

Effects of a Class III Antiarrhythmic Drug, Dofetilide, on the *In Situ* Canine Heart Assessed by the Simultaneous Monitoring of Hemodynamic and Electrophysiological Parameters

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ABSTRACT—The cardiovascular profile of dofetilide was examined using halothane-anesthetized, closed-chest *in vivo* canine model ($n=6$). Dofetilide was administered at the dose of 1, 10 or 100 $\mu\text{g}/\text{kg}$, *i.v.* over 10 min with a pause of 20 min. After the lowest infusion rate, no significant change was detected in any of the cardiovascular parameters. Infusion of 10 $\mu\text{g}/\text{kg}$ dofetilide, which was close to the submaximal clinically effective antiarrhythmic dose, decreased the heart rate and prolonged the ventricular repolarization phase and refractory period. After the highest dose of dofetilide, the cardiac output and left ventricular contraction decreased during sinus rhythm, the latter of which was not changed during the constant heart rate of 150 beats/min, while the dose-related effects were observed on the heart rate, repolarization phase and refractory period. The afterload and preload to the left ventricle and AV nodal as well as intraventricular conductions were hardly affected even at 100 $\mu\text{g}/\text{kg}$, *i.v.* These results obtained in the *in vivo* canine model support the previous reports describing that dofetilide possesses a highly selective blocking property for I_{Kr} . Moreover, the absence of effects on the afterload and preload to the left ventricle and the cardiac conduction makes dofetilide favorable as an antiarrhythmic drug because it is often used for patients with moderate to severe left ventricular dysfunction.

Keywords: Dofetilide, Monophasic action potential, Long QT syndrome, I_{Kr} blocker, Post repolarization refractoriness

In the recent DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) studies, the class III antiarrhythmic drug dofetilide was shown to possess a neutral effect on total mortality with a relatively low incidence of torsades de pointes (1). Moreover, the antiarrhythmic effects of dofetilide have been demonstrated in re-entrant tachyarrhythmias including atrial fibrillation and atrial flutter (1, 2). In the previous voltage-clamp studies (3, 4), dofetilide has been demonstrated to selectively block the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) without affecting either calcium or sodium channels. Other studies using an *in vitro* method (5–8) have suggested that dofetilide prolongs the action potential duration (APD) and the effective refractory period (ERP) without significantly affecting other cardiovascular parameters including cardiac conduction and contraction. However, precise

analysis of the electrophysiological effects of dofetilide in an *in vivo* model together with the monitoring of the cardiohemodynamic parameters is still limited (9–12), although such knowledge is obviously of major clinical importance.

The current study was designed to simultaneously assess the hemodynamic and electrophysiological effects of dofetilide using the closed-chest *in vivo* canine model (13–16). To better analyze the electrophysiological effects of the drug on the depolarization and repolarization phases, we recorded His bundle electrograms and monophasic action potentials (MAP) in addition to the standard lead II ECG. Using the same model, we recently examined several agents possessing I_{Kr} blocking activity, overdose of which has been demonstrated to be proarrhythmic in clinical practice (13, 14, 16). In this study, dofetilide in an effective antiarrhythmic dose as well as its overdose was administered under the monitoring of multiple cardiovascular parameters, and the results were

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compared with our previous reports on other drugs affecting the repolarization phase of the heart (13–16).

MATERIALS AND METHODS

Experiments were carried out using beagle dogs of either sex weighing approximately 10 kg. Animals were obtained through the Animal Laboratory for Research of Yamanashi Medical University. All experiments were performed according to Guidelines for Animal Experiments, Yamanashi Medical University. Dogs were anesthetized initially with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1.0% halothane vaporized with 100% oxygen was inhaled with a volume-limited ventilator (SN-480-3; Shinano, Tokyo). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. To prevent blood clotting, heparin calcium (100 IU/kg) was intravenously administered.

