Journal of Molecular and Cellular Cardiology 61 (2013) 44–50

Contents lists available at SciVerse ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

The late Na current as a therapeutic target: Where are we?

Lars S. Maier *, Samuel Sossalla

Abt. Kardiologie und Pneumologie/Herzzentrum, Deutsches Zentrum für Herzkreislaufforschung, Georg-August-Universität, Göttingen, Germany

ARTICLE INFO

Article history:
Received 11 January 2013
Received in revised form 26 February 2013
Accepted 4 March 2013
Available online 13 March 2013

Keywords:
$I_{Na,late}$
Ischemia
Angina
Heart failure
Arrhythmias
Ranolazine

ABSTRACT

In this article we review the late Na current which functionally can be measured using patch-clamp electrophysiology ($I_{Na,late}$). This current is largely enhanced under pathological myocardial conditions such as ischemia and heart failure. In addition, $I_{Na,late}$ can cause systolic and diastolic contractile dysfunction via a Na-dependent Ca-overload of the myocyte. Moreover, $I_{Na,late}$ plays a crucial role as ventricular and atrial proarrhythmic substrate in myocardial pathology by changing cellular electrophysiology. We summarize recent experimental and clinical studies that investigate therapeutic inhibition of this current and discuss the significance of the available data and try to answer not only the question, where we currently are but also where we may go in the near future. This article is part of a Special Issue entitled "Na^+ Regulation in Cardiac Myocytes".

Contents

1. Introduction

Sarcolemmal Na channels are responsible for the cardiac Na current (I_{Na}). Na channels mainly open transiently and are quickly inactivated thereby carrying the large peak Na current ($I_{Na,peak}$) which initiates the well-known steep upstroke of the action potential (AP). A small component of I_{Na} was named persistent or late Na current ($I_{Na,late}$) because of Na channels that remain active, inactivate with slower kinetics, or even reopen. The amplitude of $I_{Na,late}$ is very small compared to the $I_{Na,peak}$ in normal myocardium (~0.5% of $I_{Na,peak}$) [1] but may persist for hundreds of milliseconds. Coraboeuf et al. measured APs in dog Purkinje fibers and found that tetrodotoxin (TTX) abbreviated these at concentrations lower than those at which the maximum rate of AP upstroke decreased [2]. This finding leads them to conclude that this current "flows through a background Na conductance or/and a small proportion of Na channels with no inactivation mechanism (or inactivation mechanism different from normal)" which means that these authors discovered $I_{Na,late}$ [2]. Moreover, also in 1979 Attwell and coworkers described an $I_{Na,late}$ in their experiments as a current which extends to potentials well into the range of the action potential plateau and elegantly concluded: "Consequently small changes of the steady state I_{Na} might have large effects on the action potential duration" [3].

Since then, $I_{Na,late}$ was found to be elevated under several cardiac pathological conditions [4–7] and it was suggested that this may lead to intracellular Na-overload [8–10]. In addition, $I_{Na,late}$ can be

* Corresponding author at: Abt. Kardiologie und Pneumologie/Herzzentrum, Deutsches Zentrum für Herzkreislaufforschung, Georg-August-Universität Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany. Tel.: +49 551 39 6372; fax: +49 551 39 14131.
E-mail address: lmaier@med.uni-goettingen.de (L.S. Maier).

0022-2828 © 2013 Elsevier Ltd. Open access under CC BY-NC-ND license.
http://dx.doi.org/10.1016/j.yjmcc.2013.03.001

induced by several peptides, chemicals, and oxygen free radicals that slow the rate of I_{Na} inactivation [7,11–13]. Interestingly, mutations in the Na channel gene SCN5A which is associated with the long QT-3 syndrome produce slowed inactivation thereby increasing $I_{Na,late}$ [14]. Most importantly and of clinical relevance are disease states such as hypoxia, ischemia/reperfusion, myocardial infarction, and heart failure that were shown to be associated with an elevated $I_{Na,late}$ [4,15,16]. Almost fifteen years ago, Ahern and colleagues have shown that nitrosylation of SCN5A increases $I_{Na,late}$ under physiological and pathophysiological conditions [17]. Over the last few years, Ca/calmodulin-dependent kinase II (CaMKII) was found to associate and phosphorylate the cardiac Na channel which is critically involved in Na channel gating, e.g. by increasing $I_{Na,late}$ [18–22]. Interestingly, CaMKII activation occurs in a couple of myocardial pathological conditions where $I_{Na,late}$ is also elevated (e.g. heart failure and atrial fibrillation) [23]. (For the details of the molecular mechanisms underlying the origins of the $I_{Na,late}$ see review by Moreno and Clancy [24]).

In addition to the toxin TTX [25], the clinically approved anti-ischemic drug ranolazine was found to inhibit $I_{Na,late}$ [26]. In cardiac myocytes from dogs and guinea pigs, ranolazine caused a concentration-, voltage-, and frequency-dependent $I_{Na,late}$ inhibition [27]. It was suggested that ranolazine binds at the putative local anesthetic binding site of the cardiac specific Na channel isoform $Na_v1.5$ [14]. But it remains unclear how this compound produces its selectivity on $I_{Na,late}$. Inhibitory effects of ranolazine on $I_{Na,late}$ were demonstrated in multicellular myocardium and in isolated myocytes [11,13,28]. Ranolazine has also weak $I_{Na,peak}$ inhibiting effects, however with up to 38-fold higher potency for $I_{Na,late}$ than $I_{Na,peak}$ with an IC_{50} of 6.5 vs. 244 μM in dog ventricular myocytes [28]. Ranolazine was also shown to have some weak inhibitory effects on the peak and late L-type Ca current with an IC_{50} of 296 μM and 50 μM, respectively [27]. Within the therapeutic concentration range which varies between 2 and 8 μM, ranolazine inhibits the late L-type Ca current by 25–30% but at 10 μM by ~70% [27]. Thus, this could amount to non-negligible reduction in the net Ca inflow during the action potential and hence has to be taken in account with respect to antiischemic, antiarrhythmic, and effects on the failing myocardium of ranolazine. Finally, ranolazine may also have beneficial effects on $Na_v1.5$ since it was very recently shown that it inhibits stretch-induced modulation of $Na_v1.5$ [29,30].

There are also other drugs that can preferentially inhibit $I_{Na,late}$ such as the class I antiarrhythmic drugs lidocaine, mexiletine, and flecainide, and the class III antiarrhythmic drug amiodarone [31]. Recently, a novel potent and selective inhibitor $I_{Na,late}$ GS967 (6-[4-(trifluoromethoxy)phenyl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a] pyridine) was described which is currently further investigated experimentally and possibly soon clinically. F 15845 is another new compound which selectively inhibits $I_{Na,late}$ as shown by measurements in HEK293 cells [32].

