Sodium channel block by ranolazine in an experimental model of stretch-related atrial fibrillation: prolongation of interatrial conduction time and increase in post-repolarization refractoriness

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Aims

In several clinical and pre-clinical studies, application of ranolazine (RAN) led to suppression of atrial fibrillation (AF). The aim of the present study was to investigate whether RAN can suppress AF in an experimental rabbit whole heart model, in which acute haemodynamic changes trigger AF. Ranolazine was compared with flecainide and sotalol as established antiarrhythmic agents.

Methods and results

In 60 Langendorff-perfused, isolated rabbit hearts, AF episodes were evoked by burst pacing with a fixed number of stimuli at baseline and following acute atrial stretch. Data were obtained in the absence and presence of acute dilatation of the left atrium (20 mmHg) at baseline and after drug application (RAN 10 μM, n = 10; flecainide 2 μM, n = 10; sotalol 50 μM, n = 10). Application of sotalol, but not RAN or flecainide increased the atrial action potential duration at 90% repolarization (aAPD90); however, both RAN (+8 ms) and flecainide (+13 ms) increased interatrial conduction time. All three drugs caused a significant increase in atrial effective refractory period (aERP) and, thus, an increase in atrial post-repolarization refractoriness (aPRR: +11 ms each, P < 0.05). Acute dilatation of the left atrium reduced aAPD90 and aERP. The described drug effects were preserved in the setting of acute atrial dilatation. Acute atrial dilatation significantly increased the incidence of AF. Ranolazine and flecainide, but not sotalol, decreased the number of responses.

Conclusion

Ranolazine-related sodium channel block is preserved upon acute atrial stretch. Ranolazine suppresses stretch-induced AF by increasing interatrial conduction time and aPRR. These results shed further evidence on the potential role of RAN in the prevention of AF. This might also apply to clinical conditions that are associated with haemodynamic or mechanical disorders, leading to acute dilatation of the atria.

Keywords

Ranolazine • Flecainide • Atrial fibrillation • Atrial stretch

Introduction

Despite new developments in catheter ablation of atrial fibrillation (AF), antiarrhythmic drug therapy still remains a principal approach for rhythm control in AF. Currently available antiarrhythmic agents may either show proarrhythmic side effects (i.e. sotalol1) and/or are contraindicated in structural heart disease. Thus, new agents that reveal antiarrhythmic potential without affecting other organs or endangering ventricular repolarization may be attractive.

Pre-clinical2,3 and clinical4 studies have reported an antiarrhythmic potential of ranolazine (RAN) in suppressing AF. The...
What’s new?

- Ranolazine suppresses stretch-induced atrial fibrillation by exerting a described antiarrhythmic effect at therapeutic plasma concentrations of 2–10 μM, mainly due to block of peak and late INa, and delayed rectifier K+ current (IKr). Burashnikov et al. reported an atrial selectivity for use-dependent block of sodium channels by RAN, which resulted in suppression of AF in isolated atrial myocytes at a concentration causing little or no electrophysiological changes in the ventricle. A comparable antiarrhythmic effect of RAN was observed in canine pulmonary vein sleeve preparations and in intact porcine hearts. Furthermore, RAN reduced atrial proarrhythmic activity in isolated human atrial myocytes. A comparison of RAN and amiodarone for preventing AF in patients after coronary bypass surgery revealed a beneficial effect of RAN that was based on a significant reduction of AF incidence and adverse events. In addition, recent studies have shown that RAN is effective and safe in suppressing AF even in patients with structural heart disease and left atrial enlargement.

Atrial fibrillation is frequently associated with atrial dilatation caused by pressure or volume overload. Acute atrial stretch leads to modulation of atrial electrophysiology via stretch-activated channels and thereby enhances the incidence of arrhythmias. The so-called mechano-electrical feedback, which addresses electrophysiological changes in response to mechanical perturbations or changes in haemodynamic loading, may be relevant in a wide spectrum of clinical conditions such as hypertension, mitral valve disease, or cardiac failure. The effect of stretch on atrial myocardium was investigated by several groups that reported differing results. In isolated rabbit heart preparations, atrial dilatation led to a reduction of atrial action potential duration (aAPD), as well as reduced refractory period.

