Electrophysiological Effects of Dofetilide in an In Vitro Model of “Border Zone” Between Normal and Ischemic/Reperfused Myocardium

René Rouet, PhD; Sandra Picard, PhD; Christian Libersa, MD, PhD; Mathieu Ghadanfar, MD; Colin Alabaster, PhD; Jean-Louis Gérard, MD, PhD

**Background**—To evaluate both class III activity and antiarrhythmic action of dofetilide at the level of the “border zone,” we investigated its electrophysiological effects on guinea pig ventricular strips submitted partly to normoxia (normal zone, NZ) and partly to simulated severe ischemia, then reperfusion (altered zone, AZ).

**Methods and Results**—Because of the differential class III effects of dofetilide in normal and ischemic regions, the dispersion of the action potential duration at 90% repolarization (APD₉₀) between NZ and AZ was reduced by 5 nmol/L of drug during early ischemia (at 10 minutes, APD₉₀ NZ/APD₉₀ AZ was 1.68±0.22 versus 2.82±0.17 in control, P<0.05), whereas 50 nmol/L dofetilide worsened it during late ischemia (at 30 minutes, APD₉₀ NZ/APD₉₀ AZ was 4.62±0.76 versus 2.57±0.21 in control, P<0.05). Concomitantly, dofetilide at 5, 10, and 50 nmol/L abolished the early extrastimulus (ES)-induced arrhythmias, and at 10 and 50 nmol/L, it significantly enhanced the incidence of late spontaneous repetitive responses (in 86% and 75% of preparations treated with 10 and 50 nmol/L, respectively, versus 25% in control, P<0.05). During reperfusion, dofetilide at 5, 10, and 50 nmol/L exhibited concentration-dependent class III effects, as it did in the NZ, and did not modify the incidence of spontaneous arrhythmias.

**Conclusions**—Dofetilide 5 nmol/L decreased APD₉₀ dispersion between NZ and AZ and reduced the early ES-induced arrhythmias. However, dofetilide 50 nmol/L increased APD₉₀ dispersion, and at 10 and 50 nmol/L, it increased the late spontaneous arrhythmias. (Circulation. 2000;101:86-93.)

**Key Words:** antiarrhythmia agents ■ ischemia ■ reperfusion ■ myocardium

Dofetilide (UK-68,798) is a potent class III antiarrhythmic agent that inhibits the rapid component of the delayed outward potassium current (I₉₊), 1 inducing lengthening of action potential (AP) duration and effective refractory period without affecting conduction, as shown in vitro in various cardiac tissues2–5 and in vivo in anesthetized animals.6,7 Clinical studies also confirmed class III activities of dofetilide, showing significant prolongation of QT interval and ventricular effective refractory period in normal subjects8,9 and in patients with coronary artery disease.10,11 Dofetilide has been found to exert antiarrhythmic action on ventricular fibrillation in anesthetized animals7,12–14 and to show clinical efficacy for the termination of sustained atrial fibrillation and flutter15 and of ventricular tachycardias.16,17

However, clinical use of class III drugs has revealed risks in relation to their proarrhythmic effects,16–20 as recently demonstrated by the Survival With OrAl D-sotalol (SWORD) study, which reported an increased mortality in patients treated with the pure class III agent d-sotalol12 and led to the discontinuation of clinical investigation of this drug. Using an in vitro model of partial ischemia/reperfusion mimicking the “border zone” existing between normal and ischemic/reperfused ventricular regions,22 we found that the proarrhythmic effects of d-sotalol might be related to its differential class III properties on adjacent normal and ischemic zones.23 Indeed, ischemic conditions are known to be able to impair the ability of class III agents to lengthen AP.24 The border zone between normal and ischemic myocardium has been suggested to be a site promoting the emergence of arrhythmias.23,26

In view of the class III potency of dofetilide and its reported antiarrhythmic actions, it was considered useful to determine its electrophysiological effects and antiarrhythmic efficacy in a model of myocardial border zone. For this purpose, we evaluated the effects of dofetilide at 5, 10, and 50 nmol/L on the AP parameters and the incidence of arrhythmias occurring around the border zone separating normal and ischemic/reperfused adjacent tissues of guinea pig right ventricular myocardium.

