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Rate-Dependent Effects of Dofetilide on Epicardial Monophasic Action Potentials in Isolated Rabbit Heart with Atrial Pacing*

Abstract: Dofetilide (UK 68,798), a new antiarrhythmic agent, blocks potassium channels selectively and acts primarily by prolonging repolarization duration. The aim of this study was to investigate rate-dependent repolarization changes due to dofetilide in a fast beating *in-vitro* heart model.

The study was designed using Langendorff perfusion of rabbit hearts at the drug concentrations of 1 nM, 3 nM and 10 nM. The electrophysiological evaluations were performed using the recording of epicardial monophasic action potentials. Atrial pacing was set at the cycle length (ms) of 300, 325, 350, 375 and 400 so that repolarization duration could be measured in different heart rates. The study also focused on the interventricular repolarization heterogeneity between the right and left epicardial regions.

Dofetilide prolonged monophasic action potential duration at 90 % of repolarization on both sides of the epicardium in a concentration- and reverse-rate-dependent manner. However, the rate-dependent prolongation of action potential duration due to dofetilide was not accompanied by increased interventricular dispersion of repolarization. No proarrhythmia due to dofetilide was seen in our model. This may be explained by the rate-dependent stability in repolarization dispersion. Thus, the presented model indicated that dofetilide-induced prolongation of repolarization is not proarrhythmic in isolated fast beating hearts.

Key Words: Dofetilide, Rate dependency, Monophasic action potential duration, Interventricular dispersion, Langendorff perfusion

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Introduction

Dofetilide (UK 68,798) is a selective potassium channel blocker which inhibits the fast component of the delayed rectifying K^+ current (1,2) and acts primarily by prolonging repolarization duration as demonstrated in *in-vitro* preparations (3-6) in animal experiments (7,8) and in human studies (9-12). Previous investigations have shown that the dofetilide-induced prolongation of repolarization duration was prominent at longer cycle lengths (1,3-7,11,12). This phenomenon termed reverse-rate dependency in repolarization duration may induces proarrhythmia such as torsade de pointes (13).

Proarrhythmias may also be correlated with the increase in dispersion of the action potential duration, and the heterogeneity of repolarization duration in various regions of the heart (14-16). Different models have been used to assess the changes in repolarization dispersion due to dofetilide (8-11,17-20). However, there is no published data about the rate-dependent effects of dofetilide on repolarization dispersion in isolated fast beating hearts. It is considered that isolated rabbit hearts with atrial pacing may be suitable for increasing the heart rate in our model.

In recent studies, endocardial interventricular dispersion was reported to depend on heart rate and may be a relevant factor for the initiation of torsade de pointes in bradycardia (21,22). With regard to interventricular dispersion, *in-vitro* interventricular dispersion of repolarization was measured here, using the epicardial action potential recording technique for both sides of the epicardium. It is of interest to know whether dofetilide changes epicardial interventricular dispersion in a rate-dependent manner.

Methods

Isolated heart preparation

Albino rabbits of either sex, weighing 2000-2800 g, were killed by cervical dislocation. The chest was quickly opened and the heart was placed in 50 ml of ice-cold Tyrode's solution with heparin immediately after removal.

The retrograde perfusion of isolated heart began through the aorta in the Langendorff system using a modified Thyrode's solution composed of (in mM) NaCl 129, KCl 4.7, $CaCl_2$ 2.0, $MgCl_2$ 1.0, $NaHCO_3$ 14, NaH_2PO_4 1.0 and glucose 12. The perfusion pressure was adjusted to 75 ± 2 cm H_2O for all experiments. The perfusion solution was indirectly warmed to a constant temperature of 37 °C, using a pump with water circulation. The solution was saturated with a mixture of 95 % oxygen and 5 % carbon dioxide. The heart was freed from the epicardium and peripheral tissue such as lung and fat tissue. The pH value of the perfusion solution was monitored during the experiment and kept at 7.40.

Epicardial monophasic action potentials

Figure 1A shows the experimental setup for *in-vitro* recording of monophasic action potentials (MAPs). Two Ag-AgCl bipolar contact electrodes (Franz MAP probe, electrode spacing 3.5 mm, diameter 4F, EP Technologies Inc., CA) with holders, and plastic arms were positioned on the right and left epicardial surface of ventricles. The electrical continuity between the MAP reference electrode and the epicardium was provided with a sponge as described by Franz et al. (23).

