Review article

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

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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".

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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

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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,
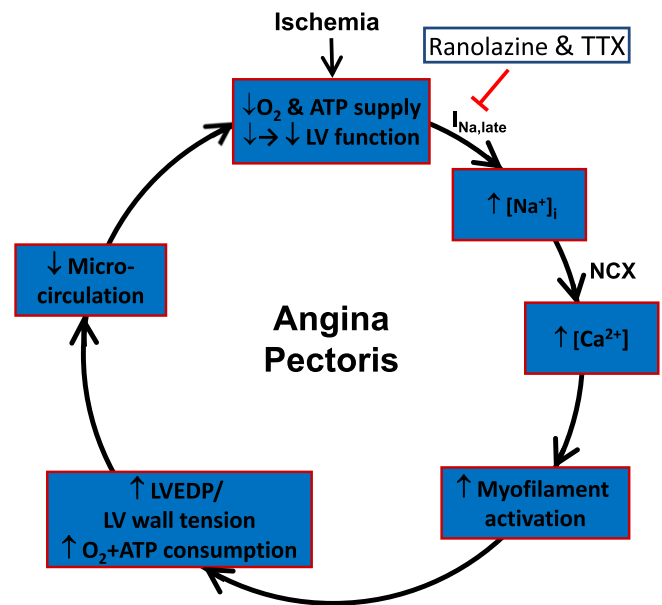

Fig. 1. Vicious circle of myocardial ischemia with a focus on $I_{Na,late}$: Ischemia enhances $I_{Na,late}$ which increases intracellular Na^+ and Ca^{2+} via Na^+/Ca^{2+} exchanger (NCX). As a consequence, Ca ions overactivate myofilaments which aggravates myocardial ischemia. Blockers of $I_{Na,late}$ 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
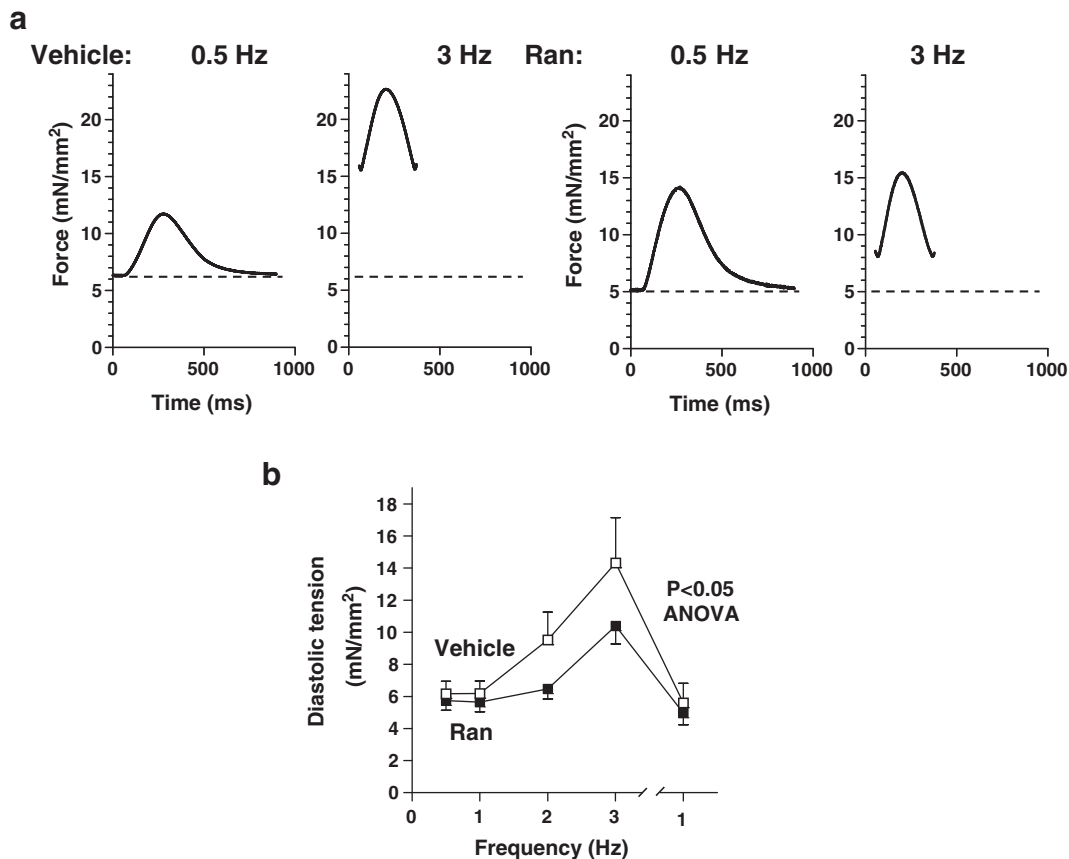
Fig. 2. Improvement of diastolic function in human failing myocardium: Effects of 10 μmol/L ranolazine (Ran) on diastolic tension during stepwise increases in stimulation rate in muscles from end-stage failing human hearts. (a) Original recordings of force at 0.5 and 3 Hz during control conditions (vehicle, 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.

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

Acknowledgments

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.

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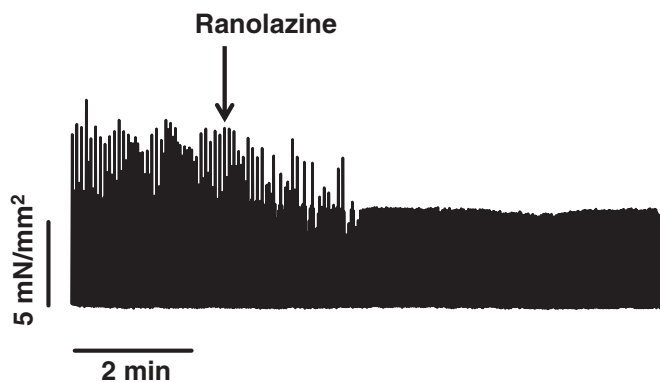
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