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Update on evidence for treatment with ranolazine in stable angina

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Abstract

Chronic angina represents a major burden for public health systems because of its poor prognosis and its high treatment costs. Ranolazine is an emerging drug recently approved for the treatment of this disease. The main molecular mechanism underlying ranolazine-mediated beneficial effects has been identified as inhibition of the late Na^+ current during the action potential, which potentially improves oxygen consumption, diastolic dysfunction and coronary blood flow. Moreover, this particular mechanism of action also confers on ranolazine a potential antiarrhythmic effect. The aim of this review is to update the evidence for ranolazine treatment in chronic angina and discuss its therapeutic perspectives based on the most recent clinical and experimental studies.

Key words: *ranolazine; stable angina; Na^+ current*

Introduction

Stable angina (SA) is one of the most common manifestations of coronary artery disease (CAD) [1]. It is characterised by elevated medical care costs [1]. Despite advances in cardiovascular disease prevention, the incidence of SA is expected to increase in the near future in developed countries. In clinical practice, the treatment goals set by guidelines are often utopian. In fact, it is recommended to (at the same time): (i.) reduce premature cardiovascular death, (ii.) prevent complications that impair the patient's functional well-being, (iii.) maintain or restore a quality of life that is satisfactory to the patient, (iv.) eliminate ischaemic symptoms and (v.) minimise costs of health care [1]. Current pharmacological approaches include: short- or long-acting nitrates, calcium-channel blockers and β-blockers [1]. However, even their intensive use is not highly effective in preventing SA [2]. Currently, N-(2-6-dimethylphenyl)-4(2-hydroxy-3-[2-methoxyphenoxy]-propyl)-1-piperazineacetamidededihydrochloride (also named ranolazine), is the most potent clinical Na^+-channel blocker. It was first approved in 2006 by the US Food and Drug Administration (FDA), and in the European Union ranolazine is approved (at a maximum dosage of 750 mg twice daily) for the symptomatic treatment of patients with inadequately controlled SA in addition to other therapies, or alone in the case of intolerance to first-line therapies [3]. The aim of this review is to explore the pathophysiological mechanisms of action of ranolazine and to update evidence from recent clinical trials on its efficacy and safety in SA.

Pathophysiology of stable angina

SA is defined as substernal chest discomfort with a characteristic quality and duration that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin [1]. Chronic SA is caused by myocardial ischaemia generally due to one or more significant obstructive lesions in the coronary arteries. During ischaemia the imbalance between the oxygen supplied and required by the myocardium leads to a dramatic reduction in myocardial contractility and impaired activity of ion pumps involved in myocardial contraction-relaxation processes. Ischaemia disrupts action potential physiology. An early event is the increase in intracellular $[Na^+]$ [4], mainly induced by an increase in the late Na^+ current (I_{Na}) [5], but also by Na^+/H^+ exchanger activation and Na^+/K^+ adenosine triphosphatase (ATPase) inhibition. The late I_{Na} delays repolarisation by increasing action potential duration. Moreover, an elevated $[Na^+]$ adversely affects cellular pathways of Ca^{++} transportation. The $[Ca^{++}]$ is mainly regulated by the Na^+/Ca^{++} exchanger, which exchanges one Ca^{++} ion for three Na^+ ions per cycle and can work in both directions: in forward mode, eliminating Ca^{++} outside the cell, or in reverse mode. Ca^{++}-carrier activity and direction depend on several factors, such as membrane potential (during the action potential it usually works in reverse mode), $[Na^+]$ and $[Ca^{++}]$. When hypoxia is established, an elevated $[Na^+]$ triggers the reverse mode Na^+/Ca^{++} exchanger [6], impairing $[Ca^{++}]$ removal from the cell [7, 8]. High $[Ca^{++}]$ keeps contractile proteins active, increasing energy consumption and diastolic tone and then impairing ventricular relaxation. These pathophysiological events are major determinants of increased ventricular wall tension [9]. This process might

create a vicious circle, potentially increasing coronary vessel resistance and decreasing coronary blood flow [10].