The epicardial monophasic action potentials were preamplified at a filter setting of 0.5-1000 Hz and displayed on an oscilloscope (Heinemann & Gregori GmbH, Kelkheim, Germany). A thermosensitive recorder (Schwarzer Cardioscript CD 6000, Picker, Germany) was used at a paper speed of 100 mm/s. The amplitude of MAP was greater than 5 mV and the isoelectric line was flat. The MAP duration was determined at 90 % of repolarization. The right and left epicardial monophasic action potential durations, $RMAPD_{90}$ and $LMAPD_{90}$, were measured using simultaneous recordings. Figure 1B shows samples of original MAP tracings obtained at different dofetilide concentrations.
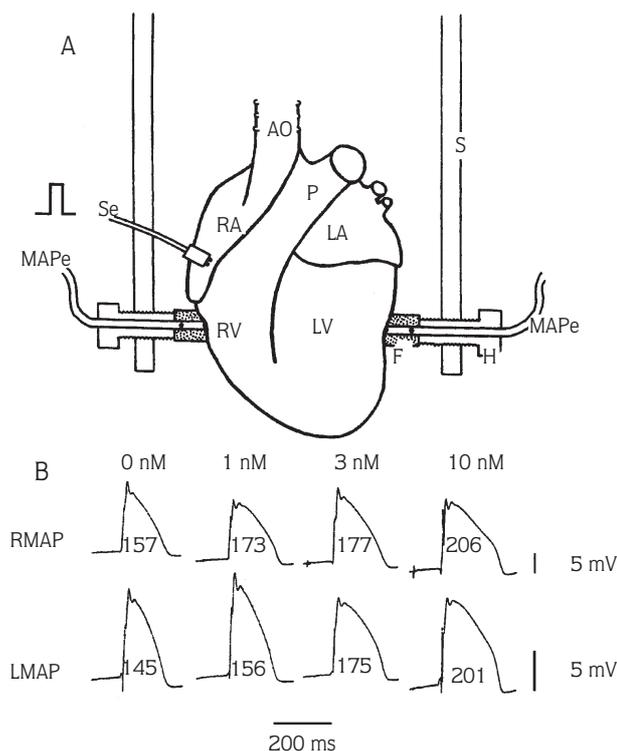

Figure 1. The experimental setup (A) and examples of monophasic action potentials during an experiment (B).
A. MAPe: the bipolar contact MAP electrode, Se: a bipolar stimulation electrode, H: holder for the MAP electrode, F: a foam rubber sponge, S: an elastic arm which allows the MAP electrode to move in accordance with the heart action, AO: the aorta, P: a. pulmonalis, RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle. B. Both right and left epicardial monophasic action potentials (RMAP and LMAP) demonstrate dose-dependent prolongation of repolarization at a constant cycle length of 375 ms. "0 nM" is the pre-drug condition. Durations at 90 % of repolarization are given in ms for each signal.

Protocol of experiments

The pre-drug perfusion lasted 45 min. After this baseline, for each experiment the heart was exposed to dofetilide at concentrations of 1 nM, 3 nM and 10 nM, respectively. Each period of drug perfusion also lasted 45 min.

The spontaneous beat to beat interval at the beginning of the experiments was between 403 and 448 ms. A bipolar silver electrode for atrial pacing was attached to the right atrial appendage and connected to a programmable stimulator (Model 5325, Medtronic Inc., USA). The stimulator generated rectangular pulses with a duration of 2 ms at twice the diastolic threshold.

For both pre-drug and post-drug conditions, the heart was stimulated at cycle lengths (CLs) of 400, 375, 350, 325 and 300 ms, respectively. The stimulation period lasted 2-3 min for each CL. The average of the last three MAP signals in a given experimental condition was used to measure the repolarization duration. In sham experiments (n = 4), no drug was added to the perfusion, but the heart rate was altered using the same CL values. The results of the sham experiments, which are not presented here, were no different from those of pre-drug conditions.

