Ranolazine in Stable Angina: Mechanism of Action and Therapeutic Implications

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Ranolazine, the first member of a newer class of medications, is a piperazine derivative that was first approved by the US Food and Drug Administration in 2006 as a treatment for chronic angina. In 2008, ranolazine received a new indication for the treatment of chronic angina, allowing for its first-line use. Ranolazine's mechanism of action differs fundamentally from that of currently available anti-ischemic drugs, thus introducing a new paradigm to complement what had been considered conventional therapy. This article outlines this mechanism of action, with a focus on myocardial ischemia and on aspects that may assist in fully exploiting ranolazine's therapeutic potential. Although the mechanism of action initially postulated to be responsible for ranolazine's antianginal effect was inhibition of fatty acid oxidation, current evidence suggests alternative explanations. Chief among them is its role as a selective inhibitor of the late component of the Na^+ current. The late sodium current has been shown, in several models, to be at the root of a wide spectrum of electrical, contractile, and metabolic derangements. Thus, ranolazine, in addition to its electrophysiologic role, has an influence on cardiomyocyte metabolism, excitation-contraction coupling, and myocardial perfusion. This explains both its efficacy as an antianginal agent and the spectrum of clinical effects observed in human trials, including electrical stabilization and glycemic effects. Accordingly, this article focuses on the current evidence that supports late sodium current inhibition as a plausible mechanism of ranolazine's therapeutic efficacy.

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KEY WORDS

Ranolazine • Fatty acid oxidation • I_{NaL} inhibition • Stable ischemic heart disease • Proarrhythmic safety

A relatively new drug, ranolazine has been commercially available since 2006 for the treatment of stable ischemic heart disease. Ranolazine's mechanism of action differs fundamentally from currently available anti-ischemic drugs, thus introducing a new paradigm to complement

what had been, up until then, considered conventional therapy. This article outlines this mechanism of action, with a focus on myocardial ischemia and on aspects that may assist in fully exploiting ranolazine's therapeutic potential. The mechanisms underlying the antiarrhythmic effect of ranolazine[1] have been discussed elsewhere[2,3] and are beyond the scope of this review. Ranolazine's electrophysiologic effects are mentioned here only with regard to safety concerns in antianginal therapy.

Targets of Ranolazine's Antianginal Effect

The mechanism of action initially proposed to be responsible for ranolazine's antianginal effect was inhibition of fatty acid oxidation (FAO). FAO may enhance glucose oxidation (GO), which is under reciprocal control according to Randle's cycle.[4] An increase in the GO:FAO ratio reduces the oxygen cost of mitochondrial adenosine triphosphate (ATP) synthesis and is therefore considered metabolically beneficial.[5] Nevertheless, this interpretation of ranolazine's effect is highly controversial[6] for the following reasons: (1) in most (but not all)[7] studies it has been demonstrated for concentrations well above those required for the anti-ischemic effects (2-6 μM, obtained by < 30 mg/ Kg/d); and (2) the causal relationship between FAO inhibition and cardioprotection in ischemia/reperfusion has been disputed.[6] Moreover, it should be considered that Na^+ and Ca^{2+} transports through the sarcolemmal and sarcoplasmic reticulum (SR) membranes are fuelled mainly by nonmitochondrial (glycolytic) ATP pools[8]; therefore, modulation of mitochondrial metabolism is unlikely to account for the whole spectrum of ranolazine effects, which includes the more relevant modulation of Na^+ and Ca^{2+} cycling.

An additional action of ranolazine, more recently described and occurring at concentrations certainly compatible with its anti-ischemic effect (≤ 10 μM), is selective inhibition of the late component of the Na^+ current (I_{NaL})[9] (Table 1). In addition to its electrophysiologic role, I_{NaL} has an impact on myocyte metabolism, excitation-contraction coupling, and (indirectly) on myocardial perfusion. Therefore, I_{NaL} inhibition may well account for both the anti-ischemic and antiarrhythmic effects of ranolazine. Accordingly, we focus on I_{NaL} inhibition as a plausible mechanism of ranolazine's therapeutic efficacy, without necessarily implying its uniqueness.

As an ancillary action, partially occurring within therapeutic concentrations, ranolazine inhibits I_{Kr}, a K^+ current involved in repolarization (Table 1)[9]; because of its potential proarrhythmic risk, I_{Kr} blockade deserves to be considered. Inhibition of the reverse mode of operation of the Na^+/Ca^{2+} exchanger has been recently described at low ranolazine concentrations (IC_{50} = 1.7 μM), but not necessarily found to account for the drug's cardioprotective effect.[10] Actions of ranolazine that occur at concentrations above the therapeutic range include blockade of the Ca^{2+} current (I_{CaL})[9] and adrenergic receptor antagonism (α and β).[11] Being negligible at therapeutic concentrations, these actions are unlikely to account for therapeutic effects.