In contrast, other groups described an increase of aAPD after acute stretch of human myocardium, while Calkins et al. did not find any alterations of these parameters. However, all these studies revealed an increase of triggered activity and atrial arrhythmias in the presence of acute atrial stretch, despite the described differences in electrophysiological parameters. This points out the multifactorial impact of atrial stretch on atrial electrophysiology.

The present study was designed to test the hypothesis that sodium channel blockade (both peak and late component) by RAN is effective in suppressing AF in a whole-heart model of stretch-induced AF. Moreover, we aimed at elucidating the underlying electrophysiological mechanisms in comparison with the antiarrhythmic characteristics of the established antiarrhythmic agents, flecainide and sotalol.

Methods

All experimental protocols were approved by the local animal care committee and conformed with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Oral drug treatment and preparation of hearts for perfusion

The method of preparing the hearts has previously been described in detail. Female New Zealand white rabbits (n = 60) weighing 3.5–4.0 kg were anaesthetized with thiopental (200–300 mg intravenous). After midsternal incision and opening of the pericardium, the complete hearts were removed and immediately placed in an ice-cold Krebs–Henseleit solution (composition in mM: CaCl2 1.80, KCl 4.70, KH2PO4 1.18, MgSO4 0.83, NaCl 118, NaHCO3 24.88, Na-pyruvate 2.0, and glucose 5.55). The aorta was cannulated, the pulmonary artery was incised, and the spontaneously beating hearts were perfused at constant flow (52 mL/min) with warm (36.8–37.2°C) Krebs–Henseleit solution. Perfusion pressure was continuously measured during the experiments and stayed stable at around 100 mmHg. The hearts were placed in a heated, solution-filled tissue bath. The perfusate was equilibrated with 95% O2 and 5% CO2 (pH 7.35; 37°C). The cannulated and perfused hearts were attached to a vertical Langendorff apparatus (Hugo Sachs Elektronik). The apex of the heart was fixed loosely on the Langendorff apparatus with a surgical yarn to ensure horizontal stability.

Electrocardiographic and electrophysiological measurements

A volume-conducted electrocardiogram (ECG) was recorded by complete immersion of the heart into a bath of Krebs–Henseleit solution that had been thermally equilibrated with the myocardial perfusate. Signals from a simulated ‘Einthoven’ configuration were amplified by a standard ECG amplifier (filter settings: 0.1–300 Hz). Monophasic action potential (MAP) recordings and stimulation were accomplished simultaneously using contact MAP pacing catheters (EP Technologies). The MAP electrograms were amplified and filtered (low pass 0.1 Hz, high pass 300 Hz). Monophasic action potentials were analysed using a specifically designed software, permitting precise definition of the amplitude and duration of the digitized signals. The recordings were considered reproducible and, therefore, acceptable for analysis only if they had a stable baseline amplitude with a variation of <20% for at least 60 s during each cycle length (CL) and a stable duration with a variation of <10% in this time window measured at 90% repolarization (aERP0.95). Two MAPs were placed on each atrium for artefact-free recordings of atrial action potentials, whereas an additional atrial MAP catheter on the left atrium was used to stimulate the heart. Two further MAPs were used to record ventricular signals. Atrial pacing at twice diastolic threshold was performed for 30 s at CLs of 350, 250, and 150 ms using a computer-based stimulation protocol employing a stimulator which delivered square-wave pulses of 2 ms pulse width.

