Dispersion of Ventricular Repolarization and Ventricular Fibrillation in Left Ventricular Hypertrophy: Influence of Selective Potassium Channel Blockers

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ABSTRACT

This study tested the hypothesis that combination ion channel blockers of the transient outward current (I_{to}) and the rapid component of the delayed rectifying current (I_{Kr}) would produce greater prolongation of the ventricular action potential duration (APD) and increased dispersion of the APD in hypertrophied hearts compared with control hearts. Isolated rabbit hearts were studied 48 ± 5 days postabdominal aortic banding. Left ventricular endocardial and epicardial APDs were significantly greater at baseline in the hypertrophied group than in controls (P < .05). The magnitude of APD prolongation induced by the I_{to} blocker 4-aminopyridine (4-AP) and combination 4-AP and the I_{Kr} blocker dofetilide was greater in the hypertrophied hearts than in the normal hearts (P < .01). Mean APD dispersion was significantly greater in the hypertrophied group than in the control hearts at baseline (P < .05). 4-AP increased APD dispersion by a similar magnitude in the hypertrophied hearts (10 ± 10 ms) and the control hearts (8 ± 8 ms, P = NS), whereas the combination 4-AP and dofetilide increased APD dispersion by a greater magnitude in the hypertrophied hearts (41 ± 28 ms) than the control hearts (21 ± 11 ms, P < .05). Ventricular fibrillation occurred spontaneously in four hypertrophied hearts (40%) during combination drug perfusion and in none of the control hearts (P < .05). Thus, combination I_{to} and I_{Kr} blockers cause greater prolongation APD and increased APD dispersion in left ventricular hypertrophy, and this is associated with the development of ventricular fibrillation.

Ventricular dilation (Reiter et al., 1988; Zabel et al., 1996) and some antiarrhythmic drugs may increase dispersion of ventricular repolarization (Hii et al., 1992; Hohnloser et al., 1995; Zabel et al., 1997; Gillis et al., 1998c) and predispose to arrhythmia development. The increased prolongation of the ventricular action potential duration (APD) and increased dispersion of APD that occur in left ventricular hypertrophy may be due, in part, to changes in the spatial heterogeneity of the density of the transient outward current (I_{to}) (Hart, 1994; Tomita et al., 1994; Gillis et al., 1998a), the delayed rectifying current (I_{Kr}) (Kleiman and Houser, 1989; Fukuwaka et al., 1994), and the inward rectifying current (I_{K1}) (Brooksby et al., 1993; Gillis et al., 1998a). We have previously reported that BaCl2, in concentrations that block I_{Kr}, produces greater prolongation of the AP in hypertrophied rabbit hearts compared with control hearts (Gillis et al., 1998a). In contrast, 4-aminopyridine (4-AP) in concentrations that block I_{to} and dofetilide in concentrations that selectively block I_{Kr} did not produce such an effect on APD in hypertrophied hearts. The effects of combinations of selective potassium channel blockers on APD and dispersion of APD in hypertrophy are unknown. We hypothesized that a change in the balance of repolarizing currents that occur in hypertrophy would result in an increase in the effects of combination I_{to} and I_{Kr} blockers on APD and APD dispersion in hypertrophy compared with controls. Furthermore, we hypothesized that such an effect might be further exaggerated by increases in ventricular preload.

Accordingly, the purposes of this study were 1) to compare the effects of modest increases in ventricular preload on APD and dispersion of APD in hypertrophied rabbit hearts compared with control hearts and 2) to compare the effects of the I_{to} blocker 4-AP, the I_{Kr} blocker dofetilide, and combination 4-AP and dofetilide on APD and dispersion of APD in hypertrophied hearts with those in control hearts at baseline and during increased preload.

Materials and Methods

Animals and Surgical Procedure. Male New Zealand White rabbits weighing 2.5 to 3.0 kg were studied. Left ventricular pressure was recorded...

ABBREVIATIONS: APD, action potential duration; 4-AP, 4-aminopyridine; APD_{90}, action potential duration at 90% repolarization; APD_{epi}, epicardial action potential duration; APD_{endo}, endocardial action potential duration; I_{to}, transient outward current; I_{Kr}, rapid component of the delayed rectifying current; I_{K1}, inward rectifying current.
overload was induced by partial ligation of the abdominal aorta as previously described (Gillis et al., 1998a,b). The animals were kept in the animal care center until the day of study. Animals matched for age and weight served as controls. The day before study, arterial blood pressure was measured by inserting a 22-gauge catheter percutaneously into an ear artery. All procedures performed conformed to the guiding principals of the Canadian Council on Animal Care.

