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Investigation of a new antiarrhythmic mechanism: combined modulation of $I_{K,ATP}$ and I_{Kr} to reduce dispersion of ventricular repolarization

Background for the studies

Sudden cardiac death, which is mostly caused by malignant ventricular cardiac arrhythmias, is a leading cause of death in industrial developed countries, and in Hungary. Ventricular fibrillation, the most serious ventricular arrhythmia, kills at least 600 000 people annually in Europe and the USA combined. Most currently available antiarrhythmic drugs were designed to target ion channels, but their use has decreased over the past 15 years due to their capacity of paradoxically causing arrhythmias (1): class I/C type Na^+ channel blockers increased mortality in survivors of myocardial infarction despite their ability to reduce the incidence of premature ventricular beats (2,3). Drugs that prolonged repolarization and effective refractory period by selective inhibition of the rapid component of the delayed rectifier potassium channels (I_{Kr}), also increased mortality (4). Selective I_{Kr} blocking drugs possess a reverse use-dependent repolarization prolonging effect, that is they prolong repolarization at slow heart rate (increased cycle lengths) more than at high heart rate, when it would be most needed, in case of tachycardia or during the development of early extrasystoles. This effect can promote the development of early afterdepolarizations; moreover these drugs lengthen repolarization in a different extent in various cell types leading to an increase in dispersion of repolarization. Both effects can play a role in the occurrence of life threatening arrhythmias, including Torsades de Pointes ventricular tachycardia (TdP) and ventricular fibrillation (5).

I_{Kr} blockers prolong the action potential duration (APD) and effective refractory period (ERP) and are therefore very effective in diminishing re-entry type arrhythmias (6-10). Based on the above, a treatment that would block I_{Kr} in a less reverse use-dependent way and in similar extent in different cardiac tissue types (i.e. Purkinje fibre vs. ventricular muscle) would be far safer for the management of cardiac arrhythmias. However, reverse use-dependency seems to be an intrinsic property of cardiac tissue, a necessary consequence of selective K^+ channel block (11). Combined inward and outward current block resembling the mode of action of amiodarone was proposed to avoid this problem. Alternatively, the increase of one type of outward (K^+) current and decrease of another type of outward current can theoretically achieve APD prolongation while minimizing the proarrhythmic effect of repolarization prolongation at slow heart rates. Such combined effects would alleviate the large unmet need for the development of novel antiarrhythmic compounds that would treat arrhythmias more safely.

In the present project, we chose the activation of the ATP-sensitive K^+ (K_{ATP}) channels to activate a voltage-independent potassium current limiting the excessive prolongation of repolarization by I_{Kr} block at slow heart rate. K_{ATP} channels were first identified in cardiac muscle (12) and link cardiac metabolism to cell membrane excitability. Many studies have demonstrated that activation of sarcolemmal K_{ATP} channels under hypoxic or ischemic conditions is cardioprotective (13-17). K_{ATP} channels have also been implicated in the powerful cardioprotective phenomenon of ischemic preconditioning (18, 19). K_{ATP} openers have been shown to abolish triggered and spontaneous activity in dog Purkinje fibre (20), exerted antiarrhythmic activity in our coronary artery occlusion/reperfusion (21) and experimental acute myocardial infarction models (22). As another potential mechanism for K_{ATP} opening mediated cardioprotection, we have identified that K_{ATP} opening exerts beneficial effects on Ca^{2+} homeostasis via hyperpolarization of the resting membrane potential (23-25). On the other hand, excessive shortening of the AP and ERP in ischaemia by K_{ATP} opening may be potentially proarrhythmic and may increase the incidence of re-entry type arrhythmias, especially if the AP shortening is heterogenously distributed in the heart (26, 27).

