Frequency-Dependent Electrophysiologic Effects of Amiodarone in Humans

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Background. In general, antiarrhythmic agents that prolong the action potential duration (APD) have attenuated effects on repolarization at short cycle lengths (reverse frequency dependence), and this may limit their efficacy for controlling ventricular arrhythmias. The frequency-dependent effects of amiodarone on repolarization may differ from those of other antiarrhythmic agents and have not been determined in humans.

Methods and Results. The frequency-dependent effects of amiodarone on repolarization and conduction were determined during electrophysiologic study in 19 patients at drug-free baseline and after 11 days of amiodarone loading (1621±162 mg/d, group A) and in 15 additional patients after ≥1 year of chronic amiodarone therapy (380±56 mg/d, group B). The two groups were similar in all clinical characteristics. The ventricular APD at 90% repolarization (APD90), right ventricular effective refractory period (VERP), and QRS duration were determined at paced cycle lengths of 300 to 600 milliseconds. In group A, amiodarone significantly (10% to 13%, P<.001) increased the APD90 at all paced cycle lengths by approximately 30 milliseconds compared with baseline. Similarly, there were no frequency-dependent effects on the percent increase in VERP. However, there was greater amiodarone-induced prolongation of the VERP magnitude at longer paced cycle lengths than at shorter cycle lengths (P=.04), although the VERP remained significantly prolonged at the shortest paced cycle length (300 milliseconds) by 33±22 milliseconds (16.6% increase from baseline, P<.001). Amiodarone significantly (P<.01) increased the QRS duration at paced cycle lengths ≤500 milliseconds by a maximum of 28% compared with baseline measurements. The increase in ventricular conduction time was frequency dependent (P<.01), consistent with significant sodium channel blockade. The VERP/APD90 ratio (determined at twice diastolic threshold) was significantly prolonged by amiodarone (as compared with baseline) at cycle lengths ≥400 milliseconds, indicative of both time- and voltage-dependent effects on refractoriness. The increase in induced sustained ventricular tachycardia cycle length in group A patients after amiodarone loading was significantly correlated with the increase in VERP (r=.68, P=.044) but not with increases in QRS duration or APD90. In addition, there were no significant differences in frequency-dependent effects of amiodarone between groups A and B.

Conclusions. The frequency-dependent response of the electrophysiologic effects of amiodarone are similar after 11 days of loading or ≥1 year of chronic therapy. Amiodarone does not exert frequency-dependent effects on ventricular repolarization; it prolongs refractoriness by both time- and voltage-dependent mechanisms and exerts frequency-dependent effects on ventricular conduction. The absence of amiodarone-induced reverse frequency-dependent effects on repolarization, together with its time-dependent effects on refractoriness may account in part for the high efficacy of the drug and its low propensity to cause torsade de pointes. (Circulation. 1993;88:1063-1071.)

Key Words • arrhythmias • repolarization • refractoriness • amiodarone

Amiodarone is a highly effective antiarrhythmic agent that has a complex pharmacological profile and a low incidence of proarrrhythmia.1-3 Amiodarone has class I and class III effects but also exhibits calcium channel blocking effects and antiadrenergic actions. Recent animal studies demonstrating that amiodarone has significant frequency-dependent actions on Vemax and ventricular conduction has further complicated the understanding of its overall pharmacology.4-6

In vitro and in vivo studies in the drug-free state have shown a close correlation between ventricular action potential duration (APD) and the ventricular effective refractory period (VERP).7-10 Both parameters progressively shorten with decreases in ventricular paced cycle lengths. Numerous studies on the rate-related effects of various antiarrhythmic agents such as sotalol,11,12 seminalide,13 quinidine,14 dofetilide,15 and N-acetylprocainamide16 on repolarization have demonstrated that the prolongation of the APD by these agents is attenuated at short ventricular paced cycle lengths. This phenomenon has been termed "reverse frequency dependence."17,16 However, a recent study in open-chest pen-
tobarbitalized dogs did not find reverse frequency dependence of the repolarization interval (determined from the test site QT interval) after chronic amiodarone therapy. This is a potentially important finding because attenuation of the APD-prolonging effects of antiarrhythmic agents at short cycle lengths may decrease drug efficacy during clinical ventricular tachyarrhythmias. In addition, reentrant ventricular arrhythmias are more likely to be induced when the APD and effective refractory period are short, whereas torsade de pointes tends to occur when the APD is markedly prolonged, particularly at slow heart rates.