**Experimental Preparation.** Animals were studied 48 ± 5 days after abdominal surgery. By this time, significant left ventricular hypertrophy had developed in animals undergoing abdominal aortic constriction compared with age- and weight-matched control animals (P < .05; Table 1). On the day of study, rabbits were pretreated with heparin sulfate (75 U/kg) and then anesthetized with sodium pentobarbital (35 mg/kg). Hearts were rapidly removed through a median sternotomy incision and perfused retrogradely via the aorta with blood buffer-perfusate (10%) hematocrit. The Krebs-Henseleit buffer consisted of 118 mM NaCl, 3.3 mM KCl, 2.0 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 24 mM NaHCO₃, 10 mM glucose, 2.0 mM Na pyruvate, and 10 mg/l albumin.

A blood-buffer perfusate was used because this preparation is more stable for electrophysiologic studies (Gillis et al., 1996a). Erythrocytes isolated from blood of healthy nonanesthetized sheep were prepared the morning of study and added to oxygenated Krebs-Henseleit buffer to give a 10% hematocrit (Gillis et al., 1996a, 1998a). The blood-buffer perfusate was warmed to 37°C and equilibrated with 95% O₂/5% CO₂ in a custom-made bath containing a Henseleit buffer to give a 10% hematocrit (Gillis et al., 1996a, 1998a). The perfusion protocol was carried out at ASPET Journals on October 16, 2017 jpet.aspetjournals.org Downloaded from

A latex balloon catheter was inserted into the left ventricle via a left atriotomy for modulation of left ventricular preload (Reiter et al., 1988; Zabel et al., 1996). The volume of the intraventricular balloon was changed by hand injections of 1.5 ml of saline. A 4P open-lumen catheter was attached to the base of the balloon catheter for monitoring of left ventricular pressure and the derivative of left ventricular pressure (dP/dt). Hearts were ventriculally paced at a cycle length of 500 ms (pulse width, 2.0 ms; twice diastolic threshold intensity) via a bipolar platinum electrode on the lateral wall of the left ventricle. Platinum electrodes were positioned on the epicardial surface of the heart for monitoring of the ECG. A plastic ring with seven evenly spaced electrode holders was mounted around the heart. Monophasic action potentials were recorded from seven sites on the epicardial surface of the ventricle via custom-made Ag-AgCl contact monophasic action potential electrodes: two sites on the right ventricle and five sites on the left ventricle (Zabel et al., 1996; Gillis et al., 1998b). One endocardial monophasic action potential was recorded from the left ventricle via an electrode inserted through the left ventricular wall. Figure 1 illustrates the location of the monophasic action potential electrodes and examples of action potential recordings from each site.

**Experimental Protocol.** The perfusion protocol was carried out in 11 control hearts and 10 hypertrophied hearts. Coronary flow was maintained at 30 ml/min. Baseline electrophysiologic data were collected during a 30-min period of perfusion with blood-buffer containing no drug. Then perfusion with 0.5 mM 4-AP, a concentration that has been shown to block one component of I_{Kr} (Campbell et al., 1993), was initiated for 30 min, and electrophysiologic data were collected 15 min after initiation of 4-AP perfusion. Perfusion with the combination of 0.5 mM 4-AP and 15 mM dofetilide, a concentration that has been shown to selectively block I_{Kr} (Jurkiewicz and Sanguinetti, 1993), was then initiated for 30 min, and electrophysiologic data were collected 15 min after initiation of the drug combination. During each stage, electrophysiologic data were collected at low preload (no balloon inflation) and during inflation of the balloon to 1.5 ml. A 2-min recovery interval was allowed before the next intervention. To assess the stability of the experimental preparation over time, six additional experiments were conducted in three control hearts and three hypertrophied hearts, which were perfused with the blood-buffer perfusate without drugs for 2 h.

