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EDITORIAL

Ranolazine for atrial fibrillation: buy one get three beneficial mechanisms!

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This editorial refers to 'Further insights into the underlying electrophysiological mechanisms for reduction of atrial fibrillation by ranolazine in an experimental model of chronic heart failure', by G. Frommeyer *et al.*, published in this issue on pages 1322–1331.

Heart failure is a major problem in our societies, with high morbidity and mortality.[1] Arrhythmias are known to contribute to the progression of and even can induce heart failure. The most common arrhythmia is atrial fibrillation, but antiarrhythmic drugs in patients with heart failure are sparse, have major side effects (e.g. amiodarone), or are even contraindicated like flecainide.

Since the first report by Burashnikov *et al.* in 2007 in isolated canine atria,[2] several experimental studies in cultured cells, and in isolated animal and human tissue have investigated the mechanisms of the antiarrhythmic properties of ranolazine (for a review, see Sossalla and Maier[3]). These studies showed that ranolazine not only inhibits late Na current but it may also act as an atrial selective peak Na current blocker. The reasons for this include the fact that the half-inactivation voltage is more negative in atrial as compared with ventricular myocytes with a more depolarized resting membrane potential in atrial cells. The consequence is an increased fraction of inactivated Na channels at a given membrane potential.[3] Accordingly, ranolazine produced a use-dependent depression of several Na channel parameters[2] which can be also found in human atrial myocytes even at higher stimulation rates.[4]

Aidonidis *et al.* recently investigated right atrial monophasic action potentials in a rabbit model of inducible atrial tachyarrhythmias *in vivo* using intracardial catheters.[5] The authors showed that ranolazine has antiarrhythmic effects due to an increase in atrial post-repolarization refractoriness resulting in depressed electrical excitability and impediment of arrhythmia initiation even at higher heart rates.[5] Post-repolarization refractoriness was calculated when subtracting 75% of total monophasic action potential duration from the effective refractory period, and was suggested to be due to Na currents. Ranolazine also increased the action potential duration at any given pacing cycle length, which the authors mainly attributed to its additional effects on the main repolarizing K current I_{Kr}.

The study by Frommeyer *et al.* in this issue of the *European Journal of Heart Failure*[6] adds to the existing body of evidence and expands previous work by that group[7] by using a rabbit heart failure model investigating action potentials mapped from the epicardium of isolated Langendorff-perfused rabbit hearts *ex vivo*. Perhaps surprisingly to some clinicians, the authors found an increased action potential duration in the atria of this heart failure model, although increased ventricular action potential duration in failing hearts is a well accepted hallmark. In atrial fibrillation, however, major known determinants of electrical remodelling include (i) reduced action potential duration; (ii) decreased L-type Ca current amplitude; and (iii) altered K currents, thereby favouring a re-entry mechanism, which are underlined by reduced effective refractory periods.[8] In addition, Nattel and Dobrev in a recent review[9] stressed the importance of early and delayed afterdepolarizations and triggered activity associated with altered Ca handling, including spontaneous Ca release from the sarcoplasmic reticulum and diastolic overload. These proarrhythmogenic triggers have now been shown by several authors.[10,11] Intracellular Ca and Na handling are closely coupled and therefore it is possible that both mechanisms exist in parallel. Alternatively, altered Na handling due to increased late Na current can contribute to cytosolic Ca overload through the Na/Ca exchanger and/or thus may lead to a transient inward current with delayed afterdepolarizations.[4,5] In addition, original data from a recently published LQT3 mouse model presenting with atrial fibrillation and increased late Na current showed early afterdepolarizations in the presence of long atrial action potentials.[12] Finally, late phase 3 delayed and

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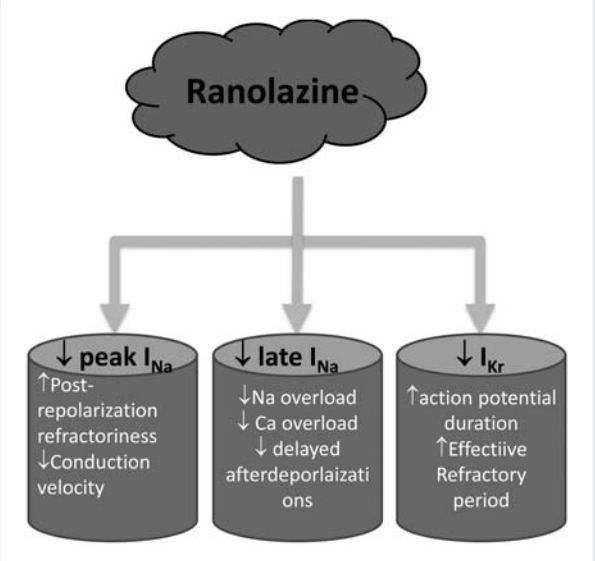