**Methods**

Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture.
Materials

Guinea pigs of either sex weighing 300 to 400 g were euthanized under anesthesia with ether. The hearts were quickly removed, and a thin longitudinal strip of the right ventricle was pinned, endocardial surface upward, in a special perfusion chamber.22–27,28 This chamber (5 mL) is bisected by a thin perforated latex membrane that allowed the preparation to be passed carefully through and divided into 2 zones, called the normal zone (NZ) and altered zone (AZ), respectively. The 2 compartments were independently superfused at the rate of 2 mL/min with Tyrode’s solution oxygenated with 95% O2 and 5% CO₂ and maintained at 36.5 ± 0.5°C (Polystat 5HP, Bio-block). The composition of the Tyrode’s solution is (in mmol/L): Na⁺ 135, K⁺ 4, Ca²⁺ 1.8, Mg²⁺ 1, H₂PO₄⁻ 1.8, HCO₃⁻ 25, Cl⁻ 117.8, and glucose 5.5. The pH was 7.35 ± 0.05. At the end of each experiment, absence of leakage between the 2 compartments was tested by a dye injection (methylene blue) in 1 of the 2 zones.

Data Acquisition and Analysis

The preparations were stimulated at a frequency of 1 Hz via a bipolar Teflon-coated steel wire electrode positioned either in the NZ or in the AZ. Rectangular pulses of 2 ms in duration and twice diastolic threshold intensity were delivered by a programmable stimulator, SMP 310 (Biologic). During the protocol, stimulation was stopped whenever spontaneous arrhythmias occurred. An extra-stimulus (ES) was applied every 4 stimulations in an attempt to elicit ES-induced repetitive responses by a progressive increase in 5-ms steps of the time interval between the stimulus and the ES. Transmembrane potentials were recorded simultaneously in both myocardial regions by use of glass microelectrodes filled with KCl 3 mol/L (tip resistance 10 to 30 MΩ) and coupled to the input stages of a home-built high-impedance capacitance-neutralizing amplifier. The recordings were displayed on a memory dual-beam storage oscilloscope (Gould Instrument Systems Inc). The following AP characteristics were automatically stored and measured by a system of cardiac AP automatic acquisition and processing devices (DATAPAC, Biologic): resting membrane potential (RMP), AP amplitude (APA), AP duration at 50% of repolarization (APD₅₀), AP duration at 90% of repolarization (APD₉₀), AP duration at 90% of repolarization (APD₉₀), and maximal upstroke velocity (Vₛᵤ). Whenever possible, the same impalement was maintained throughout the experiment; however, when it was lost, readjustment was attempted. If the readjusted parameters deviated ≤10% from the previous ones, experiments were continued; otherwise, they were terminated.

Experimental Protocol

After a 120-minute equilibration period, simulated ischemia was induced for 30 minutes in 1 compartment (AZ) by superfusion with a modified Tyrode’s solution, while the other compartment remained in normal conditions (NZ) (Figure 1). The modified Tyrode’s solution differed from normal by elevated K⁺ concentration (from 4 to 12 mmol/L), decreased HCO₃⁻ concentration (from 25 to 9 mmol/L) leading to a decrease in pH (from 7.35 ± 0.05 to 7.00 ± 0.05), a decrease in P₅₀ replacement of 95% O₂ and 5% CO₂ by 95% N₂ and 5% CO₂, and withdrawal of glucose. As previously reported,22–27,29 the present modifications are similar to those reported by Morena et al,30 which reproduced in vitro the electrophysiological abnormalities induced in vivo by ischemia. The AZ then returned to superfusion with the normal Tyrode’s solution for 30 minutes (reperfusion period).

Myocardial conduction disturbances and arrhythmias were recorded during both ischemia and reperfusion: (1) conduction blocks between the AZ and the NZ, (2) ES-induced repetitive responses defined as spontaneous extrasystoles induced by a single ES, and (3) spontaneous arrhythmias independent of the stimulation. During the ischemia and reperfusion phases, dofetilide previously diluted in ethanol-HCl (0.05N) and in Tyrode’s solution at 5 (n = 7), 10 (n = 7), or 50 (n = 8) mmol/L, or Tyrode’s solution alone (control, n = 12) was randomly superfused simultaneously in both zones. Thus, the electrophysiological effects of dofetilide were investigated (1) on AP parameters simultaneously in normal (NZ) and altered (AZ) conditions and (2) on the electrical disturbances occurring around the border zone between normal and ischemic/reperfused cardiac tissues.

Statistical Analysis

All results were expressed as mean ± SEM. Student’s t-test for paired data was performed for comparison from initial AP parameter values (measured before initiation of the ischemic period). ANOVA (2-factor analysis) was used to compare APD₉₀ changes and APD₉₀ NZ/APD₉₀ AZ ratio between the 4 experimental groups, and Fisher’s exact test for comparison of nonparametric categorical data. Differences were considered significant when P < 0.05.

