Suppression of Repolarization-Related Arrhythmias In Vitro and In Vivo by Low-Dose Potassium Channel Activators

Frank A. Fish, MD, Chandra Prakash, PhD, and Dan M. Roden, MD

Marked prolongation of cardiac action potentials and of QT intervals has been associated with early afterdepolarizations and triggered activity in vitro and with ventricular tachycardia in vivo. Because the antihypertensive potassium channel activators pinacidil and cromakalim are known to accelerate repolarization in cardiac tissues, we performed in vitro and in vivo experiments to test the hypothesis that these agents would block the arrhythmogenic effects of delayed repolarization. Early afterdepolarizations and triggered activity were elicited in canine cardiac Purkinje fibers driven at cycle lengths of 4 seconds or more (K<sub>a</sub>, 2.7 mM) during superfusion with quinidine, cesium, or sematilide, a methylsulfonylaminobenzesulfonanilide analogue of procainamide with class III antiarrhythmic activity. The potassium channel activators invariably (17 of 17) abolished this form of abnormal automaticity. This effect was observed at low concentrations that did not alter action potential characteristics at shorter cycle lengths. Intravenous Cs<sup>+</sup> (total dose, 4.5 mM/kg) was used to produce ventricular arrhythmias in anesthetized rabbits randomly pretreated in a double-blind fashion with either low-dose pinacidil (0.2 mg/kg) or vehicle. Pinacidil pretreatment resulted in significantly fewer total ventricular ectopic beats (168±157 versus 582±448, p<0.005) and episodes of ventricular tachycardia (four of nine versus nine of nine, p=0.057). At this dose, pinacidil did not alter mean blood pressure or Cs<sup>+</sup> and maximal hypertensive response after Cs<sup>+</sup>. In summary, the potassium channel activators pinacidil and cromakalim suppressed triggered activity related to prolonged repolarization at concentrations that did not affect action potential characteristics at normal rates in vitro; pinacidil blunted arrhythmias produced by cesium administration in vivo without lowering blood pressure. Potassium channel activation is a therapeutic strategy for preventing long QT-related arrhythmias and requires clinical evaluation. (Circulation 1990;82:1362–1369)

Early afterdepolarizations (EADs) and associated triggered arrhythmias have been proposed as the mechanism underlying the polymorphic ventricular arrhythmia, torsade de pointes.<sup>1–5</sup> EADs can be induced in Purkinje fibers in vitro by virtually all antiarrhythmic drugs known to cause torsade de pointes.<sup>3–5</sup> Both the in vitro and in vivo arrhythmias are favored by similar conditions: action potential–prolonging drugs, slow rates, and low extracellular potassium. Action potentials can be prolonged and EADs and triggered activity induced by interventions that either depress outward (repolarizing) currents or augment inward (depolarizing) currents. These include cesium, which blocks potassium channels<sup>6</sup>; the calcium channel activator Bay K 8644<sup>7</sup>; and agents that interfere with sodium channel inactivation such as aconitine, veratridine, and anthopleurin-A.<sup>8–10</sup> Both torsade de pointes and EADs can be suppressed by interventions that reverse or prevent action potential prolongation. Such interventions include increasing stimulation rate, increasing extracellular potassium, or adding magnesium.<sup>2,11</sup> Action potentials can be shortened and EADs suppressed by sodium channel–blocking agents such as tetrodotoxin, tetracaine, or mexiletine, which also decrease action potential duration (APD).<sup>2,12,13</sup> Interestingly, calcium channel blocking drugs such as nifedipine, verapamil, and D600 suppress EAD-associated triggered activity, often without greatly affecting APD,<sup>14–16</sup> suggesting that calcium current underlies the depolarizing upstroke of this abnormal automaticity. Similar in vitro findings have been reported with magnesium<sup>11</sup>.
also, magnesium-induced suppression of torsade de pointes is not accompanied by marked QT shortening. In addition, marked action potential prolongation by the calcium channel blockers bepridil or lidoflazine was not accompanied by EAD-associated abnormal automaticity in the absence of catecholamines. Experiments in voltage-clamped sodium-free preparations support the hypothesis that 1-type calcium channels carry the inward current responsible for triggered activity induced by Bay K 8644.