Evidence from basic research studies on the efficacy of ranolazine in ischaemic heart disease

Ranolazine is a potent late I_{Na} inhibitor. Indeed, in the therapeutic range (2–8 µmol/l), ranolazine has an almost selective action on the late I_{Na} (about 38-fold higher than on peak I_{Na}) with concentration-, frequency-, and voltage-dependent inhibitory effects [11, 12]. The mechanism of action of ranolazine is markedly different from other antianginal drugs, such as calcium-channel blockers, β-blockers and nitrates (fig. 1). The late I_{Na} inhibition by ranolazine has been observed in myocardial models exposed to lipid peroxidation [13, 14], ischaemia-reperfusion injury [15] and palmitoyl-L-carnitine [16], and in heart failure [17, 18].

Moreover, ranolazine has been shown to decrease the variability of the action potential duration in single myocytes exposed to *Anemonia sulcata* toxin (ATX-II, known to increase late I_{Na} magnitude) [19]. Ranolazine might also interfere with Ca^{++}-dependent pathways. As mentioned above, ranolazine-induced blockade of I_{Na} keeps the Na^{++}/Ca^{++} exchange in forward mode, thus preventing Ca^{++} overload [20]. Lowering the intracellular [Ca^{++}] promotes diastolic relaxation and then reduces O_2 consumption and ATP utilisation. In addition, since ranolazine improves diastolic function and reduces wall tension, this drug might indirectly increase blood flow within the ischaemic myocardial [21, 22]. Hale and coworkers showed a protective role of ranolazine in a rabbit model of ischaemia/reperfusion injury, associated with an improvement in ejection fraction and stroke volume, and less wall motion abnormality, after reperfusion [23]. Finally, Sossalla and colleagues showed that ranolazine improves diastolic function as a result of altered [Na^{+}] and [Ca^{++}] [18] (see fig. 1).

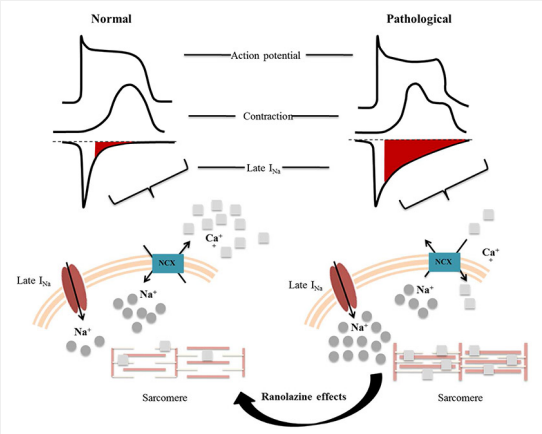

Figure 1

Abnormal function of the myocardium during ischaemia and the mechanism of action of ranolazine.

I_{Na} = late Na current; NCX = Na-Ca exchange

Ranolazine and ischaemic heart disease: evidence from clinical studies

In agreement with basic research studies, recent studies using myocardial perfusion imaging techniques confirmed that ranolazine improved coronary perfusion and oxygen supply in humans [24, 25]. Ranolazine has been extensively studied in human ischaemic heart disease, in a wide range of dosages and clinical presentations, from SA to acute coronary syndromes (ACS). The first studies, dating back to the 1990s, gave conflicting results for the small numbers of patients and low doses tested (30–60–120 mg three times daily) [26, 27]. Even the first randomised trial failed to provide definitive results, partly because the immediate-release formulation of ranolazine (at the time the only available form) was used [28, 29]. The sustained-release (SR) form of ranolazine, produced later, has been studied in several randomised, double-blind, placebo-controlled trials. These studies provided the evidence that supported the registration of ranolazine SR (Ranexa®) for clinical use in chronic ischaemic heart disease (table 1).

In the MARISA (Monotheraphy Assessment of Ranolazine in Stable Angina) trial, 191 patients with effort angina for at least 3 months (but responsive to calcium-channel blockers, β-blockers and/or nitrates) were randomised to treatment with ranolazine SR (500, 1000 or 1500 mg twice daily) or placebo. Ranolazine SR was administered as monotherapy after interruption of all other antianginal medications. After a week, the treated group reached primary endpoints: improved total exercise duration, time to onset of angina and time to ≥1 mm ST-segment depression ($p < 0.005$) at peak treadmill exercise. However, it should be noted that treatment with the higher dose of ranolazine was stopped before study end because of an increased incidence of adverse effects (such as bradycardia, hypotension and lengthening of QTc) [35].