Experimental protocol

After placing the MAP catheters, atrial pacing at described CLs was performed to obtain baseline values. Then, atrial effective refractory period (aERP) was measured. Atrial effective refractory periods were determined during atrial pacing with a basic CL of 250 ms. After an eight-beat train (S1–S1), a single premature stimulus (S2) was delivered. The S1–S2 coupling interval was decreased in decrements of 2 ms, starting with 100 ms. The shortest S1–S2 interval resulting in a propagated response was defined as aERP. Post-repolarization refractoriness (PRR) was calculated as the difference between aERP and...
Thereafter, a standardized burst pacing protocol was performed to provoke AF (Figure 1). Burst pacing was conducted at 4, 8, and 12 times diastolic threshold. For each amplitude, a train of 11 burst episodes each following 8 consecutive basic stimuli at a CL of 250 ms was delivered. The first burst started 250 ms after the last basic stimulus. Each following burst was applied 10 ms closer to the last basic stimulus, which made the final burst episode begin 150 ms after the last regular stimulus. Electric atrial activity following burst pacing was classified as ‘non-sustained’ (<1 s, minimum 5 beats), ‘sustained’ (>1 s), and ‘long-sustained’ (>20 s).

After obtaining baseline data, hearts were perfused with RAN (10 μM, n = 10) or flecainide (2 μM, n = 10), or sotalol (50 μM, n = 10) over a period of 20 min. Pacing, MAP recording, and measurement of ECG parameters were repeated 20 min after drug infusion. In 30 hearts, a small latex balloon was inserted into the left atrium and inflated with a pressure of 20 mmHg after obtaining baseline data. This acute dilatation of the atrium has been described before and is associated with an increased rate of AF episodes. The balloon was connected to a specifically designed manometer to control exact inflation pressure. Perfusion with RAN, flecainide, or sotalol was repeated as described above after an adaption period of 5 min.

In summary, data were obtained at baseline and immediate perfusion with RAN (10 μM, n = 10), flecainide (2 μM, n = 10), or sotalol (50 μM, n = 10) as well as after acute dilatation of the left atrium and consecutive RAN (10 μM, n = 10), flecainide (2 μM, n = 10), or sotalol (50 μM, n = 10) perfusion. Atrial (a)APD<sub>90</sub> was measured as the average interval between the fastest MAP upstroke and 90% repolarization. Interatrial conduction time was measured between left and right atrium.

Figure 1 Flow chart to illustrate the different consecutive parts of the experimental protocol. (A) Depicts the protocol in study groups without atrial dilatation. (B) Depicts the protocol in study groups where acute atrial dilatation was performed.
Data acquisition and statistical analysis
Data were entered into a computerized database (Microsoft Excel 2003) and statistically evaluated using SPSS Software Release 18.0.0. Categorical variables were expressed as frequency and percentage, whereas continuous variables were presented as mean ± SD. The effects of flecainide, RAN, and sotalol on CL dependence aAPD, interatrial conduction time, aERP, and PRR were assessed using the general linear model for repeated measurements. After confirming significant group differences over CL, post hoc comparisons with Bonferroni’s procedure were applied to determine differences between groups. The McNemar tests were used to compare the appearance of AF episodes. The chi² test and the Fisher’s test were used to compare AF incidence. The t-tests were used to compare the difference between two independent study groups, and the paired-samples t-test between dependent study groups. Differences were considered significant at $P < 0.05$.

Results
Effect of ranolazine, flecainide, and sotalol on atrial action potential duration and interatrial conduction time
Acute dilatation of the left atrium with intra-atrial pressure augmentation by 20 mmHg did not change aAPD and aERP. Interatrial conduction time and dispersion of atrial repolarization did not change either.

After application of RAN (10 μM) or flecainide (2 μM), aAPD remained stable. After sotalol treatment (50 μM), aAPD90 did not differ significantly from baseline values ($81 ± 21$ to $87 ± 33$ ms, $P = ns$). Ranolazine significantly augmented interatrial conduction time from baseline values of $37 ± 12$ to $41 ± 14$ ms ($P < 0.05$). Comparable results were obtained with flecainide ($32 ± 14$ ms at baseline, $45 ± 21$ ms at 2 μM flecainide, $P < 0.01$). After application of 50 μM sotalol, interatrial conduction time remained unchanged (Figure 2).