Cardiohemodynamic and electrophysiological parameters

The surface lead II ECG was obtained from the limb electrodes. The systemic blood pressure was measured at the left femoral artery. A thermodilution catheter (TC-704; Nihon Kohden, Tokyo) was inserted through the right femoral vein and positioned at the right side of the heart. The cardiac output (CO) was measured by a standard thermodilution method using a cardiac output computer (MFC-1100, Nihon Kohden). A quad-polar electrodes catheter was inserted through the right femoral artery and positioned at the non-coronary cusp of the aortic valve to obtain the His bundle electrogram. A pig tail catheter was inserted through the left femoral artery and positioned at the left ventricle to measure the left ventricular pressure. The maximum upstroke velocity of the left ventricular pressure (LVdP/dt) and the left ventricular end-diastolic pressure (LVEDP) were obtained during sinus rhythm to estimate the contractility and the preload to the left ventricle, respectively. In addition, LVdP/dt at a pacing cycle length of 400 ms was measured to get rid of the secondary effect of dofetilide derived from its negative chronotropic action.

A bi-directional steerable MAP recording/pacing combination catheter (1675P; EP Technologies, Inc., Sunnyvale, CA, USA) was inserted through the left femoral vein and positioned at the endocardium of the right ventricle to obtain MAP signals. The signals were amplified with a DC preamplifier (model 300, EP Technologies, Inc.). The amplitude of the MAP was measured as the distance from the diastolic baseline to the crest of the MAP plateau phase as reported previously (17). The duration of the MAP signals was measured as an interval, along a line horizontal to the diastolic baseline, from the

MAP upstroke to the desired repolarization level. The interval (ms) at 90% repolarization was defined as MAP₉₀.

The heart was electrically driven with a cardiac stimulator (SEC-3102, Nihon Kohden) and the pacing electrodes of the combination catheter placed in the right ventricle. The stimulation pulses were rectangular in shape, 1–2 V (about twice the threshold voltage) and of 1-ms duration. The MAP₉₀ was measured during sinus rhythm (MAP_{90(sinus)}) and at a pacing cycle length of 400 ms (MAP_{90(CL400)}) or 300 ms (MAP_{90(CL300)}). The ERP of the right ventricle was assessed by programmed electrical stimulation. The pacing protocol consisted of 10 beats of basal stimuli in a cycle length of 400 ms followed by an extra stimulus of various coupling intervals. Starting in late diastole, the coupling interval was shortened in 5- to 10-ms decrements until refractoriness occurred. The post-repolarization refractoriness (PRR), ERP – MAP_{90(CL400)}, was calculated to estimate the electrical vulnerability of the ventricular muscle (17–20).

The systemic blood pressure, left ventricular pressure, ECG, His bundle electrogram and MAP signals were monitored using a polygraph system (RM-6000, Nihon Kohden). The blood pressure, LVdP/dt and heart rate were continuously recorded on a rectilinear recorder (RJG-4124, Nihon Kohden) at a paper speed of 25 mm/min, while blood pressure, left ventricular pressure, ECG, His bundle electrogram and MAP signals were recorded on a thermal array recorder (WS-682G, Nihon Kohden) at a paper speed of 100 mm/s every 5 min. Each measurement of ECG, MAP as well as atrio-His (AH) and His-ventricle (HV) intervals was the mean of three recordings of consecutive complexes. Corrected QT (QTc) and corrected JT (JTc) intervals were obtained using Bazett's formula (21).

The cardiovascular variables were assessed in the following order: The cardiac output was measured twice. The ECG, His bundle electrogram, systemic and left ventricular pressure and MAP signal were recorded under sinus rhythm. In addition, MAP signals were recorded during the ventricular pacing at a cycle length of 400 and 300 ms. Then, the refractory period of the right ventricle was measured. All parameters described above were usually obtained within 1 min at each point.

Experimental protocol

The animals were divided into two groups: dofetilide-administered group (n=6) and vehicle-administered group (n=6). After the basal assessment, dofetilide in a dose of 1 µg/kg was administered over 10 min, and each parameter was observed 5, 10, 15, 20 and 30 min after the start of the infusion. Then, dofetilide at the higher dose of 10 µg/kg was administered over 10 min and each parameter was observed in the same manner. Finally,

dofetilide at the highest dose of 100 $\mu\text{g}/\text{kg}$ was administered over 10 min, and each parameter was observed 5, 10, 15, 20, 30, 45 and 60 min after the start of the infusion. In the control group the vehicle solution was administered instead of the drug solution to confirm the stability of the current canine model over 120 min.

