The Effects of Acute and Chronic Amiodarone on Activation Patterns and Defibrillation Threshold During Ventricular Fibrillation in Dogs

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OBJECTIVES
The goal of this study was to evaluate the effects of acute and chronic amiodarone on activation patterns during ventricular fibrillation (VF), ventricular effective refractory period (VERP) and defibrillation threshold (DFT).

BACKGROUND
Acute and chronic amiodarone may act through different mechanisms.

METHODS
The VERP, VF activation patterns and DFT were determined in 24 dogs. Twelve dogs received acute intravenous amiodarone (10 mg/kg, n = 6) or saline (n = 6), and 12 dogs received chronic oral amiodarone (20 mg/kg/day, n = 6) or placebo (n = 6). Epicardial VF activation patterns were recorded with 504 electrodes. Quantitative descriptors of VF were calculated.

RESULTS
The DFT was unchanged by acute or chronic amiodarone. Although chronic amiodarone significantly extended the VERP, acute amiodarone did not. In the mapped region, acute and chronic amiodarone decreased the number of VF wavefronts by 42% and 60%. Acute amiodarone decreased conduction block by 22%, while chronic amiodarone increased block by 41% but decreased wave fractionation by 50%. Both chronic and acute amiodarone increased the size of the core of re-entrant circuits and decreased the incidence of re-entry by 44% and 57%; however, chronic amiodarone increased wavelength, while acute amiodarone did not.

CONCLUSIONS
Neither acute nor chronic amiodarone change the DFT. While both acute and chronic amiodarone decrease the number of wavefronts, decrease the incidence of re-entry and increase the size of re-entrant cores in the mapped region during VF, they achieve these antiarrhythmic effects through different electrophysiologic mechanisms. Chronic amiodarone prolonged the VF cycle length and slowed conduction velocity, indicating it increased the wavelength and/or the excitable gap. (J Am Coll Cardiol 2002;40:375–83) © 2002 by the American College of Cardiology Foundation

Clinically, the electrophysiologic effects of amiodarone differ significantly when it is given chronically by mouth compared with an acute intravenous dose (1), a difference for which the mechanisms remain unexplained. Amiodarone is commonly prescribed for patients with an implantable defibrillator who receive frequent shocks for ventricular arrhythmias or patients with out-of-hospital cardiac arrest due to refractory ventricular arrhythmias, in whom amiodarone has been shown to increase survival to hospital admission (2). Potential effects of amiodarone on defibrillation have become increasingly important with the introduction and success of the implantable cardioverter defibrillator. However, previous studies of the effect of amiodarone on the defibrillation threshold (DFT) have yielded conflicting results (3–5).

The wavelength (6,7), incidence of conduction block (8), number and size of activation fronts and number, duration and core size of re-entrant circuits are important parameters for characterizing the effects of antiarrhythmic drugs for either atrial or ventricular fibrillation (VF). Because it is difficult and tedious to study these numerous parameters during VF solely by visual analysis, we recently developed automated methods to quantify VF activation patterns (9,10). These methods have been used to detect how activation patterns differ in the right and left ventricles (11) and how they are altered by heart failure (12). The detection of activation pattern differences during VF before and after antiarrhythmic drug administration should help us to further understand the antifibrillation mechanisms for those drugs. In this study, we quantitatively evaluated the changes in VF activation patterns caused by acute and chronic amiodarone administration to determine if they achieve their antiarrhythmic effects through the same or different mechanisms.

METHODS
All animals were managed in accordance with the guidelines established by the American Heart Association on Research Animal Use (13), and protocols were approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee.

Animal preparation. Based on the route of amiodarone administration, the animals were divided into two groups: 1) acute and 2) chronic. The same methods for preparation, ventricular effective refractory period (VERP) measurement,
DFT measurement and electrical mapping were used in both groups. Mongrel dogs 24 to 36 kg (30 ± 4 kg, mean ± SD) were anesthetized with 25 mg/kg intravenous thiopental sodium and maintained with 2% to 3% isoflurane in 100% oxygen delivered by mechanical ventilation. Succinylcholine was initially given at a dose of 1 mg/kg and followed by 0.25 to 0.5 mg/kg at about 20 min intervals to decrease skeletal muscle movement induced by defibrillation shocks. Lactated Ringers solution was continuously infused intravenously (2 to 5 ml/kg/min). Core body temperature, arterial blood gas values and serum electrolytes were maintained within normal physiologic ranges throughout the experiment. Blood pressure and the lead II surface electrocardiogram (ECG) were displayed on a monitor.

**Measurement of refractory period.** The VERP was determined using an incremental S1-S2 pacing protocol from a pair of bipolar electrodes inserted into the subepicardium for the acute group and from the tip and right ventricle electrodes (0094 Endotak, Guidant, St. Paul, Minnesota) for the chronic group. Both S1 and S2 stimuli (2 ms duration) were given at twice diastolic threshold. The S1-S1 interval was 300 ms (10 beats), and the initial S1-S2 interval was 140 ms. The S1-S2 interval was increased in 10-ms increments until the S2 stimulus captured the ventricles on the ECG. Then the S1-S2 interval was reset to 10 ms less than this interval and was increased in 2-ms increments until S2 again captured the ventricles. This procedure was repeated three times, with 2 min between each determination. The longest S1-S2 interval failing to capture in any of the three trials was defined as the VERP. We used VF cycle length as an index of the effective refractory period (ERP) during VF (14).

