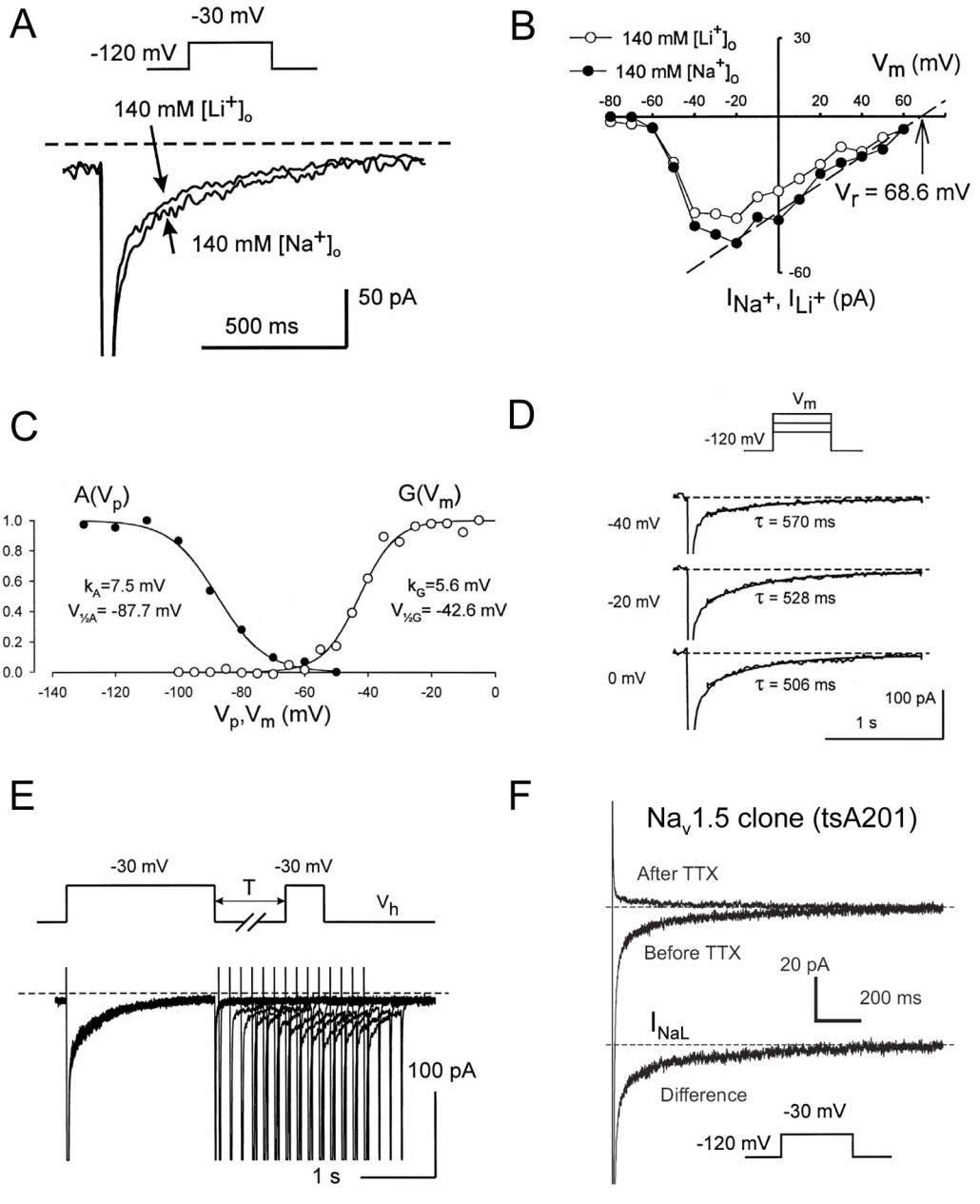

Figure (1).