Drug preparation

Dofetilide (UK-68,798, Pfizer Central Research, Kent, England) was dissolved in distilled water acidified by the addition of a solution of HCL. Thus, a stock solution (pH 3) of 10 mM dofetilide was produced and it was kept at -18 °C. The stock was diluted with Tyrode's solution to the desired concentrations of 1 nM, 3 nM and 10 nM on the day of the experiment.

Data analysis

Data are represented as mean ± SEM. The statistical comparisons were performed using one-way ANOVA. Comparison of repolarization duration between the pre-drug and post-drug period was done by the paired t-test. Student's t-tests, non-paired or also paired, were used for rate-dependent changes in prolongation of repolarization and for dispersion changes. Significance was accepted at the 0.05 level of probability.

Results

The repolarization durations

The monophasic action potential durations for both the pre- and post-drug conditions are given in the Table. Firstly, the monophasic action potential duration in the pre-drug condition depended on the heart rate. The $RMAPD_{90}$, which was found to be 153 ± 3 ms at a CL of 300 ms, increased to 172 ± 4 ms at a CL of 400 ms. The $LMAPD_{90}$ was 163 ± 4 ms in pre-drug condition at a CL of 400 ms. This value decreased to 145 ± 3 ms at a CL of 300 ms.

Secondly, the $RMAPD_{90}$ and $LMAPD_{90}$ were prolonged due to dofetilide concentration. The dofetilide perfusion even at the lowest concentration (1 nM) causes significant lengthening of repolarization on both sides of the epicardium. Exceptionally, at a CL of 325 ms and of 300 ms, the drug-induced prolongation of $LMAPD_{90}$ due to the concentration of 1 nM is not statistically significant (Table).

Dose and rate dependency of dofetilide-induced repolarization prolongation

Figures 2A and B show dose- and rate-dependent changes in monophasic action potential duration ($MAPD_{90}$). Firstly, for each CL, the difference between the pre-drug value (0 nM) and post-drug values (1 nM, 3 nM and 10 nM) was calculated to find the prolongation of repolarization. Secondly, to assess the rate-dependency of repolarization prolongation for each drug

Table.   Effects of dofetilide on monophasic action potential durations of right epicardium ($RMAPD_{90}$) and of left epicardium ($LMAPD_{90}$). The values are given as mean ± SEM (n = 7). The post-drug durations of monophasic action potential (1 nM, 3 nM, 10 nM) are significantly greater than the pre-drug duration (0 nM) (* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$, with paired t-test). N.S.: non-significant increase.

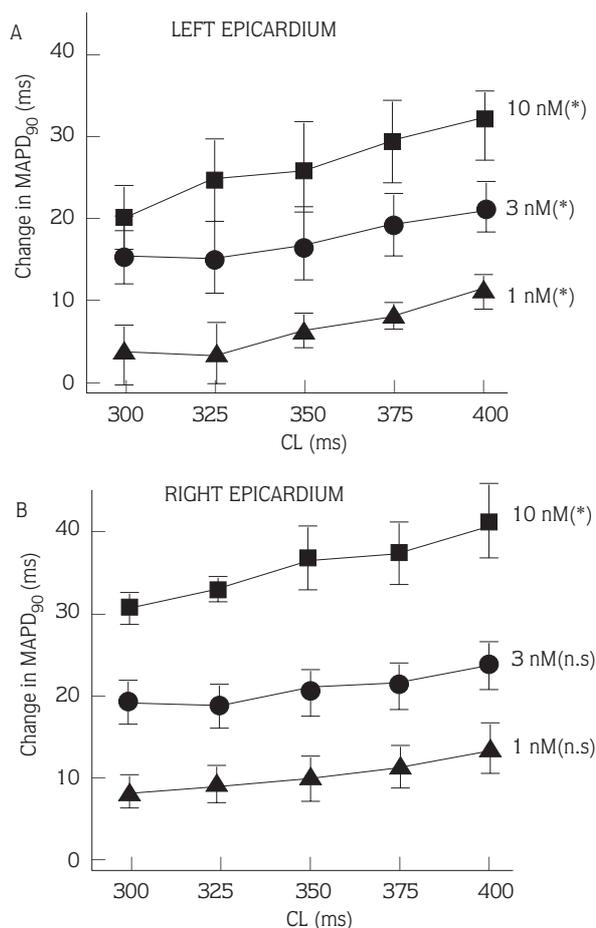| Cycle Length (ms)	400	375	350	325	300
$RMAPD_{90}$ (ms)					
0 nM	172 ± 4	169 ± 4	165 ± 4	159 ± 3	153 ± 3
1 nM	185 ± 2 **	180 ± 2 **	172 ± 3 *	168 ± 3 **	160 ± 3 **
3 nM	195 ± 4 ***	190 ± 4 ***	183 ± 5 ***	177 ± 4 ***	171 ± 4 ***
10 nM	212 ± 4 ***	206 ± 3 ***	200 ± 2 ***	191 ± 2 ***	182 ± 2 ***
$LMAPD_{90}$ (ms)					
0 nM	163 ± 4	160 ± 4	157 ± 4	152 ± 4	145 ± 3
1 nM	174 ± 3 **	168 ± 4 ***	163 ± 4 *	156 ± 4 (n.s.)	149 ± 5 (n.s.)
3 nM	182 ± 4 ***	178 ± 4 **	174 ± 6 **	169 ± 6 *	161 ± 5 **
10 nM	195 ± 3 ***	189 ± 4 ***	183 ± 4 **	177 ± 4 **	166 ± 4 **