The vasodilators pinacidil and cromakalim increase resting membrane potassium conductance in vascular smooth muscle and decrease cardiac APD. Despite dissimilar structures, both appear to mediate their cardiac effects by activating the ATP-dependent potassium current. Both drugs also demonstrate relative selectivity for vascular tissues, producing vasodilation at concentrations below those that substantially shorten cardiac APD. Nevertheless, Schotysik showed that at sufficient concentrations, cromakalim not only shortened APD but also reversed APD prolongation due to the class III agent ICS 205-930 in guinea pig papillary muscles. Although high concentrations of these agents have been used to substantially shorten cardiac APD in vitro, we hypothesized that even slight increases in potassium current(s) during repolarization by low concentrations might be sufficient to suppress EADs and triggered activity. We report here a series of experiments assessing the antiarrhythmic effects of a range of concentrations of these agents in both the in vitro and in vivo settings.

Methods

In Vitro Studies

Mongrel dogs (15–35 kg) were deeply anesthetized with intravenous sodium pentobarbital (30 mg/kg), and the heart was excised and immersed in cold Tyrode’s solution (mM, NaCl 138, NaHCO₃ 22, dextrose 5.5, MgCl₂ 0.5, Na₂HPO₄ 1.8, KCl 4, and CaCl₂ 2.7) that had been gassed with 95% O₂–5% CO₂. Free running false tendons were dissected and stored at room temperature in gassed Tyrode’s solution for 1–5 hours before they were mounted in the Lucite tissue bath. The bath was perfused with gassed Tyrode’s solution altered from the above to contain 2.7 mM KCl and warmed to 37±1°C. The measured pH of the perfusate was 7.35±0.05 for all experiments.

A pair of Teflon-coated wires scraped bare at the ends was connected to a stimulator with isolated output for field stimulation of the tissue. Stimuli were 2 msec in duration or less, and current was 1.5–2 times threshold. Purkinje cells were impaled with glass microelectrodes filled with 3 M KCl selected for tip resistances of 10–20 MΩ. The microelectrodes were connected through silver-silver chloride connections to a WPI (World Precision Instruments, New Haven, Conn.) model 750 operational amplifier with variable input capacitance. The bath was grounded through a similar 3 M KCl–silver–silver chloride junction. The amplified transmembrane potential signal was displayed on one channel of a dual time-base oscilloscope (model 5113, Tektronix Inc., Beaverton, Ore.) and recorded on a strip-chart recorder (model 2400, Gould Instruments Inc., Cleveland). The signal from the amplifier and a sawtooth signal (200 V/sec) were input into an analog differentiator whose output was linear in the 100–1,000 V/sec range. The differentiated phase zero of the action potential and the calibration signal also were displayed on the oscilloscope at a faster sweep. The oscilloscope screen was photographed and the following action potential characteristics were derived from off-line digitized tracings: takeoff potential, action potential amplitude, overshoot, and APD at 50% repolarization (APD₅₀) and at 90% repolarization (APD₉₀). Maximum upstroke slope of phase zero (Vmax) was determined directly from the oscilloscope screen and the photographed records.

All tendons first were stimulated at a basic cycle length (CL) of 500–1,000 msec for 20–30 minutes to ensure stable action potential characteristics. Baseline action potential recordings were obtained at CL 1,000, 4,000, and 8,000 msec, allowing a minimum of 60 seconds at each CL. The effective refractory period was determined by inserting extra stimuli every eighth action potential while stimulating at CL 1,000 msec (10–20-msec decrements). Fibers with spontaneous automaticity at CL<4,000 msec were not used, and fibers with spontaneous automaticity at CL between 4,000 and 8,000 msec were used to assess the electrophysiological actions of cromakalim alone at CL 1,000 and 4,000.

After baseline data were obtained, fibers were exposed to action potential–prolonging interventions while stimulation was continued at CL 1,000 msec. These interventions included quinidine (3–10 μM); the 4-[(methylsulfonyl)amino]benzamide analogue of procainamide, sematilide (CK 1752a; 10 μM); or CsCl (3–10 mM). After 60–90 minutes of exposure to one of these agents, data were obtained again at each CL (1,000, 4,000, and 8,000 msec). If triggered activity then was present, cromakalim or pinacidil was added at increasing concentrations (15 minutes exposure at each concentration while maintaining superfusion with the action potential–prolonging agent) until no triggered activity was present at CL≤8,000 msec. The effect of increasing concentrations of potassium channel activators on action potential characteristics also was assessed in preparations in which triggered activity was not elicited in the presence of action potential–prolonging agents. Also, the effects of a range of concentrations of cromakalim alone were assessed in a separate series of experiments. All data represent continuous impalements maintained throughout each experiment.