2. $I_{Na,late}$ in myocardial ischemia

An accumulation of metabolites such as palmitoyl-L-carnitine, lysophosphatidylcholine, and reactive oxygen/nitrogen species occurs during myocardial ischemia and reperfusion thereby increasing $I_{Na,late}$ [5,6] thus causing intracellular Na overload [9,13]. Inhibition of $I_{Na,late}$ reduces the rise in $[Na]_i$ [12,13]. Usually, elevated Na levels lead to intracellular Ca overload due to reduced efflux of Ca-ions through the forward mode of the Na/Ca-exchanger (NCX) and/or a larger influx of Ca-ions through the reverse mode of the NCX. In addition to changes in $[Na]_i$ and $[Ca]_i$, the NCX also produces an electrogenic current and hence generates an electrical potential because three Na ions are exchanged for each Ca ion [33]. Na accumulation and prolonged AP duration are known to be potent triggers of reverse mode NCX which occurs during myocardial hypoxia [8]. The result is an impaired overall capacity of the cell to eliminate Ca. This leads to contractile protein activation and hypercontraction of cardiac myocytes [34]. As a result, increased wall tension occurs which induces compression of intramural vessels leading to impaired oxygen supply (see Fig. 1) [35].

The majority of experimental studies that investigated the relevance of $I_{Na,late}$ modulation with respect to myocardial ischemia are derived from experiments using ranolazine. Ranolazine and TTX reverse the rise in $[Na]_i$ caused by simulated ischemia, ATX-II and oxygen free radicals [12,13,36]. Moreover, inhibition of $I_{Na,late}$ reduces reverse mode NCX and consequently diastolic Ca accumulation during ischemia/reperfusion and in the presence of ischemic metabolites, ATX-II, and reactive oxygen species [12,13,37]. The net result is an improved diastolic function [13,38–41]. A recent clinical study investigated ranolazine in patients with coronary heart disease subjected to quantitative analysis of serial myocardial perfusion images and found a reduced perfusion defect sizes during exercise and thus improved myocardial perfusion [42]. A reduced diastolic wall tension is regarded to decrease oxygen consumption and ATP utilization due to reduced myofilament activity and lower diastolic Ca levels. Ranolazine has been shown to counteract the decrease in tissue ATP in an isolated rabbit heart model of ischemia/reperfusion [43]. This observation was paralleled by an improved LV pressure, reduced release of creatine kinase, and less reperfusion injury.

The safety and efficacy of ranolazine are well investigated and its use as an antianginal agent was clinically established. An early study compared atenolol and ranolazine in patients who had limited exercise capacity due to symptomatic angina pectoris in a randomized double-blind, placebo-controlled crossover study [44]. Treatment with ranolazine or atenolol improved time onset of angina and ST-segment depression. In addition, ranolazine increased exercise duration compared to atenolol. Unlike atenolol, the effects of ranolazine occurred without changes of the rate-pressure product indicating that the antiischemic effect of ranolazine does not depend on a decrease in cardiac work. Further studies such as MARISA, CARISA und ERICA were performed in order to investigate the sustained release formulation of ranolazine (for review see [26]).

The MERLIN TIMI-36 trial investigated the effect of clinical outcome and safety of ranolazine therapy in >6000 acute coronary syndrome (ACS) patients [45]. Treatment with ranolazine did not significantly reduce the composite primary combined endpoint of cardiovascular death, myocardial infarction, or recurrent ischemia. Nevertheless,

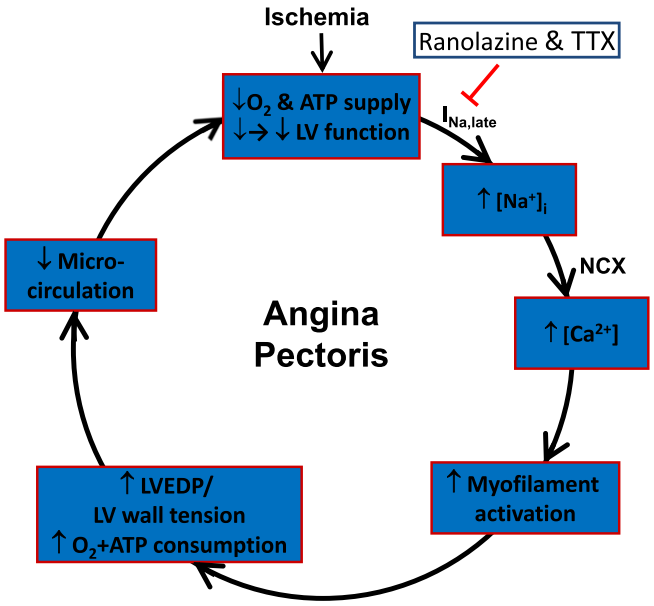

Fig. 1. Vicious circle of myocardial ischemia with a focus on $I_{Na,late}$: Ischemia enhances $I_{Na,late}$ which increases intracellular Na^+ and Ca^{2+} via Na^+/Ca^{2+} exchanger (NCX). As a consequence, Ca ions overactivate myofilaments which aggravates myocardial ischemia. Blockers of $I_{Na,late}$ are capable to attenuate this pathological cascade.

separate analyses revealed a 13% relative reduction in the risk of recurrent ischemia. Although the findings of MERLIN do not indicate the use of ranolazine for acute management of ACS patients the results demonstrate safety and underline the benefit of ranolazine as an antianginal agent for a broad population of patients with angina pectoris.

3. Contractile dysfunction — heart failure

Cellular Na and Ca handling is important for the regulation of myocardial contractile function. An excessive accumulation of intracellular Ca is known to induce diastolic and systolic dysfunction. Ca overload can be linked to an elevation of $[Na]_i$ caused in part by an enhanced $I_{Na,late}$. Indeed, $I_{Na,late}$ has been shown to be largely elevated in the pathology of heart failure [15,18,41,46,47]. Therefore, it was hypothesized that the inhibition of this current attenuates LV mechanical dysfunction (systolic and diastolic) in the failing heart by a similar mechanism as it is explained above for myocardial ischemia.

Two experimental studies report on beneficial effects of $I_{Na,late}$ inhibition using ranolazine in vivo in canine heart failure models. In dogs with coronary microembolization-induced heart failure acute infusion of ranolazine reduced LVEDP but increased LV ejection fraction and stroke volume [48]. In the same model, ranolazine was investigated as a chronic treatment option in combination with metoprolol or enalapril [40]. Ranolazine prevented progressive LV dysfunction as well as global and cellular myocardial remodeling. In combination with enalapril or metoprolol ranolazine improved LV function beyond that observed with ranolazine alone.