Because of loss of microelectrode impalments, the AP parameters were analyzed for 29 preparations (8 control and 7, 6, and 8 for 5, 10, and 50 mmol/L dofetilide, respectively).

Results

Effects of Dofetilide on the AP Parameters in Normoxic and Simulated Ischemic/Reperfused Conditions

As summarized in Table 1, in normoxic conditions (NZ), dofetilide did not significantly modify RMP, Vₛᵢₚ (except for the dofetilide 10 nmol/L group), or APA (except for the
dofetilide 5 nmol/L group), whereas AP lengthening was obtained with dofetilide (P<0.05) in a concentration-dependent manner (after 60 minutes, APD₉₀ was +18±3%, +36±3%, and +42±8% in the presence of 5, 10, and 50 nmol/L dofetilide, respectively, and APD₉₀ was +22±5%, +36±4%, and +48±8% in the presence of 5, 10, and 50 nmol/L dofetilide, respectively).

As shown in Table 2, simulated ischemia induced significant membrane depolarization and decreases of Vₘₐₓ, APA, APD₅₀, and APD₉₀ (P<0.05 versus initial values). These AP alterations were similar for all groups; in particular, the AP shortening measured at the end of the ischemic period was not significantly modified by the class III agent (after 30 minutes of simulated ischemia, APD₅₀ was reduced by 53±7%, 52±5%, and 67±7% in the presence of 5, 10, and 50 nmol/L of dofetilide, respectively, versus 61±4% for control). In all groups, reperfusion allowed recovery of AP parameters close to initial values for RMP, Vₘₐₓ, and APA. APD₅₀ and APD₉₀ also returned to initial values in the control group, whereas they were decreased by dofetilide (P<0.05) in a concentration-dependent manner (after 30 minutes of reperfusion, APD₅₀ was +8±3%, +25±5%, and +61±24% in the presence of 5, 10, and 50 nmol/L of dofetilide, respectively, and APD₉₀ was +13±4%, +35±5%, and +64±13% in the presence of 5, 10, and 50 nmol/L of dofetilide, respectively).

However, as illustrated in Figure 1 (bottom), the kinetics of the ischemia-induced AP shortening (ANOVA for time, P<0.0001) were significantly different between control and treated groups (ANOVA for group, P=0.001). APD₉₀ reduction occurred rapidly in the control group, namely, over the first 10 minutes of simulated ischemia, whereas it was significantly delayed in the presence of 5 nmol/L dofetilide (ANOVA, P<0.0001 versus control group). Conversely, in the NZ (top) during the 30 minutes of simulated ischemia, dofetilide exhibited class III effects (ANOVA for time, P<0.0001 and group, P<0.0001) at the 2 highest concentrations only (ANOVA versus control group, P<0.0001 for 50 nmol/L, P=0.0001 for 10 nmol/L).

The APD₉₀ dispersion occurring between both normal and ischemic regions was affected by the presence of dofetilide, as illustrated in Figure 2, which shows examples of AP recorded simultaneously in the NZ and AZ during early (10 minutes) and late (30 minutes) ischemia (middle and right panels, respectively), in the absence (top) or in the presence of dofetilide at 5 nmol/L (middle) and 50 nmol/L (bottom). As summarized in Figure 3, the APD₉₀ dispersion, measured as the ratio APD₉₀NZ/APD₉₀AZ, was significantly modified by 5 and 50 nmol/L dofetilide (P<0.05 and P<0.005, respectively, ANOVA versus control). Dofetilide at 5 nmol/L reduced the APD₉₀ dispersion during the first 10 minutes of simulated ischemia (P<0.05). Conversely, the high concentration of the class III agent significantly worsened the APD₉₀ dispersion during the late phase of ischemia (after 20 minutes, P<0.05). No significant variation was observed with the
intermediate concentration (10 nmol/L) compared with control.

Effects of Dofetilide on the Incidence of Electrical Disturbances During Simulated Ischemia/Reperfusion

The different types of electrical disturbances occurring in this in vitro model of border zone are illustrated in Figures 4 and 5, which show APs recorded simultaneously in the NZ and AZ during simulated ischemia and reperfusion. We recorded (1) myocardial conduction blocks, either unidirectional, for example from the AZ toward the NZ (Figure 4A), or bidirectional between the 2 ventricular regions (Figure 4B); (2) repetitive responses induced by an ES (Figure 4C); and (3) spontaneous repetitive responses independent of stimulation (Figure 5). We subdivided the severity of the spontaneous repetitive responses into 1, 2, or 3 spontaneous extrasystoles (Figure 5A, 1 spontaneous AP), salvos (Figure 5B, 7 spontaneous extrasystoles), and sustained activities (Figure 5C, >10 spontaneous APs).