In Vivo Studies

New Zealand White rabbits (3.1–3.6 kg) were anesthetized with intravenous sodium pentobarbital...
(30–45 mg/kg delivered slowly over 15–30 minutes). A tracheostomy was performed, and the rabbits were mechanically ventilated. A femoral arterial catheter was placed for arterial blood gas analysis (Corning model 158, CIBA-Corning, Medfield, Mass.) and continuous arterial blood pressure monitoring. The electrocardiogram (ECG) was monitored in the standard or augmented limb leads selected for the most distinct P wave. A 6F bipolar electrode catheter was inserted through the right jugular vein and positioned in the right atrium to record discrete atrial and far-field ventricular electrograms. Supplemental pentobarbital was administered if required.

Preliminary (unblinded) experiments indicated that cumulative cesium doses (as CsCl) of 4–5 mM/kg administered over 5 minutes produced sustained ventricular tachycardia (>30 sec) in eight of nine rabbits. Twenty rabbits then were randomized to either pinacidil or placebo pretreatment. Intravenous pinacidil (0.2 mg/kg) or an equivalent volume of vehicle (3% EtOH, 2 ml) was given at time zero and 5 minutes. CsCl was given as two boluses, 3 mM/kg at 2 minutes and 1.5 mM/kg at 7 minutes. Investigators were blinded to the administration of pinacidil or vehicle throughout the experiment and subsequent ECG analysis. The surface and intracardiac ECGs were displayed on a multichannel recorder (VR12, Electronics for Medicine) and recorded on a Gould strip-chart recorder along with the arterial blood pressure tracings (10–25 mm/sec). Rhythms were characterized as supraventricular or ventricular on the basis of QRS morphology and atrioventricular synchrony as determined by the surface ECG and atrial electrograms. Total ventricular ectopic beats were tabulated at 1-minute intervals for the 10-minute period starting at the time of the first dose of pinacidil or vehicle. Only ventricular beats that occurred prematurely or during ventricular tachycardia were included; ventricular “escape” beats after sinus arrest or atrioventricular block were excluded. Ventricular tachycardia was defined as more than three consecutive ectopic beats and was characterized as nonsustained (<30 seconds) or sustained (≥30 seconds). The coded drug assignment was unblinded after ECG analysis.

Drugs
Quinidine and cesium were obtained from Sigma Chemical Co., St. Louis. Sematilide was synthesized using the method of Lumma et al.29 Cromakalim was kindly provided by Dr. John McCullough, Bristol-Myers Squibb Pharmaceuticals, Princeton, N.J., and was prepared as a 10⁻² M solution in 100% ethanol. Pinacidil was kindly provided by Eli Lilly, Indianapolis, Ind., and prepared as a 10⁻³ M stock solution (fresh every 3–5 days) in 3% ethanol (0.2–0.5 ml 0.1N HCl added per 100 ml) for in vitro experiments. For in vivo experiments, pinacidil was prepared as 0.3 mg/ml in 3% ethanol.

Data Analysis
Action potential parameters as a function of drug concentration were compared by General Linear Models analysis of variance (ANOVA) testing (Number Crunching Statistical Systems, Ogden, Utah). The incidence of ventricular tachycardia among rabbits receiving pinacidil was compared with that in rabbits receiving placebo by two-tailed Fisher’s exact test. Frequencies of ventricular ectopic beats were compared for the total 10-minute study period by Student’s unpaired t test and at each 1-minute interval using General Linear Models ANOVA. Changes in blood pressure (precesium and postcesium) were compared by Student’s paired t test. All values are given as mean±SD.

Results
In Vitro Studies
Dose-response experiments were performed in six fibers exposed to cromakalim alone (10⁻⁹–10⁻⁵ M). As shown in Figure 1, cromakalim shortened APD₀₀ in a concentration-related fashion; at 10⁻⁵ M, APD₀₀ was shortened 39±19%. Similar concentration-dependent effects on APD₀₀ and effective refractory period were observed (Table 1), whereas cromakalim did not alter takeoff potential or Vₘₐₓ.
TABLE 1. Electrophysiological Changes Produced by Cromakalim