We examined isolated myocardial trabeculae from human end-stage failing hearts that exhibited frequency-dependent diastolic dysfunction [13] (see Fig. 2). Ranolazine did not cause negative inotropy but reduced the increase in diastolic tension, i.e. improved diastolic dysfunction. In a non-ischemic heart failure model we isolated papillary muscles from transgenic mice overexpressing CaMKII [49]. Exposure to ranolazine markedly reduced present diastolic dysfunction under frequency-induced stress suggesting that CaMKII which can induce $I_{Na,late}$ may be activated by increased Ca levels (and hence Ca overload) [13,41]. Indeed, the direct effects of CaMKII on Na channels (and thus $I_{Na,late}$) were reported previously [18] and even effects of reactive oxygen species on $I_{Na,late}$ were shown to be mediated by CaMKII [50].

The underlying mechanism causing improved contractile function in heart failure due to inhibition of $I_{Na,late}$ was investigated in isolated cardiomyocytes which were exposed to ATX-II [13]. The increase in cytosolic Na was paralleled by an elevated diastolic [Ca]. Treatment with ranolazine attenuated the effects of ATX-II leading to markedly reduced diastolic Ca levels and lower Na levels. We consider an increase in NCX forward mode as the link between cytosolic Na and Ca. However, there is a need for future studies that should investigate the influence of $I_{Na,late}$ modulation on NCX function and transport direction especially in cardiac pathology. Our findings with respect to improved diastolic function are consistent with the studies in animals showing that ranolazine attenuates diastolic dysfunction during ischemia/reperfusion [37,43], in the presence of ischemic metabolites [51], or reactive oxygen species [52], and in dogs with heart failure [28]. In summary, most of the experimental studies in heart failure models report on beneficial effects on diastolic performance than on positive inotropic effects.

In contrast to the large experimental knowledge, clinical investigations on $I_{Na,late}$ in patients suffering from heart failure are limited. In 1994, there was a first in vivo study showing an improved diastolic function in non-infarcted ischemic hearts in 15 patients before and in

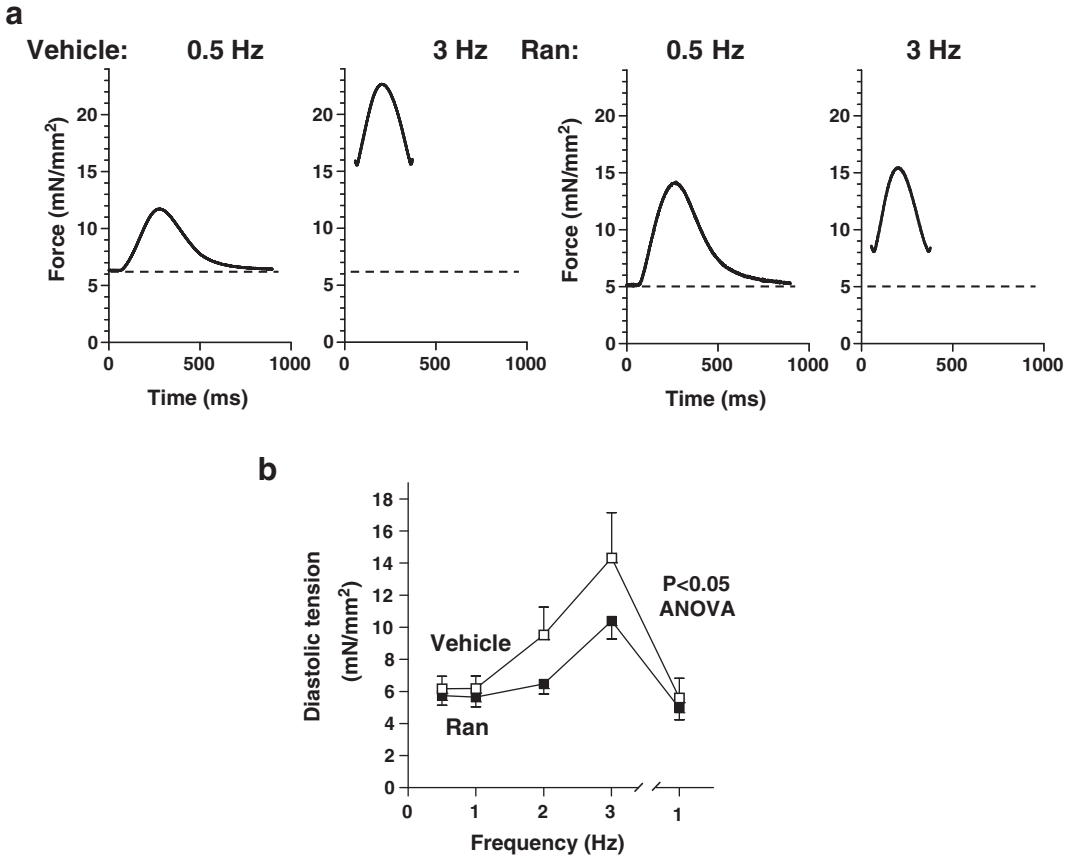

Fig. 2. Improvement of diastolic function in human failing myocardium: Effects of 10 μmol/L ranolazine (Ran) on diastolic tension during stepwise increases in stimulation rate in muscles from end-stage failing human hearts. (a) Original recordings of force at 0.5 and 3 Hz during control conditions (vehicle, left panels) and in the presence of ranolazine (right panels). (b) Mean data for diastolic tension (n = 14 each), p<0.05 (ANOVA).
Modified from Sossalla et al., JMCC, 2008

the presence of intravenous application of ranolazine [53]. Moreover, acute infusion of ranolazine in patients with type-3 long-QT syndrome where $I_{Na,late}$ is increased caused an improvement in diastolic relaxation [54]. We performed the first prospective, randomized, double-blind, placebo-controlled small proof-of-concept study in 20 patients with diastolic heart failure and showed that ranolazine improved measures of hemodynamics including LVEDP and PAP, but there was no improvement in relaxation parameters [55]. Coppini and coworkers recently investigated functional changes in myocardium from human hypertrophic cardiomyopathy, showing a complex remodeling process involving alterations of CaMKII-dependent signaling, rather than being a direct consequence of the causing sarcomeric mutations [56]. They found an enhanced $I_{Na,late}$ to be a major contributor to the electrophysiological abnormalities of ventricular myocytes and trabeculae from these patients, suggesting a potential therapeutic role of $I_{Na,late}$ inhibition. These findings are the basis for the recently initiated pilot study RESTYLE which investigates ranolazine in patients with symptomatic hypertrophic cardiomyopathy with respect to exercise capacity, diastolic function, and symptomatic status (EudraCT-Nr. 2011-004507-20).

