

Synergistic Effect of Dofetilide and Mexiletine on Prevention of Atrial Fibrillation

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Background—Although atrial fibrillation (AF) is the most common abnormal heart rhythm and its prevalence continues to rise, there is a marked paucity of effective and safe antiarrhythmic drugs for AF. This study was done to test whether combined use of dofetilide and mexiletine exhibits not only a synergistic effect on AF suppression but also a safer profile in drug-induced ventricular proarrhythmias.

Methods and Results—The effects of dofetilide plus mexiletine on atrial effective refractory period (ERP), AF inducibility, QT, and QT-related ventricular arrhythmias were studied using the isolated arterially perfused rabbit atrial and ventricular wedge preparations. Dofetilide or mexiletine alone mildly to moderately prolonged atrial ERP, but their combined use produced a markedly rate-dependent increase in atrial ERP. Dofetilide (3 nmol/L) plus mexiletine (10 μ mol/L) increased the ERP by 28.2% from 72.2 ± 5.7 to 92.8 ± 5.9 ms ($n=9$, $P<0.01$) at a pacing rate of 0.5 Hz and by 94.5% from 91.7 ± 5.2 to 178.3 ± 12.0 ms ($n=9$, $P<0.01$) at 3.3 Hz. Dofetilide plus mexiletine strongly suppressed AF inducibility. On the other hand, dofetilide at 10 nmol/L produced marked QT and T_{p-e} prolongation, steeper QT-BCL and T_{p-e} -BCL slopes, and induced early afterdepolarizations and torsade de pointes in the ventricular wedges. Mexiletine at 10 μ mol/L reduced dofetilide-induced QT and T_{p-e} prolongation, QT-BCL and T_{p-e} -BCL slopes, and abolished early afterdepolarizations and torsade de pointes.

Conclusions—In rabbits, combined use of dofetilide and mexiletine not only synergistically increases atrial ERP and effectively suppresses AF inducibility, but also markedly reduces QT liability and torsade de pointes risk posed by dofetilide alone. (*J Am Heart Assoc.* 2017;6:e005482. DOI: 10.1161/JAHA.117.005482.)

Key Words: atrial fibrillation • dofetilide • mexiletine • QT prolongation • torsade de pointes

Atrial fibrillation (AF) is the most common abnormal heart rhythm affecting ≈ 5.2 million people in United States, more than 10 million in China^{1,2}, and 33 million worldwide.³ Despite improvements in primary and secondary prevention of coronary artery disease, and effective treatment of

hypertension and other heart diseases, the AF prevalence continues to rise. The rise in AF may, at least in part, be attributable to the longer average life span of humans. It is projected that AF prevalence will increase to 12.1 million cases in 2030 in the United States.⁴ AF predisposes patients, particularly the elderly, to a higher risk for stroke, heart failure, and death.

One of the important treatments for AF is to restore and maintain a normal heart rhythm. Currently, there are 2 clinical approaches for this purpose: (1) antiarrhythmic drug therapy; and (2) radiofrequency catheter ablation. Both approaches have advantages and disadvantages, and both are insufficient to eliminate AF. There is a higher reoccurrence rate of AF when patients are treated with an antiarrhythmic drug than radiofrequency catheter ablation because of relatively inconsistent efficacy and incidence of adverse effects of antiarrhythmic drugs.⁵

While there are relatively more selections of antiarrhythmic drugs for the patients with AF who have a structurally normal heart, few are available for the patients with a depressed left ventricular systolic function despite the fact that AF is more common in these patients. For example, in patients with heart

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failure, amiodarone is the only choice for these patients according to the guideline of European Society of Cardiology for the management of AF in 2012,⁶ and dofetilide, which is available in United States but not Europe, together with amiodarone are the only 2 listed in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline.⁷ Amiodarone is the most effective antiarrhythmic drug, but it has several serious extracardiac adverse effects including thyroid dysfunction, lung toxicity, and liver injury. Dofetilide is, on the other hand, a well-tolerated antiarrhythmic drug, and as a pure I_{Kr} blocker its efficacy in AF treatment is dose dependent (ie, a higher dose was associated with a higher rate of conversion and maintaining sinus rhythm).⁸ In parallel with increased efficacy, dofetilide at higher doses results in more prominent QT prolongation that may lead to a life-threatening ventricular arrhythmia termed torsade de pointes (TdP).^{8,9} Because of this, dofetilide is often used at suboptimal doses in order to reduce its proarrhythmic risk. Ironically, clinicians want larger doses for better inhibition of AF on the one hand, but are afraid of its cardiac toxicity on the other hand. This dilemma has greatly limited clinicians' ability to treat AF.

Our and others' recent clinical study demonstrates that Class Ib antiarrhythmic drugs such as mexiletine and lidocaine that inhibit fast as well as late sodium current¹⁰ can significantly attenuate acquired QT prolongation and acutely terminate TdP episodes including those induced by dofetilide.^{11,12} This naturally raised an interesting question of whether mexiletine and dofetilide could work together to more effectively treat AF and to markedly reduce TdP risk. To test this hypothesis, we tested the effects of combined use of mexiletine and dofetilide on atrial effective refractory period, on AF inducibility and TdP incidence in the arterially perfused rabbit atrial and ventricular wedge preparations.

Methods and Materials

Arterially Perfused Rabbit Atrial, Ventricular Wedge Preparations and Electrophysiologic Recordings

All procedures were performed in accordance with institutional guidelines and approved by the Committee on the Ethics of Animal Experiments of the Medical School of Xi'an Jiaotong University. Rabbits (New Zealand White) of either sex, weighing 2.0 to 2.8 kg were injected with heparin (800 U/kg) via an ear vein and anesthetized by intramuscular injection of xylazine (5 mg/kg) and intravenous administration of ketamine HCl (30–35 mg/kg, IV). The chest was opened via a left thoracotomy, and the heart was excised and placed in a cardioplegic solution consisting of cold (4°C) normal Tyrode solution.