Although frequency-related electrophysiologic effects of amiodarone may play an important role in the antiarrhythmic efficacy of this compound and its low incidence of proarrhythmia, no study has reported the frequency-dependent actions of amiodarone on ventricular repolarization in humans. The purpose of this study was twofold: (1) to determine the frequency-dependent actions of amiodarone on ventricular repolarization and conduction and (2) to delineate potential differences in frequency-dependent actions between patients treated short term versus those treated long term with amiodarone.

Methods

Patient Population

Patients with sustained symptomatic ventricular tachycardia (VT), ventricular fibrillation, aborted sudden death, or syncope secondary to ventricular arrhythmias were studied. Those with unstable angina, myocardial infarction within the previous month, and sustained ventricular arrhythmias occurring only in the setting of an acute myocardial infarction were excluded. Two groups of patients undergoing electrophysiologic studies for the evaluation of malignant clinical ventricular arrhythmias were examined: Group A consisted of consecutive patients undergoing electrophysiologic study both at baseline in the drug-free state and after approximately 11 days of oral amiodarone loading at 1600 mg/d, and group B was a separate patient cohort undergoing electrophysiologic study after treatment for ≥1 year with chronic amiodarone at a maintenance dose of 300 to 400 mg/d after a loading regimen. All patients were chemically and clinically euthyroid at the time of their electrophysiologic evaluation. The study was approved by the West Los Angeles VA Medical Center Human Investigations Committee, and all patients gave informed consent.

Electrophysiologic Study

Electrophysiologic study was performed in all patients after the discontinuation of β-blockers, diltiazem, verapamil, and all other antiarrhythmic agents for more than six half-lives. Electrophysiologic study was performed in the baseline drug-free preabsorptive state 6 to 8 hours after the last dose of amiodarone. A 7F catheter with two platinum ring electrodes for pacing (located 2 mm from the catheter tip) and a pair of silver–silver chloride electrodes (at the distal tip and 5 mm proximal from the tip) (EP Technology, Palo Alto, Calif) was used for the recording of the right ventricular monophasic action potential (MAP) and was placed at the right ventricular (RV) apex. This catheter permits the determination of both the VERP and the MAP duration at the same location.

Pacing Protocol

All pacing was performed at twice the diastolic threshold at a pulse width of 2 milliseconds. Tracings were recorded at paper speeds of 100 to 150 mm/s (PPG VR-16 or MIDAS, Lenexa, Kan). The right ventricular MAPs were recorded using the silver–silver chloride electrode catheter. MAP recordings and right VERP determinations were obtained in the group A patients both at baseline and after approximately 11 days of oral loading with amiodarone. The catheter position was recorded in these patients during the baseline electrophysiologic study and placed in a similar position doing subsequent electrophysiologic testing on amiodarone. Group B patients underwent a single electrophysiologic study during chronic dosing of amiodarone. MAP duration was determined after steady-state ventricular pacing at cycle lengths of 600, 500, 400, 350, and 300 milliseconds for 200 complexes at twice diastolic threshold. The amplitude of the MAP was determined from the diastolic baseline to the plateau and the APD90 from the initial MAP upstroke to the point where repolarization was 90% complete. MAP recordings of <10 mV were excluded. Two blinded observers measured three APD complexes at each paced cycle length. Interobserver and intraobserver variability was <5%.

The right VERP was determined at the same catheter position as the MAP recordings after a basic drive run of 14 beats and applying an extrastimulus during late diastole and successively decrementing the coupling interval of the extrastimulus by 5 milliseconds. A 1-second pause was used between runs. The effective refractory period was reached when the extrastimulus failed to provoke a propagated response on two successive attempts.

QRS duration was determined after steady-state ventricular pacing by measuring the beginning to the end of the QRS duration in lead II. Two blinded observers measured two QRS complexes at each paced cycle length, and the interobserver and intraobserver variability was <5%.