Taken together, there is an increasing evidence that the inhibition of $I_{Na,late}$ using ranolazine may have a future therapeutic role for the treatment of systolic and diastolic heart failure. Since there is not one evidence-based compound for the treatment of diastolic heart failure up to date further clinical trials are indicated to evaluate the safety and efficacy of $I_{Na,late}$ inhibition in patients with diastolic, and possibly systolic heart failure.

4. $I_{Na,late}$ and ventricular arrhythmias

An elevated $I_{Na,late}$ is potentially involved in ventricular and atrial arrhythmogenesis by changing cellular electrophysiology. Early afterdepolarizations (EADs) are more likely to occur during a prolonged AP as a possible consequence of increased $I_{Na,late}$ [11]. Transmural differences of $I_{Na,late}$ and hence AP duration might increase dispersion of repolarization and QT interval, which underlies the development of torsade de pointes tachyarrhythmias [57].

Independent of AP prolongation, Ca overload resulting from elevated $I_{Na,late}$ [13], and leakiness of the ryanodine receptor are believed to participate as crucial events in the initiation and propagation of spontaneous SR Ca release events [33]. The consequence may be the elimination of cytosolic Ca via NCX which generates a depolarizing current (transient inward current, I_{Ti}) giving rise to delayed afterdepolarizations (DADs) [58]. The crucial importance of $I_{Na,late}$ for arrhythmias was demonstrated in guinea pig myocytes [59]. An increased $I_{Na,late}$ leads to development of EADs and DADs as well as triggered activity through I_{Ti}. These effects could be suppressed by ranolazine or TTX. Ca chelating agents, NCX blockers and the SR Ca release inhibitor ryanodine could prevent DADs and triggered activity. Since EADs could not be prevented using these agents, it is suggested that the prolongation of AP causes EADs in a Ca-independent manner.

There are several reports showing potent antiarrhythmic effects of $I_{Na,late}$ inhibition in ventricular cardiomyocytes and tissue. Ranolazine has demonstrated striking effects on afterdepolarizations as arrhythmic triggers and the transmural and temporal dispersion of repolarization in models with elevated $I_{Na,late}$ [11,28,60,61]. Ranolazine prevented pacing-induced re-entrant and multifocal ventricular fibrillation [62].

Ranolazine also inhibits I_{Kr} [27] which causes alone a prolongation of the ventricular AP, whereas the inhibition of $I_{Na,late}$ has the opposite effect and abbreviates AP. Thus, the net effect of ranolazine on AP duration is driven by the relative magnitude of $I_{Na,late}$ (inward) and I_{Kr} (outward) currents during the repolarization period. Ranolazine inhibits I_{Kr} with a potency of ~11.5 μM, but only weakly interacts with I_{Ca} (~300 μM) or NCX (~90 μM) [27]. Therefore, we consider $I_{Na,late}$ as the major target of ranolazine for the prevention and termination of ventricular arrhythmias. Of note, another new antiischemic compound F 15845 which blocks $I_{Na,late}$ was effective at preventing fatal ventricular fibrillation and ventricular tachycardia during coronary ligation [32].

Interestingly, there are studies showing antiarrhythmic effects of ranolazine under conditions without elevated $I_{Na,late}$ as it was shown for I_{Kr} blocker-induced arrhythmogenic triggers and arrhythmias [27,63–65]. $I_{Na,late}$ is largest in midmyocardial myocytes, that can be characterized by having APs that prolong disproportionately compared to the APs of other left ventricular cell types in response to many QT-prolonging drugs [66,67]. These cardiomyocytes are more likely to develop EADs in response to triggers that reduce the repolarization reserve. Accordingly, it was shown that ranolazine induces a preferential abbreviation of midmyocardial cell AP duration (where $I_{Na,late}$ is most prominent), causing a reduction in transmural dispersion of repolarization [27].

In contrast to the large number of experimental reports, there are only a few studies that investigate the antiarrhythmic potential of ranolazine in patients. Ranolazine is known to cause a slight prolongation of the QTc interval due to the inhibition of I_{Kr} [68]. In a small study in patients with type-3 long-QT syndrome where $I_{Na,late}$ is increased, ranolazine shortened the QT interval in a concentration-dependent manner [54]. Thus the net effect of ranolazine on ventricular repolarization appears to depend on the amplitude of $I_{Na,late}$.

A seven-day Holter monitoring in ACS patients of the MERLIN-TIMI 36 study revealed a reduction of ventricular tachycardia (VT) lasting ≥8 beats in ranolazine treated patients [69]. In a small observational study ranolazine reduced VT burden and ICD shocks in patients with antiarrhythmic-drug-refractory VT and previous ICD shocks [70]. Although promising, studies designed to evaluate the potential clinical role of ranolazine as an antiarrhythmic agent in ventricular arrhythmias are warranted.

5. $I_{Na,late}$ and atrial fibrillation

Atrial fibrillation (AF) causes electrical remodeling of the atria. Major and well investigated determinants include i) reduced AP duration, ii) diminished L-type Ca current amplitude, and iii) altered K currents [71,72]. These changes can explain a reduced refractory period which provides the possibility of high frequencies during AF. We investigated atrial myocytes from AF patients and found that $I_{Na,late}$ was increased in myocytes while $I_{Na,peak}$ was reduced [38]. Cardiomyocytes were exposed to ranolazine and showed a reduction of $I_{Na,late}$ in cells from AF patients. Although $I_{Na,late}$ integral per beat decreases with increasing frequencies the very high frequency and thus an increase of the number of $I_{Na,late}$ per minute during AF could largely counteract this effect thereby causing a Na-dependent Ca-overload. Therefore, we suggest that at least some anti-AF effects of ranolazine are independent of AP duration and $I_{Na,peak}$ modulation in human AF myocytes where Ca-overload has been shown to be present [73]. Nevertheless, there is a need for further investigations on $I_{Na,late}$ and its relevance for AP duration vs. Na- and Ca-homeostases especially in models of chronic AF and thus remodeled myocytes.

