Amiodarone-Induced Postrepolarization Refractoriness Suppresses Induction of Ventricular Fibrillation

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ABSTRACT
It is still incompletely understood why amiodarone is such a potent antiarrhythmic drug. We hypothesized that chronic amiodarone treatment produces postrepolarization refractoriness (PRR) without conduction slowing and that PRR modifies the induction of ventricular arrhythmias. In this study, the hearts of 15 amiodarone-pretreated (50 mg/kg p.o. for 6 weeks) rabbits and 13 controls were isolated and eight monophasic action potentials were simultaneously recorded from the epicardium and endocardium of both ventricles. Steady-state action potential duration (APD), conduction times, refractory periods, and dispersion of action potential durations were determined during programmed stimulation and during 50-Hz burst stimuli, and related to arrhythmia inducibility. Amiodarone prolonged APD by 12 to 15 ms at pacing cycle lengths of 300 to 600 ms (p < 0.05) but did not significantly increase conduction times or dispersion of APD. Amiodarone prolonged refractoriness more than action potential duration, resulting in PRR (refractory period – APD at 90% repolarization, 14 ± 10 ms, p < 0.05 versus controls). PRR curtailed the initial sloped part of the APD restitution curve by 20%. During burst stimulation, pronounced amiodarone-induced PRR (40 ± 15 ms, p < 0.05 versus controls) reduced the inducibility of ventricular arrhythmias (p < 0.05 versus controls). Furthermore, in 35% of bursts only monomorphic ventricular tachycardias and no longer ventricular fibrillation were inducible in amiodarone-treated hearts (p < 0.05 versus controls). Chronic amiodarone treatment prevents ventricular tachycardias by inducing PRR without much conduction slowing, thereby curtailing the initial part of APD restitution. PRR without conduction slowing is a desirable feature of drugs designed to prevent ventricular arrhythmias.

The need to prevent frequent appropriate discharges of implantable defibrillators, the side effects of long-term defibrillator therapy, and the increasing economic constraints in several health care systems have reemphasized the need for antiarrhythmic agents that prevent ventricular arrhythmias. Chronic amiodarone treatment reduces recurrent ventricular tachyarrhythmias (Connolly, 1999) and, in contrast to other antiarrhythmic agents, including potassium channel blockers, does not increase mortality or sudden death rates (Echt et al., 1991; Singal et al., 1995; Waldo et al., 1996; Wyse et al., 2001). Therefore, amiodarone is one of the few remaining treatment options to prevent recurrent ventricular arrhythmias (Connolly, 1999). Although amiodarone blocks multiple ion currents in the heart (Kamiya et al., 2001; Maltsev et al., 2001), the electrophysiological effects by which amiodarone exerts this unique antiarrhythmic action are not well understood.

A series of premature stimuli applied at the shortest possible coupling interval allow earlier capture of each consecutive stimulus. This shortening of the effective refractory period (ERP) is not only caused by rate-dependent decrease in action potential duration (APD) (Franz et al., 1988) but also because each additional premature stimulus captures the myocardium at an earlier repolarization level than the previous one (Koller et al., 1995). This phenomenon called “progressive encroachment” or “facilitated excitability during repetitive extrastimulation” (Koller et al., 1995) is accompanied by a progressive slowing of impulse conduction velocity, a predictor of ventricular inducibility (Koller et al., 1995; Kirchhof et al., 1998). Sodium channel...
blocks can prevent progressive encroachment by prolonging refractoriness beyond repolarization, an effect that has been called postrepolarization refractoriness (PRR; Kirchhof et al., 1998). We have previously shown that PRR induced by sodium channel blockers inhibits the induction of ventricular fibrillation, but in the case of sodium channel blockers, this effect is offset by conduction slowing, a known proarrhythmic factor that facilitates induction of monomorphic ventricular tachycardias (Kirchhof et al., 1998).

Acute administration of amiodarone can induce PRR in isolated cells (Mason et al., 1983; Varro et al., 1985; Yabek et al., 1986; Nanas and Mason, 1995). Based on these findings and on our previous studies (Kirchhof et al., 1998), we hypothesized that amiodarone may induce PRR without much conduction slowing and that this electrophysiological effect prevents the induction of ventricular arrhythmias. Because the electrophysiological effects of chronic amiodarone treatment differ from its acute effects (Mason et al., 1983; Varro et al., 1985; Yabek et al., 1986; Nanas and Mason, 1995), we used a model of chronic amiodarone treatment to measure action potential durations, effective refractory periods, PRR, and conduction times in the intact heart.