In the setting of acute atrial dilatation, the described drug effects were preserved. Atrial dilatation alone did not significantly alter aAPD90 and interatrial conduction time. In the presence of acutely dilated atria, application of flecainide ($+8$ ms) or RAN ($+9$ ms) increased conduction time ($P < 0.05$) while sotalol ($+2$ ms) did not significantly affect this parameter.

Atrial refractory period and post-repolarization refractoriness
Administration of all three drugs augmented aERP (measured as S2 refractory period at CL of 250 ms) (Figure 3A). Pharmacological intervention also increased atrial post-repolarization refractoriness (aPRR) in all groups in an equal manner [RAN: $9 ± 2$ ms at baseline to $20 ± 4$ ms (CL of 250 ms); flecainide to $20 ± 3$ ms; sotalol (50 μM) to $20 ± 5$ ms; Figure 4A]. Acute dilatation of the left atrium reduced mean aERP from baseline values of $92 ± 17$ to $82 ± 14$ ms, but did not significantly decrease mean aPRR ($9 ± 2$ to $6 ± 2$ ms, $P = ns$). Consecutive application of RAN, flecainide, or sotalol again increased aERP and aPRR significantly (Figures 3B and 4B).

Atrial fibrillation
Acute atrial dilatation led to a significant increase of AF episodes (Figure 5) in all study groups. Acute treatment with RAN significantly lowered the rate of AF in non-dilated hearts as well as in hearts with dilated atria (Figure 6A). Administration of flecainide showed a comparable reduction of irregular activity (Figure 6B) while treatment with sotalol did not significantly reduce response rates compared with both baseline and dilated heart values (Figure 6C).

Discussion
Atrial fibrillation frequently occurs in situations associated with atrial dilatation, suggesting a role of mecano-electrical feedback. The results of the present study showed a preserved therapeutic potential of $I_{Na}$ inhibition by RAN when clinical conditions were simulated that are associated with an acute pressure overload. Ranolazine led to an increase in interatrial conduction time and in aPRR, accompanied by a suppression of AF in the presence of an acute atrial stretch of the left atrium.

The pharmacological profile of RAN includes inhibition of $I_{Na}$, $I_{K}$, and $I_{Ca}$, Its rapid unbinding kinetics from the sodium channel thought to be responsible for avoiding ventricular proarrhythmia and its particular atrial-selective block of sodium-channel-dependent parameters suggest a potential role for therapy of AF even in the presence of acute atrial dilatation.

Mechano-electrical feedback and atrial fibrillation
Mechano-electrical feedback has been proposed as an important arrhythmogenic mechanism because stretch is able to induce afterdepolarizations and triggered arrhythmias probably due to an abnormal prolongation of inward currents carried by sodium or calcium channels. The important role of sodium channels in atrial arrhythmogenesis was also confirmed by an experimental study of acute stretch-related AF in isolated rabbit hearts, where the effect of sodium channel blockade was strongly enhanced upon acute atrial stretch.
In our study, acute atrial dilatation led to a reduction of aERP and aPRR, thereby favouring generation and perpetuation of AF. This model of acute electrophysiological changes has been well established by other groups and different drugs have been examined in a comparable setup. Although the electrophysiological effects of volume and pressure overload are not completely understood, previous studies reported an increased rate of AF after acute atrial stretch due to an increase in the atrial surface area available for wandering atrial wavelets. In addition, a stretch-induced shortening of ERP leads to a shortening of the wavelength of the atrial impulse. This might increase the average number of wavelets simultaneously present in the atria, thereby enhancing the vulnerability of the atria to fibrillation. In addition to alterations of aAPD and aERP, the occurrence of triggered activity in dilated atria as described by Nazir et al. plays a major role in the generation of AF. In accordance, Yamane et al. reported triggered activity originating from pulmonary veins in the presence of atrial dilatation as a crucial trigger of AF.