Ranolazine is the only potent $I_{Na,late}$ inhibitor approved for clinical purposes and thus the majority of AF studies were performed using this compound. However, as already mentioned above, ranolazine also has inhibitory effects on I_{Kr} which would prolong the APD in cardiomyocytes. Indeed, it was shown that ranolazine does not shorten but rather even slightly prolongs APD leading to prolonged atrial refractoriness [74]. Since this study did not investigate remodeled cardiomyocytes, the net effect of ranolazine on APD in most AF patients with already shortened APD remains a controversial issue [26].

Independent of $I_{Na,late}$ inhibition, ranolazine seems to act as an atrial selective $I_{Na,peak}$ inhibitor [74] although selectively inhibiting $I_{Na,late}$ in ventricular myocytes [27]. While the cause of this difference remains unclear the ability of ranolazine to inhibit $I_{Na,peak}$ in atrial myocytes was largely attributed to electrophysiological differences between atrial and ventricular myocardium [74]. Reasons for this are a more negative

half inactivation voltage and a more depolarized resting membrane potential in atrial myocytes compared to ventricular myocytes. These electrophysiological differences have been suggested to go along with an increased percentage of inactivated Na channels at a given membrane/resting or take off potential which makes them more sensitive to ranolazine.

Accordingly, it was shown that ranolazine produces a marked use-dependent depression of Na channel parameters in atria but not in ventricles [74]. In line with this, we could demonstrate that ranolazine inhibits $I_{Na,peak}$ in human atrial myocytes [38].

Several studies revealed that ranolazine exerts potent effects against AF in multicellular preparations, in vitro hearts, and in animal models (see Fig. 3). The first report indicated that ranolazine produces concomitant suppression of in vitro acetylcholine-induced AF [74]. Likewise, in vitro studies using intact porcine hearts and in in vivo pigs ranolazine was found to increase atrial effective refractory period, prolong conduction time and decrease acetycholine-induced duration and inducibility of AF [65,75,76]. Since AF is often associated with heart failure a recent study investigated ranolazine in an experimental rabbit model of heart failure with present AF. The potent antiarrhythmic effect against AF was mainly explained by the development of atrial post-repolarization refractoriness and a moderate increase in conduction time [77].

AF triggers are considered to be derived from pulmonary veins. Ranolazine causes a reduction of excitability, conduction slowing, and suppression of triggered activity in canine pulmonary vein sleeve preparations [78]. There is also an increasing recognition that either amiodarone or dronedarone in combination with ranolazine produces a synergistic atrial-selective depression of Na channel-dependent parameters and AF in coronary-perfused right atrial and superfused left atrial pulmonary vein sleeves isolated from dogs [79,80].

There are a few studies that investigated ranolazine in patients with respect to AF. The already above mentioned MERLIN TIMI-36 trial revealed a reduction of supraventricular tachycardias in patients that were treated with ranolazine after ACS. Although a very low incidence of AF, subjects treated with ranolazine were less likely to experience new onset of AF ($p = 0.08$) [69]. It has to be stated, that this trial was neither designed nor powerful enough to investigate a valid effect of ranolazine on AF.

Another study found that 72% of their patients with paroxysmal AF converted to sinus rhythm after application of 2 g of ranolazine [81]. The same group also found that ranolazine was helpful in maintaining sinus rhythm in patients with resistant AF [54]. A prospective randomized pilot study compared the safety and efficacy of ranolazine plus amiodarone versus amiodarone alone for the conversion of recent-onset AF. Treatment with ranolazine to standard amiodarone therapy appeared to be more effective compared to amiodarone alone for conversion of recent-onset AF (88% vs. 65%, $p = 0.056$) [82].

Two larger clinical phase II proofs of concept trials currently investigate the effects of ranolazine on AF. On the one hand, the RAFFAELLO trial (EudraCT-Nr: 2011-002789-18) which is a dose-ranging study testing the efficacy and safety of the three doses of ranolazine versus placebo in maintaining sinus rhythm after successful electrical cardioversion in subjects with persistent AF. This study was designed as a randomized, double-blind, double-dummy, placebo-controlled, dose-ranging trial. In addition, the HARMONY trial (EudraCT-Nr: 2011-001134-42) evaluates whether treatment with ranolazine and dronedarone when given alone and in combination suppresses AF burden in subjects with paroxysmal AF and implanted pacemakers. This trial is a randomized, double-blind, placebo-controlled, parallel-arm trial. It remains interesting what new information these studies will add to the current knowledge.

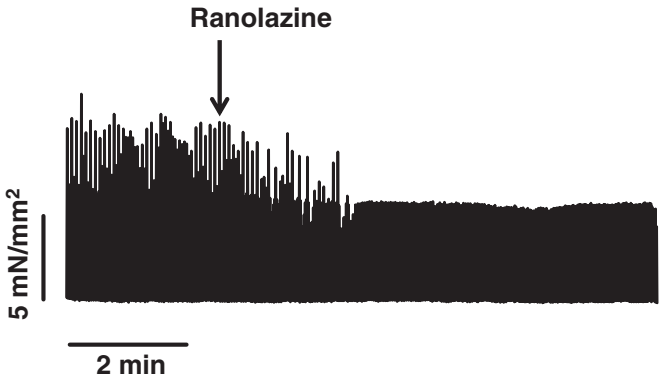

Fig. 3. Ranolazine terminates arrhythmias in an isolated human atrial muscle strip preparation: Representative recording of an experiment using an isometrically twitching human atrial muscle strip preparation. Premature contractions were induced using high extracellular [Ca2+].Application of 10 μmol/L ranolazine potently terminates these arrhythmias leading to a constant stimulation-dependent contraction pattern. Modified from Sossalla et al., J Am Coll Cardiol, 2010.

6. Conclusions

An elevated $I_{Na,late}$ causes Na-dependent Ca-overload and hence electrophysiological changes that are critically involved in ischemia, systolic and diastolic heart failure, as well as arrhythmias. Ranolazine as a clinical approved $I_{Na,late}$ inhibitor for angina pectoris has been shown to exert beneficial effects on systolic and diastolic heart failure. At this time, there is not one recommended and evidence-based agent for the treatment of diastolic heart failure and therefore a huge clinical need. Thus, appropriate randomized clinical trials are indicated to investigate the safety and efficacy of ranolazine in subjects suffering from heart failure.

Ranolazine has the potential for dual suppression of atrial and ventricular arrhythmias. While ranolazine exerts ventricular antiarrhythmic effects most likely via inhibition of $I_{Na,late}$ a "multichannel inhibitory profile" consisting of $I_{Na,peak}$, $I_{Na,late}$, and I_{Kr} blockade is regarded to be responsible for its anti-AF effects. Future work should concentrate on these detailed pharmacodynamic actions of ranolazine to terminate or prevent AF. Up to now clinical data regarding antiarrhythmic effects are sparse. Therefore prospective randomized trials are currently recruiting patients with a focus on the role of ranolazine in AF in order to corroborate the experimental and preliminary clinical findings.

