Effects of Long-term Oral Administration of Amiodarone on the Ventricular Repolarization of Rabbit Hearts

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The chronic effects of amiodarone on ventricular repolarization were investigated in Langendorff-perfused rabbit hearts in comparison with the acute effects of other Class III antiarrhythmic drugs. Forty to fifty electrograms were recorded through modified bipolar electrodes from the anterior to the lateral epicardial surface of the ventricles under His-bundle pacing (1.0 Hz). In control hearts, epicardial activation proceeded from the apex to the base. The interval from the initial sharp negative deflection of the QRS complex to the apex of the T-wave (Q-aT), which reflects the action potential duration (APD) at the recording site, was longest in the apex and shortest in the base. Therefore, repolarization proceeded from the base to the apex. In hearts treated with oral amiodarone (100 mg/kg, 4 weeks), Q-aT was uniformly prolonged by 14—16% throughout the entire mapped area, whereas the activation sequence was unaffected, and a normal Q-aT gradient was well preserved from the apex to the base. The spatial inhomogeneity of left ventricular repolarization was not enhanced by drug treatment. Acute application of sotalol (30 μmol/L), E-4031 (0.1 μmol/L) or MS-551 (1.0 μmol/L) caused a much greater Q-aT prolongation in the apex than in the base, resulting in a marked enhancement of the spatial inhomogeneity of repolarization. These findings suggest that the propensity of chronic amiodarone to induce torsade de pointes less often than other Class III agents may result at least in part from its favorable effect on the spatial homogeneity of ventricular repolarization.

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Antiarrhythmic drugs which prolong repolarization of the cardiac action potential (Class III drugs) are currently receiving renewed interest because they do not inhibit the excitability, the conductivity or the contractility of cardiac muscle, unlike sodium channel blockers (Class I drugs). However, their usefulness is limited by a different shortcoming; under certain clinical conditions, they produce a varied incidence of the polymorphic ventricular tachycardia known as "torsade de pointes". The clinical incidence of torsade de pointes for sotalol, clofilium, N-acetyl procainamide (NAPA) and several newly developed Class III drugs has been shown to be 3—10%, whereas the incidence with chronic amiodarone is unexpectedly low (<1.0%) despite similar QT-interval prolongation in body surface electrocardiograms (ECGs). Therefore, despite its undesirable extracardiac side-effects, amiodarone seems to be more useful than any other Class III drug in terms of the balance between antiarrhythmic potency.

Key words:
Amiodarone
Class III action
Ventricular repolarization
Proarrhythmia

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and proarrhythmic propensity. An understanding of why chronic amiodarone shows such a low proarrhythmic potential could provide a basis for the development of ideal Class III drugs.

With regard to the pathogenesis of drug-induced torsade de pointes, there are 2 major theories, which are not mutually exclusive; early after depolarization (EAD) and regional dispersion of repolarization. The former would lead to focal triggered activity, and the latter would set the stage for reentry by producing a critical spatial inhomogeneity of refractoriness. While each theory has its proponents, each also has its limitations, and the true mechanism remains to be identified. Hii et al demonstrated that chronic amiodarone therapy in patients with a history of Class Ia drug-induced torsade de pointes induces neither torsade de pointes nor QT-interval dispersion in precordial leads of ECGs. Therefore, they hypothesized that chronic amiodarone, unlike Class Ia drugs, causes spatially homogeneous prolongation of ventricular repolarization. To our knowledge, however, no experimental data have been presented to substantiate this hypothesis.

In the present study, we investigated the effects of chronic amiodarone on depolarization and repolarization of the rabbit ventricle by epicardial surface potential mapping, and compared them with the acute effects of other Class III drugs; sotalol, E-4031 and MS-551. We were primarily interested in regional differences in their Class III action (APD prolongation) and the resultant inhomogeneity of ventricular repolarization as a potential substrate for torsade de pointes.