I_{NaL} in Cardiac Pathophysiology

In cardiomyocytes, the voltage-dependent Na^+ current (I_{Na}) is best known for supporting autoregenerative membrane depolarization (action potential upstroke). I_{Na} consists of a large transient component (I_{NaT}), which is terminated within several milliseconds by inactivation, and the much smaller sustained or late component (I_{NaL}), which reflects incomplete sodium

TABLE 1

Comparison of Blocking Potencies on I_{NaT}, I_{NaL}, and I_{Kr}

Drug	Study	I_{NaT}	I_{NaL}	I_{Kr}	I_{NaT}/I_{NaL}	I_{Kr}/I_{NaL}
Ranolazine	Antzelevitch C et al,[9] Undrovinas AI et al[37]	294	6.5	11.5	45.5	1.8
Amiodarone	Kodama I et al,[38] Maltsev VA et al[39]	87	6.7	10	12.9	1.5
Lidocaine	Persson F et al,[40] Paul AA et al[41]	367	29	263	12.6	9.1
Flecainide	Persson F et al,[40] Paul AA et al[41]	5.2	3.4	3.9	1.5	1.1
Tetrodotoxin	Persson F et al[40]	2.2	1.7	NA	1.3	NA
Propafenone	Persson F et al,[40] Paul AA et al[41]	1.1	1.1	0.4	1.0	0.4

First three columns from left: concentrations for 50% inhibition (IC_{50} in μM) of each current; in these columns a higher value reflects lower potency of inhibition. Last two columns: IC_{50} for I_{NaT} and I_{Kr} normalized to the IC_{50} for I_{NaL}; in these columns a higher value reflects stronger selectivity for inhibition of I_{NaL} (vs I_{NaT} and I_{Kr}, respectively). NA, not available.

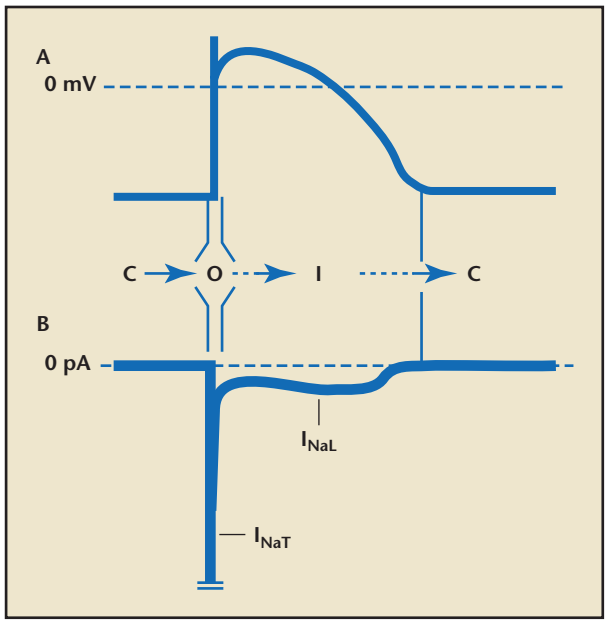


Figure 1. Components of the Na^+ current. **(A)** Action potential of a normal ventricular myocyte. **(B)** I_{Na} (recorded as tetrodotoxin-sensitive current) during the action potential in panel A; the transient component (I_{NaT}) is truncated to allow appreciation of the late one (I_{NaL}). The relationship between Na^+ channel gating transitions and the phases of the electrical cycle is shown in the middle. The transition from the closed state (C) to the open one (O; the only conductive state) is induced by membrane depolarization and quickly occurs during the action potential upstroke. Depolarization also induces the transition from the O to the inactivated state (I). However, the latter takes place with a delay of several milliseconds, thus allowing a large I_{Na} to flow transiently (I_{NaT}). The I state can be normally removed only by membrane repolarization (mostly enacted by K^+ currents). Channel opening from the I state during the action potential occurs with a very low probability, but is still adequate to generate a small sustained component (I_{NaL}).

channel inactivation (Figure 1). Both components can be carried by the same sodium channel,[12] represented in cardiac myocytes by the $Na_v1.5$ protein. I_{NaT} has a crucial physiologic role in supporting excitability and impulse propagation. I_{NaL}, almost negligible in generic working myocytes, is physiologically present in Purkinje[13] and midmyocardial cells,[14] where it contributes to their peculiarly long repolarization. Although of lesser physiologic relevance under normal circumstances, I_{NaL} may be markedly enhanced under common disease/stress conditions, including ischemia, thus acquiring a major pathophysiologic role. Hence, at least for practical purposes, I_{NaL} can be viewed as a pathologic current.