The CARISA (Combination Assessment of Ranolazine in Stable Angina) trial investigated the effects of 12 weeks of ranolazine treatment (750 or 1000 mg twice daily), in association with other classical antianginal therapy. This placebo-controlled study enrolled 823 patients. Treatment with Ranolazine SR met the primary endpoints (i.e., increase of total exercise duration at both trough [$p = 0.03$ for 750 mg] and peak levels [$p = 0.001$ for 750 mg], increase of time to onset of angina and increase of time to ≥1 mm ST-segment depression at peak exercise [$p = 0.02$ and $p < 0.001$, respectively, for 750 mg]). A prolonged treatment duration was associated with a reduction in angina episodes and nitrate consumption ($p < 0.02$) [36]. A recent *post-hoc* analysis of the CARISA trial confirmed the effectiveness of ranolazine in symptomatic patients with SA who were also on background therapy with maximally-tolerated doses of first-line antianginal therapies [37].

The ERICA (Efficacy of Ranolazine in Chronic Angina) trial compared treatment with ranolazine with placebo in 565 patients persistently symptomatic (>3 angina attacks per week) despite a maximal dose of amlodipine. Patients were randomised to receive ranolazine SR 1000 mg twice daily or placebo for 6 weeks. The primary endpoints of this study were: decrease in angina attacks ($p = 0.02$) and

concurrently in nitrate consumption (p= 0.01) as compared with placebo [38].

The MERLIN (Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-Elevation Acute Coronary Syndrome) TIMI-36 trial was designed to prove the efficacy of ranolazine in unstable angina / non-ST-elevation acute coronary syndrome (NSTEMI-ACS). In contrast to the CARISA and ERICA trials, this study was designed to assess clinical outcomes over 1 year. The patients (n = 6,560) were randomised, within 48 hours of angina onset, to ranolazine (intravenously for the first 96 hours and then orally 1000 mg SR twice daily) or placebo treatment. Treatment was continued for a median of 348 days, in addition to standard antiangina therapy. This study did not demonstrate a beneficial effect of ranolizine on its primary composite endpoint of cardiovascular death, myocardial infarction or recurrent ischaemia. However, the incidence of recurrent ischaemia was significantly lower in the ranolazine group (p= 0.03) [30]. Subsequent *post-hoc* analyses confirmed these results. In a subgroup of patients with a previous history of chronic angina, the primary endpoints were observed less frequently in the ranolazine-treated group (hazard ratio [HR] 0.86, confidence interval [CI] 0.75–0.97; p = 0.01) compared with placebo. This effect was placed in relation to the reduction in recurrent ischaemia (HR 0.78, CI 0.67–0.91; p = 0.002). Moreover, in the ranolazine-treated group, worsening angina (HR 0.77, CI 0.59–1.00; p = 0.04) and the intensification of antianginal therapy (HR 0.77, CI 64–0.92; p = 0.005) were also reduced. In addition, treadmill exercise tests at 8 months (total exercise duration, mean time to angina onset and ≥1 mm ST-segment depression; p <0.01) were also improved [31] in the ranolazine group as compared with placebo. Furthermore, only in the subgroup of patients with previous angina, ranolazine improved health status, according to various scores [39]. In a separate analysis by gender of the MERLIN-TIMI 36 trial data, ranolazine-treated women showed a more significant reduction of recurrent ischaemia (p = 0.024), as well as fewer angina attacks (p <0.001) and reduced requests for antianginal therapy intensification (p = 0.003) [34].

In addition, treatment with ranolazine reduced the risk for primary composite endpoints (at 30 days and 1 year) in the subgroup of patients with brain natriuretic peptide (BNP) level at baseline >80 pg/ml compared with those having BNP ≤80 pg/ml [33]. Finally, a *post-hoc* analysis in the subgroup of diabetic patients showed that treatment with ranolazine significantly improved glycated haemaoglobin (HbA1c) as well as recurrent ischaemia [32].

The Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) trial is the most recent study investigating the clinical efficacy of ranolazine treatment. A total of 949 patients with diabetes, coronary artery disease and SA treated with two antianginal drugs were included in the study. After a single-blind, 4-week placebo run-in, patients were randomised to 8 weeks of treatment with ranolazine SR 1000 mg twice daily or placebo. The primary outcome was the average weekly number of angina episodes recorded by an electronic diary. The ranolazine-treated arm had a significantly lower weekly angina frequency (p= 0.008) and sublingual nitroglycerin use (p = 0.003) [40] as compared with placebo.

Ranolazine and diastolic dysfunction

The management of diastolic dysfunction represents one of the most serious challenges for the cardiologists. Treatment options are limited by lack of knowledge of the mechanisms underlying the prolonged relaxation of the myocardium. Among several potential mechanisms already identified, increased Ca^{++} current [23] and oxidative stress [19] might play a relevant role in slowing ventricular relaxation of the failing heart. Since both mechanisms are coupled with an increased I_{Na}, (which is abnormally elevated in heart failure), a pathophysiological rationale exists for the investigation of ranolazine for treating diastolic dysfunction and failure. In preclinical studies, ranolazine improved diastolic performance as monotherapy [12, 41] or in association with metoprolol [42]. Moreover, these effects were achieved without inducing a negative inotropic effect. In addition, Lovelock and coworkers recently reported that ranolazine might also have a direct effect on the contractile

Table 1: Ranolazine SR efficacy in MERLIN-TIMI 36 trial and in the subsequent *post-hoc* analyses.

Author	Year	Number of patients	Population	Treatment groups	Primary endpoint		CV death		Recurrent ischaemia	
					(%pz)	HR (95% CI)	(%pz)	HR (95% CI)	(%pz)	HR (95% CI)
Morrow et al. [30]	2007	6,560	MERLIN-TIMI 36 trial	Ranolazine vs placebo	21.8% 23.5%	0.92 (0.83–1.02) p = 0.98	4.4% 4.5%	1.00 (0.79–1.25) p = 0.98	13.9% 16.1%	0.87 (0.76–0.99) p = 0.03
Wilson et al. [31]	2009	3,565	Prior chronic angina in MERLIN-TIMI 36 trial	Ranolazine vs placebo	25.2% 29.4%	0.86 (0.75–0.97) p = 0.017	11.9% 12.5%	0.97 (0.80–1.16) p = 0.71	16.5% 21.1%	0.78 (0.67–0.91) p = 0.002
Morrow et al. [32]	2009	2,220	Diabetic population in MERLIN-TIMI 36 trial	Ranolazine vs placebo	– –	1.09 (0.86–1.38) p = 0.46	– –	0.76 (0.41–1.39) p = 0.37	15.1% 19.2%	0.75 (0.61–0.93) p = 0.008
Morrow et al. [33]	2010	1,935	BNP >80 pg/ml in MERLIN-TIMI 36 trial	Ranolazine vs placebo	23% 29%	0.79 (0.66–0.94) p <0.05	7.1% 8.9%	0.83 (0.66–1.05) p >0.05	14.3% 18%	0.78 (0.62–0.98) p <0.05
Mega et al. [34]	2010	2,291	Women in MERLIN-TIMI 36 trial	Women vs men	23.9% 22.1%	0.83 (0.10–0.99) p <0.05	5.3% 4%	0.97 (0.68–1.39) p >0.05	15.7% 14.6%	0.71 (0.57–0.88) p = 0.002

Primary endpoint: composite endpoint of cardiovascular death, myocardial infarction or recurrent ischaemia.
%pz = incidence; BNP: brain natriuretic peptide; CI = confidence interval; CV = cardiovascular; HR: hazard ratio

apparatus through the modulation of myofilament Ca^{++} sensitivity [43]. Twenty years ago, Hayashida and coworkers showed an improvement of diastolic function in human noninfarcted ischaemic hearts [44]. Similarly, two other studies showed the beneficial effects of ranolazine in improved left ventricular diastolic dysfunction [22] and dyssynchrony [45]. Based on these findings, the Ranolazine in Diastolic Heart Failure (RALI-DHF) trial (NCT01163734) was designed as a prospective, single-centre, randomised, double-blind, placebo-controlled proof-of-concept study, in order to investigate the effectiveness of ranolazine in improving diastolic dysfunction in patients with heart failure with preserved ejection fraction. Twenty patients were randomised to receive ranolazine or placebo (12 patients receiving ranolazine vs 8 patients treated with placebo). The treatment schedule consisted of an intravenous infusion of the study drug or placebo for 24 hours, followed by oral treatment for a total of 14 days [46]. Treatment with ranolazine improved haemodynamic measurements (left ventricular end-diastolic pressure and pulmonary capillary wedge pressure), but relaxation parameters remained unaltered as compared with the placebo group [47]. Therefore, the RALI-DHF study failed to bridge the gap between evidence from basic studies of ranolazine and human treatment.