METHODS

Experimental Protocol

Nine Japanese white rabbits of either sex weighing 1.8 to 2.2 kg were treated for 4 weeks with oral amiodarone at a dose of 100 mg/kg daily. On the last day of drug treatment, peripheral venous blood sampling was carried out to measure serum amiodarone concentrations. Scalar electrocardiograms (ECGs) of extremity leads (I, II) were also recorded from the conscious rabbits caged in a small dark box. The rabbits were then killed by intravenous administration of pentobarbital sodium (30 mg/kg) and the hearts were quickly removed. Twenty-two untreated rabbits of corresponding weights were used as controls. A cannula was inserted into the aorta for Langendorff perfusion and the heart was perfused at a constant flow (20 ml/min) with Krebs-Ringer solution gassed with 95% O2 + 5% CO2. The composition of the perfusate was as follows (mmol/L): NaCl 120.0, KCl 4.0, CaCl2 1.2, MgSO4 1.3, NaHCO3 25.2 and glucose 5.8 (pH 7.4). The temperature of the perfusate was maintained at 32°C.

In experiments to test the effects of the drug on atrio-ventricular (A-V) conduction, His-bundle electrograms (HBEs) were recorded using a pair of bipolar stainless steel electrodes with an interpolar distance of 1.0 mm. The electrodes were inserted through an incision made in the right atrium. A pair of stimulating electrodes (interpolar distance of 1.0 mm) made of stainless steel wire were placed on the right atrium close to the sinus node. HBE signals were amplified at a frequency response from 100 to 500 Hz with a time constant of 0.03 sec.

To study the effects on ventricular depolarization and repolarization at a slow driving frequency, the lower part of the A-V node was ligated with fine silk thread so that complete A-V block was produced, and the heart was constantly driven at a cycle length of 1,000 msec (1.0 Hz) from the proximal end of the His-bundle through the pair of HBE recording electrodes. Pulses used for stimulation were 2 msec in duration with an intensity of 1.2 times the diastolic threshold. Distant bipolar electrograms (DBEs) were recorded through a pair of Ag-AgCl plate electrodes placed 1.0 cm from the basal and apical side of the heart.

The epicardial mapping technique was essentially the same as that in our previous study? In brief, 40 to 50 electrograms on the anterior to lateral surface of both ventricles were recorded through a pair of modified bipolar electrodes made of stainless steel wires. The shorter reference lead of the electrodes was positioned 2 mm above the epicardial surface, and the signal was amplified with a time constant of 0.01 sec. The interval from the initiation of a ventricular complex in DBE to the initial sharp negative
deflection of the QRS in each epicardial electrogram was defined as the activation time (AT). The interval from the sharp negative deflection to the positive peak (apex) of the T-wave in the epicardial electrogram (Q-aT) was also measured as an index of the action potential duration at the recording site, and the algebraic sum of AT and Q-aT was defined as the repolarization time (RT).

Blood samples withdrawn into heparinized tubes were centrifuged at room temperature, and the serum was removed and frozen. Both ventricles were also frozen after the mapping experiments. Amiodarone and its major active metabolite, desethylamiodarone, were measured in serum and ventricular myocardial tissue by the same method as in our previous study. The limit of sensitivity for amiodarone and desethylamiodarone was 0.025 μg/ml of serum and 0.1 μg/g wet weight of ventricular tissue.

Drugs and Data Analysis

Amiodarone HCl was kindly donated by Taisho Pharmaceutical Co, Ltd. (Tokyo, Japan). E-4031 (N-[4-[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl] carbonyl] phenyl]methane sulphonamide dihydrochloride dihydrate), and MS-551 (1,3-dimethyl-6-[2-[N-(2-hydroxyethyl)-3-(4-nitrophenyl) propylamino] ethylamino]-2, 4 (IH, 3H)-pyrimidinedione hydrochloride) were donated by Eisai Pharmaceutical Co, Ltd. (Tokyo, Japan) and Mitsui Pharmaceutical Co, Ltd (Tokyo, Japan) respectively. Sotalol was purchased from Sigma Chemical Co, Ltd. E-4031 (0.1 μmol/L), MS-551 (1.0 μmol/L) and sotalol (30 μmol/L) were added to the perfusate of the normal untreated hearts for 30 to 40 min to test their acute effects on ventricular depolarization and repolarization.

All of the electrical data were digitized at a sampling interval of 5 kHz, and recorded on a magnetic tape (SONY PC-108M) for off-line computer analysis (NEC 9801-DA). From 16-sec consecutive ECG records of each rabbit, mean values of RR, PQ, QT and QRS intervals were calculated using ECG processing software (Softron EP98-1). The mean QT interval was divided by the root mean of the RR interval to provide the corrected QT interval (QTc). Parameters in HBEs, DBEs, and modified bipolar electrograms were also measured by using a manual mode of the same software.