<table>
<thead>
<tr>
<th>Concentration (M)</th>
<th>Control</th>
<th>10⁻⁹</th>
<th>10⁻⁸</th>
<th>10⁻⁷</th>
<th>10⁻⁶</th>
<th>10⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD₉₀ (msec)</td>
<td></td>
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<tr>
<td>CL 1,000</td>
<td>177±9</td>
<td>180±12</td>
<td>171±13</td>
<td>169±18</td>
<td>150±14</td>
<td>65±24</td>
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<tr>
<td>CL 4,000</td>
<td>205±28</td>
<td>205±32</td>
<td>187±27</td>
<td>183±22</td>
<td>157±17</td>
<td>70±32</td>
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<td>APD₉₀ (msec)</td>
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<tr>
<td>CL 1,000</td>
<td>292±8</td>
<td>308±18</td>
<td>303±26</td>
<td>296±22</td>
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<td>160±23</td>
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<tr>
<td>CL 4,000</td>
<td>344±38</td>
<td>363±52</td>
<td>357±61</td>
<td>347±45</td>
<td>293±28</td>
<td>173±21</td>
</tr>
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<td>TOP (mV)</td>
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<td></td>
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<td></td>
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<tr>
<td>CL 1,000</td>
<td>-104±3</td>
<td>-103±3</td>
<td>-101±4</td>
<td>-99±5*</td>
<td>-101±4</td>
<td>-102±5</td>
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<td>CL 4,000</td>
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<td>-101±2</td>
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<td>Vₑ (V/sec)</td>
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<td>CL 1,000</td>
<td>480±120</td>
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<td>470±100</td>
<td>440±130</td>
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<tr>
<td>CL 4,000</td>
<td>470±120</td>
<td>440±120</td>
<td>460±120</td>
<td>500±200</td>
<td>520±170</td>
<td>540±190</td>
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<td>ERP (msec)</td>
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<tr>
<td>CL 1,000</td>
<td>237±9</td>
<td>243±12</td>
<td>238±11</td>
<td>235±17</td>
<td>212±27*</td>
<td>105±34*</td>
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</tbody>
</table>

Values are given as mean±SD. APD₉₀, action potential duration at 50% repolarization; CL, cycle length; APD₉₀, action potential duration at 90% repolarization; TOP, takeoff potential; Vₑ, maximum upstroke slope (phase 0); ERP, effective refractory period.

**p<0.05 vs. control (ANOVA).**

*p<0.01 vs. control (ANOVA).

In preparations pretreated with quinidine, cromakalim similarly shortened APD₉₀ (Figure 2). At higher concentrations, quinidine-induced prolongation of APD₉₀ was completely reversed, and APD₉₀ was shortened by 10⁻³ M cromakalim to 43±10% quinidine control at CL 4,000 msec. In contrast, quinidine-induced triggered activity was reversed by lower concentrations of cromakalim (10⁻⁹–10⁻⁷ M), at which no change in APD₉₀ at the faster rates was found. This effect was observed in six of six preparations with quinidine-induced triggered activity exposed to cromakalim. Importantly, when triggered activity was abolished, quinidine-induced action potential prolongation was still evident at shorter CLs (Figure 2). Quinidine increased APD₉₀ from 343±51 to 390±26 msec at CL 1,000 msec. When triggered activity at longer CLs was abolished, APD₉₀ at CL 1,000 msec was 401±41 msec (p<0.05 versus baseline).

EAD-associated triggered activity was observed in 17 preparations: seven of 14 treated with quinidine, six of nine with cesium, and four of five with sematilide. Each of these 17 preparations then was exposed to cromakalim (n=13) or pinacidil (n=4) and the triggering abolished. As described above, APD₉₀ remained prolonged over baseline when this effect was observed (Figure 3). At CL 1,000, baseline APD₉₀ was 309±44 msec and was increased to 400±33 msec by the action prolonging intervention; treatment with cromakalim or pinacidil at a concentration sufficient to reverse triggering shortened APD₉₀ to 397±67 msec (p<0.05 versus baseline). The corresponding data at 4,000 msec were 362±95 msec (baseline), 549±100 msec (action potential prolongation), and 479±95 msec (cromakalim or pinacidil, p<0.05 versus baseline). The cromakalim concentrations that suppressed triggered activity were 10⁻⁷–10⁻⁵ M in the four sematilide experiments, 10⁻⁹–10⁻⁷ M in the six quinidine experiments, and 10⁻⁶ M in three cesium experiments. The concentrations of pinacidil that suppressed triggered activity were 3×10⁻⁷–3×10⁻⁵ M in three cesium experiments and 3×10⁻⁷ M in one quinidine experiment.
In *Vivo* Studies