Several mechanisms may underlie pathologic I_{NaL} enhancement; however, the one most relevant to myocardial ischemia is instability of the channel inactivated state. This can be envisioned as defective closure of the inactivation gate, which results in a significant Na^+ leak throughout repolarization, when Na^+ channels should be effectively sealed.

Conditions and Mechanisms of I_{NaL} Enhancement

Although the interest in the pathophysiologic role of I_{NaL} was mostly triggered by identification of Na^+ channel mutations leading to arrhythmogenic QT prolongation,[15] secondary I_{NaL} enhancement occurs in association with a surprisingly large number of common disease states,[2] including cardiac hypertrophy/failure and ischemia, not necessarily related to each other in terms of primary pathogenesis. Such a pattern suggests that I_{NaL} enhancement may be a common response to cell stress and dysfunction. Accordingly, in cardiac myocytes, I_{NaL} is enhanced by reactive oxygen species (ROS),[16] whose generation is generally associated with cell distress. The question of whether ischemia can enhance the pathologic I_{NaL} can be answered only indirectly, because membrane currents can be recorded only in isolated myocytes, which cannot be subjected to ischemia. Nevertheless, I_{NaL} is enhanced by myocyte exposure to hypoxia[17] or ischemic metabolites[18] and I_{NaL} blockade effectively prevents ischemia/reperfusion damage in the intact heart.[6]

The search for a common mechanism mediating I_{NaL} enhancement by cellular stress of heterogeneous etiology has highlighted the role of Ca^{2+}-calmodulin kinase (CaMKIIδ) activation. This is a Ca^{2+}- and ROS-activated cytosolic enzyme that may, among other targets, phosphorylate $Na_v1.5$ channels. Converging evidence indicates that CaMKIIδ overexpression (or activation) enhances I_{NaL} and produces cardiac abnormalities that are reversed by I_{NaL} blockade.[19] Although this does not rule out further modes of I_{NaL} enhancement, CaMKIIδ activation is particularly relevant because its relation to I_{NaL} may set up a vicious feedback loop (as illustrated in Figure 2), and is very likely to contribute to the evolution of cell dysfunction and damage in response to stress. Although CaMKIIδ inhibition is not available for therapeutic use yet, I_{NaL} blockade may disrupt such a vicious loop.[19]

To summarize, with the exception of primary (genetic) Na^+ channel defects, I_{NaL} enhancement can be viewed as a generic response to cellular stress that is secondary in origin, but has a pivotal role in mediating functional derangements and disease progression.

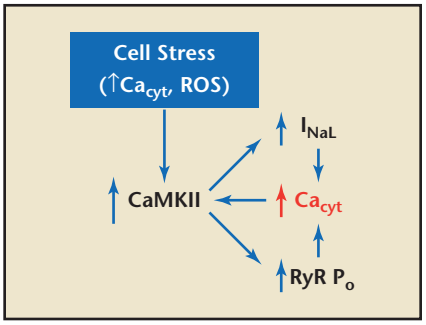


Figure 2. Positive feedback interactions initiated by cell stress and supported by Ca^{2+}-calmodulin kinase (CaMKII). Initial CaMKII activation by cell stress (eg, increased ROS) may enhance I_{NaL} and facilitate RyR opening. The resulting increase in cytosolic Ca^{2+} supports further CaMKII activation, thus setting up an autoregenerative cycle. Ca_{cyt}, cytosolic Ca^{2+}; cyt, cytosol; ROS, reactive oxygen species; RyR P_o, open probability of RyR channels.