Results

Combined modulation of $I_{K,ATP}$ and I_{Kr} reduces reverse use-dependency and repolarization heterogeneity, but the beneficial effects are limited by vasorelaxation

The effects of activation of the cardioprotective outward $I_{K,ATP}$ current, that could ideally limit the excessive repolarisation prolongation of I_{Kr} blockers and could also decrease heterogeneity of repolarisation in various types of cardiac tissues were investigated in our present study. These beneficial effects could contribute to a new and safer therapeutic option for the management of ventricular arrhythmias. Action potential measurements were carried out in dog and rabbit Purkinje fibre and ventricular muscle preparations by conventional intracellular microelectrode technique. For I_{Kr} block dofetilide (50 and 300 nM in dogs; 12.5 nM in rabbits) and for $I_{K,ATP}$ activation pinacidil (1 and 3 uM in dogs; 20 uM in rabbits) and P-1075 (10-75 nM) were used. Vasoreactivity was investigated on endothelium deprived isolated rat aortas and porcine coronary arteries. Arterial rings were contracted with KCl and relaxed by pinacidil in the presence and absence of dofetilide. Repolarization was significantly prolonged at all applied stimulation frequencies by dofetilide and combination of dofetilide + pinacidil or P-1075 as well. In rabbit preparations, the action potential duration, primarily at slow stimulation frequency (40/min), was increased at lesser degree by the combination of dofetilide + pinacidil than with dofetilide alone (46.1 ± 7.3 ms (31.6 %) vs. 59.2 ± 7.6 ms (41.5 %) in left ventricular muscle and 67.2 ± 14.8 ms* (32.6 %) vs. 97.2 ± 21.5 ms (47 %) in Purkinje fibres; *p<0.05).