Attempts were made to induce ventricular tachycardia using programmed ventricular stimulation at two right ventricular sites and up to three premature extrastimuli as previously described. Sustained VT morphology was analyzed by comparing the morphology of the tachycardia in leads I, AVF, V1, and V6. Sustained VT morphologies were defined as the same if there was concordance in all of the examined leads. Sustained VT was defined as VT that lasted ≥30 seconds or that required earlier termination because of hemodynamic compromise.

Data Analysis

Categorical data were analyzed using Fisher’s exact test. The changes in the APD90, VERP, QRS duration, and the consistency of these changes compared with baseline measurements as a function of cycle length were determined using repeated-measures ANOVA with the Greenhouse-Geisser correction for within-subject correlations. Changes in the VERP/APD90 ratios compared with baseline were analyzed using repeated-measures multivariate ANOVA because the assumption
of compound symmetry was violated. The increase in \( APD_{90} \), VERP, or QRS duration were compared with the increase in sustained VT cycle length during amiodarone therapy in group A patients using linear regression analysis. The electrophysiologic parameter that was measured at the cycle length that most closely approximated the baseline sustained VT cycle length was used for this analysis.\(^{30}\) Data are expressed as mean±SD except for the figures where mean±SE was used. \( P \leq .05 \) was considered to be significant.

**Results**

**Patient Population**

Nineteen patients were treated with amiodarone for a mean of 11 days (group A, 1621±162 mg/d), and 15 patients were treated for ≥1 year (group B, 380±56 mg/d). Except for the number of days of therapy and treatment dose, there were no significant differences between the two groups' clinical characteristics (Table).

**APD and VERP in Group A**

After amiodarone loading, group A patients had a significant (10% to 13%, \( P < .001 \)) prolongation of the \( APD_{90} \) (Fig 1) compared with baseline of approximately 30 milliseconds during ventricular pacing at all cycle lengths tested (300 to 600 milliseconds). The percent increase from baseline in the \( APD_{90} \) in group A patients was 11.4%, 10.1%, 13.0%, 13.0%, and 12.3% during ventricular paced cycle lengths of 600, 500, 400, 350, and 300 milliseconds, respectively. Thus, the degree of \( APD_{90} \) prolongation compared with baseline was relatively constant, and no frequency-dependent effects of amiodarone on the APD were observed.

As with the \( APD_{90} \), the VERP in group A was also prolonged by amiodarone (\( P < .001 \)) at all paced cycle lengths compared with baseline (Fig 2). The increase in VERP magnitude during amiodarone therapy in group A patients was examined over the range of paced cycle lengths using repeated-measures ANOVA. This demonstrated a significantly greater prolongation of the VERP magnitude at longer as compared with shorter paced cycle lengths (\( P = .04 \)). The percent increase (Fig 2) from baseline in the VERP was 21.8%, 22.6%, 21.0%, 19.8%, and 16.9% during ventricular paced cycle lengths of 600, 500, 400, 350, and 300 milliseconds, respectively. There were no significant differences in the percent increase in VERP at any of the examined cycle lengths. Thus, at short paced cycle lengths there was a significant attenuation of the magnitude of amiodarone-induced VERP prolongation but not in the relative increase in the VERP, and the VERP during amiodarone therapy remained significantly prolonged at the shortest paced cycle length (300 milliseconds) by 33±20 milliseconds (16.9%, \( P < .001 \) compared with baseline).

**Effects on Conduction in Group A**

Compared with baseline, amiodarone significantly (\( P < .01 \)) increased the QRS duration (Fig 3) at all paced cycle lengths ≤500 milliseconds. The maximal prolongation of the QRS duration compared with baseline was 28%. The degree of QRS prolongation was significantly greater at shorter than at longer paced cycle lengths (\( P < .01 \)), indicative of frequency-dependent effects of amiodarone on ventricular conduction.