### Materials and Methods

**Experimental Preparation and Data Acquisition.** The study conformed with the Guide for the Care and use of Laboratory Animals published by the National Institutes of Health (NIH publication 85-23, revised 1986). Fifteen male New Zealand White rabbits (mean body weight 3.9 ± 0.5 kg) received oral amiodarone treatment (50 mg/kg b.wt./day) for 6 weeks. The drug was mixed into the normal food. Thirteen rabbits of comparable weight and equal sex served as controls. After the end of the treatment period, the hearts were isolated and retrogradely perfused via the aorta on a modified vertical Langendorff apparatus using a 37°C warm, oxygenated modified Krebs-Henseleit solution. Details of the isolated heart setup have been described previously (Kirchhof et al., 1998, 2003). In brief, eight monophasic action potential (MAP)-pacing combination catheters were simultaneously placed onto the epicardium of both ventricles and into the right ventricular cavity. We used MAP combination catheters because they allow for stimulation and recording of an action potential at the same site. A custom-designed latex balloon was connected to a pressure transducer and placed into the left ventricle to monitor left ventricular pressure. A volume-conducted six-lead ECG was recorded from a solution-filled tissue bath (Kirchhof et al., 1998). All data were acquired using a 24-channel EP lab system (EP system version 2.51; Bard Electrophysiology, Unterschächen, Germany). The atroventricular node was crushed to allow pacing at slow ventricular rates.

**Electrophysiological Protocol.** One of the left ventricular epicardial MAP catheters was used for pacing and burst stimulation. The pacing threshold was checked repetitively during the stimulation protocol. All pacing stimuli were of 2-ms duration. First, the ventricle was paced at twice diastolic threshold for >1 min at 200-, 300-, 400-, and 600-ms pacing cycle length, respectively, to determine steady-state action potential durations and conduction times. Programmed stimulation was performed using up to three extra stimuli at 400- and 600-ms basic drive cycle length. The coupling interval of the extra stimuli was decreased in steps of 5 ms. The effective refractory period was defined as the longest coupling interval not eliciting a premature response and was determined twice for each extra stimulus. For determination of the ERP of S3, the coupling interval of the previous extra stimulus was set at ERP (S2) plus 5 ms.

**Burst Stimulation.** To determine the vulnerability of the ventricles to extremely premature stimulation, the heart was stimulated for 5 s using 50-Hz burst stimuli at 2, 3, and 5 times diastolic threshold, and at maximal output strength (corresponding to 8–20 times diastolic threshold). This stimulation frequency is the most effective to induce ventricular arrhythmias in this model (Kirchhof et al., 1998). Each burst stimulus was repeated three times to assess the probability of arrhythmia induction. Burst stimulation allows for multiple consecutive premature stimuli as close to refractoriness as possible. For assessment of arrhythmia inducibility, we chose burst stimulation and not conventional programmed stimulation because this technique can be repeated multiple times within a short time period (Kirchhof et al., 1998). The entire stimulation protocol was performed via a single MAP catheter to be able to compare the measurements during programmed stimulation and during burst stimulation.