Biophysical properties of the slowly inactivating, late Na^+ current (I_{NaL}) evaluated by whole cell patch clamp in human ventricular cardiomyocytes (A-E) and human cloned $Na_v1.5$ expressed in tsA201 cells (F). A-B: I_{NaL} can be carried either by Na^+ or Li^+. B: I-V relation for I_{NaL}. C: examples of steady-state activation and availability curves, $G(V_m)$ and $A(V_p)$, respectively. D: Examples of original traces illustrating voltage-independent I_{NaL} decay. E: slow reactivation of I_{NaL}. F: I_{NaL} produced by $Na_v1.5$ was assessed as difference current before application of a selective Na^+ channel blocker tetrodotoxin (TTX, 30 μM) and after TTX. Voltage protocols are shown at the traces. Recording was performed at 24°C. Modified from [11] (A-E) and [65](F), used with permission.

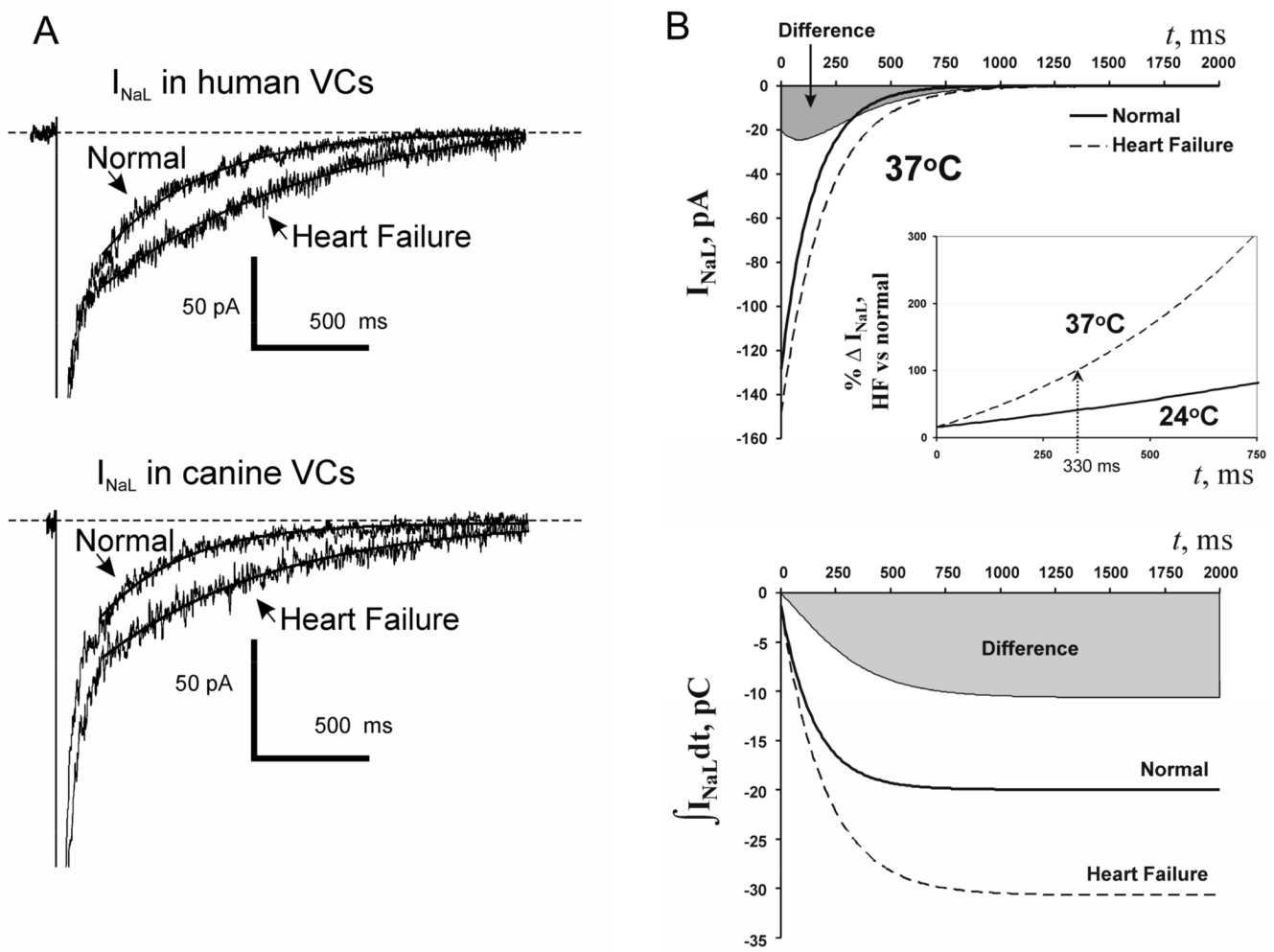

Figure (2).