**Ratio of VERP and \( APD_{90} \) in Group A**

The VERP/\( APD_{90} \) ratio, measured at twice diastolic threshold, is illustrated in Fig 3. Under basal conditions, as the pacing rate was increased, the \( APD_{90} \) and effective refractory period shortened. Since the effective refractory period shortened to a lesser degree, the ratio increased toward unity at the shortest paced cycle lengths. In the presence of amiodarone, the ratio was increased at long cycle lengths and approached unity as the cycle length was decreased. However, compared with baseline, the ratio was significantly (\( P < .05 \)) increased in the amiodarone groups at cycle lengths ≥400 milliseconds. Thus, at the longer cycle lengths examined, amiodarone-induced prolongation of the VERP was not solely secondary to increases in the \( APD_{90} \). Therefore, at cycle lengths ≥400 milliseconds, the ac-

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**Clinical Characteristics of Study Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>( n )</th>
<th>Amiodarone Rx (d)</th>
<th>Amiodarone dose (mg)</th>
<th>Age of patient (y)</th>
<th>Clinical sustained VT/VF</th>
<th>Hx of MI</th>
<th>Congestive cardiomyopathy</th>
<th>LVEF (%)</th>
<th>LVESD (mm)</th>
<th>LVEDD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>19</td>
<td>11.0±2.6</td>
<td>1621±162</td>
<td>62±10</td>
<td>74%</td>
<td>80%</td>
<td>16%</td>
<td>58%</td>
<td>49±10</td>
<td>63±6</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>820±638</td>
<td>380±56</td>
<td>63±7</td>
<td>93%</td>
<td>100%</td>
<td>0%</td>
<td>40%</td>
<td>50±10</td>
<td>64±9</td>
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\( P < .001 \) on the action potential duration at 90% repolarization (\( APD_{90} \)) after 11 days of amiodarone administration (group A, AMIO) compared with drug-free baseline. The \( APD_{90} \) was increased by a relatively fixed amount of approximately 30 milliseconds at each paced cycle length.
tions of amiodarone on the VERP are secondary to time-dependent as well as voltage-dependent effects.

Ventricular Tachycardia Induction in Group A

In group A patients, 4 of 19 (21%) patients had no sustained VT induced during their follow-up electrophysiologic study on amiodarone therapy. Of the 15 patients with persistently inducible sustained VT, VT of the same morphology was induced in an individual patient at baseline and on amiodarone therapy in 11 patients. The sustained VT cycle length of morphologically similar VTs increased from 240±33 to 336±53 milliseconds (P<.001) during amiodarone therapy. By linear regression analysis (at the paced cycle length closest to the baseline VT cycle length), the change in VERP was significantly correlated with the increase in sustained VT cycle length (r=.68, P=.044). There was no significant correlation for the change in QRS duration (r=.06, P=NS) or APD90 (r=−.096, P=NS).

Frequency-Dependent Electrophysiologic Effects in Group B

During amiodarone therapy, group B patients had a similar pattern of change in the mean values of the APD90, VERP, VERP/APD90, and QRS duration at the different paced cycle lengths, as did group A patients (Fig 4). In addition, there were no significant differences in the mean values of any of the electrophysiologic parameters during amiodarone therapy between groups A and B.

![Graphs showing frequency-dependent effects of 11 days of amiodarone administration (group A, AMIO) on the VERP and percent increase in RVERP.](image)

**Fig 2.** Graphs show the frequency-dependent effects of 11 days of amiodarone administration (group A, AMIO) on the magnitude of the right ventricular effective refractory period (RVERP) (left) and on the percent change from baseline (right). Amiodarone significantly increased the RVERP with an attenuation of amiodarone-induced RVERP prolongation at short paced cycle lengths (P=.04). There were no significant frequency-dependent effects on the percent increase in RVERP.