Atrial dilatation has been proven to ascent activity of K+-selective and cationic non-selective channels and thereby to enhance atrial arrhythmias. However, sodium channel blockade failed to reverse this pathophysiological mechanism. In contrast, a beneficial effect of sodium channel block by flecainide in the setting of acute atrial stretch has been reported before. In the present study, RAN, a late I_{Na} blocking agent, demonstrated efficacy in suppressing AF. This is most likely related to voltage-dependent block of peak I_{Na} on top of I_{Kr} blockade.

Effect of ranolazine on atrial conduction time, effective refractory period, and atrial post-repolarization refractoriness in acute stretch-induced atrial fibrillation

The increase of conduction time is a crucial mechanism that accounts for the antifibrillatory effect of class-IC-antiarrhythmic drugs such as flecainide. In the present study, a slowed
conduction was observed after application of RAN or flecainide. The antiarrhythmic potential of RAN showed no significant difference as compared with the established antiarrhythmic potential of flecainide, whereas application of the $I_{Kr}$-blocker sotalol did not influence conduction time. In a previous study by Eijsbouts et al., blockade of sodium channel by flecainide caused a higher degree of conduction delay in dilated than in non-dilated atria, a finding that has been confirmed in the present study. Ranolazine and flecainide caused a significant increase in conduction time as compared with untreated hearts as well as compared with untreated hearts after acute atrial dilatation.

Previous studies demonstrated a shortening of ERP by increasing atrial pressure in the isolated rabbit heart. This effect may be due to stretch-activated channels or mechanical modulation of intracellular calcium concentration. Shortening of the ERP by stretch contributed to an increase of AF in previous isolated rabbit heart studies and in humans, by shortening the wavelength of atrial impulses, and thus by increasing the number of wavelets. Moreover, stretch in the rabbit heart is a key arrhythmogenic factor, since the rabbit atrium in normal conditions is not as vulnerable to sustained atrial arrhythmias. Besides, the maximal number of wavelets that such a small atrial mass may contain may be below the fibrillation threshold.

Our data showed an increase of aERP that led to an increase of PRR with the sodium-channel blocking agent flecainide. An increase in aPRR has been identified as an important therapeutic approach for atrial and ventricular arrhythmias. The observed increase by RAN might be explained by a slowing of recovery of $I_{Na}$ from inactivation. It has been shown that RAN prolongs the recovery of $I_{Na}$ from inactivation in both canine myocytes and HEK293 cells expressing a LQT3 mutation, R1623Q. Slowing of the recovery of $Na^{+}$ channels from the inactivation process may thus explain the antifibrillatory effect of antiarrhythmic agents. Flecainide revealed a comparable effect on aPRR as compared with RAN. In addition, sotalol also led to an increase in PRR in our model, although sotalol had no effect on $I_{Na}$. This finding can be explained.

Figure 5 Representative example of sustained AF provoked by burst pacing.
by a residual, slowly deactivating $K^+$ conductance ($G_K = G_{Kr} + G_{Ks}$) activated during the action potential. The time course of deactivation is slower than the time course of repolarization, thus most of the deactivation takes place during the diastolic interval, which is amplified by sotalol in the present study. This led to an increase in APD, but a more marked increase in ERP.

Of note, experimental studies revealed beneficial effects of blocking $I_{KUR}$ and $I_{KACH}$ against AF in heart failure models. However, these targets need clinical validation.

As compared with RAN or flecainide, sotalol exerted the weakest antiarrhythmic effect and did not result in a significant reduction of AF episodes. Although flecainide was more effective than RAN in our experimental model of AF, the clinical use of flecainide is very limited in the setting of structural heart disease.