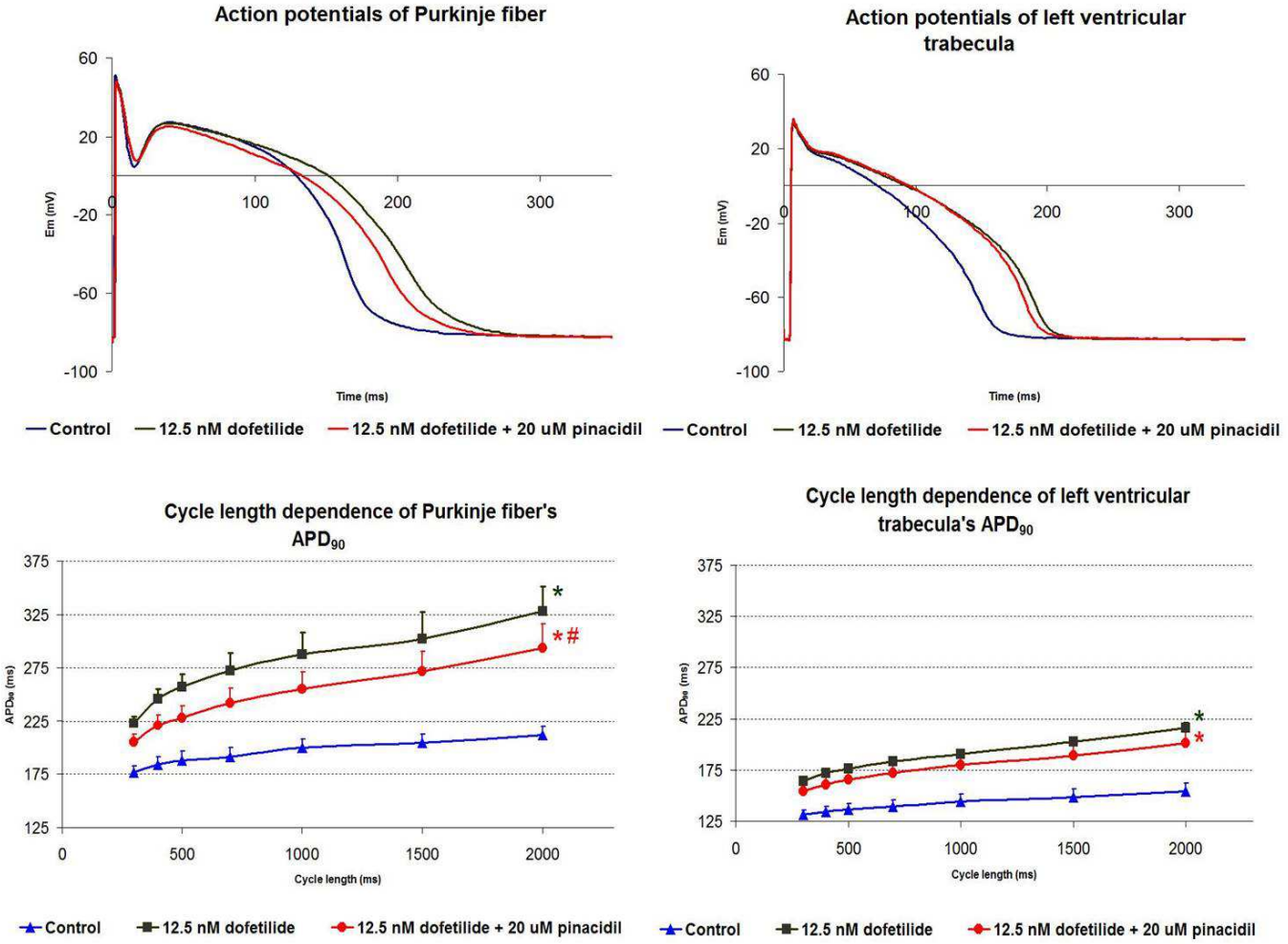

Figure 1. Representative action potential recordings (top panels) and cycle length dependence of action potential durations at 90% repolarization in rabbit Purkinje fibers and left ventricular muscles (bottom panels) following I_{Kr} block (dofetilide) and combination of I_{Kr} block and $I_{K,ATP}$ activation (pinacidil).

A reduction of repolarization heterogeneity was observed by application of combination of dofetilide + pinacidil compared with dofetilide alone. Results obtained from dog preparations showed similar results. Importantly, different sensitivities of Purkinje fibers and papillary muscle preparations to potassium channel modulators were

identified. We concluded that the proarrhythmic reverse use-dependent effects of I_{Kr} blockers and the increased repolarization heterogeneity may be reduced by simultaneous activation of $I_{K,ATP}$. For this aim, cardioselective $I_{K,ATP}$ activators, devoid of reflex tachycardia due to extensive vasodilating effects, would be preferred, since currently available $I_{K,ATP}$ activators cause significant vasorelaxation alone and in combination with I_{Kr} blockers (**Figs 1-3,** not all results are shown due to space limitation).