Consequences of I_{NaL} Enhancement

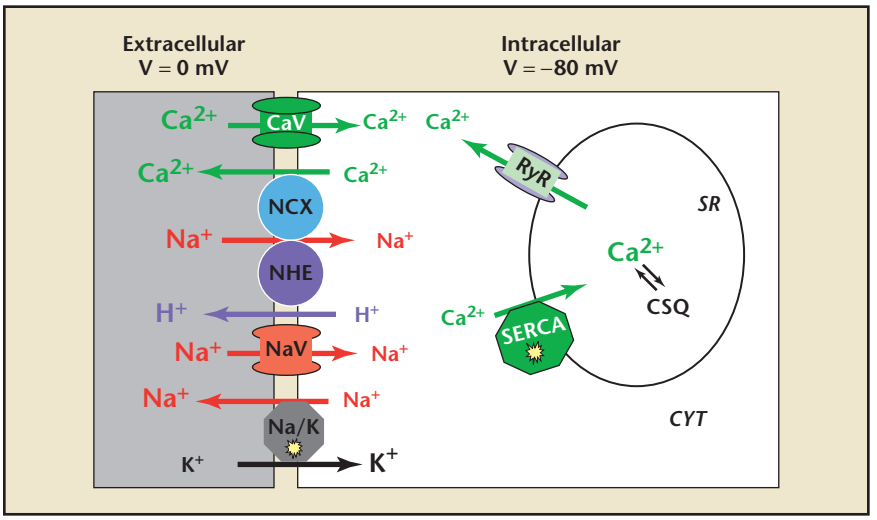
I_{NaL} enhancement generates an inward current during repolarization (Figure 1) and supports extra Na^+ entry into the cell. The excess inward current prolongs and destabilizes repolarization (prolongs the QT interval), thus facilitating arrhythmias. However, the effect most relevant to myocardial ischemia is the augmentation of Na^+ influx, which increases energy consumption, limits coronary flow, and may impair myocyte function and survival during ischemia. Altogether, the consequences of increased sodium influx set the stage for progression of ischemic disease and qualify I_{NaL} as a target for antianginal therapy.

Na^+ is normally extruded from the cell by the ATP-powered Na^+/K^+ pump. Therefore, excess Na^+ influx increases ATP consumption as this pump is activated; furthermore, if the influx of sodium exceeds the pump maximal transport rate, Na^+ accumulates in the cytosol and its transmembrane gradient is dissipated. As the latter energizes many secondary membrane transport mechanisms, most importantly the Na^+/Ca^{2+} exchanger (NCX) and the Na^+/H^+ exchanger (NHE) (Figure 3), a pivotal consequence of intracellular Na^+ accumulation is the perturbation of intracellular Ca^{2+} and H^+ homeostasis.

Reduced Ca^{2+} extrusion by NCX results in diastolic dysfunction. Accordingly, blockade of pathologically enhanced I_{NaL} improves diastolic relaxation[20] and increases coronary flow,[21] conceivably by relieving intramural vessels from extrinsic compression.[22] This implies that I_{NaL} enhancement may cause a microvascular perfusion defect, independent of intrinsic vascular tone, likely to be unresponsive to standard vasodilator therapy or angioplasty. Furthermore, increased cytosolic Ca^{2+} promotes opening of SR Ca^{2+} release channels, thus destabilizing the Ca^{2+} store and short-circuiting ATP-powered Ca^{2+} uptake by the SR Ca^{2+} pump (Figure 3). Extra ATP consumption may therefore be required to maintain SR Ca^{2+} content adequate for contraction and to support normal diastolic sarcomere activation. High cytosolic Ca^{2+} also impairs mitochondrial function, particularly if Na^+ is simultaneously elevated.[23] During ischemia/reperfusion, I_{NaL} blockade limits mitochondrial Ca^{2+} overload and ROS generation at the same time, thus delaying opening of the mitochondrial permeability transition pore.[24] Because the latter leads to osmotic disruption of mitochondrial membrane and release of proapoptotic signals (cytochrome C), I_{NaL} enhancement may impact on cell survival.

Under normal conditions, cellular H^+ homeostasis may be less sensitive than Ca^{2+} homeostasis to I_{NaL} enhancement, because mechanisms other than NHE contribute to H^+ extrusion. During abrupt reperfusion following acute coronary occlusion, massive H^+ extrusion through NHE contributes to intracellular Na^+ loading, which explains why direct NHE inhibition paradoxically improves Ca^{2+} handling and limits myocardial injury.[25] Nevertheless, the situation