Surgical preparation of the rabbit atrial and ventricular wedge preparation was essentially similar to that described in our previous studies.^{13,14} Briefly, the atrial wedge preparation was dissected from the left rabbit atria and cannulated via a coronary artery branch, and perfused with a cardioplegic solution. Similarly, the left ventricular wedge preparation was dissected from the rabbit heart and arterially cannulated via a branch of the left coronary artery. The atrial or ventricular wedge preparation was then placed in a small tissue bath and arterially perfused with Tyrode solution containing 4.0 mmol/L K^+ buffered with 95% O_2 and 5% CO_2 at a temperature of $35.7 \pm 0.1^\circ C$. The arterially perfused rabbit atrial preparations were paced at basic cycle lengths (BCLs) of 300, 500, 1000, and 2000 ms, whereas the rabbit left ventricular wedge was paced at 500, 1000, and 2000 ms.

Two extracellular silver/silver chloride electrodes were placed on the endocardial or epicardial surfaces to record bipolar atrial electrograms. A transmural ECG was recorded in the left ventricular wedge preparation using 2 extracellular silver/silver chloride electrodes placed in the bath 0.5 to 1.5 cm from the epicardial and endocardial surfaces of the preparation (Epi: "+" pole). Transmembrane action potential was recorded from the atrial and ventricular wedges using the floating glass microelectrodes. Atrial action potential duration at 90% repolarization (APD_{90}) was used for data analysis. Ventricular action potential was recorded for identification of early afterdepolarization (EAD) induced by dofetilide.

Atrial effective refractory period (ERP) was measured by introducing an extrastimulus (S2) repeatedly every 10 pulses (S1) at 2 times the pacing threshold. ERP was defined as the longest S1–S2 interval that failed to capture the atrial wedge preparation. In the preparations that lost excitation intermittently after drug interventions, the ERP was then considered to be equal to the S1–S1 interval. AF was induced by programming stimulation using single or double extrastimuli (S2 and S3) following BCLs (S1 and S1) of 1000 and 500 ms.

Measurement of QT and T_{p-e} intervals in the isolated arterially perfused ventricular wedge was described in detail previously.^{15–18} Rate-dependent changes in QT and T_{p-e} (ie, QT-BCL and T_{p-e} -BCL slopes) were examined and determined as well.

EAD, EAD-dependent R-on-T extrasystoles and TdP were induced by dofetilide in the rabbit left ventricular wedges, which were paced at a BCL of 2000 ms and perfused with Tyrode solution containing 3 mmol/L K^+ , which is equivalent to hypokalemia in humans. Lower K^+ potentiated the effect of dofetilide to induced EAD, R-on-T, and TdP. The K^+ concentration in Tyrode solution remained the same when the effect of mexiletine on dofetilide-induced EAD, R-on-T, and TdP was examined. TdP score, an index of drug-induced TdP risk, was calculated based on drug-induced changes in QT, T_{p-e} , and appearance of EAD-dependent arrhythmias as described previously.^{16,17}

Study Groups

In the present study, only 1 atrial or ventricular preparation was obtained from each rabbit. The study was divided into the following groups:

1. Effects of dofetilide and dofetilide plus mexiletine on atrial APD₉₀: dofetilide at 3 nmol/L and dofetilide 3 nmol/L plus mexiletine 10 μmol/L (n=9 rabbits); dofetilide at 10 nmol/L and dofetilide 10 nmol/L plus mexiletine 30 μmol/L (n=5 rabbits).
2. Effects of dofetilide and dofetilide plus mexiletine on atrial ERP: dofetilide 3 nmol/L and dofetilide 3 nmol/L plus mexiletine 10 μmol/L (n=9 rabbits); dofetilide 10 nmol/L and dofetilide 10 nmol/L plus mexiletine 30 μmol/L (n=7 rabbits).
3. Effect of dofetilide, mexiletine, and dofetilide plus mexiletine on AF inducibility: dofetilide at 3 nmol/L, mexiletine 10 μmol/L, and dofetilide 3 nmol/L plus mexiletine 10 μmol/L (n=10 rabbits).
4. Effects of dofetilide and dofetilide plus mexiletine on QT, T_{p-e}, and TdP incidence in the rabbit ventricular wedge preparations: dofetilide 10 nmol/L and dofetilide 10 nmol/L plus mexiletine 10 μmol/L (n=9 rabbits).

Data Analysis

Data were expressed as mean ± SEM. Student *t* test was used to determine the statistical significance of differences between control and test conditions. Fisher exact analysis was used to compare statistical difference in incidences between control and test conditions. Significance was defined as a value of *P*<0.05. Both *t* test and Fisher exact analysis

were performed using SigmaPlot version 11.0. N indicates number of rabbits used in each group.

Results

Effects of Dofetilide Plus Mexiletine on the Rabbit Atrial APD and ERP

Mexiletine at 10 μmol/L alone appeared to produce no significant effect in rabbit atrial APD₉₀. Atrial APD₉₀ changed from 91.9±4.3 and 99.6±5.2 ms in control perfusion to 90.0±4.7 and 99.6±5.1 ms at BCLs of 1000 and 500 ms, respectively (n=6, *P*>0.05). As shown in Figure 1, on the other hand, dofetilide (D) at 3 and 10 nmol/L significantly increased atrial endocardial APD₉₀ at BCLs of 1000 and 500 ms, and addition of mexiletine (10 and 30 μmol/L) exhibited no significant additional effect on prolonged atrial APD₉₀ by dofetilide.