Figure 2.   Rate-dependent changes in monophasic action potential duration (MAPD$_{90}$).
The change means dofetilide-induced prolongation of both left epicardial MAPD$_{90}$ (A) and right epicardial MAPD$_{90}$ (B). The values at a CL of 300 ms were compared to those at a CL of 400 ms. * change in MAPD$_{90}$ is significant (p < 0.05). N.S.: non-significant.

In the case of 10 nM dofetilide, drug-induced prolongation at a CL of 400 ms was found to be greater on both sides of the ventricle in comparison with that of a CL of 300 ms (p < 0.05, Figures 2A and B). The reverse-rate-dependency was also found with relatively lower drug concentrations (1 nM and 3 nM) on the left ventricle, but not on the right ventricle (p < 0.05). In other words, reverse-rate- dependent prolongation on the left side was statistically significant at all the concentrations tested (1 nM, 3 nM, 10 nM). In contrast, only a 10 nM concentration caused reverse-rate-dependent prolongation of repolarization on the right ventricle.

Interventricular dispersion of repolarization

The interventricular dispersion was defined as the absolute value of the difference between RMAPD$_{90}$ and LMAPD$_{90}$. Figure 3 shows the rate-dependent dispersion of repolarization duration for both pre-drug (0 nM) and post-drug conditions. Dofetilide at concentrations of 1 nM and 3 nM did not increase the dispersion of repolarization compared to those of pre-drugs (0 nM). Although the dispersion seems to be enhanced by the

concentration, the prolongation at a CL of 300 ms was statistically compared to that at a CL of 400 ms.

The maximum prolongation of RMAPD$_{90}$ was obtained with 10 nM dofetilide (Figure 2B). This value was 40.4 ± 4.3 ms at a CL of 400 ms. In contrast, 1 nM dofetilide prolonged the RMAPD$_{90}$ only 12.7 ± 2.9 ms at a CL of 400 ms. The maximal change in LMAPD$_{90}$ after the application of 10 nM dofetilide was 32.1 ± 3.4 ms at a CL of 400 ms (Figure 2A). At the same CL, 1 nM dofetile caused 11.0 ± 1.9 ms prolongation of repolarization on the left side. As a result, a higher dose of dofetilide caused greater prolongation of repolarization on both sides of the epicardium.
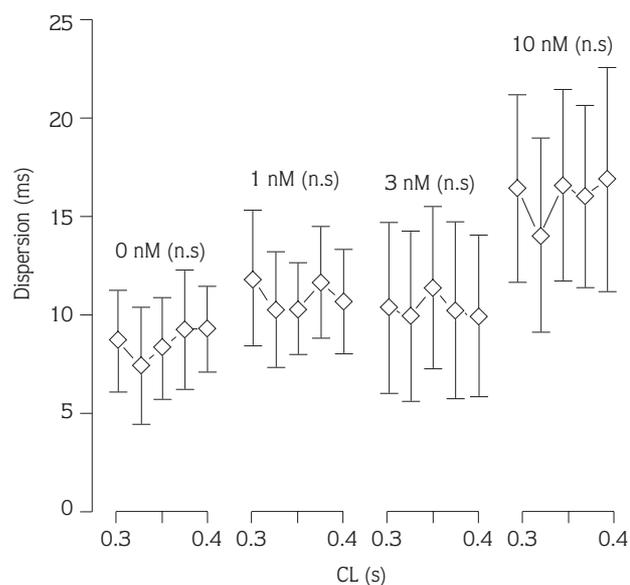