As summarized in Table 3, dofetilide at 5 nmol/L significantly decreased the incidence of ischemia-induced conduction blocks (P<0.05) and delayed their occurrence (at 27.5±1.7 minutes of the ischemic phase versus 17.1±1.7 minutes with no drug, P<0.05), whereas at 10 and 50 nmol/L, no significant effect was observed either on the incidence of blocks or on their occurrence time (at 19.9±4.0 minutes and 19.5±1.4 minutes in the presence of dofetilide at 10 and 50 nmol/L, respectively).

Figure 2. Representative AP recordings obtained simultaneously in normal and simulated ischemic conditions in absence of drug (control, top) and in presence of dofetilide at 5 (middle) and 50 (bottom) nmol/L. Traces show examples of AP recorded in same cell in each myocardial zone (NZ and AZ) in initial conditions (before initiation of ischemia, left) and during early (at 10 minutes, middle) and late (at 30 minutes, right) ischemic phases. Dispersion of APD\(_{90}\) between NZ and AZ (r) is measured as ratio APD\(_{90}\)NZ/APD\(_{90}\)AZ. Note that during early simulated ischemia (at 10 minutes, middle traces), APs in AZ were shortened less in presence of dofetilide than in control, leading to a decreased dispersion of APD\(_{90}\) (low r value), especially with 5 nmol/L dofetilide, whereas during late ischemia (at 30 minutes, left traces), APs were shortened in AZ and lengthened in NZ, leading to an increase of APD\(_{90}\) dispersion with 50 nmol/L dofetilide (high r value).

Figure 3. Effects of dofetilide at 5, 10, and 50 nmol/L on dispersion of APD\(_{90}\) between normal and ischemic myocardial zones. Data are expressed as mean±SEM. Dispersions of APD\(_{90}\) are represented by ratio APD\(_{90}\)NZ/APD\(_{90}\)AZ. For each group: control (n=8) and dofetilide 5 (n=7), 10 (n=6), and 50 (n=8) nmol/L. Ratio values are given in initial conditions (0 minutes) and at 5, 10, 20, and 30 minutes of simulated ischemic phase. Results of ANOVA are given for group and time factors. *P<0.05, Student’s t test vs control. Note APD\(_{90}\) dispersion is reduced by 5 nmol/L dofetilide during early ischemic phase (at 5 and 10 minutes) and enhanced by 50 nmol/L dofetilide during late ischemic phase (at 20 and 30 minutes).
During ischemia, dofetilide at all concentrations completely abolished the occurrence of ES-induced repetitive responses, whereas the incidence of spontaneous arrhythmias was significantly enhanced by 10 and 50 nmol/L of drug (P<0.05 each; P<0.07 for the dofetilide 5 nmol/L group). The percentage of preparations with severe spontaneous arrhythmias (sustained type) appeared to be higher in treated groups than in control, although this was not significant. The spontaneous repetitive responses occurred significantly later during simulated ischemia than those of ES-induced type (at 17.4±3.0 versus 9.8±2.1 minutes in control group, P<0.05), and their occurrence time was similar in all groups (at 15.9±2.7, 14.4±1.8, and 17.9±2.3 minutes in the presence of 5, 10, and 50 nmol/L dofetilide, respectively, versus 17.4±3.0 minutes during ischemia alone).

During reperfusion, all myocardial conduction blocks disappeared with a similar delay for all groups (at 1.5±0.3, 1.6±0.5, and 1.6±0.2 minutes after the reperfusion onset in the presence of 5, 10, and 50 nmol/L dofetilide, respectively, and 2.0±1.0 minutes in control). Dofetilide at 50 nmol/L prevented the occurrence of ES-induced repetitive responses, whereas it was already low in control. The incidence of spontaneous arrhythmias remained high for all treated groups, as did the percentage of preparations exhibiting severe spontaneous arrhythmic events. The occurrence time of spontaneous repetitive responses also was similar among groups (at 11.7±2.2 minutes of the reperfusion phase in control and 14.8±1.8, 15.9±1.2, and 14.9±2.1 minutes in the presence of dofetilide at 5, 10, and 50 nmol/L, respectively, P=NS).