Values represent the means or means ± SEM. A one-way analysis of variance with an F-test was used to evaluate the chronic effects of amiodarone in comparison with control animals. Dunnet's test was also used and differences were considered significant at p < 0.05.

RESULTS

Electrocardiograms and Amiodarone Concentration

ECGs recorded from the 9 rabbits that received oral amiodarone for 4 weeks at a dose of 100 mg/kg daily showed significantly longer values of RR, QT, and corrected QT (QTc) intervals than those from the 22 control rabbits: RR, 310±12 msec vs 245±6 msec; QT, 184±5 msec vs 140±2 msec; QTc, 332±8 msec vs 288±5 msec. In contrast, there was no significant difference between the 2 groups in PQ (46±2 msec vs 44±2 msec) or QRS (41±3 msec vs 39±2 msec).

Serum and ventricular tissue concentrations of amiodarone in the rabbits which received oral amiodarone (100 mg/kg) were 0.16±0.04 μg/ml (n=9) and 3.70±1.23 μg/g (n=9), respectively. Concentrations of desethylamiodarone were 0.03±0.01 μg/ml in serum (n=9) and 1.80±0.53 μg/g wet weight in myocardium (n=9). These values are comparable to those we reported previously.

Atrio-Ventricular Conduction

His-bundle electrograms (HBEs) were measured under constant right atrial pacing at a cycle length of 450 msec (2.2 Hz) to estimate the effect of amiodarone on atrioventricular (A-V) conduction. Atrio-His bundle (A-H) and His-ventricular (H-V) intervals in the hearts treated with chronic oral amiodarone (A-H, 37.9±1.9 msec and H-V, 26.2±2.0 msec, n=7) were similar to those in the control hearts (A-H, 39.3±1.8 msec and H-V, 27.6±1.9 msec, n=11).

There was no significant difference in either parameter between the 2 groups.

Ventricular Depolarization and
Effects of Amiodarone on Ventricular Repolarization

Repolarization

Epicardial mapping under His-bundle pacing (1.0 Hz) was performed in the 9 hearts treated with chronic amiodarone and in the 22 control hearts. Representative results are shown in Fig 1. In the control heart, the initial activation (epicardial breakthrough) appeared near the apex of the right ventricle. This activation then proceeded nearly centrifugally and reached the base of both ventricles within 20 msec. Q-aT intervals, which reflect the action potential duration at the recording site, were almost always longer in the apex than in the base. Consequently, repolarization proceeded from the base to the apex.

In the 9 hearts treated with oral amiodarone, no arrhythmias were induced during His-bundle pacing (1.0 Hz). Epicardial activation proceeded, as in the control, from the apex to the base with a similar propagation speed. Q-aT intervals were prolonged throughout the entire mapped area, but the normal Q-aT gradient from the apex to the base, and the normal direction of repolarization from the base to the apex, were well preserved.

The entire mapped area of the epicardial surface of each heart was divided into 3 regions, one third from the apex, one third from the base, and the remaining third in the middle, to estimate regional differences in Q-aT intervals and regional differences in the effects of amiodarone on Q-aT intervals. The results are summarized in Table I. In control hearts, average Q-aT intervals were longest in the apex and shortest in the base of both the right and left ventricles. In hearts treated with chronic amiodarone, Q-aT was moderately prolonged, but its extent in the base, middle and apex was fairly uniform (14–16%). The Q-aT gradient from the apex to the base was analogous to that in control hearts.

We also examined the acute effects of 3 other Class III drugs, sotalol, E-4031 and MS-551, on ventricular depolarization and repolarization in Langendorff-perfused hearts by adding these compounds to the perfusate. Twenty hearts from untreated
TABLE I  EFFECTS OF AMIODARONE ON Q-aT INTERVALS OF THE RIGHT AND LEFT VENTRICLES

<table>
<thead>
<tr>
<th></th>
<th>RV (msec)</th>
<th>LV (msec)</th>
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<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Middle</td>
</tr>
<tr>
<td>Control (n=22)</td>
<td>313 ± 6</td>
<td>334 ± 5*</td>
</tr>
<tr>
<td>Amiodarone (n=9)</td>
<td>364 ± 13*</td>
<td>382 ± 12*</td>
</tr>
<tr>
<td>% change</td>
<td>+16</td>
<td>+14</td>
</tr>
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</table>

Anterior and lateral epicardial surface of the right and left ventricles was divided into three regions, one third from the apex, one third from the base, and the remaining third in the middle. Average Q-aT intervals of 4 to 7 data in the respective zone were obtained in each heart and means ± SEM of 22 untreated (control) hearts and 9 hearts treated with oral amiodarone (100 mg/kg daily, 4 weeks) were calculated. Percentage change of means was presented at the bottom. *: Significantly different from control at p<0.05. #: Significantly different from the base in the respective ventricle at p<0.05.