Figure 3.   Pre- and post-drug epicardial interventricular dispersions of repolarization at different heart rates.
The values at a CL of 300 ms were compared to those at a CL of 400 ms, for a given concentration. N.S: non-significant rate dependency in dispersion (p < 0.05, paired t-test). In comparison with pre-drug dispersion (0 nM), the increased dispersion at a concentration of 10 nM is also not statistically significant (p = 0.064, ANOVA)

highest concentration of dofetilide (10 nM), this change was not statistically significant because of greater standard deviations. In the pre-drug, dispersion was not dependent on the CL. Similarly, there was no correlation between the heart rate and interventricular dispersion in the cases of dofetilide perfusions at concentrations of 1 nM and 3 nM. The interventricular dispersion of repolarization at the highest concentration (10 nM) seems to be prominent, but this prominent dispersion was also not clearly dependent on heart rate.

Discussion

As shown in the Table, dofetilide caused lengthening in MAP duration even at the lowest concentration (1 nM) tested. Dofetilide-induced prolongation of repolarization depended on both cycle length and drug concentration. The prolongation was greater with increased cycle lengths (Figures 2A and B).

In comparison to previous microelectrode studies (3-6), the absolute change in CL was relatively smaller in the present model. For example, Tande et al. (3) performed stimulation at a CL of 500 ms up to 2000 ms to assess rate-dependent prolongation of action potential duration with a wide range. In contrast, we used faster pacing rates depending on the presence of spontaneous sinoatrial nodal activity. Although the maximal change in CL was only 100 ms, it was possible to show the reverse-rate- dependent changes in repolarization duration in the presented model. Thus, the data obtained here by monophasic action potential recording may confirm that dofetilide causes in-vitro reverse- or negative-rate-dependent prolongation of repolarization (3-6).

On the other hand, we have limited the increase in drug concentration with 10 nM. It was found that a high dosage of dofetilide, being 0.1 µM, caused second degree A-V blocks in isolated rabbit heart, if the CL was shortened by atrial pacing, but no proarrhythmic activity such as extrasystol or ventricular tachycardia was seen due to 0.1 µM dofetilide (un-published data). AV conduction was affected by the high dosage of dofetilide in both the closed-chest dog model of Satoh et al. (24) and the in-vivo rabbit experiments of Lu et al. (25). The increased concentration dofetilide also induces polymorphic ventricular tachycardia as well as ventricular fibrillation (25).

In healthy volunteers, dofetilide caused prolongation of the QT interval in a reverse- rate- dependent manner (11,12). In contrast, dofetilide did not produce rate-dependent changes in the prolongation of the QT interval in patients with ischemic heart disease (9). It was also reported that dofetilide did not induce reverse- rate-dependent prolongation of monophasic action potentials in patients with ventricular tachycardia (10).

The present study is limited as it is an in-vitro model and does not simulate heart disease. The main purpose of this study was to investigate not only rate-dependent prolongation but also rate-dependent changes in repolarization dispersion inducing faster heart rates.

The drug-induced increase in dispersion of ventricular repolarization may heighten the risk of ventricular proarrhythmia (15,16). Therefore, the antiarrhythmic efficacy of the drug is probably decreased (15,16). The effects of dofetilide on the dispersion of repolarization were assessed in patients (9,10), healthy subjects (11) and in-vivo animal models (8,17). Gwilt et al. (17) have reported that dofetilide reduced the pacing- induced heterogeneity of epicardial repolarization in open- chest dogs. No effect of dofetilide on repolarization dispersion was determined in humans (9-11) or in post-infarcted anaesthetized dogs (8). These previous dispersion results were obtained using monophasic action potential recording from the right ventricular endocardium (10) or using surface ECG recordings for QT interval measurement (8,9,11,17).