**Discussion**

The main findings of this study may be summarized as follows: (1) Dofetilide at 5 nmol/L prevented early ischemia-induced AP shortening, whereas at 10 and 50 nmol/L, it exerted class III effects in normal conditions; (2) as a result of its differential class III efficacy in the NZ and AZ, dofetilide at 5 nmol/L prevented the early APD₉₀ dispersion (10 minutes) between zones, whereas at 10 and 50 nmol/L it worsened it during the late ischemic phase (20 to 30 minutes); (3) dofetilide at all concentrations inhibited the early ES-
TABLE 3. Effects of Dofetilide on the Incidence of Conduction Blocks and Arrhythmias During Simulated Ischemia and Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>Dofetilide, nmol/L</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (n=7)</td>
<td>10 (n=7)</td>
<td>50 (n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction blocks</td>
<td>83</td>
<td>29*</td>
<td>57</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Triggered repetitive responses</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Spontaneous repetitive responses</td>
<td>25</td>
<td>71</td>
<td>86*</td>
<td>75*</td>
<td></td>
</tr>
<tr>
<td>Sustained activities</td>
<td>17</td>
<td>29</td>
<td>43</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triggered repetitive responses</td>
<td>17</td>
<td>29</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Spontaneous repetitive responses</td>
<td>92</td>
<td>86</td>
<td>100</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Sustained activities</td>
<td>67</td>
<td>71</td>
<td>86</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Values are % of preparations with disturbances. *P<0.05, exact Fisher’s test vs control.

induced arrhythmias, but at 10 and 50 nmol/L it increased the spontaneous repetitive responses occurring later during the ischemic phase; and (4) dofetilide did not significantly affect the incidence of arrhythmias induced by reperfusion.

In this in vitro model, dofetilide did not antagonize the AP shortening that developed after 20 minutes of exposure to simulated ischemic conditions. This inability to prevent the late APD₉₀ decrease is most likely related to the high K⁺ concentration in the ischemia-mimicking solution (12 mmol/L). It has been clearly established that hyperkalemia is able to impair the class III efficacy of dofetilide and that the Iᵦ block induced by this agent in AT-1 cells is strikingly reduced by elevated extracellular K⁺ content. In addition, the ischemia-induced AP shortening has been attributed mainly to the activation of an ATP-dependent potassium conductance (Iᵦ,ATP). These potassium channels are not affected by dofetilide, and the Iᵦ,ATP-induced changes in AP shape observed during the late ischemic phase may override any effect of Iᵦ, blockade. More interestingly, this study demonstrated that dofetilide delayed the decrease in APD₉₀ during the early ischemic period (until 15 minutes, Figure 1B), suggesting that the class III efficacy of dofetilide might be different and more beneficial under less severe ischemic conditions, as might occur in patients with chronic coronary artery disease. It is unclear, however, why this protective effect of dofetilide was obtained only with the low concentration (5 nmol/L). Further investigations would be needed to clarify this point.

The present study also showed that the dispersion of APD₉₀ around the border zone was affected differently depending on the concentration of dofetilide, which prevented it at 5 nmol/L during the early ischemic phase, worsened it at 50 nmol/L during the late ischemic phase, and had no significant effect at 10 nmol/L. The dispersion of repolarization is implicated in the generation of arrhythmia, as suggested by a previous study using simultaneous monophasic AP recordings from 2 sites of the right ventricle in human heart that has clearly proposed a link between the dispersion of repolarization and the inducibility of monomorphic ventricular tachycardia. Injury currents with the border zone, as established in isolated porcine and canine hearts, are thought to be a possible mechanism responsible for some arrhythmias such as automatic activities, focal reexcitation, reentry arrhythmias, or triggered activities.