Atrial ERP exhibited a flattened but “bell-shaped” response to pacing rates: ERP was mildly shorter at 0.5 and 1 Hz, reached its highest value at 2 Hz, and slightly reduced at 3.3 Hz (Figure 2), which was paralleled to that of APD to pacing rates. Similar blunted responses of rabbit atrial APD and ERP to rate changes were reported previously.^{19–21} The ionic mechanisms responsible for this “bell-shaped” response may be attributable to a much larger transient outward current and a much smaller late sodium current in the rabbit atria compared with the ventricles.^{14,19}

Although mexiletine or dofetilide alone mildly to moderately prolonged atrial ERP, combined use of both produced a marked increase in atrial ERP that was rate dependent (Figure 2). In other words, atrial ERP increased with

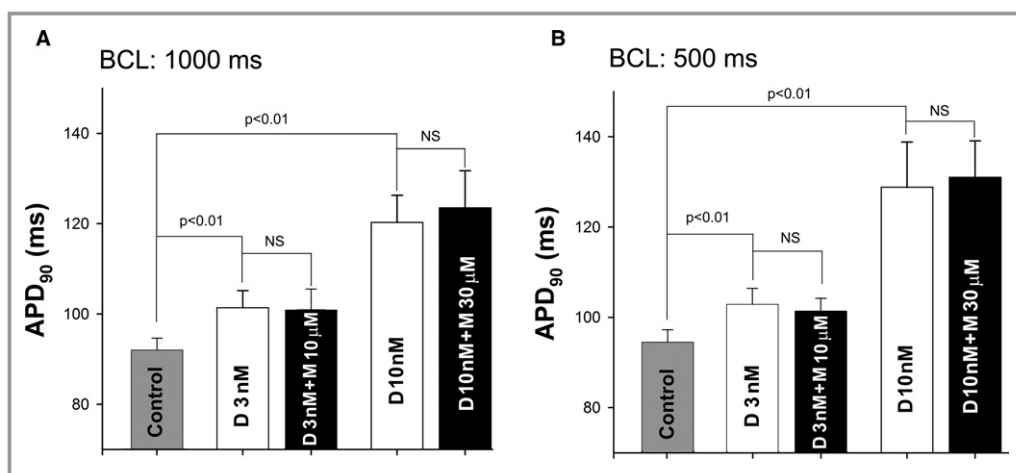


Figure 1. The effect of dofetilide (D) and dofetilide plus mexiletine (M) on rabbit atrial action potential duration at 90% of repolarization (APD₉₀) at basic cycle lengths (BCL) of 1000 ms (A) or 500 ms (B). NS indicates no statistical significance, SEM for error bars, n=9 for dofetilide at 3 nmol/L and dofetilide at 3 nmol/L plus mexiletine at 10 μmol/L, n=5 for dofetilide at 10 nmol/L and dofetilide 10 nmol/L plus mexiletine at 30 μmol/L.

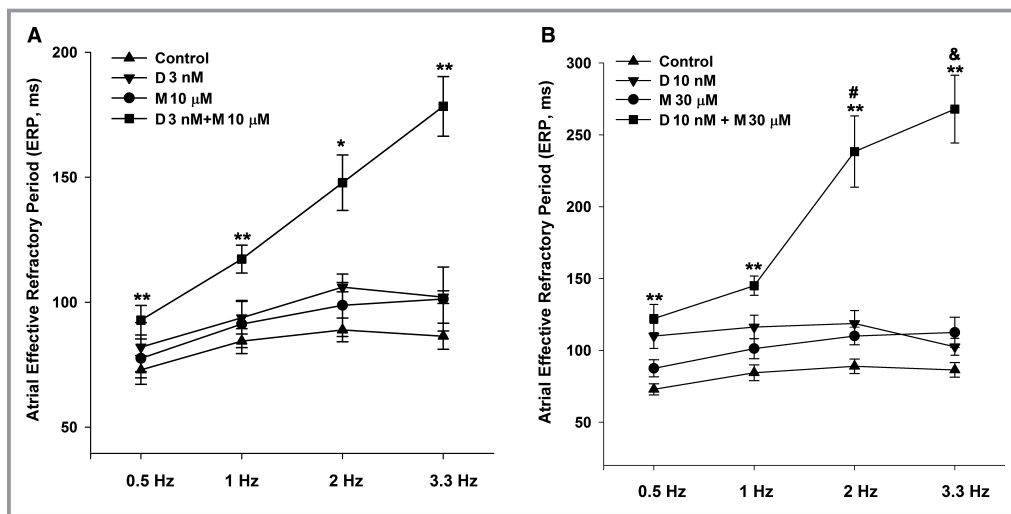


Figure 2. The effect of dofetilide (D), mexiletine (M), and dofetilide plus mexiletine on rabbit atrial effective refractory period (ERP) at different pacing rates. A, Dofetilide at 3 nmol/L or mexiletine at 10 μ mol/L produced a small but statistically significant increase in atrial ERP. Dofetilide at 3 nmol/L plus mexiletine at 10 μ mol/L markedly amplified their individual effects on atrial ERP. B, At relatively higher concentrations, dofetilide at 10 nmol/L plus mexiletine at 10 μ mol/L exhibited more prominent synergistic effect on atrial ERP. * P <0.05 and ** P <0.01 as compared with the ERP in the dofetilide group; #1 out of 9 atrial wedge preparations paced at 2 Hz lost excitation; &4 out of 7 atrial wedge preparations paced at 3.3 Hz lost excitation. Note also that the y -axis scales are different in (A and B). For statistical differences among the study groups and sample size in each group related to this figure, please see the information in the Results section.

increasing pacing rates in the presence of both dofetilide and mexiletine. This was different from atrial ERP changes in response to dofetilide or mexiletine alone in which an increase in atrial ERP reached a plateau at pacing rates of 2 and 3.3 Hz (Figure 2). Dofetilide at 3 nmol/L and mexiletine at 10 μ mol/L are close to their respective therapeutic plasma concentrations in humans.^{22–25} At these concentrations, dofetilide plus mexiletine increased the atrial ERP by 28.2% from 72.2 ± 5.7 to 92.8 ± 5.9 ms ($n=9$, P <0.01) at a pacing rate of 0.5 Hz (ie, BCL: 2000 ms), by 39.7% from