TABLE II  EFFECTS OF SOTALOL, E-4031 AND MS-551 ON Q-aT INTERVALS OF THE RIGHT AND LEFT VENTRICLES

<table>
<thead>
<tr>
<th></th>
<th>RV (msec)</th>
<th>LV (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Middle</td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>307 ± 11</td>
<td>329 ± 9*</td>
</tr>
<tr>
<td>Sotalol (30 μmol/L)</td>
<td>378 ± 15*</td>
<td>416 ± 16*</td>
</tr>
<tr>
<td>% change</td>
<td>+23</td>
<td>+26</td>
</tr>
<tr>
<td>Control (n=5)</td>
<td>328 ± 9</td>
<td>341 ± 8</td>
</tr>
<tr>
<td>E-4031 (0.1 μmol/L)</td>
<td>458 ± 15</td>
<td>505 ± 16*</td>
</tr>
<tr>
<td>% change</td>
<td>+40</td>
<td>+48</td>
</tr>
<tr>
<td>Control (n=5)</td>
<td>319 ± 9</td>
<td>334 ± 9*</td>
</tr>
<tr>
<td>MS-551 (1.0 μmol/L)</td>
<td>410 ± 13*</td>
<td>441 ± 13*</td>
</tr>
<tr>
<td>% change</td>
<td>+29</td>
<td>+32</td>
</tr>
</tbody>
</table>

Anterior and lateral epicardial surface of the right and left ventricles was divided into three regions, one third from the apex, one third from the base, and the remaining third in the middle. Average Q-aT intervals of 4 to 7 data in the respective zone were obtained in each heart. Values presented are means ± SEM before (control) and after application of either sotalol (30 μmol/L), E-4031 (0.1 μmol/L) or MS-551 (1.0 μmol/L). Percentage changes of means after each drug treatment are also presented. *: Significantly different from control at p<0.05. #: Significantly different from the base in the respective ventricle at p<0.05.

(control) rabbits were used for this series of experiments. Four of the 20 hearts often showed ventricular arrhythmias (isolated premature complexes) during His-bundle pacing after application of either drug; one of 7 with sotalol, one of 6 with MS-551, and 2 of 7 with E-4031. These preparations were neglected, and the remaining 16 hearts were used for data analysis.

Application of these 3 Class III compounds to the untreated hearts did not affect the depolarization sequence from the apex to the base. All 3 drugs caused a significant Q-aT prolongation throughout the entire mapped area, but its extent was always greater in the apex than in the base (Table II).

Spatial Inhomogeneity of Ventricular Repolarization
The effect of chronic amiodarone on the spatial inhomogeneity of ventricular repolarization was estimated by measuring the maximal difference in Q-aT (MaxΔQ-aT) and the maximal difference in RT (MaxΔRT) in the left ventricle of each heart. These values were not measured in the right ventricle due to the large variability among the control hearts. Fig 2 shows an example of a heart treated with oral amiodarone. MaxΔQ-aT and MaxΔRT in this case were 26 msec and 23 msec, respectively. The average values of

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**Fig 2.** Spatial inhomogeneity of depolarization and repolarization in the left ventricle of amiodarone-treated hearts. The maximal difference in Q-aT (MaxΔQ-aT) and the maximal difference in RT (MaxΔRT) in the left ventricle were measured. Isochrone is 5 msec for AT and 10 msec for Q-aT and RT. Solid arrows indicate the global direction of depolarization and repolarization.