Our findings show that dofetilide exerted antiarrhythmic and proarhythmic effects around the border zone during ischemia depending on the type of arrhythmia, reducing the ES-induced arrhythmic events and enhancing the incidence of those of the spontaneous type at all concentrations, although significantly only at 10 and 50 nmol/L. Antiarrhythmic effects of the class III agents have been reported, especially in ventricular fibrillation models. Chen et al demonstrated in dogs that dofetilide exerted no benefit on arrhythmias linked to abnormal automaticity but suppressed the reentry arrhythmias induced by programmed electrical stimulation. Our results might be compared with these latter findings, although a difference in mechanism responsible for the arrhythmias in the 2 different models may exist. Indeed, as previously discussed, the ES-induced arrhythmias recorded in our model are probably due to reentry between normal and ischemic myocardial zones. Briefly, the increase of myocardial conduction times and the occurrence of conduction blocks between the two regions would favor the emergence of reentry movements. In addition, it is known that single or multiple premature impulses, such as extrastimuli, are able to either provoke or inhibit reentrant circuits by altering refractory periods of the tissue involved. The decrease of the incidence of myocardial conduction blocks around the border zone observed with 5 nmol/L dofetilide might explain its preventive action on the ES-induced repetitive responses. Our findings also suggest that the antiarrhythmic efficacy of 5 nmol/L dofetilide might be related to the lessened APD₉₀ dispersion between the two regions during the early ischemic phase. The antiarrhythmic action of 10 and 50 nmol/L dofetilide on ES-induced arrhythmias is more likely related to its significant class III effects in NZ during the early ischemic phase, thus terminating reentry circuits that traverse the normal tissue. In contrast, the border zone spontaneous arrhythmias are unlikely to be related to reentry movements, because they are independent of the stimulation. Early and delayed afterdepolarizations or abnormal automaticity, induced by injury currents originating from the border zone, cannot be excluded. Whatever the mechanisms involved, the significant increase of the incidence of spontaneous arrhythmias obtained with 10 and 50 nmol/L dofetilide might be related to its potent class III action in the normal region, unlike in the ischemic tissue.

During reperfusion, dofetilide did not affect the border zone spontaneous arrhythmias. These findings are consistent with the absence of protective effects of dofetilide against ventricular fibrillation in dogs and in minipigs, although it is difficult to compare data obtained in vivo during coronary blood flow restoration with data obtained in vitro using Tyrode’s solution simulating ischemia/reperfusion. We recently demonstrated, in this model of myocardial border zone, that another class III antiarrhythmic drug, dl-sotalol, was proarrhythmic during reperfusion, whereas dl-sotalol and propranolol, both of which exert β-blocking activities, pre-
vented the occurrence of spontaneous repetitive responses.23 These findings clearly suggested that an adrenergic stimulation by catecholamines might be responsible, at least in part, for the reperfusion-related spontaneous arrhythmias and might explain the lack of antiarrhythmic effect of dofetilide, like d-sotalol, around the border zone. Alternatively, the present in vitro model may have limitations with respect to the relevance to border zones occurring during pathophysiological conditions. Indeed, the partition between normal and ischemic/reperfused ventricular tissues was narrow and regular, whereas this border zone may be larger and more patchworked in vivo in disease states such as chronic infarction and fibrosis than in the present model. However, this does not modify the implications of our findings for the understanding of the differential antiarrhythmic and proarrhythmic effects of dofetilide, depending on the concentration used and the arrhythmia type, around the potentially crucial myocardial border zone. The validity and relevance of this in vitro model was previously discussed and recognized.22

In conclusion, the present work in an in vitro model of border zone provides evidence for benefits of a low concentration of dofetilide (5 nmol/L) in preventing both dispersion of repolarization between normal and ischemic tissues and the occurrence of ES-induced arrhythmias during myocardial acute ischemia with no significant proarrhythmic effect on either spontaneous arrhythmic events or reperfusion-induced arrhythmias. In contrast, high concentrations of dofetilide may exert proarrhythmic effects on ischemia-induced spontaneous arrhythmias around the border zone, in relation to its differential class III efficacy in normal and ischemic tissues. Interestingly, the concentration of 5 nmol/L relates closely to human plasma concentrations detected after doses of dofetilide that prevent inducible sustained ventricular tachyarrhythmia.16,41 The higher concentrations of dofetilide (10 and 50 nmol/L) used in the present study are consistent with the observations of torsades de pointes observed in patients after 15 mg/kg.41 Although the 50 nmol/L concentration of drug is beyond what is attainable with clinically recommended doses, the present data clearly indicate the need for close attention to dosage to optimize the benefit relative to the risk in patients treated with dofetilide.

Acknowledgment

This work was supported by a grant from Pfizer Central Research, Sandwich, UK.

References


Electrophysiological Effects of Dofetilide in an In Vitro Model of "Border Zone" Between Normal and Ischemic/Reperfused Myocardium
René Rouet, Sandra Picard, Christian Libersa, Mathieu Ghadanfar, Colin Alabaster and Jean-Louis Gérard

_Circulation_. 2000;101:86-93
doi: 10.1161/01.CIR.101.1.86
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/1/86