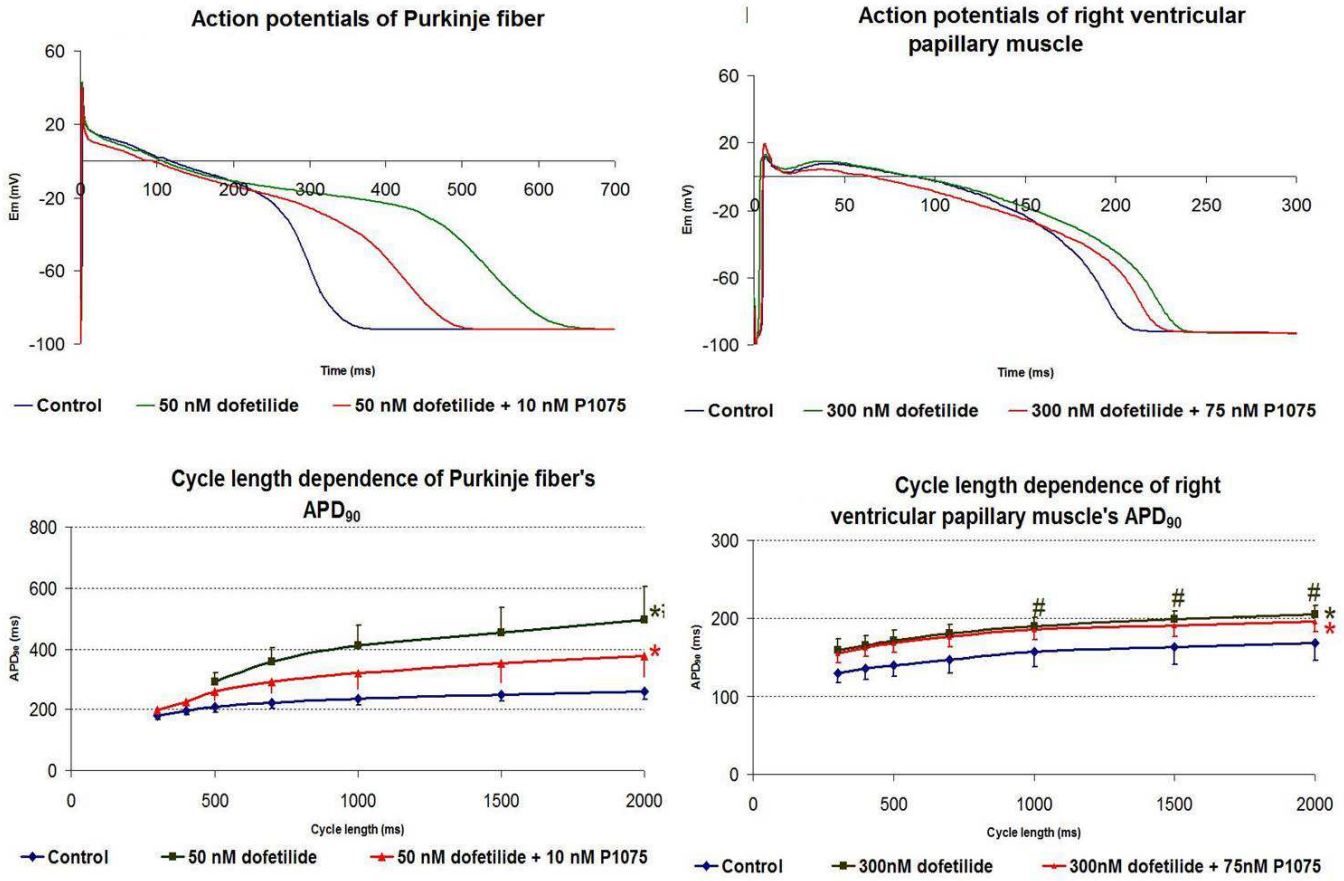

Figure 2. Representative action potential recordings (top panels) and cycle length dependence of action potential durations at 90% repolarization in dog Purkinje fibers and right ventricular papillary muscles (bottom panels) following I_{Kr} block (dofetilide) and combination of I_{Kr} block and $I_{K,ATP}$ activation (P-1075).