A: Chronic heart failure slows and increases I_{NaL}. A: examples of whole cell I_{NaL} recordings in human and dog ventricular cardiomyocytes. B: Idealized I_{NaL} and their integrals in normal and failing dog cardiomyocytes of same size (200 pF) calculated using Q_{10} factors (37°C) and average parameters of I_{NaL} density and decay time constant measured in normal and HF canine VCs. Larger and slower I_{NaL} in failing cardiomyocytes results in substantial increase in total charge (or Na^+ influx) transfer by I_{NaL}. Gray areas illustrate difference between failing and normal cells. Adapted from [13], used with permission.

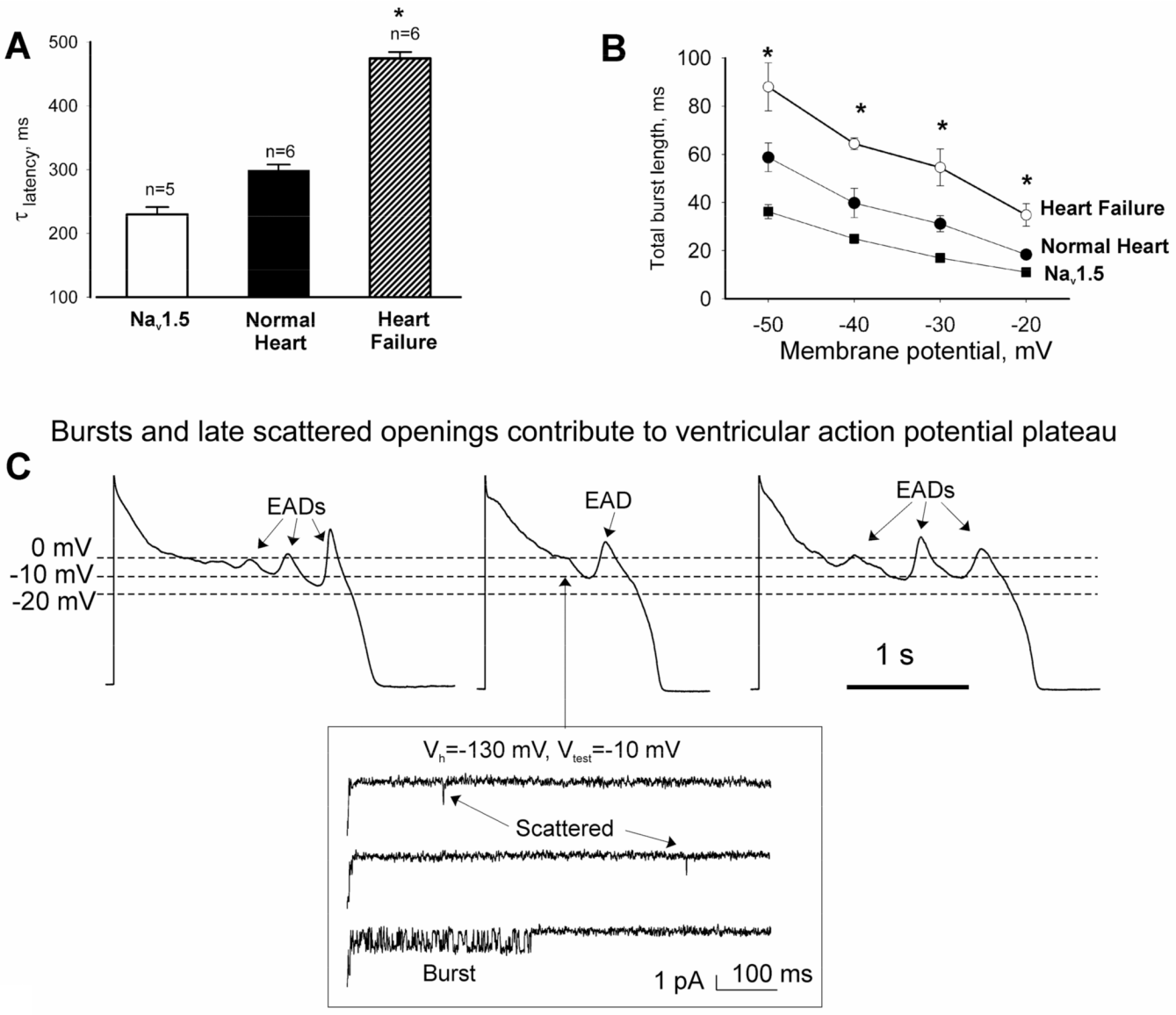