Disclosure statement

L.S.M. acknowledges research grants and funding from CVT, GILEAD, and MENARINI/Berlin-Chemie, companies that provide ranolazine. Both authors receive speaker's honoraria from Berlin-Chemie.

Acknowledgments

Both authors are supported by the Deutsche Forschungsgemeinschaft (DFG) through TPA03 SFB 1002. L.S.M. is funded by a DFG Heisenberg grant (MA 1982/4-2), the GRK 1816 RP3, the DZHK (Deutsches Zentrum für Herz-Kreislauf-Forschung), as well as the Fondation Leducq. S.S. is funded by a German Foundation of Heart Research grant.

References

[1] Saint DA, Ju YK, Gage PW. A persistent sodium current in rat ventricular myocytes. J Physiol 1992;453:219–31.
[2] Coraboeuf E, Deroubaix E, Coulombe A. Effect of tetrodotoxin on action potentials of the conducting system in the dog heart. Am J Physiol Heart Circ Physiol 1979;236:H561–7.
[3] Attwell D, Cohen I, Eisner D, Ohba M, Ojeda C. The steady state TTX-sensitive ("window") sodium current in cardiac Purkinje fibres. Pflugers Arch 1979;379:137–42.
[4] Ju YK, Saint DA, Gage PW. Hypoxia increases persistent sodium current in rat ventricular myocytes. J Physiol 1996;497:337–47.
[5] Undrovinas AI, Fleidervish IA, Makielski JC. Inward sodium current at resting potentials in single cardiac myocytes induced by the ischemic metabolite lysophosphatidylcholine. Circ Res 1992;71:1231–41.