Plasma drug concentration

A volume of 3 ml of blood was drawn from the right femoral artery to measure the plasma drug concentration. The blood samples were centrifuged at $1,500 \times g$ for 30 min at 4°C . The plasma was stored at -80°C until the drug concentration was measured. Sensitive and specific determinations of the concentrations of dofetilide were performed using a standard high-performance liquid chromatographic method at Pfizer Pharmaceuticals, Inc. (Tokyo).

Drugs

Dofetilide was obtained from Pfizer Pharmaceuticals, Inc., while the following drugs were purchased: thiopental sodium (Tanabe Seiyaku, Osaka), halothane (Takeda Chemical Industries, Tokyo) and heparin calcium (Mitsui Pharmaceuticals, Tokyo). Dofetilide was initially dissolved with 10 mM HCl in a concentration of 1 mg/ml and then diluted with 10 mM HCl to obtain 0.1 and 0.01 mg/ml solutions.

Statistical analyses

Data are presented as the mean \pm S.E.M. The statistical significance within a parameter was evaluated by one-way repeated-measures analysis of variance (ANOVA). When a P value was <0.05 by ANOVA, the drug was judged as having affected the parameter. In this case, the statistical significance between the control and a value at a particular time point after the drug administration was determined by Contrasts for mean values comparison, and a P value <0.05 was considered significant. The differences of the control values between the groups were evaluated by the unpaired t -test. The increments of $\text{MAP}_{90(\text{CL}400)}$ and $\text{MAP}_{90(\text{CL}300)}$ at each time point were compared by the paired t -test. A P value less than 0.05 is considered significant.

RESULTS

Effects of dofetilide on blood pressure and heart rate

The time courses of changes in the heart rate and the mean blood pressure are summarized in Fig. 1. The heart rate (beats/min) and the mean blood pressure (mmHg) at the pre-drug control (C) were 131 ± 7 and 121 ± 6 in the dofetilide-administered group, and 117 ± 6 and 108 ± 5 in the vehicle-administered group, respectively. There was

no significant difference in each control value between the groups. In the vehicle-administered group, no significant change was observed in these parameters during the study. In the dofetilide-administered group, the heart rate decreased and significant changes were observed from 5 min after the start of 10 $\mu\text{g}/\text{kg}$ of dofetilide infusion to the end of the experiment, while no significant change was detected in the mean blood pressure during the whole experimental period.

Plasma drug concentration

The time courses of the plasma drug concentration of dofetilide are summarized in Fig. 1 ($n=4$). The decrease of the plasma concentration of the drugs followed a pattern predicted by the two-compartment theory of pharmacokinetics. The peak plasma concentration of dofetilide after 1, 10 and 100 $\mu\text{g}/\text{kg}$ infusion were