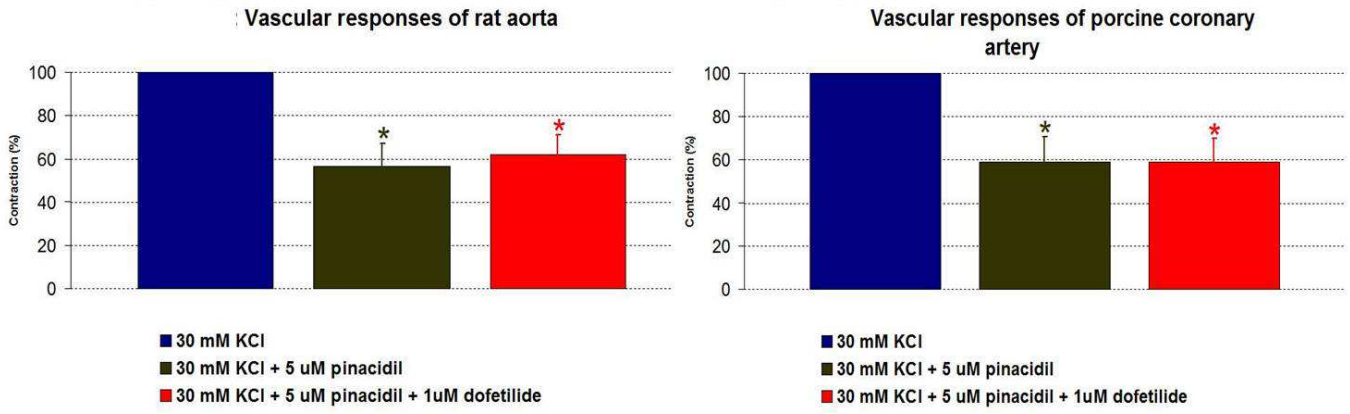

Figure 3. Relative vasorelaxation caused by the $I_{K,ATP}$ activator alone and in combination of the I_{Kr} blocker following pre-contraction by KCl (100%) in rat aorta and in porcine coronary artery. *p<0.05; n=12 and 13, respectively.

These results were continuously reported in conference abstract publications as more data became available (28-30), in 2 publications (31, 32) and another manuscript is currently being prepared. The NKFI grant ID is indicated in these publications, and will be indicated in another paper to be sumbitted by the end of November, 2016.

Investigations on species differences in repolarization reserve and arrhythmia susceptibility in the two most commonly used species for arrhythmia research: dogs and rabbits

The rabbit and the dog are two commonly used species in arrhythmia studies (also in the current project) in order to evaluate the occurrence of cardiac dysrhythmias and their underlying mechanisms. In order to evaluate the effects of combined modification of different potassium currents on arrhythmias in dogs and rabbits, differences in their arrhythmia susceptibility and repolarization characteristics must be investigated. A large and still growing number of animal experimental and clinical studies suggest that the degree of repolarization prolongation does not show a close correlation with subsequent ventricular arrhythmia development. In these cases, without marked prolongation of the QT interval, repolarization reserve may be reduced with a consequent increase in arrhythmia susceptibility. According to the concept of repolarization reserve, normal cardiac repolarization is controlled by different potassium currents in a redundant way, and congenital or acquired (e.g. mild potassium current inhibition by a non-cardiovascular drug) decrease in the function of a single repolarizing current does not always lead to marked repolarization prolongation, since other currents can compensate for the lost function. In the case of reduced repolarization reserve, additional inhibition of another repolarizing current can result in excessive prolongation of repolarization and can provoke serious ventricular arrhythmias. Evidence pointed to a critically important role for the slow component of the delayed rectifier potassium current (I_{Ks}) in ventricular repolarization reserve, however, other potassium currents may also significantly contribute to repolarization reserve. There is considerable variation in the expression of key repolarizing potassium channels in different mammalian species, including dog and rabbit that are frequently used species in pro-arrhythmia models. Therefore, it was reasonable to assume that species specific ion channel expression profiles may result in species dependent alterations in responses to potassium channel blockers. Such differences may significantly influence the value of data obtained in these models for human extrapolation, however, it is unclear how species specific potassium channel expressions translate into differences in arrhythmia development in dogs and rabbits. A possibly important role for I_{K1} has been suggested in repolarization reserve. We studied the effects of combined pharmacological inhibition of I_{K1} (by $BaCl_2$) and I_{Ks} (by HMR1556), as well as I_{K1} (by $BaCl_2$) and I_{Kr} (by dofetilide) on ECG parameters and the incidence of TdP in conscious dogs and anesthetized rabbits. We also investigated whether TdP development was paralleled by increased short-term variability of the QT interval, a novel ECG parameter suggested for more reliable prediction of drug-induced ventricular arrhythmias.

We investigated the effects of repolarization reserve impairment by pharmacological block of I_{K1} in combination with I_{Ks} and I_{Kr} on the incidence of the typical drug-induced arrhythmia, TdP, and different ECG parameters. Heart rates were significantly decreased by combined I_{K1}+I_{Kr} block in both species, while I_{K1}+I_{Ks} inhibition reduced heart rate only in rabbits. Inhibition of I_{Ks} alone as well as I_{K1} alone significantly prolonged the QTc interval in dogs but did not do so in rabbits. Increased QTc intervals by combined potassium channel inhibitions did not appear to be informative on subsequent TdP development in either species.