**Data Analysis.** All data were exported on a personal computer system and analyzed using a semiautomatic computer program for analysis of action potential duration (Franz et al., 1995). The program was used to determine action potential durations in each MAP recording at 50, 70, and 90% repolarization (APD50, APD70, and APD90), and conduction times during steady-state pacing and during programmed stimulation for the construction of APD restitution curves. Conduction times were measured as the interval from the pacing stimulus to the fastest part of the upstroke in each of the eight MAP recordings. The timing of the MAP upstroke was determined digitally under visual control of an experienced observer. The mean and maximal conduction times were calculated over all MAP recordings in every beat analyzed (Kirchhof et al., 1998). Dispersion...
Concentrations. Amiodarone prolonged APD at 300- to 600-ms basic cycle lengths (BCLs) and at all repolarization levels analyzed (Fig. 1). Dispersion of APD was not changed by amiodarone (maximal difference 6 ms, all p > 0.2). Alternans of APD did not occur at pacing cycle lengths from 200 to 600 ms. Conduction times were not significantly different in amiodarone-treated hearts compared with baseline hearts, although there was a trend toward a slight prolongation of conduction times in amiodarone-treated hearts (p = 0.07–0.14; Table 1). Conduction times during programmed stimulation did not increase in amiodarone-treated hearts (see below). Myocardial amiodarone tissue levels ranged from 5.1 ± 0.9 to 13.1 ± 2.3 μg of amiodarone per gram of myocardium. The mean amiodarone tissue concentration was 7.9 ± 0.6 μg of amiodarone per gram of myocardium, comparable with myocardial tissue concentrations in human hearts during chronic amiodarone treatment (Candinas et al., 1998; Anastasiou-Nana et al., 1999). Amiodarone tissue concentrations were not different between right and left ventricular specimens.

APD Restitution Curve, Refractoriness, and Conduction Times. During programmed stimulation, the initial portion of the APD restitution curve was significantly curtailed by −20% of its total duration in amiodarone-treated hearts (Fig. 2, p < 0.05). This curtailment of the APD restitution curve was due to postrepolarization refractoriness (see below) and resulted in a lesser degree of APD shortening during programmed stimulation [600-ms BCL: shortest APD after S2 amiodarone 150 ± 9 ms; baseline 135 ± 15 ms, p < 0.05; 400-ms BCL: amiodarone 121 ± 16 ms; baseline 110 ± 19 ms, p = 0.07]. The remaining portion of the restitution curve was not significantly changed by amiodarone treatment (Fig. 2, A and B). Upon inspection of the restitution curves, a small upward deviation was noted in amiodarone-treated hearts for long S2 coupling intervals at a pacing cycle length of 600 ms (Fig. 2B), probably caused by the potassium

**Results**

**Steady-State Action Potential Durations and Tissue Concentrations.** Amiodarone prolonged APD at 300- to 600-ms basic cycle lengths (BCLs) and at all repolarization levels analyzed (Fig. 1). Dispersion of APD was not changed by amiodarone (maximal difference 6 ms, all p > 0.2). Alternans of APD did not occur at pacing cycle lengths from 200 to 600 ms. Conduction times were not significantly different in amiodarone-treated hearts compared with baseline hearts, although there was a trend toward a slight prolongation of conduction times in amiodarone-treated hearts (p = 0.07–0.14; Table 1). Conduction times during programmed stimulation did not increase in amiodarone-treated hearts (see below). Myocardial amiodarone tissue levels ranged from 5.1 ± 0.9 to 13.1 ± 2.3 μg of amiodarone per gram of myocardium. The mean amiodarone tissue concentration was 7.9 ± 0.6 μg of amiodarone per gram of myocardium, comparable with myocardial tissue concentrations in human hearts during chronic amiodarone treatment (Candinas et al., 1998; Anastasiou-Nana et al., 1999). Amiodarone tissue concentrations were not different between right and left ventricular specimens.

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**Fig. 2.** Amiodarone curtails APD restitution curves at 600- and 400-ms BCL. Action potential duration of the premature response (APD) is given on the ordinate, and the coupling interval of the extra stimulus on the abscissa. A, APD restitution curve at 400-ms BCL. B, APD restitution curve at 600-ms BCL. Amiodarone curtailed the initial, steep portion of the APD restitution curve. C and D, initial sloped portion of the APD restitution curve at 400-ms BCL (C) and at 600-ms BCL (D). Horizontal black bars highlight the curtailed initial portion of the APD restitution curve in amiodarone-treated hearts.
channel-blocking properties of amiodarone. In contrast to the curtailing of the initial part of the restitution curve, these subtle changes did not reach statistical significance, thereby demonstrating the relevance of the initial portion of the restitution curve for the antiarrhythmic action of amiodarone.