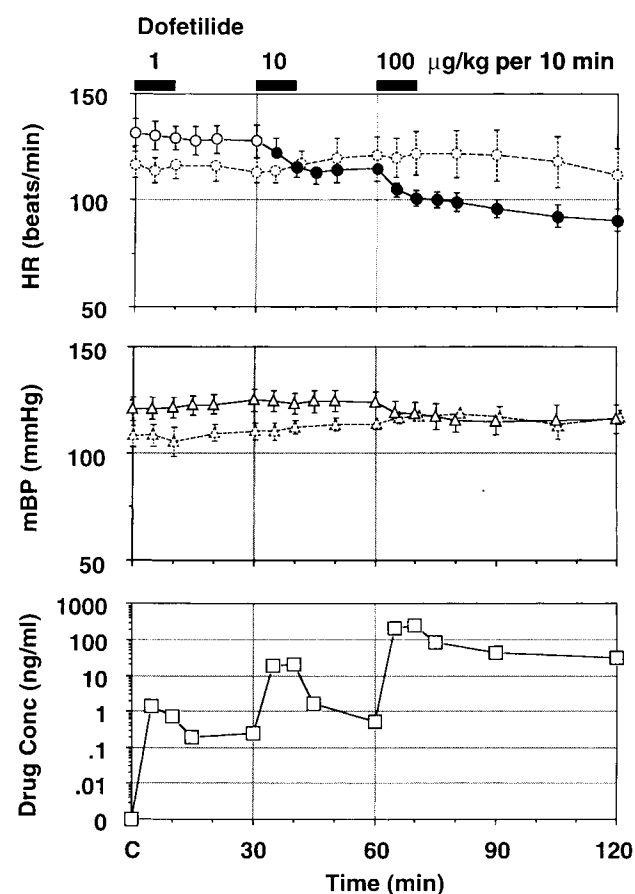


Fig. 1. Time courses of heart rate: HR (circles) and mean blood pressure: mBP (triangles) in the vehicle-administered group (dashed line) ($n=6$) and dofetilide-administered group (solid line) ($n=6$) (top and middle); and plasma concentration of dofetilide: Drug Conc (square) ($n=4$) (bottom). Data are presented as the mean \pm S.E.M. The closed symbols represent the significant differences from each control value ($P < 0.05$).

1.5 ± 0.5 , 20.3 ± 1.2 and 255.3 ± 13.7 ng/ml, respectively.

Effects of dofetilide on LVdP/dt, LVEDP and CO

The time courses of changes in the LVdP/dt, LVEDP and CO are summarized in Fig. 2. The LVdP/dt (mmHg/s), LVEDP (mmHg) and CO (L/min) at the pre-drug control were 2000 ± 202 , 7.2 ± 1.1 and 1.62 ± 0.06 in the dofetilide administered group, and 1817 ± 140 , 5.7 ± 1.5 and 1.50 ± 0.09 in the vehicle-administered group, respectively. There was no significant difference in each control value between the groups. In the vehicle administered group, no significant change was observed in these parameters during the study. In the dofetilide administered group, the LVdP/dt and CO decreased and significant changes were observed in the LVdP/dt for 5–60 min and in the CO for 20–60 min after the start of the highest dose of $100 \mu\text{g/kg}$ of dofetilide infusion, while no significant change was observed in LVEDP. In addition, LVdP/dt was measured during the pacing cycle

length of 400 ms. The LVdP/dt at the pre-drug control period was 2145 ± 125 mmHg/s. Dofetilide did not affect this LVdP/dt during the whole observation period of this study.

Effects of dofetilide on ECG

The time courses of changes in PR interval, QRS width, JTc and QTc are summarized in Fig. 3. The PR interval (ms), QRS width (ms), JTc (ms/s^{1/2}) and QTc (ms/s^{1/2}) at the pre-drug control were 100 ± 5 , 58 ± 4 , 210 ± 18 and 393 ± 18 in the dofetilide-administered group and 95 ± 6 , 68 ± 3 , 271 ± 10 and 366 ± 8 in the vehicle-administered group, respectively. There was no significant difference in each control value between the groups. In the vehicle-administered group, no significant change was observed in these parameters during the study. In the dofetilide-administered group, JTc and QTc were prolonged, while no significant change was observed in the PR interval and QRS width. Significant changes were observed in both JTc and QTc from 5 min after the start of $10 \mu\text{g/kg}$ of dofetilide infusion to the end of the ex-