Two animals (one in each group) died immediately after the first dose of CsCl, one (vehicle-pretreated) because of polymorphic ventricular tachycardia and one (pinacidil-pretreated) because of complete heart block. Among the remaining 18 animals, pinacidil-pretreated animals developed 168±157 total ventricular ectopic beats during the 10-minute study period, compared with 582±448 in those receiving vehicle (*p*<0.005). The frequencies of ventricular ectopic beats became significantly different (*p*<0.05, ANOVA) at the time of the second pretreatment dose; frequency decreased among those receiving pinacidil but continued to increase among those receiving vehicle (Figure 4). Two pinacidil-pretreated rabbits developed sustained ventricular tachycardia, two developed nonsustained ventricular tachycardia, and five had no ventricular tachycardia, compared with six, three, and zero, respectively, in vehicle-pretreated animals (*p* = 0.057).

Rabbits became markedly hypertensive after cesium infusion. However, blood pressure before the first cesium dose and the maximum response to cesium were similar in the pinacidil-pretreated and vehicle-pretreated animals. In vehicle-pretreated animals, cesium increased blood pressure from 93±16 to 165±35 mm Hg, whereas in the pinacidil-pretreated group, the precesium blood pressure was 98±10 mm Hg and rose to 168±18 mm Hg. Thus, at these doses, pinacidil exerted an antiarrhythmic effect without a major hypotensive action.

Discussion

These studies have demonstrated that the potassium channel activators pinacidil and cromakalim reversed abnormal automaticity induced by action potential–prolonging drugs in canine cardiac Purkinje fibers. Although this effect was predictable in view of the known action potential shortening effects of the drugs, it was interesting that action potentials remained prolonged at concentrations at which the antiarrhythmic effect was observed. Similarly, the cromakalim concentrations that exhibited this antiarrhythmic effect were an order of magnitude (or more) lower than those that significantly shortened APD<sub>90</sub>. These in vitro results suggest a protective
effect against ventricular arrhythmias related to abnormal repolarization in vivo. Indeed, pinacidil decreased the frequency of cesium-induced ventricular arrhythmias in anesthetized rabbits. Furthermore, as in the in vitro studies, this antiarrhythmic effect was observed at a low dose of pinacidil, which did not significantly decrease blood pressure.

The ability of potassium channel activators to suppress arrhythmias in vitro at concentrations that minimally shortened APD$_{90}$ could be explained by two mechanisms. Potassium channel activators may sufficiently accelerate repolarization to prevent the activation or reactivation of the inward current responsible for the depolarizing upstroke of a triggered beat, possibly a calcium current. Alternatively, drugs might serve as specific blockers of this depolarizing current, although theoretical and experimental data in support of this possibility have not been presented. The same mechanism probably accounted for the protective effects of pinacidil in vivo. Although the importance of changes in loading conditions on ventricular arrhythmias are becoming recognized, the blood pressure data demonstrated no effect due to pinacidil before cesium administration, nor was the marked hypertensive response to cesium blunted. This would suggest the antiarrhythmic effect was independent of vasodilation or altered loading.

The effects of potassium channel activators on vascular and cardiac tissue have been studied in vitro, including in single-cell preparations. Their vasodilatory action appears to be predominately mediated by increasing Ca$^{2+}$-dependent potassium current, which results in hyperpolarization and decreased vascular tone. A possible secondary mechanism, stimulation of Ca$^{2+}$ transport out of the cell or reuptake by the sarcoplasmic reticulum, also has been suggested for pinacidil. Potassium channel activation also accounts for at least some of the vasodilatory properties of nicorandil (which may exert an additional G-protein effect) and minoxidil. In cardiac tissue, pinacidil and cromakalim markedly reduce APD in a concentration-dependent fashion (e.g., Figure 1), and as discussed above, this effect appears to be mediated by activation of the ATP-dependent potassium current.

Reversal of drug-induced action potential prolongation and potentially antiarrhythmic effects of potassium channel activators in vitro have been reported by other groups. Action potentials in guinea pig ventricular muscle initially prolonged by the serotonin antagonist ICS 205-930 were restored to control values by cromakalim. Similar results were obtained when cromakalim was added after action potentials were prolonged by sotalol, an agent that has been associated with torsade de pointes. Imanishi et al demonstrated that nicorandil suppressed spontaneous automaticity induced by barium or markedly reduced potassium. Nicorandil also decreased refractory periods in cardiac Purkinje fibers, presumably reflecting decreased APD. Premature depolarizations thus arose at more negative potentials with a more rapid upstroke (an effect that should improve conduction and propagation). Finally, nicorandil suppressed repetitive activity induced by depolarizing current.