Figure (3).

Inactivation of both late scattered mode (A) or burst mode (B) of the late openings of Na^+ channel was slowest in failing human cardiomyocytes compared with those from normal human hearts or heterologously expressed $Na_v1.5$. *P<0.05, heart failure *vs*. normal heart or clone (Mean±SEM). Cell-attached patches, 24°C. (Adapted from [12]). C: recordings of action potentials in failing human cardiomyocytes are shown along with the late scattered mode and burst mode openings occurring at -10 mV, i.e. within the voltages of the action potential plateau. Adapted from [12,40], used with permission.

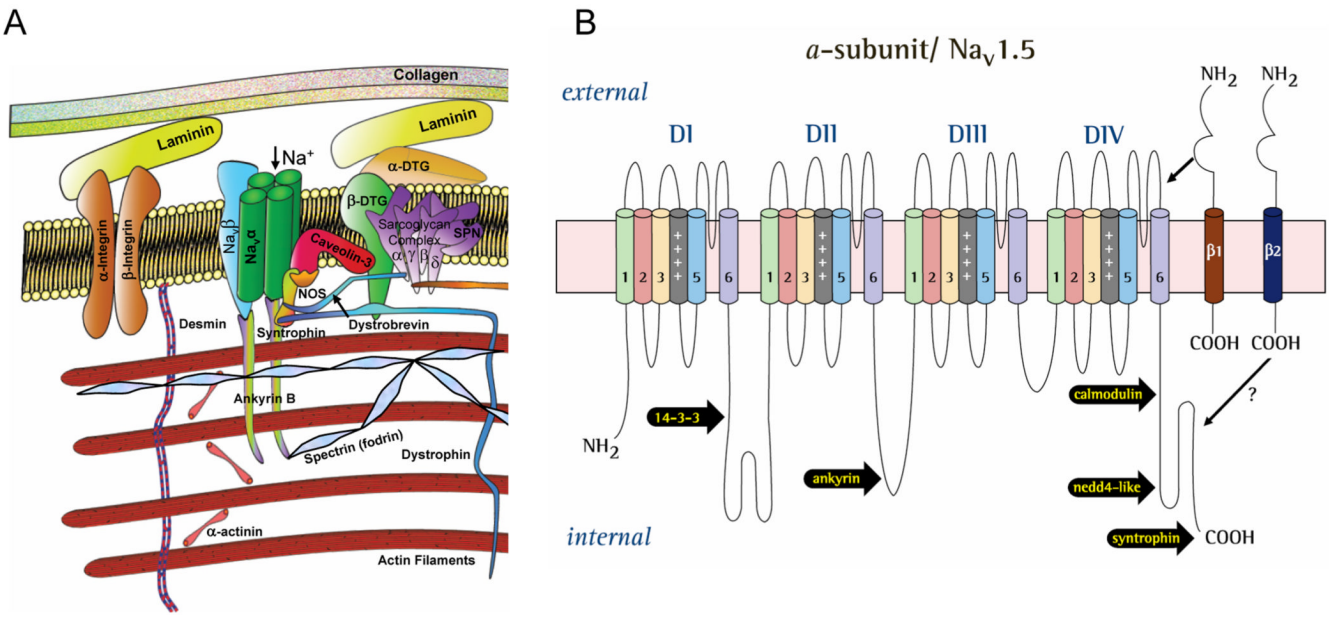

Figure (4).