We found that combined pharmacological inhibition of I_{K1}+I_{Kr} and I_{K1}+I_{Ks} led to repolarization reserve impairment and high incidence of TdP in conscious dogs and anesthetized rabbits. However, dogs and rabbits exhibited markedly different patterns of TdP suggesting that at least some of these currents may play different relative roles in repolarization reserve in the two species. In contrast, our laboratory showed in previously published experiments that both species responded with a high incidence of TdP paralleled by significant increases of short-term variability of the QT interval (STV_{QT}) following I_{Ks}+I_{Kr} inhibitor administration. In this study, a high TdP incidence was observed following inhibition of I_{K1}+I_{Ks} in dogs (67% vs 14% in rabbits). Rabbits exhibited higher TdP incidence after I_{K1}+I_{Kr} block (72% vs 14% in dogs). Increased TdP incidence was associated with significantly larger STV_{QT} in both models.

We concluded that rabbit pro-arrhythmia models based on pharmacologically impaired repolarization reserve may present greater arrhythmia susceptibility and may be more useful than canine models in predicting human electrophysiological responses to drugs affecting cardiac ventricular repolarization. These results also warrant cautious evaluation of the potential pro-arrhythmic adverse effects and cardiovascular safety of candidate compounds in rabbit and dog models. These results were published and discussed in (33, 34). The NKFI grant ID was indicated in the publications.

In vivo and in vitro cardiac electrophysiological effects of chronic amiodarone and desethylamiodarone administration in dogs

Amiodarone (AMIO) is a multi-ion channel modulator (modulating both I_{Kr} and $I_{K,ATP}$) and is considered to be one of the most effective antiarrhytmic agents with lower proarrhythmic risk compared to other currently used antiarrhythmics, however, it possesses serious extracardiac adverse effects which greatly limit its clinical use. It has been suggested that desethylamiodarone (DEA), the active metabolite of AMIO might have similar cardiac electrophysiological effects to the parent compound. We proposed that chronic DEA treatment would exert similar electrophysiological properties compared to chronic AMIO application, albeit without AMIO related adverse effects. Electrocardiograms (ECGs) were recorded from conscious dogs, RR, QT, QT_c intervals were measured, short-term variability of the QT interval (STV_{QT}) was calculated. Action potential (AP) (V_{max}, APD_{90}) parameters and cardiac ionic currents were measured by conventional microelectrode and patch-clamp techniques, respectively, to assess the *in vitro* cardiac electrophysiological effects of chronic (4 weeks) oral DEA (30 mg/kg/day) and AMIO (45 mg/kg/day) administration in Beagle dogs. AMIO and DEA tissue levels were also measured. Significantly increased RR (by 13.3 %; 39.4 %) and prolonged QT (by 14.5 %; 23.1 %) and QTc (by 9.6 %; 11.3 %;) intervals were measured following both 4-week DEA and AMIO administration compared to their respective baseline values. No differences were observed in STV_{QT} values. V_{max} values were significantly reduced by 21.0 % and 14.4 %, moreover APD_{90} was slightly but significantly prolonged by 6.0 % and 10.0 % as a result of DEA or AMIO application compared to the control group receiving vehicle. Decreased It_o current in the AMIO group, significantly reduced I_{Kr} current and a decreasing trend in I_{KAch} current in both DEA and AMIO groups were demonstrated by patch-clamp experiments. The tissue levels for DEA both in DEA and AMIO treated groups were similar (10.5 ± 6.8 vs. 14.7 ± 9.0 in right atrium and 22.2 ± 12.0 vs. 29.7 ± 17.0 μg/tissue g in left ventricle), but the AMIO treatment resulted in higher kidney (+ 61.8 %) and lung (+ 55.9 %) DEA levels and certainly led to high AMIO levels as well in all tissue types.