**Electrophysiologic, Hemodynamic, and Morphologic Measurements.** The monophasic action potential recordings, left ventricular pressure, and derivative of left ventricular pressure (dP/dt) were digitally acquired at 100 Hz/channel on a Compaq 386 system with a data translation (DT 2821) analog and digital input-output board (Gillis et al., 1998a,b). This board provides a 12-bit resolution, 50-Hz throughput, and software-programmable gains. APDs recorded by the monophasic action potential electrodes were measured from the steepest part of the action potential upstroke to the level of 90% repolarization. We defined the distance from the diastolic baseline to the crest of the plateau as the total action potential amplitude (Gillis et al., 1998b). Ventricular activation times were measured from the pacing stimulus to the most rapid rise of the onset of the local monophasic action potential (Zabel et al., 1986; Gillis et al., 1998b). Left ventricular end-diastolic pressure, peak left ventricular systolic pressure, and

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**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics of rabbit hearts</th>
<th>Control (n = 11)</th>
<th>Hypertrophy (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit weight (kg)</td>
<td>3.2 ± 0.3</td>
<td>3.5 ± 0.2*</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>11.3 ± 1.0</td>
<td>14.4 ± 2.5b</td>
</tr>
<tr>
<td>Left ventricle weight (g)</td>
<td>10.0 ± 0.9</td>
<td>12.9 ± 2.2c</td>
</tr>
<tr>
<td>Heart weight/body weight (mm Hg)</td>
<td>0.0035 ± 0.0003</td>
<td>0.0040 ± 0.0006c</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>85 ± 4</td>
<td>132 ± 15c</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>100 ± 6</td>
<td>161 ± 21d</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>77 ± 4</td>
<td>117 ± 3e</td>
</tr>
<tr>
<td>Myocyte cell diameter (μm)</td>
<td>11.5 ± 1.0</td>
<td>13.3 ± 0.8f</td>
</tr>
</tbody>
</table>

* P < .05, b P < .01, c P < .001, versus control.
peak positive dP/dt were continuously monitored. Coronary flow was measured as the coronary sinus effluent ejected via the pulmonary artery. APDs at 90% (APD_{ept}) repolarization, left ventricular pressures, and dP/dt were measured semiautomatically with a custom-designed software program. An average of five complexes were measured at each sampling time. Dispersion of the APD was defined as the difference between the maximal and minimal recorded APD intervals (Zabel et al., 1996; Gillis et al., 1998b). Dispersion of ventricular activation time was defined as the difference between the maximal and minimal recorded activation times.

Hearts were blotted and weighed at the end of each experiment. Transverse sections of the heart were cut at the midventricular level at the end of each study and fixed in 10% buffered formalin for light-microscopic study. Sections of paraffin block were stained with H&E or Gomori trichrome (Gillis et al., 1998a). Other sections were stained by periodic acid Schiff with or without diastase to outline the cell membranes. Histologic sections were imaged on a television monitor at \( \times 1000 \) magnification, and the diameter across the nucleus of longitudinally oriented myocytes located in the interventricular septum was measured semiautomatically by marking two points with a light pen with a Bioquant 4 Image Analysis System (Rand M Biometrics Inc., Nashville, TN) (Hoshino et al., 1983; Schoen et al., 1984). The diameters of 80 myocytes were averaged for each experiment.

Statistical Analysis. Data are presented as means \( \pm \) S.D. Electrophysiologic and hemodynamic parameters were compared between the sham and hypertrophied hearts. The effects of increasing preload, 4-AP, and the combination of 4-AP and dofetilide were compared within and between groups. Differences between groups were compared with the paired \( t \) test, unpaired \( t \) test, or factorial ANOVA for repeated measures (Montgomery, 1991) where appropriate. Differences were considered statistically significant at \( P < .05 \).

### Results

The characteristics of the control and hypertrophied hearts are shown in Table 1. The hypertrophied animals were slightly heavier than control animals on the day of study (\( P < .05 \)). The heart mass, left ventricular mass, and ventricular myocyte diameter were significantly (\( P < .01 \)) greater in the hypertrophied than the control group. The heart-to-body weight ratio was also greater in the hypertrophied group than the control group (\( P < .05 \)). The mean arterial blood pressure was significantly greater in the hypertrophied animals. Significant histologic abnormalities were not observed in the hypertrophied hearts compared with the control hearts.