[6] Wu J, Corr PB. Palmitoyl carnitine modifies sodium currents and induces transient inward current in ventricular myocytes. Am J Physiol 1994;266:H1034–46.
[7] Ward CA, Giles WR. Ionic mechanism of the effects of hydrogen peroxide in rat ventricular myocytes. J Physiol 1997;500(Pt 3):631–42.
[8] Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. Heart 2006;92(Suppl. 4):iv6–iv14.
[9] Makielski JC, Farley AL. Na^+ current in human ventricle: implications for sodium loading and homeostasis. J Cardiovasc Electrophysiol 2006;17(Suppl. 1):S15–20.
[10] Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol 2008;97:222–6.
[11] Song Y, Shryock JC, Wu L, Belardinelli L. Antagonism by ranolazine of the pro-arrhythmic effects of increasing late I_{Na} in guinea pig ventricular myocytes. J Cardiovasc Pharmacol 2004;44:192–9.
[12] Song Y, Shryock JC, Wagner S, Maier LS, Belardinelli L. Blocking late sodium current reduces hydrogen peroxide-induced arrhythmogenic activity and contractile dysfunction. J Pharmacol Exp Ther 2006;318:214–22.
[13] Sossalla S, Wagner S, Rasenack EC, Ruff H, Weber SL, Schondube FA, et al. Ranolazine improves diastolic dysfunction in isolated myocardium from failing human hearts — role of late sodium current and intracellular ion accumulation. J Mol Cell Cardiol 2008;45:32–43.
[14] Fredj S, Lindegger N, Sampson KJ, Carmeliet P, Kass RS. Altered Na^+ channels promote pause-induced spontaneous diastolic activity in long QT syndrome type 3 myocytes. Circ Res 2006;99:1225–32.
[15] Maltsev VA, Silverman N, Sabbah HN, Undrovinas AI. Chronic heart failure slows late sodium current in human and canine ventricular myocytes: implications for repolarization variability. Eur J Heart Fail 2007;9:219–27.
[16] Huang B, El-Sherif T, Gidh-Jain M, Qin D, El-Sherif N. Alterations of sodium channel kinetics and gene expression in the postinfarction remodeled myocardium. J Cardiovasc Electrophysiol 2001;12:218–25.
[17] Ahern GP, Hsu SF, Klyachko VA, Jackson MB. Induction of persistent sodium current by exogenous and endogenous nitric oxide. J Biol Chem 2000;275:28810–5.
[18] Wagner S, Dybkova N, Rasenack EC, Jacobshagen C, Fabritz L, Kirchhof P, et al. Ca^{2+}/calmodulin-dependent protein kinase II regulates cardiac Na^+ channels. J Clin Invest 2006;116:3127–38.
[19] Hund TJ, Koval OM, Li J, Wright PJ, Qian L, Snyder JS, et al. A beta(IV)-spectrin/CaMKII signaling complex is essential for membrane excitability in mice. J Clin Invest 2010;120:3508–19.
[20] Aiba T, Hesketh GG, Liu T, Carlisle R, Villa-Abrille MC, O'Rourke B, et al. Na^+ channel regulation by Ca^{2+}/calmodulin and Ca^{2+}/calmodulin-dependent protein kinase II in guinea-pig ventricular myocytes. Cardiovasc Res 2010;85:454–63.
[21] Yao L, Fan P, Jiang Z, Viatchenko-Karpinski S, Wu Y, Kornyeyev D, et al. Nav1.5-dependent persistent Na + influx activates CaMKII in rat ventricular myocytes and N1325S mice. Am J Physiol Cell Physiol 2011;301:C577–86.
[22] Ashpole NM, Herren AW, Ginsburg KS, Brogan JD, Johnson DE, Cummins TR, et al. Ca2 +/calmodulin-dependent protein kinase II (CaMKII) regulates cardiac sodium channel NaV1.5 gating by multiple phosphorylation sites. J Biol Chem 2012;287:19856–69.
[23] Fischer TH, Maier LS, Sossalla S. The ryanodine receptor leak: how a tattered receptor plunges the failing heart into crisis.Heart Fail Rev 2012 [Epub ahead of print Aug 30].
[24] Moreno JD, Clancy CE. Pathophysiology of the cardiac late Na current and its potential as a drug target. J Mol Cell Cardiol 2012;52:608–19.
[25] Wasserstrom JA, Salata JJ. Basis for tetrodotoxin and lidocaine effects on action potentials in dog ventricular myocytes. Am J Physiol 1988;254:H1157–66.
[26] Sossalla S, Maier LS. Role of ranolazine in angina, heart failure, arrhythmias, and diabetes. Pharmacol Ther 2012;133:311–22.
[27] Antzelevitch C, Belardinelli L, Zygmunt AC, Burashnikov A, Di Diego JM, Fish JM, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.
[28] Undrovinas AI, Belardinelli L, Undrovinas NA, Sabbah HN. Ranolazine improves abnormal repolarization and contraction in left ventricular myocytes of dogs with heart failure by inhibiting late sodium current. J Cardiovasc Electrophysiol 2006;17(Suppl. 1):S169–77.
[29] Beyder A, Strege PR, Reyes S, Bernard CE, Terzic A, Makielski J, et al. Ranolazine decreases mechanosensitivity of the voltage-gated sodium ion channel Na(v) 1.5: a novel mechanism of drug action. Circulation 2012;125:2698–706.
[30] Strege P, Beyder A, Bernard C, Crespo-Diaz R, Behfar A, Terzic A, et al. Ranolazine inhibits shear sensitivity of endogenous Na + current and spontaneous action potentials in HL-1 cells. Channels (Austin) 2012;6:457–62.
[31] Belardinelli L, Antzelevitch C, Fraser H. Inhibition of late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodiumdependent calcium overload and its detrimental effects on cardiomyocyte function. Eur Heart J 2004;6(Suppl. I):13–7.
[32] Pignier C, Rougier JS, Vie B, Culie C, Verscheure Y, Vacher B, et al. Selective inhibition of persistent sodium current by F 15845 prevents ischaemia-induced arrhythmias. Br J Pharmacol 2010;161:79–91.
[33] Bers DM. Excitation–contraction coupling and cardiac contractile force. 2nd ed.Dordrecht, Netherlands: Kluwer Academic Publishers; 2001.
[34] Wagner S, Seidler T, Picht E, Maier LS, Kazanski V, Teucher N, et al. Na^+–Ca^{2+} exchanger overexpression predisposes to reactive oxygen species-induced injury. Cardiovasc Res 2003;60:404–12.
[35] Wang P, Fraser H, Lloyd SG, McVeigh JJ, Belardinelli L, Chatham JC. A comparison between ranolazine and CVT-4325, a novel inhibitor of fatty acid oxidation, on cardiac metabolism and left ventricular function in rat isolated perfused heart during ischemia and reperfusion. J Pharmacol Exp Ther 2007;321:213–20.
[36] Zhang XQ, Yamada S, Barry WH. Ranolazine inhibits an oxidative stress-induced increase in myocyte sodium and calcium loading during simulated-demand ischemia. J Cardiovasc Pharmacol 2008;51:443–9.
[37] Fraser H, Belardinelli L, Wang L, Light PE, McVeigh JJ, Clanachan AS. Ranolazine decreases diastolic calcium accumulation caused by ATX-II or ischemia in rat hearts. J Mol Cell Cardiol 2006;41:1031–8.
[38] Sossalla S, Kallmeyer B, Wagner S, Mazur M, Maurer U, Toischer K, et al. Altered Na^+ currents in atrial fibrillation effects of ranolazine on arrhythmias and contractility in human atrial myocardium. J Am Coll Cardiol 2010;55:2330–42.
[39] Hwang H, Arcidi Jr JM, Hale SL, Simkhovich BZ, Belardinelli L, Dhalla AK, et al. Ranolazine as a cardioplegia additive improves recovery of diastolic function in isolated rat hearts. Circulation 2009;120:S16–21.
[40] Rastogi S, Sharov VG, Mishra S, Gupta RC, Blackburn B, Belardinelli L, et al. Ranolazine combined with enalapril or metoprolol prevents progressive LV dysfunction and remodeling in dogs with moderate heart failure. Am J Physiol Heart Circ Physiol 2008;295:H2149–55.
[41] Sossalla S, Maurer U, Schotola H, Hartmann N, Didie´ M, Zimmermann W, et al. Diastolic dysfunction and arrhythmias caused by overexpression of CaMKIIδC can be reversed by inhibition of late Na^+ current. Basic Res Cardiol 2011;106:263–72.
[42] Venkataraman R, Belardinelli L, Blackburn B, Heo J, Iskandrian AE. A study of the effects of ranolazine using automated quantitative analysis of serial myocardial perfusion images. JACC Cardiovasc Imaging 2009;2:1301–9.
[43] Gralinski MR, Black SC, Kilgore KS, Chou AY, McCormack JG, Lucchesi BR. Cardioprotective effects of ranolazine (RS-43285) in the isolated perfused rabbit heart. Cardiovasc Res 1994;28:1231–7.
[44] Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. Am J Cardiol 2005;95:311–6.
[45] Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775–83.
[46] Maltsev VA, Undrovinas A. Late sodium current in failing heart: friend or foe? Prog Biophys Mol Biol 2008;96:421–51.
[47] Maltsev VA, Reznikov V, Undrovinas NA, Sabbah HN, Undrovinas A. Modulation of late sodium current by Ca2 +, calmodulin, and CaMKII in normal and failing dog cardiomyocytes: similarities and differences. Am J Physiol Heart Circ Physiol 2008;294:H1597–608.
[48] Sabbah HN, Chandler MP, Mishima T, Suzuki G, Chaudhry P, Nass O, et al. Ranolazine, a partial fatty acid oxidation (pFOX) inhibitor, improves left ventricular function in dogs with chronic heart failure. J Card Fail 2002;8:416–22.
[49] Sossalla S, Fluschnik N, Schotola H, Ort KR, Neef S, Schulte T, et al. Inhibition of elevated Ca^{2+}/calmodulin-dependent protein kinase II improves contractility in human failing myocardium. Circ Res 2010;107:1150–61.
[50] Wagner S, Ruff HM, Weber SL, Bellmann S, Sowa T, Schulte T, et al. Reactive Oxygen Species-Activated Ca/Calmodulin Kinase II Is Required for Late I_{Na} Augmentation Leading to Cellular Na and Ca Overload. Circ Res 2011;108:555–65.
[51] Wu Y, Song Y, Belardinelli L, Shryock JC. The late Na^+ current (I_{Na}) inhibitor ranolazine attenuates effects of palmitoyl-L-carnitine to increase late I_{Na} and cause ventricular diastolic dysfunction. J Pharmacol Exp Ther 2009;330:550–7.
[52] Maruyama K, Hara A, Hashizume H, Ushikubi F, Abiko Y. Ranolazine attenuates palmitoyl-L-carnitine-induced mechanical and metabolic derangement in the isolated, perfused rat heart. J Pharm Pharmacol 2000;52:709–15.
[53] Hayashida W, van Eyll C, Rousseau MF, Pouleur H. Effects of ranolazine on left ventricular regional diastolic function in patients with ischemic heart disease. Cardiovasc Drugs Ther 1994;8:741–7.
[54] Moss AJ, Zareba W, Schwarz KQ, Rosero S, McNitt S, Robinson JL. Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long-QT syndrome. J Cardiovasc Electrophysiol 2008;19:1289–93.
[55] Maier LS, Layug B, Karwatowska-Prokopczuk E, Belardinelli L, Lee S, Sander J, et al. RAnoLazIne for the treatment of Diastolic Heart Failure in pa-tients with preserved ejection fraction: The RALI-DHF proof-of-concept study. JACC: Heart Fail in press.
[56] Coppini R, Ferrantini C, Yao L, Fan P, Del Lungo M, Stillitano F, et al. Late sodium current inhibition reverses electro-mechanical dysfunction in human hypertrophic cardiomyopathy. Circulation 2012;127:575–84.
[57] Antzelevitch C, Belardinelli L. The role of sodium channel current in modulating transmural dispersion of repolarization and arrhythmogenesis. J Cardiovasc Electrophysiol 2006;17(Suppl. 1):S79–85.
[58] Cheng H, Lederer WJ. Calcium sparks. Physiol Rev 2008;88:1491–545.
[59] Song Y, Shryock JC, Belardinelli L. An increase of late sodium current induces delayed afterdepolarizations and sustained triggered activity in atrial myocytes. Am J Physiol Heart Circ Physiol 2008;294:H2031–9.
[60] Wu L, Shryock JC, Song Y, Li Y, Antzelevitch C, Belardinelli L. Antiarrhythmic effects of ranolazine in a guinea pig in vitro model of long-QT syndrome. J Pharmacol Exp Ther 2004;310:599–605.
[61] Dhalla AK, Wang WQ, Dow J, Shryock JC, Belardinelli L, Bhandari A, et al. Ranolazine, an antianginal agent, markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion. Am J Physiol Heart Circ Physiol 2009;297:H1923–9.
[62] Morita N, Lee JH, Xie Y, Sovari A, Qu Z, Weiss JN, et al. Suppression of re-entrant and multifocal ventricular fibrillation by the late sodium current blocker ranolazine. J Am Coll Cardiol 2011;57:366–75.
[63] Wu L, Shryock J, Song Y, Belardinelli L. An increase in late sodium current potentiates the proarrhythmic activities of low-risk QT-prolonging drugs in female rabbit hearts. J Pharmacol Exp Ther 2006:718–26.