Potential antiarrhythmic role of ranolazine treatment

Ranolazine appears to have potential effects on myocardial conduction activity and related metabolic pathways. The increase in late I_{Na} might directly affect myocyte electrophysiology, lengthening the action potential and hence increasing transmural dispersion of repolarisation and the QT interval [48]. At the same time, the induction of intracellular Ca^{++} overload can give rise to a delayed after-depolarisation [49]. These abnormalities might predispose to the onset of ventricular arrhythmias, especially "torsades de pointes". Ranolazine might reduce the transmural and temporal dispersion of repolarisation, which are proarrhythmic triggers [50]. These effects were shown in several animal models, especially in suppressing arrhythmogenic potential in long QT3 syndrome (where a mutation in the Na^+ channel induces an I_{Na}) [51–53] and also in a pilot study in human beings [54]. In the framework of the MERLIN-TIMI 36 trial, the potential antiarrhythmic effects of ranolazine were shown for the first time (although only as a safety and not as a primary endpoint). A reduced incidence of ventricular/supraventricular tachycardia ($p<0.001$) and, especially, atrial fibrillation ($p= 0.01$) were observed in the ranolazine groups as compared with placebo [55]. The therapeutic benefits of the blockade of I_{Na} peak in the setting of atrial fibrillation were widely recognised [56]. This action is largely due to a rate-dependent reduction of excitability, prolongation of the effective refractory period (secondary to the development of postrepolarization refractoriness), and blockade of conduction in a critical part of the reentrant circuit. Reduction of I_{Na} peak can also significantly decrease intracellular [Na] and, thus, Ca^{++} overload-mediated triggered activity. Recently, Milber and coworkers reported that ranolazine-related Na^+-channel blockade also suppresses stretch-induced atrial fibrillation by increasing the interatrial conduction time and atrial postrepolarisation refractoriness [57].

Accordingly, the impact of ranolazine in prevention and treatment of atrial fibrillation was investigated as a primary endpoint in clinical trials that showed ranolazine was effective as maintainance therapy [58] as well as a "pill-in-the-pocket" strategy [59]. Ranolazine has been shown to favour successfully electrical cardioversion [60]. A clinical trial investigating this primary endpoint was recently finished and results will be available soon, potentially clarifying this issue (Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion [RAFFAELLO]) [61].

Importantly, class-III antiarrhythmic drugs were not superior to ranolazine in preventing atrial fibrillation in patients after coronary artery bypass surgery [62] or coronary revascularisation surgery [63]. Amiodarone plus ranolazine resulted in a significantly higher conversion rate of new-onset atrial fibrillation than amiodarone alone in both experimental models [64] and in humans [65]. Finally, a sponsored trial to assess a ranolazine-dronedarone combination versus dronedarone alone in paroxysmal atrial fibrillation was recently approved [66]. The results of this study will be available in the near future.

Conclusions

As was the case with treatments for ACS [67, 68], the development of new drugs might provide additional therapeutic options in the treatment of SA. Compared with the other drugs, ranolazine provides an anti-ischaemic effect without haemodynamic changes such as bradycardia or hypotension. This allowed the safe use of ranolazine in addition to other drug classes, improving control of anginal symptoms and representing a useful option in the presence of several comorbidities such as diabetes. Treatment with ranolazine was shown to be generally well tolerated, although it remains contraindicated in severe renal failure or moderate to severe hepatic impairment, and also has potential drug interactions through CYP450 enzymes [3]. The strength of the data reported from different clinical trials and the good pharmacological profile might suggest a potential extension of the use of ranolazine for the treatment of SA. Furthermore, it has been reported that treatment with ranolazine might be cost effective, since a better outcome brings lower costs of care [69]. On the other hand, additional data are needed potentially to recommend the use of ranolazine in the treatment of arrhythmias and heart failure. If the preliminary data discussed above are confirmed, we might have a single drug (ranolazine) that is effective on different aspects (both electrical and mechanical dysfunction) in SA, potentially improving patient quality of life and healthcare costs.