![Graphs showing frequency-dependent effects of 11 days of amiodarone administration (group A, AMIO) on the QRS duration and VERP/APD90 ratio.](image)

**Fig 3.** Graphs show frequency-dependent effects of 11 days of amiodarone administration (group A, AMIO) on the QRS duration (left) and the ventricular effective refractory period/action potential duration at 90% repolarization (VERP/APD90) ratio (right). Amiodarone increased the QRS duration in group A at a paced cycle length ≤500 milliseconds and significantly increased the VERP/APD90 ratio at cycle lengths ≥400 milliseconds.
Discussion

This is the first study to systematically determine the frequency-dependent effects of amiodarone on cardiac repolarization in humans. The principal findings are that (1) amiodarone significantly prolongs the ventricular APD₉₀, and VERP and slows ventricular conduction; (2) although the effects on QRS duration are frequency dependent, amiodarone does not exert frequency-dependent effects on repolarization; and (3) the effects on refractoriness are secondary to both time- and voltage-dependent effects.

Effects on Conduction

Amiodarone blocks the sodium current that underlies \( V_{\text{max}} \), the upstroke velocity of phase 0 of the APD, and the major determinant of ventricular conduction. In the present study, this general effect was manifest by the increase in the QRS duration observed at each paced cycle length. In addition, and consistent with in situ studies, the relative increase in the QRS duration as a function of the paced cycle length reflects the ability of the drug to slow sodium current recovery during the interpulse interval.

Whereas under drug-free conditions, ventricular conduction time is unaltered over the range of pacing cycle lengths between 600 and 300 milliseconds, in the presence of amiodarone, the QRS duration increased markedly as the cycle length decreased. Our results are also consistent with those reported in anesthetized dogs in which the longitudinal conduction was unaltered at cycle lengths >1000 milliseconds but decreased by 13% when the cycle length was further decreased to 300 milliseconds. Similarly, we observed a 19% increase in QRS duration in group A patients when the pacing cycle length was shortened to 300 milliseconds from 600 milliseconds. Likewise, Varro et al observed a significant reduction in \( V_{\text{max}} \) only at cycle lengths <600 milliseconds in isolated dog Purkinje and guinea pig ventricular muscle fibers.

Effects on Refractoriness

The major focus of this study was on the rate-related change in ventricular repolarization and the effective refractory period during ventricular pacing. Agents that lengthen the APD by blocking outward current potassium channels (eg, the delayed rectifier \( I_{\text{K}} \)), usually exhibit marked APD lengthening at long cycle lengths, an effect that is significantly attenuated at shorter cycle lengths. Hondeghem and Snyder have defined this reduction in the magnitude of APD prolongation at short cycle lengths as reverse frequency dependence and have suggested that such a loss of class III actions at the short cycle lengths commonly associated with clinical ventricular arrhythmias may lead to a corresponding decrease in efficacy. It is noteworthy that the phenomenon of reverse frequency dependence of the APD₉₀ has been demonstrated for sotalol, sematilide, quinidine, dofetilide, and \( N \)-acetyl procanidamide. Although the mechanism underlying this phenomenon is unclear, theoretical considerations suggest that an increase in APD₉₀ over all range of frequencies, but especially at fast rates, is a desirable electrophysiologic property for the control of cardiac ventricular arrhythmias. The lack of rate-related effects of amiodarone on repolarization in humans thus may be of significant electropharmacological importance.
We found that amiodarone-induced prolongation of the APD₉₀ occurred over a wide range of frequencies without significant attenuation during rapid ventricular pacing. Similar findings evaluating repolarization intervals (derived from the test site QT interval) in pentobarbitalized dogs have been reported.² Both of these observations are most likely secondary to block of Iₖ.¹,³,³⁶-³⁸ Although other processes also may be involved. The unique frequency-dependent features of amiodarone on repolarization may be related to the findings of Balser et al¹⁰ that amiodarone-induced block of outward currents in guinea pig ventricular cells occurs throughout the cardiac cycle, mildly increasing during depolarization and slightly decreasing during repolarization. This would allow relatively steady-state block of outward currents during the interpulse interval, and it would not be expected that Iₖ block would be reduced during short cycle lengths. In addition, the nonselective block by amiodarone of potassium currents may contribute to the lack of frequency-dependent effects on repolarization.³⁶-⁴⁰

In contrast to the APD₉₀, there was an attenuation in the magnitude of amiodarone-induced VERP prolongation at short cycle lengths, although the VERP nevertheless remained significantly prolonged at the shortest cycle length examined. No frequency-dependent effects on the percent increase in the VERP by amiodarone were observed, and it is unclear whether the absolute or relative prolongation of the VERP is the more clinically meaningful parameter.