Max ΔQ-aT = 26 msec  Max ΔRT=23 msec

**TABLE III** EFFECTS OF AMIODARONE, SOTALOL, E-4031, AND MS-551 ON THE SPATIAL INHOMOGENEITY OF THE LEFT VENTRICLE

<table>
<thead>
<tr>
<th></th>
<th>Max ΔQ-aT (msec)</th>
<th>Max ΔRT (msec)</th>
</tr>
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<tbody>
<tr>
<td>Control (n=22)</td>
<td>29.4±2.2</td>
<td>25.3±2.3</td>
</tr>
<tr>
<td>Amiodarone (100 mg/kg) (n=9)</td>
<td>21.7±3.1</td>
<td>20.9±2.8</td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>31.0±4.2</td>
<td>26.8±5.4</td>
</tr>
<tr>
<td>Sotalol (30 μmol/L)</td>
<td>60.2±12.1*</td>
<td>54.4±12.4*</td>
</tr>
<tr>
<td>Control (n=5)</td>
<td>27.2±4.1</td>
<td>22.8±4.4</td>
</tr>
<tr>
<td>E-4031 (0.1 μmol/L)</td>
<td>66.6±8.7*</td>
<td>62.6±7.8*</td>
</tr>
<tr>
<td>Control (n=5)</td>
<td>29.0±2.8</td>
<td>26.2±2.8</td>
</tr>
<tr>
<td>MS-551 (1.0 μmol/L)</td>
<td>46.8±5.0*</td>
<td>43.6±3.6*</td>
</tr>
</tbody>
</table>

Maximal difference of Q-aT (Max ΔQ-aT) and maximal difference of RT (Max ΔRT) were obtained in each heart. Control data for amiodarone were obtained from untreated hearts, and those for sotalo, E-4031 (0.1 μmol/L) and MS-551 (1.0 μmol/L) were obtained before application of respective drug. Values are presented as means ± SEM. *: Significantly different from control at p<0.05.

Max ΔQ-aT and Max ΔRT in the 9 hearts treated with amiodarone were 21.7±3.1 msec and 20.9±2.8 msec, respectively. These values were slightly less than those obtained from the 22 control hearts, but the differences were not statistically significant (Table III). Thus, the spatial inhomogeneity of repolarization in the left ventricle was not enhanced by chronic amiodarone.

Fig 3 shows an experiment with sotalol. The maps show activation time (AT), Q-aT intervals and repolarization time (RT) of the left ventricle before (control) and 40 min after application of sotalol (30 μmol/L). Sotalol (30 μmol/L) caused Q-aT prolongation without affecting AT. The Q-aT prolongation was greater in the apex than in the base. Max ΔQ-aT in the left ventricle increased from 36 msec to 63 msec, and Max ΔRT increased from 28 msec to 57 msec.

Qualitatively similar results were obtained with E-4031 (0.1 μmol/L) and MS-551 (1.0 μmol/L). Thus, acute treatment with either of the 3 compounds resulted in a marked enhancement of the spatial inhomogeneity of repolarization due to a greater Q-aT prolongation in the apex than...
Fig 3. Effects of sotalol on the depolarization and repolarization sequences of the left ventricle. Maps of activation time (AT), Q-aT interval, and repolarization time (RT) in the left ventricle were obtained before (control, upper panels) and after application of sotalol (30 μmol/L, lower panels). Isochrone is 5 msec for AT maps and 10 msec for Q-aT and RT maps. Solid arrows indicate the global direction of depolarization and repolarization. The maximal difference of in Q-aT (Max ΔQ-aT) and the maximal difference in RT (Max ΔRT) were calculated from maps before (control) and 40 min after application of sotalol.

in the base (Table II). Pooled data of Max ΔQ-aT and Max ΔRT obtained from 5 or 6 hearts are summarized in Table III. Both of these parameters were significantly increased by 1.6- to 2.7-fold after the application of sotalol (30 μmol/L), E-4031 (0.1 μmol/L) or MS-551 (1.0 μmol/L).

**DISCUSSION**

**Q-aT Interval in the Surface Potential**

In the present experiments, we measured Q-aT intervals in the epicardial surface potential as an index of action potential duration (APD) at the recording site. This parameter corresponds to the "activation-recovery interval" measured from unipolar electrograms by other investigators. In our previous experiments using rabbit ventricular preparations, the initial sharp negative deflection of the ORS complex and the positive peak of the T-wave (aT) in modified bipolar electrograms coincide well with the upstroke phase and terminal repolarization of transmembrane action potentials recorded through a glass micro-electrode from a site as close as possible to the tip of the surface electrodes; there was a very good correlation (r=0.98) between the Q-aT interval and APD at 90% repolarization.