We concluded that chronic DEA treatment in dogs resulted in similar cardiac electrophysiological changes compared to AMIO administration without potentially harmful tissue AMIO accumulation. It might be possible to substitute chronic AMIO treatment with chronic DEA application that could represent a similarly effective but significantly safer therapeutic option for the management of cardiac arrhythmias. The results have been presented in abstract form (35) and the manuscript will be submitted published by the end of November, 2016. The NKFI grant ID was indicated in the abstract publication and will be included in the final paper as well.

Validation of our rabbit in vivo proarrhythmia model with cisapride, a known drug with proarrhythmic adverse effects

The reliable assessment of proarrhythmic side effects of drugs in development is essential but remains elusive. Recently, in addition to conventional ECG measurements, the short-term beat-to-beat variability of the QT interval (STV_{QT}) has been suggested as a novel parameter to predict drug induced ventricular arrhythmias due to repolarization disturbances. We have recently created a rabbit proarrhythmia model based on impaired repolarization reserve due to the pharmacological block of the slow component of the delayed rectifier potassium current (I_{Ks}).

To test whether this model would identify a drug with known Torsades des Pointes (TdP) liability, cisapride, a prokinetic agent withdrawn from the market in many countries due to its proarrhythmic adverse effects, was administered to anaesthetized rabbits (n=10 in all groups) with and without pre-treatment with the I_{Ks} blocker HMR-1556 (0.1 mg/kg; i.v.). HMR-1556 on its own did not prolong the QTc interval, did not increase STV_{QT} and did not cause any TdP. Cisapride on its own (1 mg/kg; i.v.) moderately increased the QTc interval, STV_{QT} and caused TdP in 10% of the animals. The combination of HMR-1556 and cisapride further and significantly increased STV_{QT} (4.4 ± 0.34 vs. 2.3 ± 0.34 ms in controls) and incidence of TdP (50%) compared to cisapride alone.

We concluded that these results confirmed that our rabbit proarrhythmia model with impaired repolarization reserve may be useful in identifying compounds with drug induced ventricular arrhythmia provoking adverse effect liability. The NKFI project ID was indicated in the abstract publication of these results (36).

Dissemination of Results

The results of the studies were presented at national and international scientific meetings. The results were published in high impact international scientific journals. In addition to the above mentioned papers, the PI also

published a review paper on aspects of atrial arrhythmias and multi-ion channel modulation (37), indicating the NKFI grant ID. The studies of the project will contribute to the PhD thesis of Tibor Hornyik, Viktor Juhász and Richárd Varga (project participants and PhD students of the PI). They are expected to defend their thesis in the next 5-6 months.

Possible Exploitation of the Results

The described synergistic antiarrhythmic mechanisms could be utilized in new treatment strategies of arrhythmias associated with heart failure. The performed studies were basic scientific investigations, however, the results may offer new mechanisms for the development of novel antiarrhythmic drugs based on the investigated synergistic mechanisms having a markedly reduced proarrhythmic risk compared to previous pharmacological antiarrhythmic interventions. This novel concept would hold significant market value, since current antiarrhythmic pharmacological compound development is hampered by proarrhythmic side effects. It should be noted, that we presently lack K_{ATP} channel openers with sufficient cardiac selectivity (as also shown by our studies). The development of cardiac selective $I_{K,ATP}$ activators would require an industrial project, where molecular libraries should be subjected to high-throughput screening to identify molecules that open cardiac K_{ATP} channels at significantly lower concentrations than those found in vascular smooth muscle.

Alterations in the Budget

There were unforseen service costs due to the malfunction of the micromanipulators on the elecrophysiological setup, and their service was essential for the project.
The foreign conference travel and accomodation costs were not exactly as originally planned, due to unforseen changes in the number of conference participations. Importantly, the overall budget spending did not exceed the planned amount. These budget alterations did not affect the completion of the studies.

Alterations in the Project

The project was delayed due to laboratory and building construction delays (beyond the control of the project personnel) and therefore the project was extended by 6 months based on the written permission by NKFI (Dec 17, 2015).

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