VERP prolongation did not appear to be fully accounted for by APD₉₀ prolongation in our study. The significant prolongation of the VERP/APD₉₀ ratio (measured at twice diastolic threshold) compared with baseline at long cycle lengths appears to reflect a composite of time-dependent as well as voltage-dependent effects. The result of these time-dependent effects is a significant lengthening of the VERP at long cycle lengths (about 50 milliseconds, compared with baseline) without an equivalent increase in APD₉₀, which was prolonged by approximately 30 milliseconds. These time-dependent effects (at twice diastolic threshold) most likely reflect the incomplete recovery of sodium channel blockade after repolarization.⁸,¹⁴,⁴¹-⁴³ The relatively rapid kinetics of sodium channel block during depolarization probably results in a high degree of sodium channel block at the end of the plateau, which does not fully dissipate by the end of repolarization.⁸,⁴¹-⁴³ Subsequently, the VERP is prolonged to a greater extent than the APD₉₀. Such time-dependent effects on refractoriness have been demonstrated in guinea pig ventricular free wall tissues for lidocaine,⁴¹ a drug with sodium channel blocking kinetics similar to amiodarone,³¹ and that also preferentially binds to inactivated sodium channels.⁴⁴ During rapid pacing the QRS duration is markedly prolonged, reflecting the shortened diastolic interval and less dissipation of amiodarone-induced sodium channel block at phase 0 of the APD, whereas time-dependent effects on refractoriness are not increased at short cycle lengths. This most likely reflects a balance during rapid pacing between less amiodarone binding during the shortened plateau and frequency-dependent accumulation of sodium block, resulting in an overall lack of further enhancement of sodium block during the terminal portions of phase 3 (where the VERP is determined) compared with long paced cycle lengths. Our findings are in agreement with those in a chronic amiodarone dog model that demonstrated significant time-dependent effects on the VERP at cycle lengths of 300 to 1000 milliseconds.³ The increase observed at drug-free baseline in the VERP/APD₉₀ ratio at short cycle lengths in the current study probably reflects lack of full recovery of sodium channels during rapid pacing.⁴¹,⁴³

Increases in the VERP but not in the APD₉₀ or the QRS duration were shown to correlate with the observed increase in sustained VT cycle length in group A patients, suggesting that changes in refractoriness are important in determining the rate of VT. Similar findings have been reported by Chiamvimonvat et al⁴⁵ during amiodarone therapy. Increases in QRS duration were not correlated with changes in VT cycle length, and this may represent the fact that we did not measure conduction changes directly in the arrhythmic circuit.

**Frequency-Dependent Effects of Amiodarone in Groups A and B**

We observed a similar pattern of change at the different paced cycle lengths in the APD₉₀, VERP, VERP/APD₉₀, and QRS duration in patients after either an amiodarone loading regimen or treatment for >1 year with amiodarone. In addition, the mean values of the electrophysiologic parameters during amiodarone treatment were very similar in the two groups, as were their clinical parameters. It is unlikely that both groups' baseline electrophysiologic values were significantly different (we have analyzed the baseline values in 26 additional patients, and they are very similar to those of group A [unpublished results]). Thus, the data suggest that the unusual frequency-dependent actions of amiodarone occur early and do not appear to change significantly over time.

Previous studies have not consistently demonstrated a greater effect on ventricular refractoriness as a function of time in patients receiving amiodarone.⁴⁶-⁵¹ Several studies⁴⁶-⁵⁰ have shown no significant change in the VERP between 1 and 2 weeks of amiodarone therapy as compared with 1 to 4 months of therapy, whereas another group⁵⁰ reported a significant (6%) increase in VERP after a mean of 5 months of therapy. Mitchell et al⁵¹ studied patients at 2 and 10 weeks and found significant increases in the RV functional but not the effective refractory period. Thus, in general, studies performed between 1 and 2 weeks and after the first several months of amiodarone therapy have not shown significant time-dependent increases in the VERP.

