REVIEW

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Mechanism of action of the new anti-ischemia drug ranolazine

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■ **Abstract** Myocardial ischemia is associated with reduced ATP fluxes and decreased energy supply resulting in disturbances of intracellular ion homeostasis in cardiac myocytes. In the recent years, increased persistent (late) sodium current was suggested to contribute to disturbed ion homeostasis by elevating intracellular sodium concentration with subsequent elevation of intracellular calcium. The new anti-ischemia drug ranolazine, a specific inhibitor of late sodium current, reduces sodium overload and hence ameliorates disturbed ion homeostasis. This is associated with symptomatic improvement of angina in patients. Moreover, ranolazine was shown to exhibit anti-arrhythmic effects. In the present article, we review the relevant pathophysiological concepts for the role of late sodium inhibition and summarize the most recent data from basic as well as clinical studies.

■ **Key words** angina – ischemia – sodium current – calcium overload

Current therapeutic strategies

According to the 2006 guidelines of the European Society of Cardiology [16], therapeutic goals of medical treatment of coronary heart disease can be partitioned into (1) immediate short-term relieve, (2) treatment aimed at relieve of symptoms, and (3) treatment aimed at improving prognosis. Interestingly, there is no overlap between drugs that improve prognosis and drugs that relieve symptoms with the exception of β-blockers after myocardial infarction. This suggests that ischemia which causes symptoms may not be a major mechanism relevant to prognosis, whereas mechanisms which influence thrombocyte function and anti-inflammatory or cytokine-neuro-humoral actions may be beneficial for survival.

Current strategies of drug-induced relieve of symptoms aim to improve the imbalance between oxygen supply of the heart and oxygen demand which is relevant to myocardial ischemia and angina pectoris [16]. All agents in this category: β-blockers, calcium channel antagonists, nitrates, K-channel openers, and sinus node inhibitors reduce myocardial oxygen demand. This occurs either by direct myocardial effects or indirectly by complex effects on hemodynamic determinants [13]. Calcium channel antagonists, nitrates, and K-channel openers in
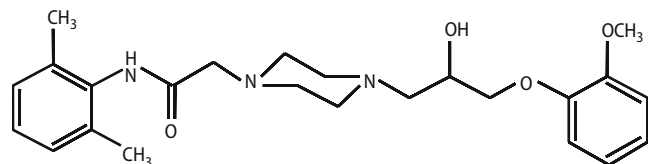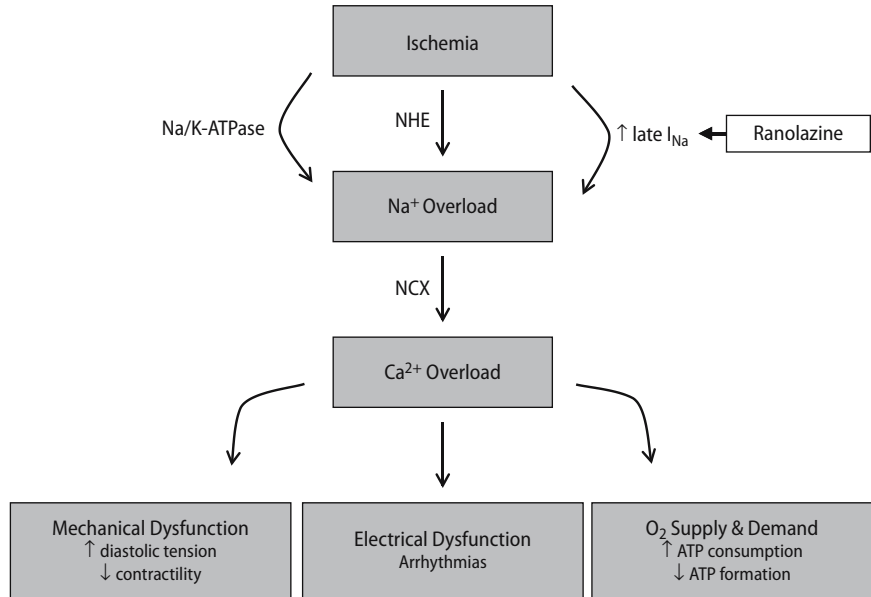

Fig. 1 Ranolazine, structure

Fig. 2 Scheme for the pathophysiology of myocardial ischemia and the role of late I$_{Na}$ inhibition with ranolazine


addition may improve blood flow and thus oxygen supply to the heart.