Conduction times increased during premature stimulation both in controls and in amiodarone-treated hearts. Neither mean conduction times nor the increase in conduction time during programmed stimulation was different between amiodarone-treated hearts and controls (conduction times at BCL = 600 ms: amiodarone increase from 38 ± 1 ms (at diastolic intervals >150 ms) to 54 ± 4 ms (refractory period ± 5 ms), baseline increase from 36 ± 1 to 54 ± 4 ms; BCL = 400 ms: amiodarone increase from 41 ± 2 to 56 ± 3 ms, baseline increase from 32 ± 3 to 50 ± 3 ms]. Amiodarone induced PRR during programmed stimulation (p < 0.05 versus base for S1 = 600 ms; Table 1).

**Ventricular Arrhythmias during Burst Stimulation.** A total of 1189 burst stimulation episodes were analyzed. In 282 episodes (24%), sustained ventricular arrhythmias were induced. Arrhythmia induction was more likely at higher stimulus strengths (Fig. 3A). Amiodarone reduced arrhythmia inducibility at all stimulus strengths (Fig. 3A, p < 0.05). The number of arrhythmia-free hearts was higher in the amiodarone-treated group (Fig. 3B). Furthermore, 35% of burst stimuli induced monomorphic ventricular tachycardias instead of ventricular fibrillation in amiodarone-treated hearts (Figs. 3C and 4, p < 0.05). During monomorphic tachycardias, the left ventricle still generated pressure, suggesting a residual systolic left ventricular function (Fig. 4, Amio).

**Amiodarone-Induced PRR Prevents Arrhythmia Induction.** Amiodarone induced PRR during programmed stimulation (Table 1; Fig. 5A). During burst stimulation, PRR was more pronounced than during programmed stimulation (mean PRR during bursts irrespective of stimulus strength: amiodarone 40 ± 15 ms versus controls 22 ± 13 ms, p < 0.05). Presence of PRR during burst stimuli prevented induction of ventricular fibrillation (Fig. 5C). Higher burst stimulus strengths reduced PRR and reverted PRR to progressive encroachment (Fig. 5, B and C), concurrent with increased arrhythmia inducibility (Fig. 3A).

Burst stimulation episodes that did not induce arrhythmias showed marked PRR (Fig. 5D). Induction of ventricular fibrillation, in contrast, was associated with progressive encroachment, or lack of PRR. Of note, the bursts that induced monomorphic ventricular tachycardias showed PRR that was not significantly different from form bursts not inducing arrhythmias. Thus, amiodarone-induced PRR prevented induction of ventricular fibrillation in favor of no arrhythmias at all or in favor of hemodynamically better tolerated monomorphic ventricular tachycardias.

**Discussion**

**Main Findings.** Chronic amiodarone treatment induced marked PRR (Figs. 3 and 5). Amiodarone-induced PRR prevented the induction of ventricular arrhythmias and furthermore reduced the incidence of ventricular fibrillation in favor of monomorphic ventricular tachycardias (Figs. 3–5). PRR prevented excitation during the vulnerable period and curtailed the initial, steep portion of the APD restitution curve (Figs. 2 and 5). PRR without conduction slowing is a desirable effect of drugs designed to prevent ventricular arrhythmias.

**Relation of Refractoriness and Repolarization.** The effective refractory period is known to relate to repolarization levels between 75 and 85% in different animal models and in human (Franz et al., 1988, 1990; Lee et al., 1992). Premature stimulation alters this fixed relationship between APD and refractory period (Koller et al., 1995; Kirchhof et al., 1998): closely coupled extra stimuli shorten the refractory period of the premature responses due not only to a parallel decrease in the concomitant APD but also because premature excitation is possible at increasingly less complete repolarization levels (progressive encroachment; Davidenko and Antzele-
PRR. Progressive encroachment of excitation (Koller et al., 1995) can be prevented by the sodium channel blocker propafenone (Kirchhof et al., 1998). In our previous study, propafenone-induced PRR prevented ventricular fibrillation, but this apparently antiarrhythmic effect was offset by marked conduction slowing that promoted monomorphic ventricular tachycardias (Kirchhof et al., 1998). Chronic amiodarone treatment, in contrast, induced PRR without a high degree of conduction slowing in this study, and reduced the inducibility of ventricular arrhythmias (Figs. 3 and 4). PRR was present both during programmed stimulation and during burst stimulation in amiodarone-treated hearts. These findings provide direct evidence that PRR has antiarrhythmic effects in the intact heart in the absence of conduction slowing.