The present data showed that Q-aT intervals of both ventricles were moderately prolonged (14−16%) by long-term treatment with oral amiodarone (100 mg/kg daily, 4 weeks) without any changes in the epicardial activation sequence. Atrio-ventricular conduction measured by His-bundle electrograms (HBEs) was also unaffected by amiodarone treatment. These findings are
consistent with our previous study on right ventricular papillary muscles isolated from rabbits treated with oral amiodarone (50 mg/kg or 100 mg/kg daily, 4 weeks), in which drug treatment prolonged the action potential duration (APD) by 13 to 20% with a minimal decrease in the maximum upstroke velocity (Vmax) of the action potential and the contractile force. These findings may indicate that a major and consistent electrophysiological effect of chronic amiodarone is repolarization delay (Class III action), whereas its Class I action is minimal or negligible.

**Q-aT Gradient in the Rabbit Ventricle**

In control rabbit hearts, the Q-aT interval was longer in the apex than in the base. Consequently, ventricular repolarization proceeded from the base to the apex, opposite the direction of the activation sequence (Fig 1, Table I). This characteristic is consistent with our previous finding. This Q-aT gradient in the ventricle is most likely due to regional differences in ionic currents responsible for the action potential duration. The repolarization of mammalian ventricular cells is determined by a fine balance between inward and outward currents. Inward currents can be carried through Na⁺ and Ca²⁺ channels (particularly the slowly inactivating and window current components) and the Na⁺–Ca²⁺ exchange current. Among the several outward currents, the delayed rectifier potassium current (Iₖ), transient outward current (Iₒ₁) and inward rectifier potassium current (Iₒ₂) are considered to be the most important for repolarization under physiological conditions. There is a considerable difference in the current density of Iₒ₁ (4-aminopyridine-sensitive and Ca²⁺-insensitive component of Iₒ₁) in ventricular cells of endocardial and epicardial origin. In experiments using rabbit left ventricles, Feddida and Giles showed an approximately 50% decrease in Iₒ₁ density from epicardium to endocardium. In dogs, the magnitude of Iₒ₁ has been shown to be several times greater in epicardial myocytes and in the unique cell population in the deep subepicardial to midmyocardial layers (M region) than in the endocardial myocytes. A greater magnitude of Iₒ₁ in epicardial than endocardial ventricular cells has also been observed in cats. Such a regional difference in Iₒ₁ density has been suggested to be an important and perhaps major determinant of regional variation in action potential configuration. In epicardial mapping experiments in rabbit hearts, we observed that 1 to 2 mmol/L 4-aminopyridine (4-AP) caused a much greater Q-aT prolongation in the base than in the apex (unpublished data), suggesting a larger Iₒ₁ density in the base than in the apex. This could be responsible for the Q-aT gradient (APD gradient) between the apex and the base. However, we cannot eliminate other possible mechanisms for the Q-aT gradient. There might be a regional difference in Iₖ and Iₒ₂ as observed in cat hearts or in some unique cell population, such as M cells, in dog hearts. More extensive electrophysiological studies on rabbit ventricular cells will be required to clarify these possibilities.

**Regional Differences in Class III Action**

The present study indicated that the Class III action (APD prolongation) of chronic amiodarone was nearly uniform throughout the entire ventricle, whereas the acute Class III action of sotalol, E-4031 and MS-551 was non-uniform (greater APD prolongation in the apex than in the base). Consequently, the spatial inhomogeneity of ventricular repolarization was unaffected by amiodarone, whereas it was greatly enhanced by the 3 reference drugs. This regional difference in Class III action could be explained by the channel-specificity of the individual drugs action. Only limited information is available regarding the ionic mechanism responsible for APD prolongation by chronic amiodarone. In voltage clamp studies using ventricular myocytes isolated from rabbits that received long-term oral amiodarone (100 mg kg⁻¹ daily, 4 weeks), we observed that the Iₖ density and Iₒ₁ density in treated cells were significantly decreased (46–63% and 29–61%, respectively) compared to control cells. It is now acknowledged that there are 2 subtypes of Iₖ in mammalian cardiac cells, in terms of different gating kinetics, different voltage-dependencies and different rectification properties: Iₖ,rapid (Iₖr) and Iₖ,slow (Iₖs). In rabbit ventricular cells, Iₖ is composed predominantly of Iₖr, and the

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contribution of $I_{Ks}$ is negligible. Therefore, chronic amiodarone may inhibit both $I_{Kr}$ and $I_{to1}$ to a similar extent. In contrast, sotalol and E-4031 have been shown to be highly specific $I_{Kr}$ blockers; they have no inhibitory effects on other types of potassium channels at therapeutic concentrations. MS-551 at concentrations of less than 3 $\mu$mol/L has been shown to block $I_{Kr}$ with no significant effect on $I_{to1}$ or $I_{K1}$. 