Figure 3. The main membrane mechanisms linking Na^+ to Ca^{2+} movements between compartments. The size of the ion symbol represents the direction of its electrochemical gradient (from large to small); the actual flux direction is shown by the *arrows*. The intracellular compartment is divided into CYT and SR. The *yellow flash symbol* denotes mechanisms directly consuming ATP, transports driven by Na^+ gradient are shown as *circles*. ATP consuming mechanisms (Na^+/K^+ and SERCA ATP-ases) generate ion concentration gradients that are exploited as chemical energy to fuel other active transport mechanisms (NCX, NHE) and passive ion flux through channels (Ca_v, Na_v, RyR). ATP, adenosine triphosphate; Ca_v and Na_v, V-gated Ca^{2+} and Na^+ channels; CSQ, calsequestrin (SR Ca^{2+} buffering protein); CYT, cytosol; NCX, Na^+/Ca^{2+} exchanger; NHE, Na^+/H^+ exchanger; Na/K, Na^+-K^+ ATPase; SERCA, SR Ca^{2+} ATPase; RyR, Ca^{2+}-gated Ca^{2+} release channels of the SR; SR, sarcoplasmic reticulum.



might be different in the presence of chronic partial ischemia. Similar to what occurs in ouabain-induced Na^+ overload,[26] reduced H^+ export by NHE might lead to persistent intracellular acidosis, thus contributing to impaired force development and relaxation. This hypothesis awaits experimental confirmation.

To summarize, I_{NaL} enhancement is at the root of a wide spectrum of electrical, contractile, and metabolic derangements. Accordingly, the pleiotropic effect of selective I_{NaL} blockers, rather than arguing against drug specificity, is fully expected.

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I_{NaL} Pharmacology

Mechanism and Implications of Selective I_{NaL} Blockade

According to the mechanism underlying I_{NaL} just outlined, selectivity (vs I_{NaT}) of I_{NaL} inhibition can be theoretically achieved by drugs (1) making the intrinsic channel inactivated state more stable (by affecting protein conformational stability), or (2) selectively binding to the inactivated state (a specific protein conformation) and physically blocking Na^+ permeation. Notably, to achieve I_{NaL} selectivity, the latter mechanisms require the channel to completely recover from inactivation during diastole and the subsequent drug unbinding to occur swiftly; this is necessary to make the channel fully available to conduct I_{NaT} during the subsequent action potential upstroke. In practical terms, I_{NaL} versus I_{NaT} block selectivity may be diminished whenever diastolic potential is partially depolarized (leading to incomplete channel recovery from inactivation), or diastole is short as compared with the time required for drug unbinding (eg, at fast heart rates or prolonged action potential duration).[3] Whereas the level of diastolic membrane potential is a myocyte property, potentially affected by disease states (eg, acute ischemia), the rate of unbinding is mostly a drug property (possibly affected by local pH), perhaps the most relevant in differentiating currently available agents in terms of I_{NaL} versus I_{NaT} selectivity.

I_{NaL} is significantly inhibited by most Na^+ channel blockers (ie, local anesthetics) at concentrations blocking I_{NaT} (Table 1), the therapeutic effect initially sought. Nevertheless, clinical studies have dramatically unveiled the unexpected proarrhythmic effect of local anesthetic agents in the setting of coronary artery disease.[27] Why concomitant ischemia makes propagation impairment (the effect of I_{NaT} blockade) particularly dangerous has never been demonstrated. Nevertheless, there are several plausible explanations and the empiric evidence of risk is compelling. On the other hand, substantial evidence indicates that selective I_{NaL} blockade (by ranolazine) does not entail proarrhythmic risk in the setting of ischemic heart disease; to the contrary, a significant antiarrhythmic effect has been observed.[1] This implies that selectivity (relative to I_{NaT}) is the prerequisite for exploiting I_{NaL} blockade as an anti-ischemic intervention. Incidentally, amiodarone, currently the only antiarrhythmic drug considered relatively safe in coronary artery disease, is second only to ranolazine in terms of I_{NaL} versus I_{NaT} selectivity (Table 1).

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I_{NaL} Enhancers

A number of natural and synthetic molecules, anemone toxin and veratridine being the most frequently used, cause I_{NaL} enhancement. Their interest is experimental, rather than therapeutic, and they are mentioned here only because they are widely exploited to generate experimental models of I_{NaL} enhancement. The consequences of I_{NaL} enhancement by these toxins and by naturally occurring disease are reasonably similar, thus making toxin-based models pathophysiologically sound.