83.9 ± 5.0 to 117.2 ± 5.6 ms ($n=9$, P <0.01) at 1 Hz, by 60.2% from 92.2 ± 4.7 to 147.8 ± 11.1 ms ($n=9$, P <0.05) at 2 Hz, and by 94.5% from 91.7 ± 5.2 to 178.3 ± 12.0 ms ($n=9$, P <0.01) at 3.3 Hz. With combined use of dofetilide and mexiletine at relatively higher concentrations of 10 nmol/L and 30 μ mol/L, respectively, there was intermittent loss of excitation in 4 of 7 atrial wedge preparations at a pacing rate of 3.3 Hz (Figure 3). This indicates that the increase in ERP was underestimated at 3.3 Hz (Figure 2, right panel). At these relatively higher concentrations, none of the atrial

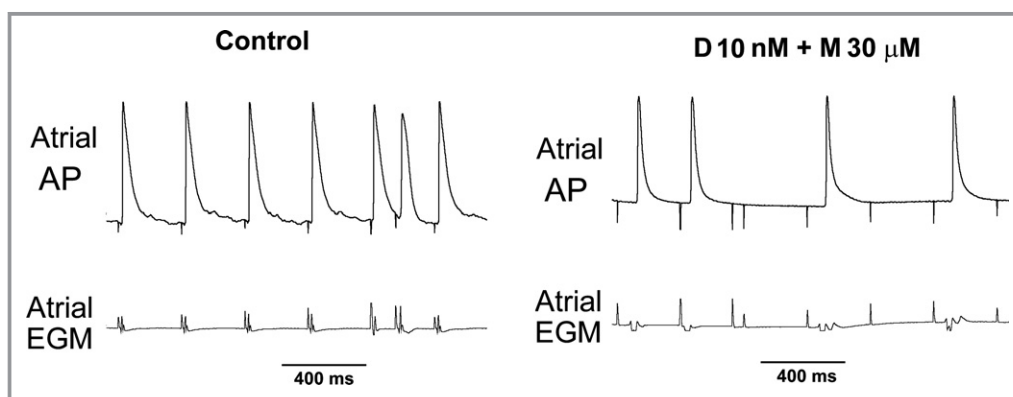


Figure 3. Intermittent loss of excitation was observed in the presence of dofetilide (D) plus mexiletine (M) at relative higher concentrations (10 nmol/L and 30 μ mol/L, respectively) at a pacing rate of 3.3 Hz. AP indicates action potential; EGM, atrial electrogram.

preparations lost excitation when dofetilide or mexiletine was used alone.

Effects of Dofetilide Plus Mexiletine on AF Inducibility

As shown in Figure 4, nonsustained AF in the isolated arterially perfused rabbit atrial wedge preparation could be induced by programmed stimulation with up to 2 extrastimuli (S2 and S3). While mexiletine at 10 $\mu\text{mol/L}$ had little effects on AF induction, dofetilide at concentrations from 3 nmol/L partially suppressed AF inducibility and reduced AF duration (Table 1). Combined use of dofetilide at 3 nmol/L and

mexiletine at 10 $\mu\text{mol/L}$ (n=10), however, completely suppressed AF inducibility (Table 1). The effect of dofetilide plus mexiletine on AF inducibility could be partially washable (ie, after reperfusion of normal Tyrode solution for 30 minutes, AF could be induced in some of the preparations) (data not shown).

Effects of Mexiletine on Dofetilide-Induced QT and T_{p-e} Prolongation and Proarrhythmias

The major issue that limits clinical use of dofetilide is that dofetilide can produce marked QT prolongation and induce a QT-related life-threatening proarrhythmia TdP.^{9,11} In this