In vivo antiarrhythmic effects of pinacidil have been demonstrated previously in a dog model of ischemia-related arrhythmia. Cumulative doses of 0.1–2.0 mg/kg increased the percentage of sinus beats 22–24 hours postinfarction. However, these doses also produced an average 30% decrease in blood pressure. Coadministration of the $\alpha$-agonist phenylephrine offset the antiarrhythmic effects of pinacidil, whereas $\beta$-blockade did not augment the antiarrhythmic effect. Based on the response to phenylephrine, these authors concluded that the antiarrhythmic effect of pinacidil was related to
systemic and possibly coronary vasodilation, rather than to a direct myocardial effect. However, the doses of pinacidil used here did not alter blood pressure. Two mechanisms might explain the cesium-induced arrhythmias in these experiments. First, monophasic action potential recordings in dogs have suggested that cesium does produce triggering associated with marked action potential prolongation. Another group recently has reported similar findings in rabbits treated with clofibrate; interestingly, arrhythmias in that model also were abolished by pinacidil. Alternatively, it is possible that the decreased potassium conductance caused by cesium leads to enhanced “normal” automaticity similar to that seen with barium. The presence of abnormalities on a monophasic action potential record would not exclude such a mechanism, and nicorandil does suppress barium-induced automaticity in vitro. Our experiments demonstrate conclusively that an in vivo arrhythmia related to potassium channel block was significantly attenuated by pinacidil pretreatment at doses that did not alter blood pressure, suggesting a direct antiarrhythmic effect of this potassium channel activator in this setting.

In human subjects, pinacidil and cromakalim cause modest but significant increases in resting heart rate at effective vasodilating doses. Although more significant sinus tachycardia (>100 beats/min standing) has been seen in some patients receiving pinacidil doses exceeding 25 mg twice daily, serious proarrhythmic effects have not been reported in preliminary human studies. Non-specific T wave changes (flat, inverted, or biphasic) have been observed in normal volunteers receiving pinacidil, whereas T wave abnormalities present at baseline have been reported to normalize during therapy. No data on the effects of pinacidil or other agents of this type on normal or abnormal QT intervals have been reported.

Clinical observations have consistently identified diuretic-induced hypokalemia as one of the common features of patients who develop torsade de points during treatment with QT-prolonging agents. This study suggests that potassium channel activators may offer preferable alternative antihypertensive therapy for patients receiving QT-prolonging agents, at least to avoid the potassium-wasting effects of diuretics. Furthermore, our in vitro and in vivo data also suggest that arrhythmias related to abnormal repolarization may be suppressed by potassium channel activators. Thus, potassium channel activation also might prove beneficial in other subsets identified at risk for ventricular arrhythmias related to excessive QT prolongation, such as in patients with congenital long QT syndromes and possibly even in late postmyocardial infarction patients. On the other hand, like any drug with electrophysiological activity, potassium channel activators also may potentiate arrhythmias under certain conditions, perhaps as a result of excessive or inhomogeneous shortening of refractoriness.

The effects of potassium channel activation on APD in these experiments was frequency dependent. At low concentrations, action potentials were shortened (and related arrhythmias reversed) at slow rates, whereas action potentials were not shortened at faster rates (Figures 2 and 3). Thus, we speculate that an appropriate degree of potassium channel activation might control arrhythmias related to prolonged repolarization but not interfere with increased repolarization thought to contribute to arrhythmia suppression at faster rates (a class III action). Indeed, the occasional development of bradycardia-dependent torsade de pointes appears to be the single greatest liability of agents with pure class III properties. Otherwise, compared with sodium channel block, action potential prolongation as a therapeutic strategy produces less hemodynamic compromise, greater efficacy against sustained ventricular tachyarrhythmias related to recent coronary occlusion in dogs, and desirable effects on the energy required for defibrillation. Hondeghem and Snyders have recently proposed that the “ideal” class III agent should produce its greatest action potential–prolonging actions at fast rates and have indicated that an open-state potassium channel blocker would satisfy this requirement. Until such agents are developed, the combination of available action potential–prolonging drugs with low-dose potassium channel activators may produce a similar desirable electrophysiological profile.

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**KEY WORDS** quinidine · cesium · pinacidil · cromakalim · potassium · afterdepolarizations
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*Circulation*. 1990;82:1362-1369
doi: 10.1161/01.CIR.82.4.1362

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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