Interaction Between I_{NaL} and I_{Kr} Blockade

The interaction between the main and ancillary actions of ranolazine (I_{NaL} and I_{Kr} blockade, respectively), albeit not directly involved in the anti-ischemic effect, is highly relevant to drug safety. I_{Kr} blockade is well known to prolong action potential duration (APD) and reduce repolarization stability. Although APD prolongation is theoretically antiarrhythmic (by prolonging refractoriness), its benefit is outweighed by repolarization instability, which facilitates early afterdepolarizations (EADs) and the resulting arrhythmias (mostly torsades de pointes tachycardias). Therefore, it is important to consider that concomitant I_{NaL} inhibition strikingly counters the effect of I_{Kr} blockade on duration of repolarization, including its "reverse rate dependency,"[28] and particularly on repolarization stability.[29] Longer action potentials

are intrinsically more sensitive to perturbations,[30] and susceptible to develop EADs[31]; therefore, APD shortening itself may contribute to the stabilizing effect of I_{NaL} blockade. Nevertheless, the large difference between the effect of I_{NaL} inhibition in control and during I_{Kr} blockade on repolarization stability might suggest the involvement of additional, still undefined mechanisms.

The practical counterpart of the interaction between I_{NaL} and I_{Kr} inhibition is that, despite its ancillary I_{Kr} blockade, ranolazine minimally modifies APD in normal myocardium, shortens it in diseased myocardium (when I_{NaL} is enhanced), and it has, under both conditions, a stabilizing effect on repolarization. Consistent with these experimental observations, significant QT prolongation and torsadogenic effect are conspicuously absent from the response to ranolazine in the clinical setting.

Therapeutic Perspective

Because I_{NaL} enhancement is at the root of many manifestations of myocardial disease, I_{NaL} blockade potentially has multiple therapeutic indications (eg, antiarrhythmic, lusitropic), many of them awaiting validation in the clinical setting. Such validation is already available, through clinical evaluation of ranolazine, for its anti-ischemic effect; acquaintance with its mechanism leads to predictions potentially useful in optimizing its therapeutic use.

The mechanism by which I_{NaL} inhibition improves the balance between myocardial blood supply and demand is independent of hemodynamic load. Because heart rate, systemic arterial resistance, and venous return are virtually unaffected at therapeutic concentrations, ranolazine exerts its anti-ischemic effect without decreasing cardiac mechanical work.[32] This mode of action differs from that of all current anti-ischemic agents, thus predicting the effect of I_{NaL} inhibition to be fully additive when combined with standard therapy. Furthermore, by relieving intramural vessels from extrinsic compression, I_{NaL} inhibition might specifically target microvascular insufficiency, particularly the one associated with diastolic dysfunction. If confirmed in the clinical setting by specifically designed studies, the antiarrhythmic potential of I_{NaL} inhibition may be highly relevant to the overall therapeutic approach to ischemic heart disease.

Finally, improvement of glycemic control in patients with type 2 diabetes mellitus (DM) has been serendipitously observed while testing ranolazine in ischemic heart disease.[33] Although improvement of insulin secretion seems to be involved,[34] and voltage-dependent Na^+ channels do contribute to control of insulin secretion by pancreatic islet cells,[35] it is still unclear whether I_{NaL} inhibition may account for this unpredicted effect. Irrespective of the underlying mechanism, improvement of glycemic control would be an obvious advantage in the management of the large cohort of ischemic patients also affected by DM and the metabolic syndrome.

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Therapeutic concentrations of ranolazine do not affect intrinsic vascular tone. Moreover, there is

MAIN POINTS

- Although the mechanism of action initially postulated to be responsible for ranolazine's antianginal effect was inhibition of fatty acid oxidation, current evidence suggests alternative explanations; chief among them is its role as a selective inhibitor of the late component of the Na^+ current. The late sodium current has been shown, in several models, to be at the root of a wide spectrum of electrical, contractile, and metabolic derangements.
- Therapeutic concentrations of ranolazine selectively inhibit the late component of the NA^+ current (I_{NaL}). In addition to its electrophysiologic role, I_{NaL} has an impact on myocyte metabolism, excitation-contraction coupling, and (indirectly) on myocardial perfusion; therefore, I_{NaL} inhibition may well account for both the anti-ischemic and antiarrhythmic effects of ranolazine.
- By relieving intramural vessels from extrinsic compression, I_{NaL} inhibition might specifically target microvascular insufficiency, particularly the one associated with diastolic dysfunction. If confirmed in the clinical setting by specifically designed studies, the antiarrhythmic potential of I_{NaL} inhibition may be highly relevant to the overall therapeutic approach to ischemic heart disease.

nothing to suggest that I_{NaL} may have a role in vascular plaque genesis, stability, or thrombus formation. Therefore, the failure of ranolazine to affect the incidence of acute coronary events (unstable angina and myocardial infarction)[36] is expected from its mechanism of action and does not conflict with its efficacy in the treatment of stable angina. ■

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