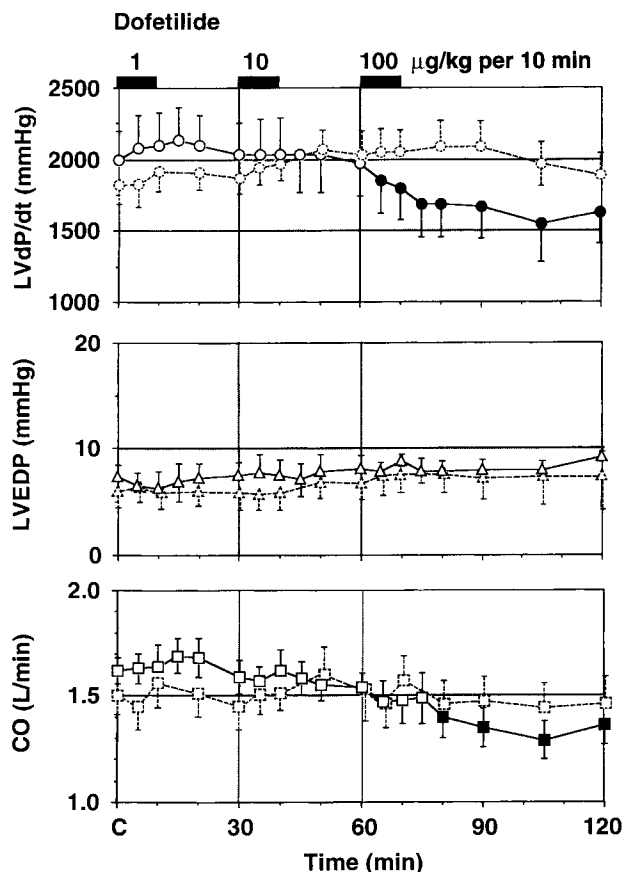


Fig. 2. Time courses of maximum upstroke velocity of left ventricular pressure: LVdP/dt (circles) (top), left ventricular end-diastolic pressure: LVEDP (triangles) (middle) and cardiac output: CO (squares) (bottom). Other details are as described in the legend of Fig. 1.

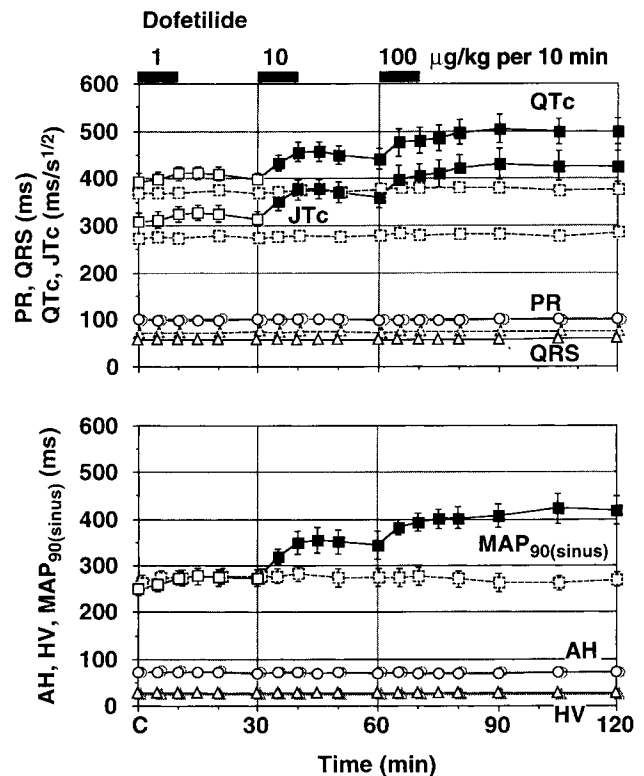


Fig. 3. Time courses of PR interval (circles), QRS width (triangles), QTc and JTc (squares) (top); and atrio-His interval: AH (circles), His-ventricular interval: HV (triangles) and MAP₉₀ during the sinus rhythm: MAP_{90(sinus)} (squares) (bottom). MAP₉₀ represents the duration of monophasic action potential at a level of 90% repolarization. Other details are as described in the legend of Fig. 1.

periment. No ventricular premature beat was observed during the whole experimental period.

Effects of dofetilide on AH and HV intervals

The time courses of changes in AH and HV intervals during the sinus rhythm are summarized in Fig. 3. The AH and HV intervals (ms) at the pre-drug control period were 72 ± 7 and 29 ± 1 in the dofetilide-administered group and 72 ± 5 and 25 ± 2 in the vehicle-administered group, respectively. There was no significant difference in each control value between the groups. In the vehicle-administered group as well as the dofetilide administered group, no significant change was detected in these parameters during the study.