Limitations and Clinical Implications

In the present study, epicardial depolarization and repolarization sequences were examined by recording 40 to 50 electrograms in sequence by moving the exploring modified bipolar electrodes, since a delicate and fine attachment of the electrode tip was required to obtain good signals for precise measurement of the Q-aT interval. It was difficult to establish this condition in simultaneous recordings of multiple electrograms. A possible beat-to-beat variability in depolarization and repolarization would invalidate the data obtained by such sequential mapping experiments. To avoid this problem, we monitored the QRS-T configuration of distant bipolar electrograms (DBEs) throughout each mapping procedure, and only the data associated with a constant DBE morphology were used for measurement.

We examined the chronic effects of amiodarone and the acute effects of 3 other Class III drugs (sotalol, E-4031, MS-551) on ventricular repolarization under His-bundle pacing at 1.0 Hz. This ventricular rate is much less than the rabbit heart rate in vivo (3.2–3.9 Hz). It has been shown in previous studies that APD prolongation (Class III action) in ventricular muscle with chronic amiodarone is unaffected by stimulation frequencies whereas that with acute sotalol, E-4031 and MS-551 is largely enhanced at lower stimulation frequencies, giving rise to a marked “reverse frequency-dependence.” Accordingly, the greater Q-aT prolongation with sotalol, E-4031 and MS-551 in the apex than at the base, which leads to a greater spatial inhomogeneity of ventricular repolarization (in contrast to hearts treated with amiodarone), could be attenuated at higher (more physiological) ventricular rates.

Another limitation of the present study is the doses of the individual drugs. Oral amiodarone at 100 mg/kg was applied to rabbits daily for 4 weeks, since this dosing protocol was previously found to cause sufficient electrophysiologic changes in isolated papillary muscles. With the other 3 drugs (sotalol, E-4031 and MS-551), only 1 concentration near the middle of their therapeutic or effective plasma levels in human patients or animal arrhythmia models was tested. Therefore, we cannot rule out the possibility that these compounds have different effects on the spatial inhomogeneity of ventricular repolarization at other concentrations.

Many recent clinical studies have suggested that interlead QT variability on body surface electrocardiograms (ECGs), defined as QT dispersion, may reflect regional variation in ventricular repolarization, which represents an electrophysiological substrate for arrhythmia. QT dispersion (the difference between the max and mini QT in 12-lead ECG) has been shown to be increased in patients with long QT syndromes, myocardial infarction, chronic heart failure, ventricular hypertrophy or antiarrhythmic (Class Ia) drug therapy, all of whom are at high risk for ventricular arrhythmias or sudden cardiac death. In contrast, QT dispersion was shown to be reduced or unaffected by amiodarone treatment for arrhythmias. The present data on amiodarone agree with these clinical reports, and provide the first experimental evidence that long-term treatment with oral amiodarone does not increase the spatial inhomogeneity of ventricular repolarization despite substantial APD prolongation. This pharmacological characteristic of amiodarone might underlie its high antiarrhythmic activity with minimal proarrhythmic potential. Nevertheless, we cannot extend the present data directly to interpret the minimal clinical incidence of torsade de pointes with amiodarone because our experiments were carried out in normal rabbit hearts, whereas the clinical benefit of amiodarone has been demonstrated in patients under various pathological conditions.

Day et al. reported that QT dispersion in 12-lead ECGs from patients with postmyocardial infarction was reduced by long-term treatment with oral sotalol.
apparent discrepancy between their results and the present data for sotalol could be due to different conditions of the heart and/or different dosing protocols. The effects of sotalol on the heart in vivo might be modulated by its potent beta-blocking action. Furthermore, the electrophysiologic effect of sotalol on ventricular cells in the border zone of infarction might be different from that on normal cells. These possibilities should be investigated in future experimental and clinical studies.

REFERENCES


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