[64] Antoons G, Oros A, Beekman JD, Engelen MA, Houtman MJ, Belardinelli L, et al. Late Na^+ current inhibition by ranolazine reduces torsades de pointes in the chronic atrioventricular block dog model. J Am Coll Cardiol 2010;55:801–9.
[65] Kumar K, Nearing BD, Bartoli CR, Kwaku KF, Belardinelli L, Verrier RL. Effect of ranolazine on ventricular vulnerability and defibrillation threshold in the intact porcine heart. J Cardiovasc Electrophysiol 2008;19:1073–9.
[66] Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, et al. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. Circ Res 1991;69:1427–49.
[67] Zygmunt A, Goodrow R, Antzelevitch C. I_{NaCa} contributes to electrical heterogeneity within the canine ventricle. Am J Physiol Heart Circ Physiol 2000:H1671–8.
[68] Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwatowska-Prokopczuk E, Buros JL, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 trial. J Am Coll Cardiol 2009;53:1510–6.
[69] Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. Circulation 2007;116:1647–52.
[70] Bunch TJ, Mahapatra S, Murdock D, Molden J, Weiss JP, May HT, et al. Ranolazine reduces ventricular tachycardia burden and ICD shocks in patients with drug-refractory ICD shocks. Pacing Clin Electrophysiol 2011;34:1600–6.
[71] Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca^{2+} currents and human atrial fibrillation. Circ Res 1999;85:428–36.
[72] Nattel S, Dobrev D. The multidimensional role of calcium in atrial fibrillation pathophysiology: mechanistic insights and therapeutic opportunities. Eur Heart J 2012;33:1870–7.
[73] Neef S, Dybkova N, Sossalla S, Ort KR, Fluschnik N, Neumann K, et al. CaMKII-dependent diastolic SR Ca^{2+} leak and elevated diastolic Ca^{2+} levels in right atrial myocardium of patients with atrial fibrillation. Circ Res 2010;106:1134–44.
[74] Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C. Atrium-selective sodium channel block as a strategy for suppression of atrial fibrillation: differences in sodium channel inactivation between atria and ventricles and the role of ranolazine. Circulation 2007;116:1449–57.
[75] Kumar K, Nearing BD, Carvas M, Nascimento BC, Acar M, Belardinelli L, et al. Ranolazine exerts potent effects on atrial electrical properties and abbreviates atrial fibrillation duration in the intact porcine heart. J Cardiovasc Electrophysiol 2009;20:796–802.
[76] Carvas M, Nascimento BC, Acar M, Nearing BD, Belardinelli L, Verrier RL. Intrapericardial ranolazine prolongs atrial refractory period and markedly reduces atrial fibrillation inducibility in the intact porcine heart. J Cardiovasc Pharmacol 2010;55:286–91.
[77] Frommeyer G, Schmidt M, Clauss C, Kaese S, Stypmann J, Pott C, et al. Further insights into the underlying electrophysiological mechanisms for reduction of atrial fibrillation by ranolazine in an experimental model of chronic heart failure. Eur J Heart Fail 2012;14:1322–31.
[78] Sicouri S, Glass A, Belardinelli L, Antzelevitch C. Antiarrhythmic effects of ranolazine in canine pulmonary vein sleeve preparations. Heart Rhythm 2008;5:1019–26.
[79] Sicouri S, Burashnikov A, Belardinelli L, Antzelevitch C. Synergistic electrophysiologic and antiarrhythmic effects of the combination of ranolazine and chronic amiodarone in canine atria. Circ Arrhythm Electrophysiol 2010;3:88–95.
[80] Burashnikov A, Sicouri S, Di Diego JM, Belardinelli L, Antzelevitch C. Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. J Am Coll Cardiol 2010;56:1216–24.
[81] Murdock DK, Kersten M, Kaliebe J, Larrain G. The use of oral ranolazine to convert new or paroxysmal atrial fibrillation: a review of experience with implications for possible “pill in the pocket” approach to atrial fibrillation. Indian Pacing Electrophysiol J 2009;9:260–7.
[82] Fragakis N, Koskinas KC, Katritsis DG, Pagourelias ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. Am J Cardiol 2012;110:673–7.