Figure 1 Schematic summary of some of the possible antiarrhythmic effects of ranolazine in atrial fibrillation. Reduced peak Na current, thereby increasing post-repolarization refractoriness. Reduced late Na current, thereby normalizing intracellular Na and Ca overload and reducing delayed afterdepolarizations. Reduced I_{Kr}, thereby increasing the action potential duration and effective refractory period.

early afterdepolarizations as well as automatic beats serving as triggers were reduced in the presence of ranolazine.[13]

Now, Frommeyer *et al.*[6] not only show increased action potential duration in their rabbit heart failure model but also an increase in the effective refractory period as compared with control hearts. Upon acetylcholine and isoproterenol infusion, atrial fibrillation occurred with a shortening of action potential duration as well as a reduction in the atrial effective refractory period, whereas post-repolarization refractoriness was unaltered. Most importantly, ranolazine led to a reduction in atrial arrhythmias due to an increase in the effective refractory period and post-repolarization refractoriness without changes in action potential duration. The underlying mechanism of this finding may be a combination of an inhibition of late Na current and an inhibition of I_{Kr}, the main repolarizing K current of the myocytes. On the other hand, a slowed conduction time as found by the authors probably results from an inhibition of atrial peak Na current. Perhaps this mixture of inhibitory effects on atrial myocytes is the key success of the antiarrhythmic effects of ranolazine in animal models (see *Figure 1*). In the clinical setting, an atrial selective antiarrhythmic drug without significant changes in action potential duration but prolonging repolarization is needed.

The findings of Frommeyer *et al*. may not be surprising *per se* but are an important step towards a novel antiarrhythmic approach in the setting of severe heart failure because many patients with heart failure also suffer from atrial arrhythmias leading to decompensation. If these findings translate into humans, this could be a step towards a novel and safe antiarrhythmic treatment in heart failure patients. Ranolazine most importantly bears no proarrrhythmic properties for the ventricle like many antiarrhythmic drugs and does not greatly prolong the QT interval due to its inhibitory effects on both late I_{Na} and I_{Kr}.

However, is there any clinical evidence for antiarrhythmic effects? Well, it was the mega trial MERLIN TIMI-36 that first presented clinical evidence for a possible antiarrhythmic role for ranolazine. A main inclusion criterion in that study was an acute coronary syndrome, and ranolazine was tested on top of optimal therapy in $>$ 6500 patients. Although the composite primary endpoint of mortality combined with angina pectoris was not significantly different between the placebo and the ranolazine group ($P = 0.08$), the authors found in one of the safety endpoints significantly less supraventricular tachycardias.[14] However, this trial with a low incidence of atrial fibrillation was not designed to test for antiarrhythmic effects of ranolazine. Therefore, based on this trial and the experimental data discussed above, two clinical trials are currently investigating the role of ranolazine in atrial fibrillation: RAFFAELLO (EudraCT-No: 2011-002789-18) is a trial in which ranolazine is being investigated in atrial fibrillation following an electrical cardioversion in patients with non-permanent atrial fibrillation. In addition, the HARMONY study is a proof of concept study to evaluate the efficacy and safety of combination therapy of ranolazine and low dose dronedarone in patients with paroxysmal atrial fibrillation and dual-chamber pacemakers (EudraCT-No: 2011-001134-42) because synergistic effects of the combination of ranolazine and dronedarone to suppress atrial fibrillation were recently described.[15]

Although both trials are phase II studies and do not include patients with heart failure of New York Heart Association class III or IV, we may soon see the first data from two randomized placebo-controlled trials in which ranolazine, a drug with several beneficial mechanisms for treating atrial fibrillation, is tested in the clinical setting and maybe in the near future even in heart failure patients.

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