Ranolazine (Fig. 1), a piperazine derivative, is a new anti-ischemic drug for the treatment of angina, whose mode of action is different from the pharmacological principals mentioned above [3].

Pathophysiology of myocardial ischemia relevant to the action of ranolazine

Myocardial ischemia immediately results in reduced ATP fluxes and reduced energy supply to various key proteins for the contraction–relaxation cycle of the individual cardiac myocyte. These include proteins which control myocyte ion homeostasis. As a consequence, intracellular sodium, and calcium concentration are disturbed, which is relevant to myocardial damage following ischemia.

There are several mechanisms by which energy lack increases intracellular sodium (Fig. 2). A large portion of the sodium enters the cell through the cardiac sodium channel following depolarisation during the initial phase (fast upstroke) of the action potential. This sodium influx causes further rapid
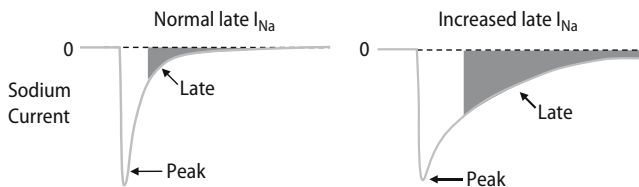
Fig. 3 Late I$_{Na}$ under normal and increased late I$_{Na}$ under pathophysiological conditions

depolarisation leading to the activation of voltage-gated L-type calcium channels causing calcium influx. Sodium channels spontaneously inactivate quickly within one to three milliseconds. Channels recycle and may be activated by the next membrane depolarisation [8, 22]. It has been shown that this typical fast sodium current may be altered during pathological conditions such as hypoxia, exposure to ischemic metabolites and reactive oxygen species. Under those conditions, there is a pronounced late opening of the sodium channel up to a few hundreds of milliseconds following depolarisation referred to as late (or persistent) sodium current (late I$_{Na}$, Fig. 3) [14, 28, 30, 31]. Late I$_{Na}$ may represent a major source for increased intracellular sodium during ischemia. Other mechanisms leading to disturbed sodium balance include sodium influx through the sodium-proton pump [7] or lack of sodium elimination through the sodium potassium ATPase.

Energy lack and the resulting decrease in the phosphorylation potential reduce free energy available for calcium transport into the sarcoplasmic reticulum and therefore intracellular calcium accumulates in the cytosol. As a consequence, elevated diastolic calcium levels activate contractile proteins even during diastole leading to diastolic dysfunction. Disturbed sarcoplasmic reticulum calcium accumulation is severely aggravated by elevated intracellular sodium. This mainly occurs through the sarcolemmal sodium–calcium exchanger, which exchanges one calcium ion for three sodium ions per cycle. The sodium–calcium exchanger can work in two different directions. In its forward mode, it eliminates calcium outside of the cell to accomplish diastolic relaxation (in addition to calcium reuptake into the sarcoplasmic reticulum). In its

reverse mode (usually during the action potential), it brings in calcium into the cell in exchange to trans-sarcolemmal elimination of sodium. The activity and direction of transport depends on the abundance of the protein as well as on the membrane potential, intracellular sodium and intracellular calcium concentration. Sodium accumulation following myocardial hypoxia (i.e., through late I_{Na}) promotes reverse mode sodium–calcium exchange and therefore reduces the overall cellular capacity to eliminate calcium outside of the cytosol. This adds to the elevated diastolic calcium due to reduced sarcoplasmic reticulum calcium pump activity and further aggravates diastolic dysfunction due to contractile protein activation. Diastolic activation of contractile proteins is associated with extra energy consumption [17]. Moreover, increased diastolic tone increases micro-circulatory resistance and further impairs energy balance of the ischemic myocardium. Therefore, diastolic dysfunction following myocardial ischemia increases energy consumption and aggravates disturbed energy balance like a vicious cycle.

Ranolazine has been shown to be a potent inhibitor of late I_{Na} and therefore interrupts a major step in the pathophysiology of myocardial ischemia [1].

Mode of action of ranolazine

In myocytes from dog and guinea pig hearts, ranolazine was shown to cause a concentration, voltage, and frequency-dependent inhibition of late I_{Na} [1]. Ranolazine also was shown to prevent H_2O_2 induced increase in late I_{Na} [25]. Most specifically, ranolazine has been shown to reverse the sustained rise in diastolic and systolic calcium caused by a well-known enhancer of late I_{Na}, the sea anemone toxin ATX-II [10, 26]. Taken together, the major mechanism of action of ranolazine is to inhibit late I_{Na} thus preventing sodium overload of the cell. As a consequence, ranolazine prevents reverse mode sodium–calcium exchange and thus diastolic accumulation of calcium possibly resulting in improved diastolic tone [12, 27] and improved coronary blood flow [10]. Accordingly, ranolazine has been shown to decrease post-ischemic contracture in rabbit isolated perfused hearts subjected to ischemia and reperfusion [11].