Conduction Times. In this model, we assessed conduction times during programmed stimulation in eight simultaneous MAP recordings that were equally spread throughout the right and left ventricular epicardium, a surrogate parameter for conduction velocity in this model (Kirchhof et al., 1998). We found a trend toward longer conduction times in amiodarone-treated hearts during steady-state pacing, compatible with the sodium channel-blocking effect of amiodarone (Mason et al., 1983; Maruyama et al., 1995). Conduction times were not significantly prolonged in amiodarone-treated hearts, probably due to the intrinsic variability of conduction times measured between different hearts by equally spread MAP recordings. Noteworthy is the fact that amiodarone did not enhance the increase in conduction times associated with programmed stimulation. This is in contrast to slowly dissociating sodium channel blockers that markedly slow conduction times during programmed stimulation in the same experimental model (Kirchhof et al., 1998) and may be attributable to the development of PRR, which prevents stimulation during relative refractoriness. Lack of conduction slowing during premature stimulation could prevent wave-length shortening and induction of monomorphic ventricular tachycardias (Kirchhof et al., 1998).

How Could PRR Prevent Arrhythmia Induction? PRR allows for full recovery of voltage-dependent sodium channels during the refractory period (Maruyama et al., 1995), as reflected by relatively rapid upstroke velocities of action potentials after an extra stimulus in isolated tissue preparations that are not different from upstroke velocities during fixed frequent pacing (Pallandi and Campbell, 1987). Previously, we hypothesized that this effect may reduce stimulation-induced conduction slowing and thereby prevent induction of ventricular tachyarrhythmias (El-Sherif, 1991; Koller et al., 1995; Kirchhof et al., 1998). In this study, however, the degree of stimulation-induced conduction slowing was similar at baseline and in amiodarone-treated hearts, potentially due to the inactivated sodium channel-blocking effect of amiodarone (Pallandi and Campbell, 1987; Maruyama et al., 1995). Preventing stimulation-induced conduction slowing can therefore not fully explain the antiarrhythmic effect of PRR. Amiodarone-induced PRR must exert other antiarrhythmic effects. These may include curtailing of APD restitution and prevention of excitation during the vulnerable period.

Due to loss of excitability during the late repolarization phase, the initial portion of the APD restitution curve was eliminated in amiodarone-treated hearts, resulting in a shorter steep portion of the APD restitution curve (Fig. 2, C and D). This effect may prevent or reduce alternans of action potential duration after premature stimuli or during high heart rates (Fox et al., 2002), a known proarrhythmic factor that precedes wave front breakup and induction of ventricular fibrillation (Weiss et al., 2000; Ohara et al., 2001). Due to the lengthy stimulation protocol for induction of arrhythmias, we could not directly quantify APD alternans in the present study. APD alternans occur, however, when a steep slope of APD restitution is present over a long range of coupling intervals (Weiss et al., 2000; Fox et al., 2002). Ami-
Amiodarone curtailed this steep portion of APD restitution in our study. Of note, the remainder of the restitution curve was not altered by amiodarone, suggesting that the curtailed portion of the restitution curve is a direct consequence of PRR.

PRR prevents electrical stimulation during the so-called vulnerable period of the heart, which is delineated by the dispersion of action potential durations from 70 to 90% repolarization (Kirchhof et al., 1996). A single strong electrical field stimulus almost inevitably induces ventricular fibrillation when it is applied during this vulnerable period at a certain range of shock strengths. In this setting, ventricular fibrillation is induced by causing micro-re-entry in regions of slow conduction and functional block (Frazier et al., 1989).

**Comparison to Other Antiarrhythmic Agents.** Potassium channel blockers prolong both repolarization and refractoriness to a similar extent, and therefore do not induce PRR (Kirchhof et al., 1996; Zabel et al., 1997). Sodium channel blockers induce PRR but markedly slow conduction velocity (Franz and Costard, 1988; Kirchhof et al., 1998). These effects may explain why both sodium and “pure” potassium channel blockers have more pro- than antiarrhythmic effects in clinical trials (Echt et al., 1991; Singh et al., 1995; Waldo et al., 1996; Wyse et al., 2001). PRR will be present when an action potential-prolonging drug, e.g., sotalol, is combined with a sodium channel blocker, e.g., mexiletine. PRR could therefore also contribute to the antiarrhythmic effects of such combinations of antiarrhythmic drugs (Breithardt et al., 1981; Chezalviel-Guibert et al., 1995; Lee et al., 1997).