**Time-Dependent Experiments.** APD measured on the epicardial surface of the heart (APD_{ept}) and on the endocardial surface (APD_{endo}) of the left ventricle remained stable over time in the absence of drug perfusion at low and high preload (Table 2). As well, left ventricular systolic pressure and end diastolic pressure remained stable over time at low and high preload (Table 2).

### Dispersion of Repolarization in Ventricular Hypertrophy

#### Changes in Left Ventricular Systolic and Diastolic Pressure. At low preload, the left ventricular systolic pressure was 19 \( \pm \) 12 mm Hg in the control hearts and 23 \( \pm \) 16 mm Hg in the hypertrophied hearts (\( P = \text{NS} \)). Increasing the preload resulted in a significant (\( P < .05 \)) increase in left ventricular systolic pressure in both the control hearts (35 \( \pm \) 22 mm Hg) and hypertrophied hearts (42 \( \pm \) 15 mm Hg). Systolic pressures remained unchanged at a given preload during the perfusion protocol. At low preload, the left ventricular end-diastolic pressure was 1 \( \pm \) 3 mm Hg in the control hearts and 3 \( \pm \) 2 mm Hg in the hypertrophied hearts (\( P = \text{NS} \)). Increasing preload resulted in a slight (\( P = \text{NS} \)) increase in the end-diastolic pressure in control hearts (2 \( \pm \) 3 mm Hg) or hypertrophied hearts (5 \( \pm \) 2 mm Hg). The left ventricular end-diastolic pressure remained unchanged at low preload during the drug perfusion protocol.

APDs. The mean APD_{ept} values measured from one site on the lateral wall of the left ventricle at baseline and during drug perfusion in the hypertrophied and control hearts are shown in Fig. 2. APD_{ept} was prolonged in the hypertrophied group compared with the control group at baseline and during perfusion with 4-AP and 4-AP plus dofetilide (\( P < .05 \)). The drug 4-AP alone and in combination with dofetilide caused significant (\( P < .001 \)) prolongation of APD_{ept} in both hypertrophied and control hearts. However, the magnitude of APD_{ept} prolongation induced by 4-AP and 4-AP plus dofetilide was greater in the hypertrophied hearts than in the control hearts (\( P < .05 \) by factorial ANOVA).

The left ventricular APD_{endo} was significantly longer than the left ventricular APD_{ept} at baseline and throughout the perfusion protocol in both hypertrophied and control hearts (Fig. 2). APD_{endo} was greater in the hypertrophied group than in the control group at baseline and during drug perfusion (\( P < .01 \)). The drug 4-AP alone and 4-AP plus dofetilide caused significant (\( P < .001 \)) prolongation of APD_{endo} in both hypertrophied and control hearts. However, the magnitude of prolongation of APD_{endo} induced by 4-AP and 4-AP plus dofetilide was greater in the hypertrophied hearts than in control hearts (\( P < .05 \) by factorial ANOVA).

The effects of increasing preload on APD_{ept} and APD_{endo} are shown in Fig. 3. Increasing preload was not associated