Schematic illustration of Na^+ channel macromolecular complex. A: The pore forming α subunit of the channel interacts with β-subunits, cytoskeleton and the extracellular matrix (Modified after [50], used with permission). B: schematic presentation of the α subunit of the cardiac Na^+ channel isoform ($Na_v1.5$) with reported sites of interaction with β subunits (restricted only to β1 and β2) and other regulatory proteins. Reprinted from [17], used with permission.

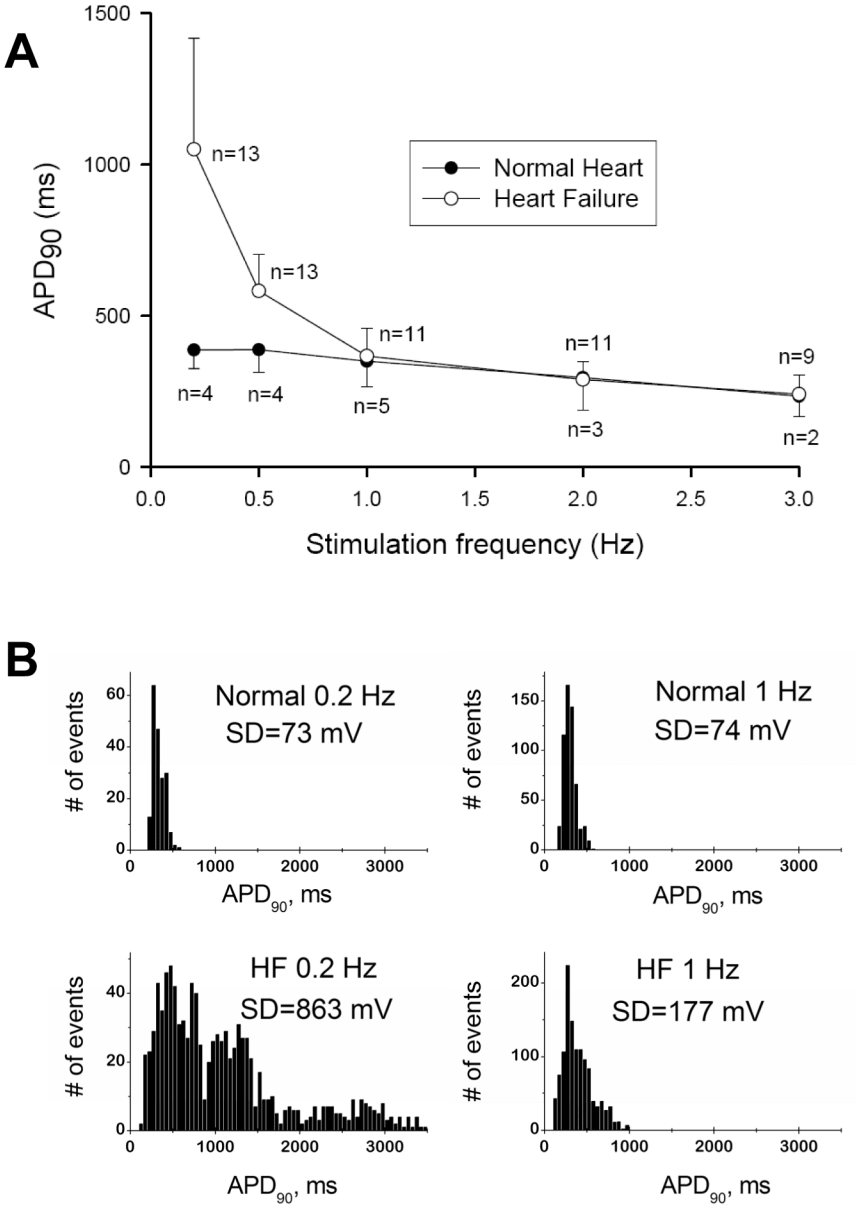

Figure (5).