Clinical impact

Our data are relevant to clinical conditions, in which atrial stretch and AF occur due to changes in atrial pressure (e.g. presence of mitral valve disease, compromised ventricular function). Ranolazine might yield a substantial prolongation of aPRR and slowing of conduction that may be comparable to the effect of flecainide, thereby suppressing AF. An important advantage of RAN in rhythm control of AF is the fact that the substance may be administered to patients suffering from structural heart disease. Murdock et al. showed a beneficial effect of RAN in converting AF with a high dose of RAN as a ‘pill in the pocket’ approach. Of note, most of the patients had enlarged left atria. The peculiar finding in this small study is the antiarrhythmic effect of RAN in structural abnormal hearts, which is a promising approach for the near future. As displayed in the current ESC guidelines for AF, amiodarone, dronedarone (with strict limitations), and sotalol are the only antiarrhythmic agents recommended in patients with coronary artery disease. For patients with relevant heart failure, amiodarone, with its well-known adverse effects, remains the only recommended antiarrhythmic agent. The results of our study may demonstrate a potential novel therapeutic role for RAN. Furthermore, in contrast to common antiarrhythmic drugs it has not displayed proarrhythmic has been found to significantly reduce ventricular arrhythmias in experimental and clinical studies.

Further clinical studies are currently conducted, i.e. the HARMONY trial which investigates the effects of a combined treatment of dronedarone and RAN for rhythm control in AF (www.clinicaltrials.gov). Therefore, RAN may be a promising drug for rhythm control of AF in heart failure.

Figure 6 (A) Occurrence of AF at baseline and after application of RAN (top), as well as at baseline, after acute atrial dilatation and after consecutive treatment with RAN (bottom). (B) Occurrence of AF at baseline and after application of flecainide (top), as well as at baseline, after acute atrial dilatation and after consecutive treatment with flecainide (bottom). (C) Occurrence of AF at baseline and after application of sotalol (top), as well as at baseline, after acute atrial dilatation and after consecutive treatment with sotalol (bottom).
Limitations of the study

The present experimental study was conducted in isolated rabbit hearts and extrapolation of the clinical situation needs to be handled carefully. Although many studies show that the electrophysiological findings in rabbit hearts are comparable with observations in humans, the present model is still an experimental model that is not able to capture the complex pathophysiology of AF in humans completely. It cannot ideally mimic the clinical situation of spontaneous occurrence of AF episodes and thereby does not consider clinical triggers of the initiation of AF. Owing to the small size of the rabbit heart, an aggressive stimulation protocol is mandatory to induce fibrillation to assess antifibrillatory effects. In addition, the autonomous nervous system plays a pivotal role in the initiation and maintenance of AF in humans, which cannot be assessed in this ex vivo experimental model. Moreover, there was no significant effect of sotalol on AF episodes, although clinical efficacy has been suggested. The present model emphasizes the importance of slowing of conduction as an important feature of antiarrhythmic drugs. Effects on ERP and PRR, shown by sotalol, are likely needed in combination with marked electrophysiological mechanisms can be analysed in this whole-heart model, where cell-to-cell coupling effects come to bear. In addition, the model is well established to examine the electrophysiological characteristics of antiarrhythmic drugs.

In contrast, as compared with single-cell studies or sleeve preparations, electrophysiological mechanisms can be analysed in this whole-heart model, where cell-to-cell coupling effects come to bear. In addition, the model is well established to examine the electrophysiological characteristics of antiarrhythmic drugs.

Conclusion

The present study sheds further light on the effects of RAN on atrial electrophysiology and suggests a possible therapeutic role in stretch-related AF. Ranolazine suppressed AF comparable to the sodium channel blocker flecainide, and is associated with slowing of intratral conduction and an increase in PRR. In contrast to ‘classic’ class IC-drugs, RAN may be a promising novel option in patients with structural heart disease.

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