In the present in-vitro model, the interventricular dispersion seems to be increased by relatively higher dosages, but this dose- dependent increase was not significant. Obviously, changes in dispersion did not depend on heart rate (p < 0.05). Thus, stable dispersion in different heart rates might explain the fact that the dofetilide does not cause proarrhythmia in isolated rabbit hearts.

Gillis et al. (18,20) and D'Alonzo et al. (19) have measured some effects of dofetilide using in-vitro rabbit hearts. In all of these studies (18-20), no measurement related to the rate- dependent repolarization changes induced by dofetilide was obtained. Dofetilide prolonged monophasic action potential duration in both sham and hypertrophied hearts at a concentration of 15 nM (18). Dofetilide was also tested in a drug combination with 4-aminopyridine (20). This combination enhanced the

dispersion of the repolarization in isolated rabbit hearts. The increase in dispersion was greater in a hypertrophied heart than the increase of dispersion in a non-hypertrophied one (20). This enhanced dispersion (20) may induce ventricular fibrillation in an isolated rabbit heart. The ventricular fibrillation in an isolated rabbit heart (20) may also be related to ventricular hypertrophy and/or drug combinations including 4-aminopyridine, because neither ventricular proarrhythmic activity nor afterdepolarization was seen in the present model even at perfusion of 0.1 μM dofetilide (unpublished data). Similarly, D'Alonzo et al. (19) found that dofetilide, at concentrations from 0.1 μM to 0.5 μM, did not induce proarrhythmia in isolated spontaneously beating rabbit hearts. However, if the acetylcholine and/or the methoxamine was combined with dofetilide, early afterdepolarization and/or torsade de pointes was induced in their model (19).

Dofetilide was found to be an effective and safe antiarrhythmic in the treatments of atrial fibrillation and atrial fatter (26-28). There was a small risk (3 %) of proarrhythmic activity in patients with atrial fibrillation or with flutter (26). It is likely that dofetilide affects the ventricular repolarization of the heart by supraventricular arrhythmia unless inducing proarrhythmia (26). It was considered that class III antiarrhythmic agents possess less proarrhythmic activity in fast beating hearts (13). On the other hand, dofetilide elevated the incidence of torsade de pointes with enhanced interventricular dispersion of monophasic action potential (MAPD) in a novel dog model (22), which is discussed below.

It was reported that the interventricular difference in MAPD showed very strong bradycardia dependence and it was much larger than intraventricular dispersion under ventricular pacing in a dog model with A-V ablation (21). Moreover, the interventricular dispersion may be more important than intraventricular dispersion for induction of torsade de pointes (21). Van Opstal et al. (22) have used a similar dog model and they have examined the dofetilide-induced rate-dependency of repolarization prolongation and of dispersion. It was demonstrated that a dofetilide-induced increase in the interventricular dispersion of endocardial repolarization elevated the incidence of torsade de pointes (22).

In our opinion, the pacing side should be considered an important factor for the evaluation of drug-induced repolarization changes and for the induction of arrhythmias, because an intact heart with atrial pacing may show a different epicardial repolarization dispersion in comparison to that with ventricular pacing (14). The atrial pacing was applied here to assess the *in-vitro* effect of dofetilide on the dispersion of repolarization in fast heart rates, in the absence of A-V ablation and ventricular pacing. Depending on our experimental procedure, the presented results are not directly comparable to those of the dog model mentioned (22).

Conclusion

Dofetilide causes reverse-rate-dependent prolongation of repolarization duration in atrial- paced isolated rabbit hearts. Parallel to this finding, the dispersion of repolarization was stable in different heart rates and no proarrhythmia was seen. Therefore, the dofetilide-induced repolarization prolongation in the presented model might indicate a safely antiarrhythmic efficacy in fast beating hearts driven from the atrium.

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