As a late I_{Na} inhibitor, ranolazine was also shown to increase action potential duration and thus modestly QT interval by 2–5 ms [5, 6]. This effect, however, is not heart rate-dependent and cannot be exaggerated during bradycardia [2, 19, 32]. Furthermore, ranolazine does not induce early after depolarisations and does not increase dispersion of repolarisation across the left ventricular wall [2]. According to this profile ranolazine does not increase the risk of Torsade de pointes tachycardia as it is observed with many other QT interval prolonging agents.

Clinical effects of ranolazine

Ranolazine has yet been studied in several clinical trials. Three initial trials have investigated the efficacy of immediate release ranolazine [9, 20, 23]. Two larger phase three studies have examined the efficacy of sustained release ranolazine in patients with chronic stable angina. MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) randomised 191 patients to placebo or ranolazine in a cross-over design with 1 week treatment period [6]. CARISA (Combination Assessment of Ranolazine in Stable Angina) randomised patients to placebo or ranolazine on top of previous anti-anginal therapy. Treatment was maintained for 12 weeks [5]. MARISA showed that ranolazine monotherapy significantly improved exercise performance in patients with stable angina. This was true for exercise duration, time to angina and time to 1 mm ST segment depression. More specifically, 70% of patients in the placebo group stopped their exercise test because of angina as compared to only 52% in the ranolazine group (1.5 g bidaily). CARISA improved peak and trough exercise duration, time to angina and time to 1 mm ST depression. These effects were sustained through a 12-week treatment. Also, ranolazine reduced the number of angina attacks from a baseline of 4.5 per week to 2.1 per week for ranolazine (1 g bidaily) compared to 3.3 per week for placebo. Most importantly, the anti-anginal effects of ranolazine in MARISA and CARISA occurred without clinical meaningful changes in heart rate or blood pressure.

In the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndrome) TIMI-36 trial, the effect of clinical outcome of ranolazine therapy was studied in patients with acute coronary syndromes [18]. MERLIN was a multi-national, double-blind, randomised, placebo-controlled, parallel-group clinical trial designed to evaluate the efficacy and safety of ranolazine during acute and long-term treatment in 6560 patients with non-ST elevation ACS treated with standard therapy. Within 48 h of the onset of angina due to ACS, eligible hospitalised patients were enrolled in the study and randomised to receive intravenous ranolazine or placebo, followed by long-term treatment with ranolazine tablets or placebo. Although ranolazine did not significantly influence the primary combined endpoint of cardiovascular death, myocardial infarction or recurrent ischemia, additional analyses revealed a 13% relative reduction in the risk of recurrent ischemia. Furthermore, ranolazine was favourable regarding

safety endpoints. In particular potential antiarrhythmic effects of ranolzine became apparent [24]. This underlines experimental data [4]. Thus inhibition of late I_{Na} with ranolazine is safe in particular regarding electrophysiological aspects. Although the results of MERLIN do not support the use of ranolazine for acute management of ACS these findings support previous finding regarding safety and benefit of ranolazine as an antianginal therapy and suggest a benefit of ranolazine as antianginal therapy in a broad population of patients with established ischemic heart disease.

Future aspects for clinical application for ranolazine

Inhibition of enhanced late I_{Na} by ranolazine may represent a new treatment option for cardiac diseases associated with disturbed myocardial ion homeostasis. Elevated intracellular sodium has been observed in human heart failure and in several animal failure models [15, 21]. It has been shown recently that increased intracellular sodium in heart failure may, in part, result from CaMKII-dependent phosphorylation of sodium channels with subsequent increase in late I_{Na} [29]. Therefore, ranolazine may be an interesting approach for the treatment of systolic heart failure by improving disturbed sodium homeostasis. Moreover, calcium overload subsequent to disturbed sodium homeostasis may also be a major pathophysiological factor in diastolic heart failure. Therefore we speculate that in diastolic heart failure due to disturbed sodium/calcium homeostasis, ranolazine may represent a new attractive treatment option. Accordingly, studies in heart failure with systolic and diastolic dysfunction are warranted to test the potential therapeutical benefit of ranolazine.

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