**Methodological Considerations.** Our data pertain to ventricular arrhythmias induced by multiple electrical stimuli and their prevention by antiarrhythmic agents in the intact rabbit heart. Although this experimental setup quantifies arrhythmia inducibility, combined with multisite assessment of conduction times, action potential durations, and refractoriness, the results cannot be directly transferred to the clinical setting in which a variety of underlying cardiac diseases and autonomic influences form additional anti- and proarrhythmic factors. Some data suggest that amiodarone may have antiarrhythmic effects in ischemic tissue or in hearts that survived a myocardial infarction (Manning et al., 1995; Aimond et al., 2000). Further studies may determine the effect of amiodarone on PRR in hearts with acute ischemia or myocardial infarction, and whether these results also pertain to arrhythmias provoked by other techniques.

Proarrhythmic effects associated with other mechanisms of arrhythmia induction than rapid ventricular stimulation and functional reentry, e.g., after depolarizations and repolarization-related arrhythmias, were not assessed in this study. Amiodarone did not increase dispersion of repolarization in this and other studies (Sicouri et al., 1997; Zabel et al., 1997), in keeping with its low proarrhythmic potential (Haverkamp et al., 2000).

Others have previously demonstrated that the acute effects of amiodarone include a prolongation of refractoriness beyond repolarization in isolated rabbit papillary muscle (Pallandi and Campbell, 1987; Maruyama et al., 1995). Maruyama et al. (1995) already suggested that the sodium channel-blocking effect of amiodarone might be one of the reasons why this drug is an effective antiarrhythmic agent. Our

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**Fig. 5.** Amiodarone-induced PRR relates to prevention of arrhythmia induction. A, example of amiodarone-induced PRR recorded in a monophasic action potential during programmed stimulation with two premature stimuli stimulated at the shortest possible coupling interval (ERP + 5 ms). Horizontal black bars indicate intervals of PRR in the amiodarone-treated heart. B, top, typical example of encroachment of excitation during burst stimulation at maximal stimulus strength without amiodarone treatment. Upward arrows indicate take-off potentials of the next action potential. Bottom, typical example of PRR during burst stimulation at maximal stimulus strength in an amiodarone-treated heart. Horizontal bars indicate intervals of PRR. Calibration bars indicate 5 mV and 100 ms (A and B). C, mean PRR during burst stimulation in amiodarone-treated and control hearts split by stimulus strength (absissa), and for all bursts (rightmost column). PRR decreased with increasing stimulus strength, related to a higher probability of arrhythmia induction (compare Fig. 3A). D, mean PRR (milliseconds) during bursts inducing ventricular fibrillation (VF), monomorphic ventricular tachycardias (mVT), or no arrhythmia (No Arrh). PRR was present when no arrhythmia was induced, less PRR when mVT was induced. Progressive encroachment was associated with induction of VF. Asterisks (*) indicate significant differences between groups.
study demonstrates that PRR mediates the antiarrhythmic efficacy of chronic amiodarone treatment in the intact heart.

Implications. In contrast to slowly dissociating sodium channel blockers and the pure potassium channel \( (K_p) \) blocker sotalol (Echt et al., 1991; Singh et al., 1995; Waldo et al., 1996; Wyse et al., 2001), amiodarone is the only antiarrhythmic drug whose antiarrhythmic potential is not offset by proarrhythmic effects in patients (Singh et al., 1995; Wyse et al., 2001). PRR can explain this unique antiarrhythmic efficacy of amiodarone, whereas lack of conduction slowing (this study) and uniform action potential prolongation (Si-couri et al., 1997) may explain the low proarrhythmic potential of the drug (Singh et al., 1995; Wyse et al., 2001). The ideal antiarrhythmic agent has yet to be designed. Such a compound should eliminate premature responses by producing PRR, without interfering with normal excitation. So far, only amiodarone approximates these criteria.

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References


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