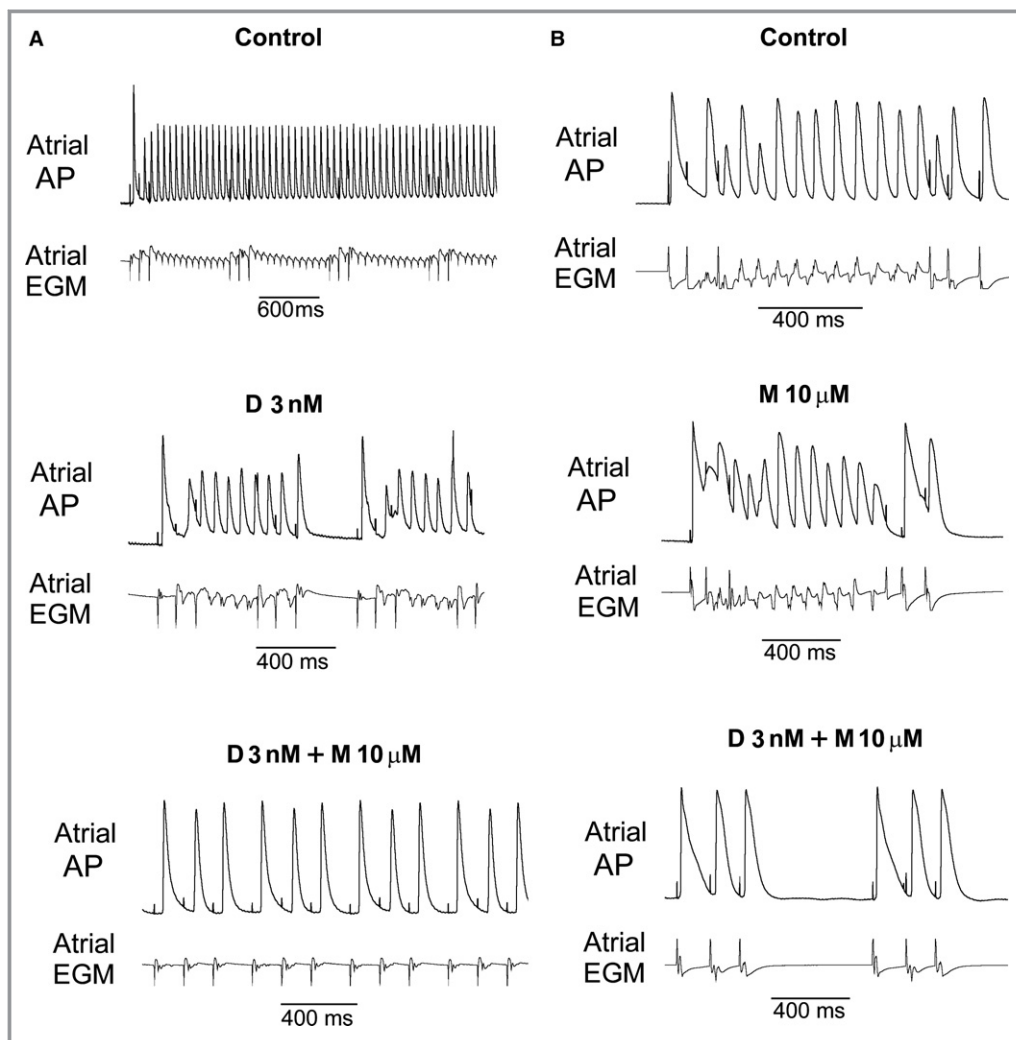


Figure 4. The effect of dofetilide (D), mexiletine (M), and dofetilide plus mexiletine on atrial fibrillation (AF) induction by programming stimulation. AF was readily induced by programmed stimulation with up to 2 extrastimuli in control conditions. A, Dofetilide at 3 nmol/L alone failed to suppress AF inducibility, while combined use of dofetilide (3 nmol/L) and mexiletine (10 $\mu\text{mol/L}$) rendered AF noninducible. B, Similarly in another atrial preparation, mexiletine at 10 $\mu\text{mol/L}$ alone could not suppress AF inducibility; and dofetilide (3 nmol/L) plus mexiletine (10 $\mu\text{mol/L}$) again prevented AF from being induced. AP indicates action potential; EGM, atrial electrogram.

Table 1. Effects of Dofetilide, Mexiletine, and Dofetilide Plus Mexiletine on AF Incidence in Arterially Perfused Rabbit Atrial Wedge Preparations

	Induced AF
Control (C)	10 of 10 preparations
Dofetilide (D) at 3 nmol/L	3 of 6 preparations*
Mexiletine (M) 10 μ mol/L	4 of 4 preparations
D 3 nmol/L+M 10 μ mol/L	0 of 10 preparations ^{†,‡}

AF, atrial fibrillation.

* $P < 0.05$ when compared with control.

[†] $P < 0.01$ when compared with mexiletine at 3 nmol/L.

[‡] $P < 0.05$ when compared with mexiletine at 10 μ mol/L.

section of the study, we tested the effect of mexiletine on the dofetilide-induced QT and T_{p-e} prolongation and proarrhythmias for which we used dofetilide at a higher concentration (10 nmol/L) than that used in atrial experiments.

Dofetilide at 10 nmol/L increased the QT interval by 110.6% from 313.9 ± 8.4 to 629.4 ± 31.7 ($n=9$, $P < 0.01$) and the T_{p-e} interval, an index of repolarization dispersion, by 220.5% from 56.2 ± 3.2 to 178.0 ± 16.4 at a BCL of 2000 ms ($n=9$, $P < 0.01$, Figure 5), leading to the development of EAD, EAD-dependent R-on-T ectopic beats, and TdP (Figure 6). Dofetilide at 10 nmol/L produced a TdP score—a semiquantitative parameter used to estimate drug-induced TdP risk in which 14 indicates the maximal TdP risk^{16,17}—of 12.0 ± 0.5 (versus 0 ± 0.0 in control, $n=9$, $P < 0.01$). In addition, dofetilide at 10 nmol/L markedly amplified rate-dependent changes in

QT and T_{p-e} intervals, resulting in much steeper QT-BCL and T_{p-e} -BCL slopes (Figure 7).

Mexiletine (10 μ mol/L) shortened QT and T_{p-e} intervals, reduced the QT-BCL and T_{p-e} -BCL slopes, and effectively abolished EAD, R-on-T, and TdP in the presence of dofetilide at 10 nmol/L (Figure 6 and Table 2). Mexiletine at 10 μ mol/L markedly reduced the TdP score from 12.0 ± 0.5 to 3.2 ± 0.7 ($n=9$, $P < 0.01$, Table 2). The effect of mexiletine on dofetilide-induced EAD, R-on-T, and TdP was washable (ie, after removal of mexiletine in the perfusate, EAD, R-on-T reoccurred) (data not shown).

Discussion

The present study has demonstrated a novel finding that there is a synergistic effect between dofetilide, a pure I_{Kr} blocker, and mexiletine, a *nonatrial* selective sodium channel blocker, on an increase in atrial ERP and suppression of AF inducibility in the isolated arterially perfused rabbit atrial wedge preparations. Furthermore, mexiletine significantly blunted dofetilide-induced QT and T_{p-e} interval prolongation, reduced the QT-BCL and T_{p-e} -BCL slopes, and suppressed dofetilide-induced EAD and EAD-dependent proarrhythmias in the rabbit ventricular wedge preparations. The evidence strongly indicates that combined use of dofetilide and mexiletine may not only significantly increase the efficacy in the treatment of atrial fibrillation but also markedly reduce proarrhythmic potentials of dofetilide.