Effects of dofetilide on MAP_{90}

The time course of changes in MAP_{90} during sinus rhythm is summarized in Fig. 3, while those during ven-

tricular pacing are shown in Fig. 4. The $MAP_{90(sinus)}$ (ms), $MAP_{90(CL400)}$ (ms) and $MAP_{90(CL300)}$ (ms) were 251 ± 15 , 247 ± 12 and 229 ± 8 in the dofetilide-administered group and 264 ± 15 , 253 ± 13 and 234 ± 9 in the vehicle-administered group, respectively. There was no significant difference in each control value between the groups. In the vehicle-administered group, no significant change was observed in these parameters during the study. In the dofetilide-administered group, these parameters increased, and significant changes were observed from 5 min after start of $10 \mu\text{g/kg}$ of dofetilide infusion to the end of the study. The time courses of the increment in $MAP_{90(CL400)}$ and $MAP_{90(CL300)}$ are also summarized in Fig. 4. Increment of $MAP_{90(CL400)}$ was greater than that of $MAP_{90(CL300)}$ from 5 min after start of $1 \mu\text{g/kg}$ of dofetilide infusion to the end of the study, indicating that dofetilide has a reverse frequency-dependent property.

Effects of dofetilide on ERP

The time courses of changes in ERP are summarized in Fig. 4. The ERP (ms) at the pre-drug control period was 221 ± 7 in the dofetilide-administered group and 217 ± 7 in the vehicle-administered group, respectively. There was no significant difference in the control value between the groups. In the vehicle-administered group, no significant change was observed in these parameters during the study. In the dofetilide-administered group, ERP increased and significant changes were observed from 10 min after the start of $10 \mu\text{g/kg}$ of dofetilide infusion to the end of the experiment.

Effects of dofetilide on post repolarization refractoriness (PRR)

The PRR value was negative during the study. The time courses of changes in the PRR are summarized in Fig. 4. The PRR at the pre-drug control period was -26 ± 7 (ms) in the dofetilide-administered group and -36 ± 7 (ms) in the vehicle-administered group, respectively. There was no significant difference in the control value between the groups. In the vehicle-administered group, no significant change was observed in this parameter during the study. In the dofetilide-administered group, the absolute value of PRR slightly increased, but significant changes were observed from 10 min after the start of $10 \mu\text{g/kg}$ of dofetilide infusion to the end of the experiment.

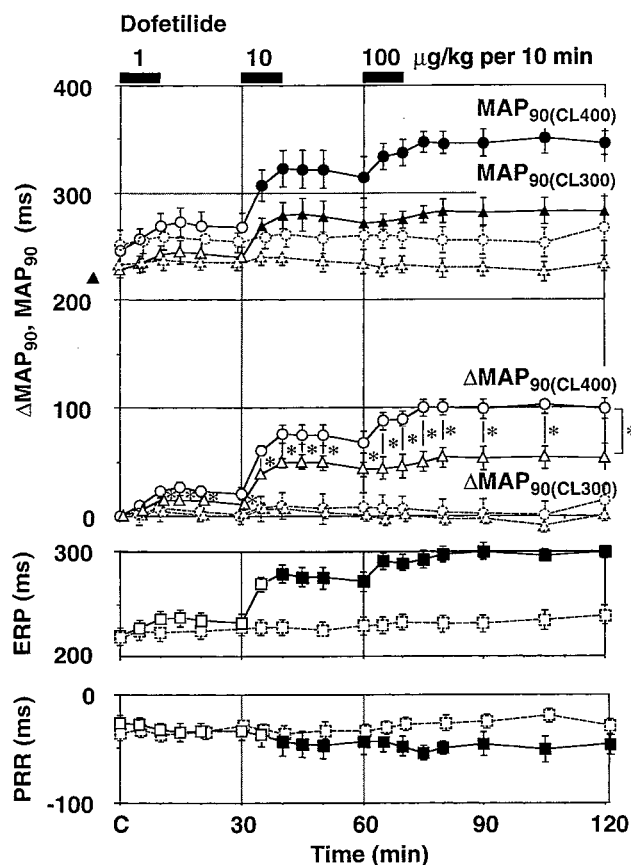


Fig. 4. Time courses of MAP_{90} during the electrical pacing at a cycle length of 400 ms: $MAP_{90(400)}$ (circles) and 300 ms: $MAP_{90(300)}$ (triangles), and the increment in MAP_{90} at a cycle length of 400 ms: $\Delta MAP_{90(400)}$ (circles) and 300 ms: $\Delta MAP_{90(300)}$ (triangles) (top); and effective refractory period: ERP (squares) (middle) and post-repolarization refractoriness: PRR (squares) (bottom). * $P < 0.05$. Other details are as described in the legend of Fig. 1.