A: Frequency-dependence of action potential duration in ventricular cardiomyocytes of normal dogs and dogs with chronic heart failure. Note that largest difference occurs at low pacing rates. B: at the low (0.2 Hz) and the physiologic (1 Hz) pacing rates, AP duration in failing myocytes exhibits significant beat-to beat variability (see respective SD values in the APD_{90} distribution histograms) Adapted from [10] with permission.

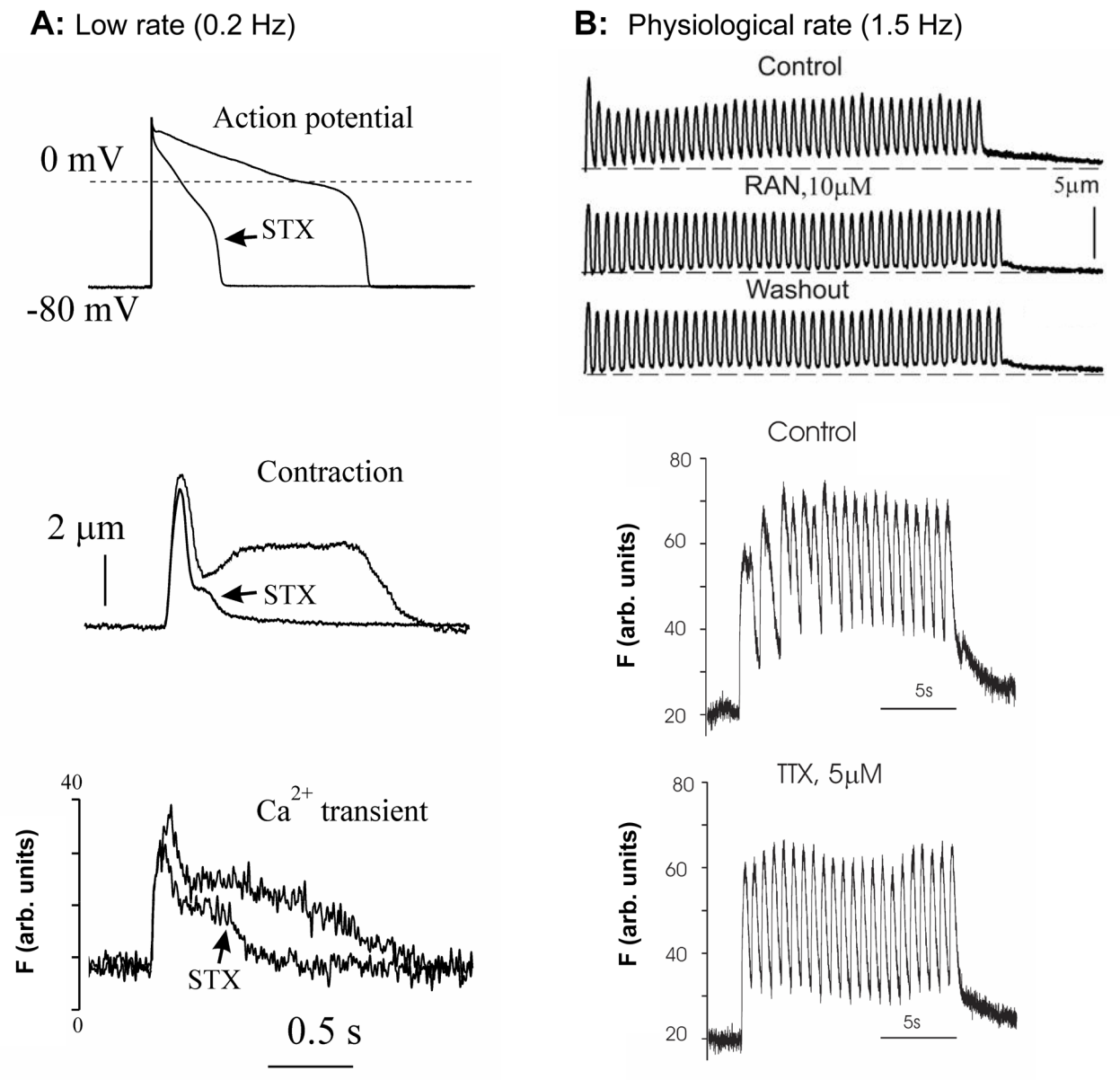

Figure (6).