The mechanisms underlying the synergistic effect between dofetilide and mexiletine on the increase in atrial ERP and

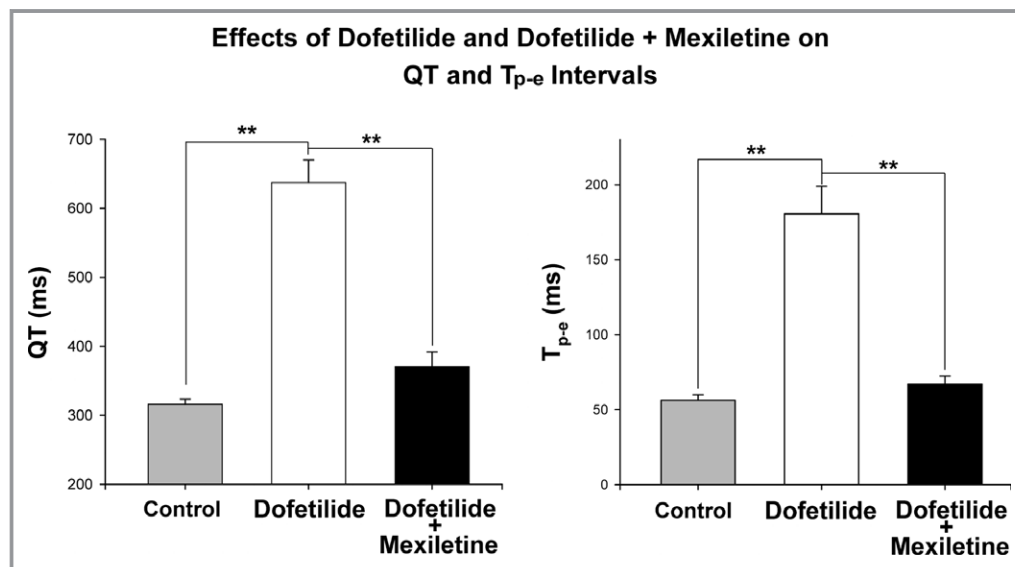


Figure 5. The effect of dofetilide at 10 nmol/L and dofetilide (10 nmol/L) plus mexiletine (10 μ mol/L) on QT and T_{p-e} intervals. BCL=2000 ms. ** $P < 0.01$; SEM for error bars for $n=9$. BCL indicates basic cycle lengths.

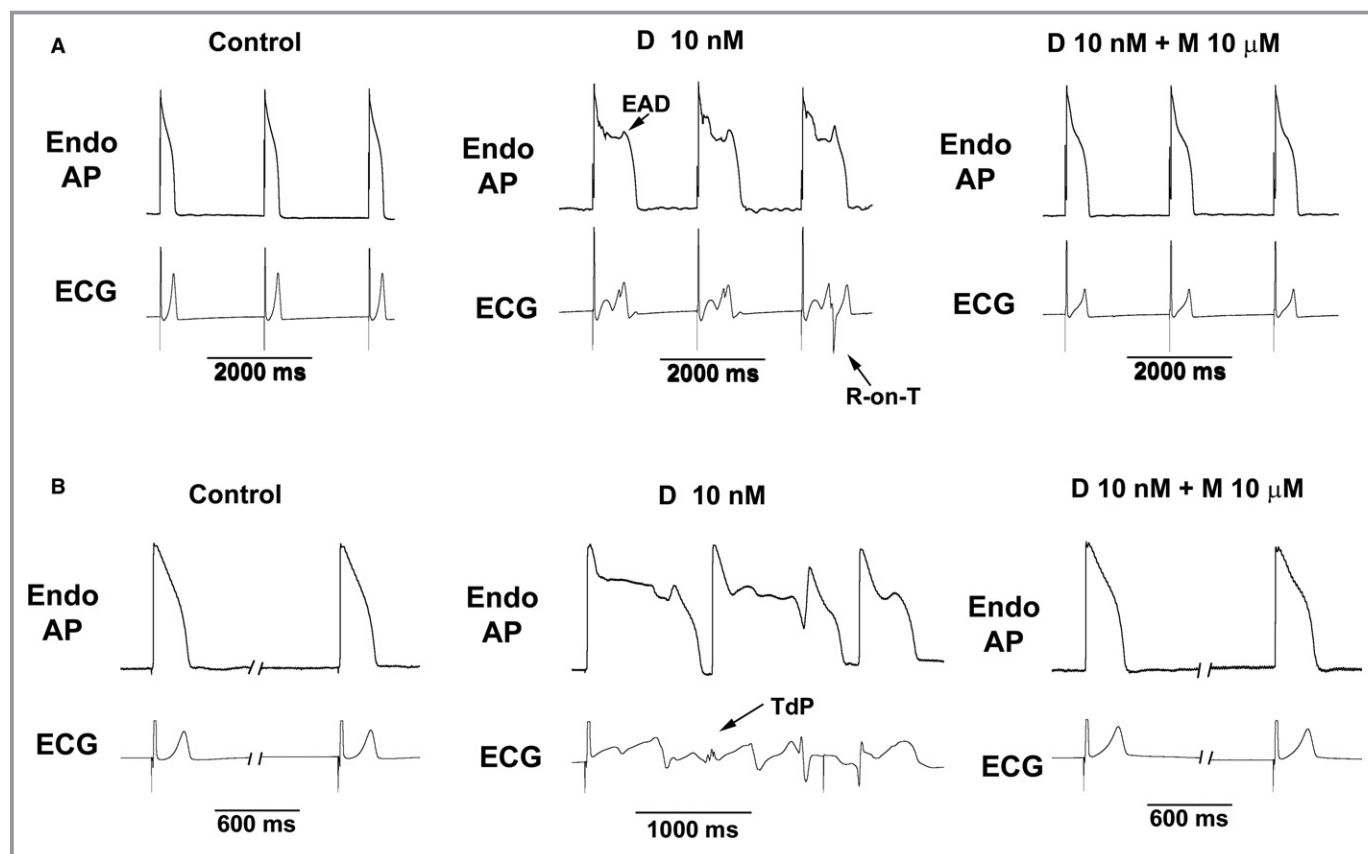


Figure 6. Examples of the effect of mexiletine (M) on dofetilide (D)-induced early afterdepolarization (EAD), EAD-dependent R-on-T extrasystoles, and torsades de pointes (TdP) in arterially perfused rabbit left ventricular wedges: (A) shows that mexiletine at 10 $\mu\text{mol/L}$ abolished dofetilide-induced EAD and R-on-T extrasystoles; (B) shows that mexiletine at 10 $\mu\text{mol/L}$ abolished dofetilide-induced EAD and TdP. AP indicates action potential.