### Table 2

**Time-dependent experiments**

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Preload</th>
<th>Control</th>
<th>Hypertrophy</th>
<th>Control</th>
<th>Hypertrophy</th>
<th>Control</th>
<th>Hypertrophy</th>
<th>Control</th>
<th>Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 min</td>
<td>10 min</td>
<td>110 min</td>
<td>120 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP</td>
<td></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 ( \pm ) 1</td>
<td>3 ( \pm ) 2</td>
<td>7 ( \pm ) 5</td>
<td>8 ( \pm ) 6</td>
<td>2 ( \pm ) 2</td>
<td>4 ( \pm ) 3</td>
<td>7 ( \pm ) 5</td>
<td>4 ( \pm ) 5</td>
</tr>
<tr>
<td>LVSP peak</td>
<td></td>
<td>10 ( \pm ) 7</td>
<td>29 ( \pm ) 12</td>
<td>17 ( \pm ) 7</td>
<td>34 ( \pm ) 10</td>
<td>7 ( \pm ) 4</td>
<td>14 ( \pm ) 3</td>
<td>25 ( \pm ) 7</td>
<td>25 ( \pm ) 5</td>
</tr>
<tr>
<td>APD_{ept}</td>
<td></td>
<td>171 ( \pm ) 18</td>
<td>182 ( \pm ) 7</td>
<td>176 ( \pm ) 19</td>
<td>173 ( \pm ) 9</td>
<td>181 ( \pm ) 25</td>
<td>186 ( \pm ) 2</td>
<td>167 ( \pm ) 5</td>
<td>182 ( \pm ) 12</td>
</tr>
<tr>
<td>APD_{endo}</td>
<td></td>
<td>204 ( \pm ) 8</td>
<td>211 ( \pm ) 9</td>
<td>206 ( \pm ) 7</td>
<td>209 ( \pm ) 11</td>
<td>209 ( \pm ) 14</td>
<td>213 ( \pm ) 9</td>
<td>204 ( \pm ) 2</td>
<td>219 ( \pm ) 11</td>
</tr>
</tbody>
</table>
with significant shortening of APD_{epi} at baseline in either the hypertrophied group (187 ± 30 to 182 ± 20 ms) or the control group (164 ± 21 to 157 ± 16 ms). During 4-AP perfusion, increasing preload tended to shorten APD_{epi} in both the hypertrophied group (216 ± 33 to 209 ± 25 ms) and the control group (177 ± 17 to 170 ± 22 ms; P < .08). During 4-AP plus dofetilide perfusion, increasing preload tended to shorten APD_{epi} in both the hypertrophied (255 ± 41 to 235 ± 50 ms) and control (209 ± 34 to 196 ± 41 ms; P = .05) groups. The magnitude of shortening was similar in both groups. Increasing preload did not significantly shorten APD_{endo} at baseline in either the hypertrophied group (194 ± 19 to 190 ± 20 ms) or the control group (232 ± 42 to 224 ± 22 ms) or during 4-AP plus dofetilide perfusion (Fig. 3).

**APD Dispersions.** Mean APD dispersions measured at baseline and during drug perfusion at low and high preload are shown in Fig. 4. APD dispersion was significantly (P < .05) greater in the hypertrophied group than in the control group at baseline and during drug perfusion. Drug perfusion with 4-AP and 4-AP plus dofetilide significantly (P < .001) increased APD dispersion in both groups, and this effect was greater in the hypertrophied hearts than in the control hearts (P < .005). 4-AP increased APD dispersion by a similar magnitude in the hypertrophied hearts (10 ± 10 ms) and the control hearts (8 ± 8 ms; P = NS), whereas 4-AP plus dofetilide increased APD dispersion by a greater magnitude in the hypertrophied hearts (41 ± 28 ms) compared with the control hearts (21 ± 11 ms; P < .05). The effect of 4-AP plus dofetilide on APD dispersion tended to be further exaggerated in hypertrophy after an increase in preload (P = .08).

**Spontaneous Ventricular Fibrillation.** Spontaneous ventricular fibrillation developed during 4-AP plus dofetilide perfusion in four hypertrophied hearts (40%) and no control hearts (P < .05). Spontaneous ventricular fibrillation did not develop during baseline or 4-AP perfusion in either group.

**Discussion**

In this study, we have demonstrated that the I_{to} blocker 4-AP and combination I_{to} and I_{Ks} blockers 4-AP plus dofetilide cause greater prolongation of left ventricular APD and increased dispersion of ventricular repolarization in left ventricular hypertrophy compared with control hearts. Modest increases in preload tended to exaggerate the drug-induced increased dispersion of APD in hypertrophied hearts. Furthermore, spontaneous ventricular fibrillation was more likely to occur in hypertrophied hearts than in control hearts during perfusion with the combination I_{to} and I_{Ks}, blockers.