A: Examples of effects of a specific Na^+ channel blocker saxitoxin (STX) on AP duration, contraction and Ca^{2+} transient in ventricular cardiomyocytes of dogs with chronic heart failure at a low pacing rate of 0.2 Hz STX reduces AP duration, abolishes "dome" phase of contraction and of Ca^{2+} transient in failing cells. B: At higher pacing rates a specific I_{NaL} blockers ranolazine reduces diastolic tension, and a specific Na^+ channel blocker tetrodotoxin (TTX) reduces Ca^{2+} accumulation (Fluo-4 signals). Adapted from [14,15,17], used with permission.

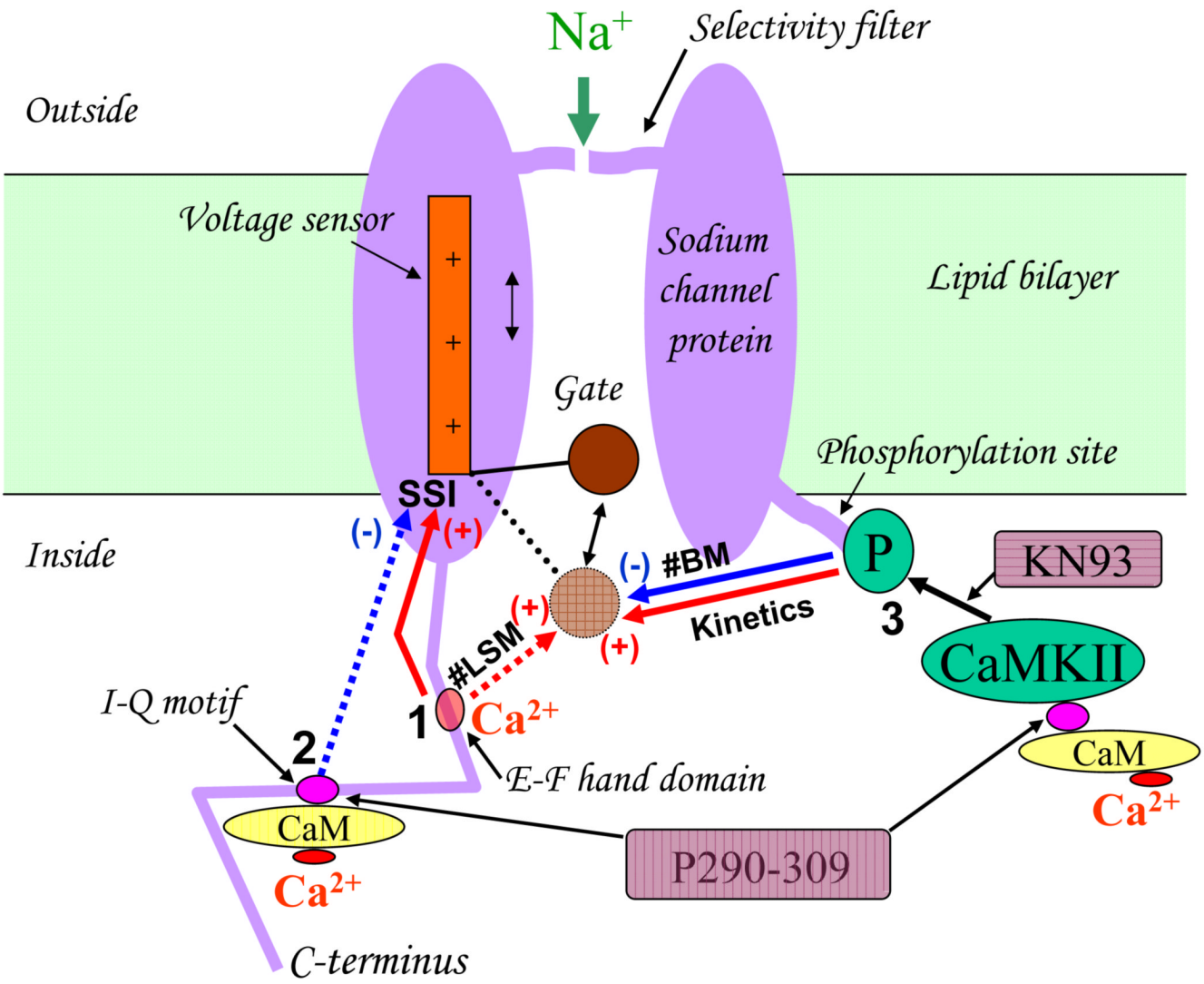

Figure (7).