suppression of AF inducibility as seen in the present study are unknown. A recent computer simulation study by Aguilar et al has shown that dofetilide potentiates pilsicainide, a Class Ic sodium channel blocker that has been used for the treatment of AF for decades,^{26,27} to block the atrial fast sodium channel, particularly at fast pacing rates.²⁸ These authors believe that prolongation of atrial action potential phase 2 by dofetilide slows recovery of the fast sodium channel from inactivation and shortens the diastolic interval that in turn decreases the time for drug unbinding from the channel. Therefore, the fraction of the available sodium channels for excitation is reduced. Indeed, these may partially explain the synergistic effect between dofetilide and mexiletine to increase the atrial ERP and to suppress AF.

However, there may be another alternative explanation for the synergistic effect of combined use of dofetilide and mexiletine. Our previous studies have shown that action potential prolongation, regardless of underlying mechanisms, increases fraction of tetrodotoxin-sensitive slowly inactivating sodium current, which is persistent through the action potential plateau phase (ie, so-called late sodium current [$I_{\text{Na-L}}$]).^{10,14,29,30}

Mexiletine preferentially blocks the late sodium current¹⁰ and may bind more of these sodium channels when action potential duration is prolonged. The total available sodium channels would become less for excitation if the fast and late sodium channels are required to remain in a constant ratio. This is indirectly supported by the fact that any sodium channel blocker more or less inhibits the late sodium current regardless of whether it binds the open state or inactivated state of the sodium channels. Because the late sodium channels remain open for tens to hundreds of ms, much longer than the fast sodium channels, one would expect that the sodium channel blockers that block the channels in their open state would have more prominent effect on the late sodium current than those blocking the channels in their inactivated state, but this is not the case. (In addition, our unpublished data (Gan-Xin Yan, MD, PhD, 2015) indicate that mexiletine produces more significant QRS widening when APD prolongation is induced by $I_{\text{Na-L}}$ enhancer than I_{Kr} blocker in the rabbit ventricular wedges.) In other words, both fast and late sodium currents may be closely linked to the same type sodium channels and potentially convert to each other.