**Clinical Implications**

The observations that at long cycle lengths the VERP is markedly prolonged by time and voltage-dependent effects, whereas the ventricular APD₉₀ is prolonged by a relatively fixed amount of approximately 30 milliseconds at all examined cycle lengths, and the lack of reverse frequency-dependence of repolarization may account in part for the high efficacy and low proarrhythmogenicity of amiodarone when compared with other antiarrhythmic agents.¹-³,³⁵,⁵²,⁵³ One important action of amiodarone is slowing of VT and making an arrhythmia hemodynamically well tolerated.⁴⁴-⁵⁶ In this study, an increase in the VERP by amiodarone was correlated...
with slowing of the induced sustained VT. The ability of amiodarone to significantly prolong the VERP even at short cycle lengths thus may contribute to tachycardia slowing. Although most of our patients still had inducible VT during amiodarone therapy, the lack of frequency-dependent effects on relative VERP prolongation and on the APD_{90} may nevertheless play a protective role against the clinical initiation or maintenance of reentrant arrhythmias\textsuperscript{17-20} since the ability to induce sustained VT during electrophysiologic study in patients receiving amiodarone does not preclude a good clinical outcome.\textsuperscript{3,50,57-61}

The lack of reverse frequency dependence of the APD_{90} by amiodarone is unique for antiarrhythmic agents and results in amiodarone having substantial pharmacological effect at the short cycle lengths commonly observed during clinical ventricular arrhythmias. The lack of a comparable increase in the APD_{90} at long cycle lengths compared with the VERP may reduce the likelihood of early afterdepolarization–driven torsade de points.\textsuperscript{23-26,36,55} Indeed, our findings suggest that amiodarone is fundamentally different from other agents that prolong the APD in not inducing marked APD prolongation at long cycle lengths.\textsuperscript{11-16} The fact that amiodarone produces a relatively greater increase in the VERP compared with the APD_{90} at long cycle lengths may decrease the likelihood of development of triggered arrhythmias, since early afterdepolarizations may fall within the effective refractory period and thus be unable to propagate.

Limitations of the Study

The group A and group B patients were different, and, although the clinical parameters of the two patient cohorts were similar, the electrophysiologic comparison is between two separate populations, and the data must be examined with this in mind. It was not feasible to wait ≥1 year to restudy the same patients because of alterations in patient therapy for clinical reasons, patients moving to a different locale, and intercurrent clinical events; thus, the major analysis of group B is in the pattern of change in their electrophysiologic parameters at different paced cycle lengths and a comparison of the electrophysiologic profile of groups A and B. It was only possible to test a relatively narrow range of cycle lengths (300 to 600 milliseconds) because of sinus interference at longer cycle lengths or hemodynamic instability at shorter cycle lengths. QRS duration was used as a measurement of ventricular conduction velocity and may not be as accurate as directly measured conduction velocity. However, the QRS duration has been shown to correlate highly with conduction changes measured by epicardial mapping.\textsuperscript{62} Furthermore, the QRS duration has been used to determine frequency-dependent conduction slowing, and, as a parameter, it correlates well with changes in V_{max} in vitro.\textsuperscript{63} The APD_{90} and VERP were measured at the same RV site; however, it is unlikely that these measurements were obtained from exactly the same cohort of cells. However, the demonstration in humans of a very linear relation between test-site APD_{90} and VERP substantiates comparing the APD_{90} with the VERP when both measurements are made at the same catheter site.\textsuperscript{57} The analysis between electrophysiologic characteristics and the increase in sustained VT cycle length during amiodarone therapy was performed in a small number of patients, and the effects of amiodarone on these parameters in the reentrant circuit may be different from those at the RV recording site. It was only possible to perform the electrophysiologic determinations at twice diastolic threshold, and the possibility cannot be excluded that other frequency-dependent relations might be observed at higher current stimulation.

Conclusions

Amiodarone does not exert frequency-dependent effects on ventricular repolarization; refractoriness is prolonged by both time- and voltage-dependent mechanisms, and amiodarone exerts frequency-dependent effects on ventricular conduction. The overall findings are unique in an antiarrhythmic agent and may contribute to the unusual efficacy of the drug combined with its low incidence of proarrhythmic effects.

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