Ventricular hypertrophy induced by pressure or volume overload is associated with alterations in cardiac electrophysiologic properties including prolongation of APD (Aaronson, 1980; Cerbai et al., 1994; Hart, 1994; Gillis et al., 1998a) and increased dispersion of ventricular repolarization (Kowey et al., 1991; Buja et al., 1993; Davey et al., 1994; Hart, 1994; Gillis et al., 1998b). Changes in ionic channel current density that are thought to contribute to these electrophysiologic abnormalities include decreases in I_{to}, I_{Ks}, and...
I$_K$$_3$ (Brooksby et al., 1993; Gillis et al., 1998a). We have previously reported that I$_K$$_1$ and I$_K$$\alpha$ but not I$_K$$\epsilon$, current densities are significantly reduced in ventricular myocytes isolated from hypertrophied rabbit hearts compared with controls (Gillis et al., 1998a). We also observed that barium in concentrations that selectively block inward rectifying currents produced greater APD prolongation in hypertrophied rabbit hearts. In contrast, dofetilide or low concentrations (0.2 mM) of 4-AP did not significantly prolong APD to a greater extent in hypertrophied hearts compared with control hearts (Gillis et al., 1998a). In this study, higher concentrations of 4-AP did produce greater prolongation of the APD in hypertrophied hearts compared with control hearts. Thus, the reduction in the two dominant repolarizing currents in hypertrophied rabbit heart, I$_K$$\alpha$ and I$_K$$_3$, is associated with an altered pharmacodynamic response: exaggeration of the effects of I$_K$$\alpha$ and I$_K$$_3$ blockers on prolongation of APD. Dofetilide in similar concentrations to those used in this study did not prolong APD to a greater extent in hypertrophied hearts (Gillis et al., 1998b). However, the combination of I$_K$$\alpha$ and I$_K$$_3$ blockade further exaggerated the prolongation of left ventricular endocardial APD in hypertrophy compared with 4-AP alone. This suggests that a change in the balance of repolarizing currents in hypertrophy, i.e., a greater dominance of I$_K$$_3$ in repolarization resulting from the decrease in I$_K$$\alpha$, could result in an increased pharmacodynamic effect of the combination ion channel blockers.

Increased dispersion of ventricular repolarization has been reported in left ventricular hypertrophy and is associated with increased risk of sudden death (Buja et al., 1993; Davey et al., 1994). We previously reported that increased dispersion of ventricular APD occurs in this rabbit model of left ventricular hypertrophy and that dofetilide in the same concentration as used in the current study did not significantly increase APD dispersion in hypertrophy compared with control hearts (Gillis et al., 1998b). In this study, 4-AP caused a greater increase in APD dispersion in hypertrophied hearts than in control hearts. Furthermore, 4-AP plus dofetilide substantially increased APD dispersion in hypertrophied hearts compared with control hearts. In another model of cardiac hypertrophy associated with complete heart block, the class III drug almokalant was reported to cause greater prolongation of APD and increased disparities of repolarization compared with controls (Volders et al., 1998).

Increased in preload have been reported to increase dispersion of ventricular repolarization in isolated perfused hearts (Zabel et al., 1996; Calkins et al., 1989) and to increase the propensity to ventricular arrhythmias (Reiter et al., 1988; Franz et al., 1992). In this study, modest increases in preload did not substantially increase APD dispersion at baseline in either control or hypertrophied hearts. However, the magnitude of APD dispersion tended to be further increased in hypertrophied hearts compared with control hearts when preload was increased during perfusion of 4-AP plus dofetilide.

Antiarrhythmic drug-induced dispersion of ventricular repolarization is associated with increased risk of ventricular proarrhythmia (Hii et al., 1992) and decreased probability of antiarrhythmic drug efficacy (Gillis et al., 1998c). In this study, the 4-AP plus dofetilide was associated with a greater frequency in the development of spontaneous ventricular fibrillation in hypertrophied hearts compared with control hearts. In our previous studies, the spontaneous occurrence of ventricular fibrillation was not observed during the perfusion of 15 nM dofetilide alone in hypertrophied hearts (Gillis et al., 1998a,b). It is likely that increased APD dispersion provided the substrate for ventricular reentry and that ventricular fibrillation may have been initiated by drug-induced afterdepolarizations. The onset of ventricular fibrillation was not recorded in this study. Dofetilide has recently been reported to be safe for use in patients with heart failure (Pedersen, 1998; Torp-Pedersen et al., 1999). In contrast, other class I and III antiarrhythmic drugs are proarrhythmic in patients with ventricular dysfunction or after myocardial infarction (The Cardiac Arrhythmia Suppression Trial Investigators, 1989; Waldo et al., 1996). Volders et al. (1998) reported that the class III drug almokalant causes greater prolongation of APD and a higher incidence of afterdepolarizations in canine myocytes isolated from hypertrophied hearts. Thus, this study suggests that combined I$_K$$\alpha$ and I$_K$$_3$ blockers might be proarrhythmic in the setting of left ventricular hypertrophy and increased dispersion of ventricular repolarization.

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References


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