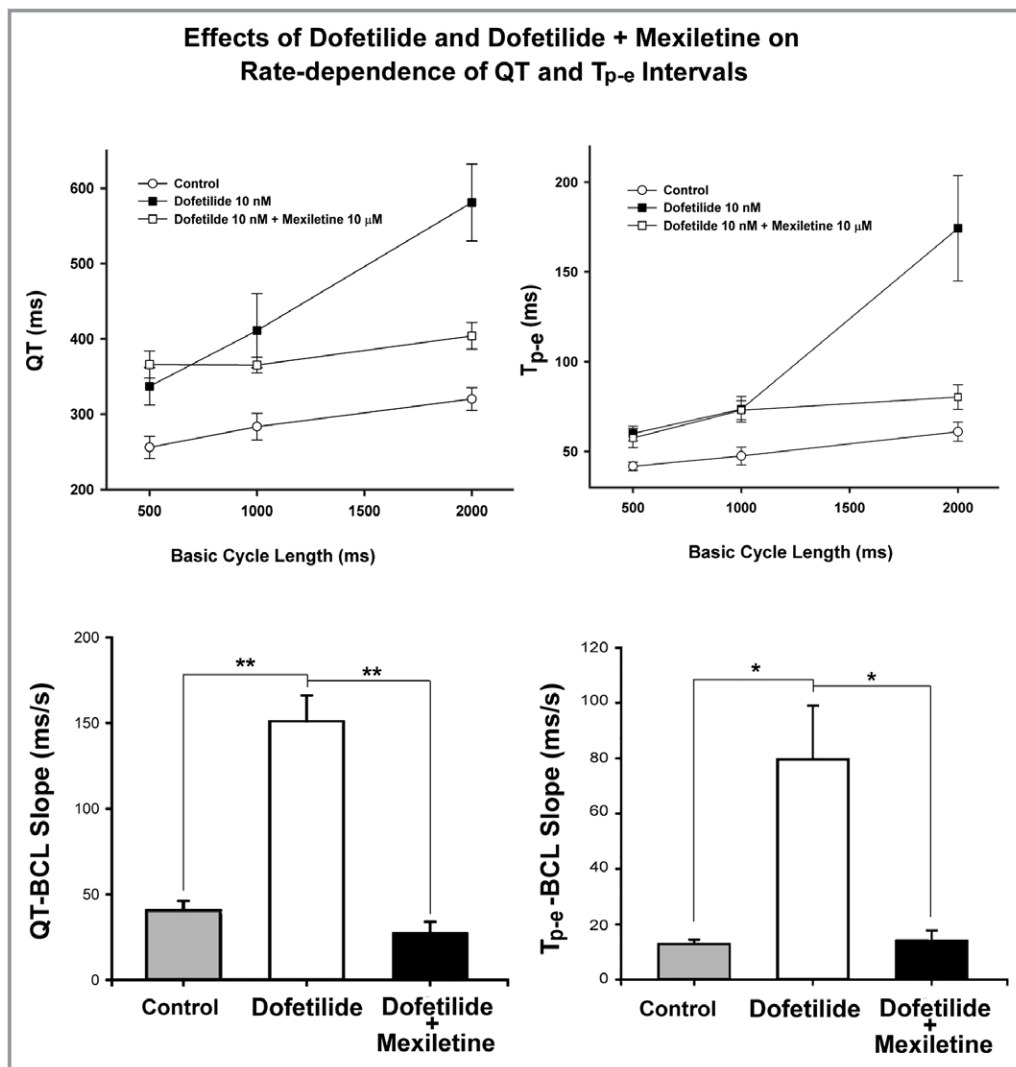


Figure 7. The effect of dofetilide at 10 nmol/L and dofetilide (10 nmol/L) plus mexiletine (10 μ mol/L) on the rate-dependent changes in QT and T_{p-e} intervals. * P <0.05, ** P <0.01; SEM for error bars for $n=4$. BCL, basic cycle lengths.

On the other hand, I_{Na-L} per se appears to play an important role in the development of AF. In humans, I_{Na-L} is significantly larger in atrial myocytes from AF than that in the

Table 2. Effects of M on D-Induced EAD, EAD-Dependent R-on-T Extrasystoles, and TdP Score in Arterially Perfused Rabbit Left Ventricular Wedges

	EAD	R-on-T	TdP	TdP Score*
Control (C)	0 of 9	0 of 9	0 of 7	0
D 10 nmol/L	9 of 9	7 of 9	2 of 9	12.0 \pm 0.5
D 10 nmol/L+M 10 μ mol/L	0 of 9 [†]	0 of 9 [†]	0 of 9	3.2 \pm 0.7 [†]

EAD, early afterdepolarization; D, dofetilide; M, mexiletine; TdP, torsade de pointes.

*TdP score was calculated based on the published criteria.^{16,17}

[†] P <0.01 when compared with dofetilide at 10 nmol/L.

myocytes from sinus rhythm.³¹ I_{Na-L} inhibition prevents ATX-II-induced AF.³² Therefore, additional synergistic actions of dofetilide plus mexiletine in AF treatment include the following: (1) I_{Na-L} inhibition by mexiletine may translate into ERP prolongation when APD is prolonged by dofetilide; (2) mexiletine via I_{Na-L} inhibition may potentially inhibit the triggered activities in the pulmonary veins because previous studies showed that the triggered activities of the pulmonary veins induced by the I_{Na-L} enhancer ATX-II can be reduced by a selective I_{Na-L} blocker, ranolazine.³³

Clinically, mexiletine as a class 1b sodium channel blocker can be used in almost all cardiac pathophysiological conditions including coronary artery disease and congestive heart failure (CHF) in which the prevalence of AF is high.^{34–37} In other words, the simultaneous presence of AF with coronary artery disease and/or CHF is common. This is particularly

important because dofetilide plus mexiletine can be a pharmacotherapeutic option for AF treatment in patients with coronary artery disease and/or CHF. A similar approach of combined use of a I_{Na-L} blocker ranolazine and dronedarone at lower than its regular doses appears promising in suppression of AF, and may also potentially reduce the side effect of dronedarone to cause CHF.^{38–40} On the other hand, it is well known that use of class Ic sodium channel blockers is contraindicated in patients with coronary artery disease and CHF.^{7,41,42} Therefore, combined use of dofetilide with a class Ic sodium channel blocker may likely have limited application in these patients.

One of the key benefits with combined use of dofetilide and mexiletine is that mexiletine can markedly reduce the TdP risk of dofetilide and improve its safety profile. Use of dofetilide is associated with QT and T_{p-e} prolongation that may lead to the development of TdP, a life-threatening ventricular arrhythmia.^{9,11} As a result, a 3-day mandatory in-hospital loading period is required for use of dofetilide by the US Food and Drug Administration, and the physician who prescribes dofetilide must have gone through special dofetilide training. However, significant reduction of the TdP risk of dofetilide by this measure comes at the cost of its efficacy because QT prolongation beyond a certain limit leads to reduction of dofetilide dose or termination of dofetilide treatment. This is likely the major reason for its low annual prescription at only 2% of the antiarrhythmic drug prescriptions versus 45% for amiodarone.⁴³ Our recent clinical study showed that mexiletine can effectively suppress TdP in patients who were treated with dofetilide and had genetic defects leading to long QT syndrome.¹¹ This is further supported by the experimental data in the present study that mexiletine attenuated dofetilide-induced QT and T_{p-e} prolongation, reduced its reverse use-dependence (ie, reducing the QT-BCL slope) and abolished EAD, R-on-T extrasystoles, and TdP in the rabbit ventricular wedge preparation.

Another novel finding in the present study is that dofetilide markedly increased the T_{p-e} -BCL slope. In other words, dofetilide amplified rate-dependent changes in the T_{p-e} interval. Increased T_{p-e} -BCL slope manifests as a marked increase in T_{p-e} during bradycardia or after pauses. This may explain why EADs, EAD-dependent R-on-T extrasystole, and TdP often occur during bradycardia or after pauses.¹¹ It is therefore important to notice that mexiletine blunted dofetilide-induced rate-dependent changes in the T_{p-e} interval and reduced the T_{p-e} -BCL slope (Figure 7).

In conclusion, combined use of dofetilide and mexiletine not only synergistically increases atrial ERP and suppresses AF inducibility, but also markedly reduces the QT liability and the TdP risk posed by dofetilide in rabbits. The information obtained from the animal experiments provides a rationale for systematic human studies with combined use of dofetilide and

mexiletine in clinical AF management. We believe that dofetilide plus mexiletine may greatly enhance the capability of clinicians to treat AF in a conservative way rather than via invasive procedures such as radiofrequency ablation because both efficacy and safety profiles of the combined use are markedly improved.

Disclosures

None.

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