DISCUSSION

The present study was designed to bridge the gap between the basic observations in vitro and the clinical electrophysiology of dofetilide using a well-established in vivo canine model under the monitoring of multiple cardiovascular parameters and plasma drug concentra-

tions. Dofetilide was infused in three doses, 1, 10 and 100 $\mu\text{g}/\text{kg}$, in this study, since its clinical effective intravenous antiarrhythmic dose has been estimated as 1.5–10 $\mu\text{g}/\text{kg}$ (2, 22–24). After the administration of 10 $\mu\text{g}/\text{kg}$ of dofetilide, the ventricular repolarization as well as refractoriness increased, while the sinus automaticity was suppressed (25). Since the C_{max} of dofetilide after 10 $\mu\text{g}/\text{kg}$, which was $20.3 \pm 1.2 \text{ ng/ml}$ ($= 50.0 \text{ nM}$), was close to the IC_{50} value of I_{Kr} (31.5 nM) in the previous report with isolated guinea pig ventricular myocytes (2), the effects of dofetilide on the repolarization phase and heart rate could be explained by its class III action (2, 5, 7, 10, 26). More importantly, the prolonging effects of the repolarization phase was more prominent at slower heart rate and thus showed a reverse frequency-dependence, suggesting that the negative chronotropic effect of dofetilide may further potentiate the prolongation of the repolarization phase in the *in situ* heart.

Meanwhile after the administration of the overdose of dofetilide, the ventricular contraction was suppressed and the cardiac output decreased during the sinus rhythm, which has not been described elsewhere as far as we know, while the dose-related changes were observed on the heart rate, repolarization phase and refractory period. More importantly, no effect was observed on the afterload and preload to the left ventricle and the cardiac conduction during the whole experimental period, which could be important in analyzing the unique cardiovascular properties of dofetilide in comparison with those of other drugs that can affect the repolarization phase of the heart besides their major pharmacodynamic effects (13–16), as described below.

To examine the proarrhythmic possibility of dofetilide, in the present study, we simultaneously measured both MAP and ERP at the same site and directly compared the drug effects on the repolarization and refractoriness, since both APD and ERP vary from site to site in the ventricle. As shown in Fig. 4, the repolarization phase was prolonged beyond the ventricular refractoriness, which may provide a substrate for re-entry arrhythmias (17, 20). In our recent studies (14, 16), a similar extent of negative PRR was also induced by cisapride and astemizole, which were not originally classified as I_{Kr} blockers, but have this effect as a "side effect". However, cisapride and astemizole decreased the blood pressure and suppressed the cardiac conduction besides such prolonging effects on the repolarization phase. Since the DIAMOND studies (1) have already demonstrated a neutral effect of dofetilide on total mortality in addition to a relatively low incidence of torsades de pointes in patients with left ventricular dysfunction, the difference in the cardiovascular profile among these drugs seems to be important. One can speculate that the conduction slowing may enhance the

formation of an unidirectional block, especially in the heart having more negative PRR, thereby providing a substrate for re-entry arrhythmias.

Many pharmacological maneuvers that prolong the action potential duration have been reported to result in a positive inotropic action via the delay of inactivation of slow calcium channels (5, 6, 27). Indeed in all previous studies, dofetilide has been reported to be devoid of negative inotropic activity (2, 3, 5, 10) even in the presence of the induced acute cardiac failure (28). However, contrary to these previous data, negative inotropic action was observed only after the administration of the highest dose of dofetilide during the sinus rhythm in our *in vivo* canine model. To further analyze the mechanism of the negative inotropic effect of dofetilide, we measured LVdP/dt at a pacing cycle length of 400 ms and found that dofetilide had little effect on the ventricular contraction under the constant heart rate. Thus, the negative inotropic effect of dofetilide observed during the sinus rhythm can be considered to be secondarily derived from its negative chronotropic action.

In summary, the cardiovascular profile of dofetilide can be explained by its selective blocking property for I_{Kr} . The absence of the effects on the afterload and preload of the left ventricle as well as the cardiac conduction would be favorable as an antiarrhythmic drug when employed in patients with left ventricular dysfunction.

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