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Figures (large format)

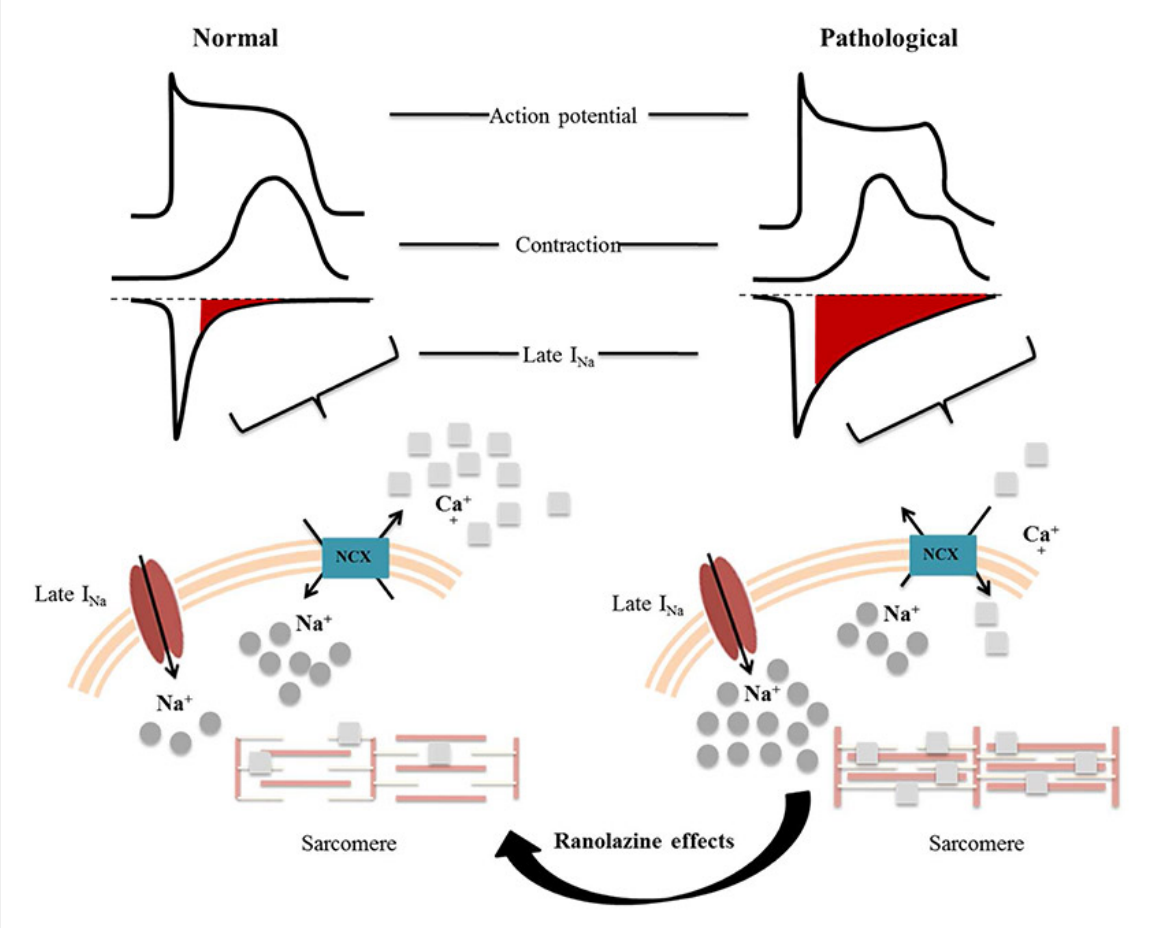

Figure 1

Abnormal function of the myocardium during ischaemia and the mechanism of action of ranolazine.
I_{Na} = late Na current; NCX = Na-Ca exchange