Simplified hypothetical diagram of the intracellular Ca^{2+} signaling pathways modulating late sodium current in normal and failing ventricular cardiac myocytes. Pathways 1, 2 and 3 (marked by black digits) represent Ca^{2+} binding to: the E-F domain, CaM-binding site (IQ motif) on C-terminus of NaCh as well as CaM/CaMKII complex, respectively. In addition, shown are the inhibitory sites of the CaM antagonist peptide P290-309 and KN93 - inhibitor of CaMKII, which were used in our original study [110] to discover the I_{NaL} modulation depicted in the diagram. Dashed line arrows indicate the regulation pathways which are operational only in heart failure. Reprinted from [110], used with permission.

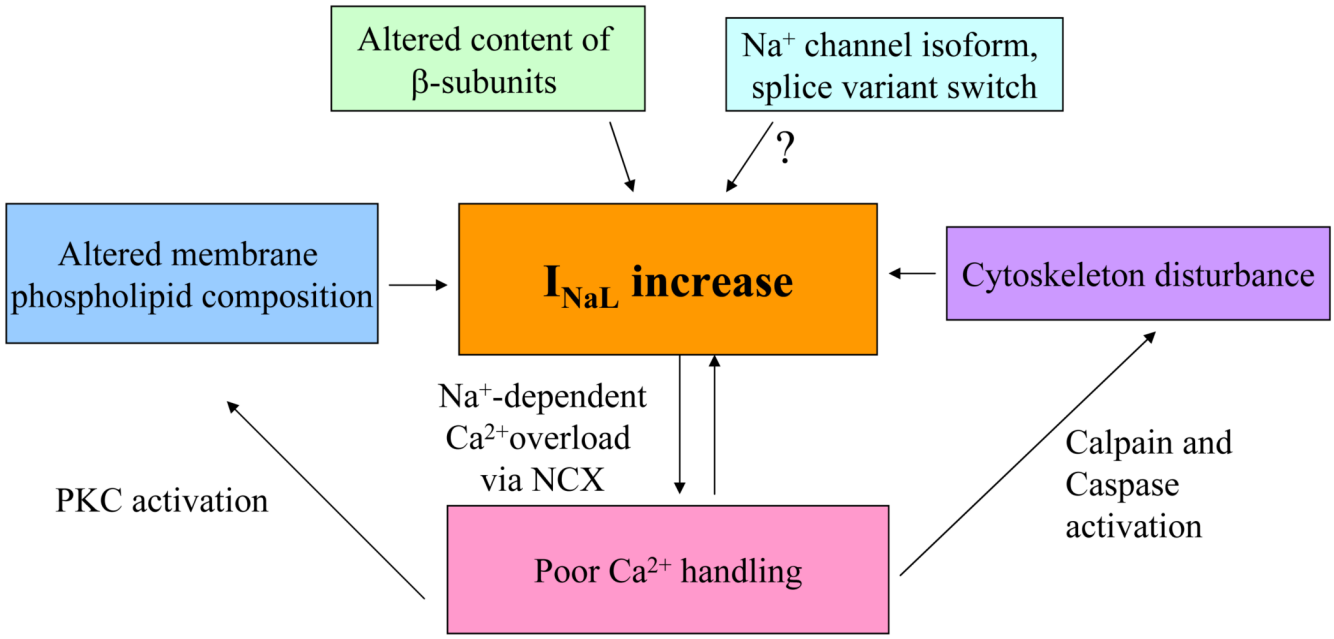

Figure (8).
Simplified diagram of the modulatory mechanisms that lead to the I_{NaL} increase in HF. These mechanisms may serve as a road map to develop new strategies for HF treatment (see text for detail).