**DFT determination.** In the chronic group, the DFT was determined for an SVC electrode and a right ventricular electrode (0094 Endotak, Guidant). Ventricular fibrillation was induced with 30-V, 60-Hz alternating current through the sensing/pacing electrode on the defibrillation catheter. After 20 s of VF, a biphasic shock (6/4 ms) was given. The leading edge voltage of the first shock was 400 V for the first animal and was the mean DFT from previous animals for the following animals. Depending on the success or failure of the shock, the leading edge voltage was decreased or increased by 40 V, respectively. The transition from failure to success or success to failure was recorded as the first data point. The up-down algorithm was continued until the third reversal of success to failure or failure to success was reached. The DFT was determined by averaging the four shock strengths that formed the three reversals (10). At least 5 min elapsed after every VF episode to allow blood pressure and heart rate to return to normal. The DFT determination protocol used for the acute group was the same as in the chronic group except that the right ventricular electrode was exchanged for an epicardial patch (10 mm in diameter) on the left ventricular apex.

**Mapping.** The heart was exposed through a median sternotomy and supported in a pericardial sling. A 504-electrode (24 × 21) plaque was sutured to the anterior right ventricular epicardium with slight overlap onto the anterior left ventricular epicardium. The electrodes were 2 mm apart and, in total, covered 20.16 cm², which is about 20% of the ventricular surface. The ground reference for the unipolar recordings was attached to the right leg.

### Amiodarone administration.

In the acute group, after baseline testing, six animals received a loading dose of amiodarone (10 mg/kg in 5 cc dimethyl sulfoxide [DMSO]) followed by a maintenance infusion of 0.03 mg/kg/min, which has been reported to cause a steady-state plasma concentration (15). In another six control animals, DMSO/saline was administered instead of amiodarone. Electrophysiologic measurements were repeated after 15 min of infusion of amiodarone or DMSO/saline.

In the chronic group, 12 dogs were randomly assigned into two subgroups. Each animal underwent closed-chest baseline VERP and DFT testing on day 1 of the study via transvenous electrodes. After testing on day 1 and throughout the subsequent 29 days, six dogs were administered amiodarone 20 mg/kg/day in divided oral doses (5). In the other six dogs, a placebo was administered instead of amiodarone. On day 30 of the study, the animals again underwent closed-chest electrophysiologic measurements, followed by open-chest mapping of VF. The investigators were blinded to whether the dogs received amiodarone or placebo.

### Amiodarone concentrations.

A 6-ml blood sample was obtained at the end of the study from the chronic amiodarone animals and three control animals. The samples were centrifuged, and serum was frozen at −20°C until analysis. A high performance liquid chromatographic technique was used to quantitate amiodarone (16). The limit of quantification was 0.3 µg/ml.

### Data acquisition.

In the acute group, the 20 s of VF before each DFT determination shock was recorded at baseline and after amiodarone administration. In the chronic group, after all other electrophysiologic tests were completed on day 30, four VF episodes separated by at least 5 min were induced and recorded for 20 s before a rescue shock was given. Unipolar electrograms were amplified, bandpass filtered between 0.5 and 500 Hz and sampled at 2 kHz. Data for 1-s intervals beginning 0 s, 5 s, 10 s, 15 s and 20 s after VF induction and for a 4-s interval beginning 15 s after...
induction were transferred to a computer workstation (Sun Microsystems Inc., Mountain View, California) for analysis.

**Quantitative analysis of VF activation.** The method of analysis of VF activation pattern has been previously described in detail (9,10,17,18). In brief, activation patterns during VF were quantified by first identifying individual wavefronts (17). From the wavefronts, the following 10 descriptors were computed for each 1-s data set:

1. **Number of wavefronts:** The number of wavefronts completely or partially within the mapped region during the 1-s interval (17).
2. **Area swept out by the wavefronts:** The mean number of electrodes that record activation from a wavefront multiplied by the area of the plaque represented by each electrode (4 mm² for our 2-mm interelectrode spacing) (17). When re-entry was present, electrodes were only counted once. Thus, the maximum area that could be swept out by a wavefront was the area of the plaque.
3. **Fractionation incidence:** Fraction of wavefronts that fragment into two or more child wavefronts (17).
4. **Collision incidence:** Fraction of wavefronts that collide and coalesce with one or more other wavefronts (17).
5. **Block incidence:** Fraction of wavefronts that block. Block was identified when a wavefront terminated without fractionating, colliding with other wavefronts or propagating out of the mapped region (17).
6. **Breakthrough or focal incidence:** A wavefront appearing on the epicardium in the mapped region without arising from a fractionation or collision or without propagating in from an edge of the mapped region. This is the logical opposite of block. Such wavefronts have either broken through to the epicardium from deeper layers or have arisen de novo (10).
7. **Repeatability:** A cross-correlation technique was used to sort the wavefronts into clusters. Each cluster represents a distinct activation pathway (18). Repeatability is the average number of wavefronts in each cluster and expresses how many wavefronts traverse each distinct pathway (10).
8. **Overall activation rate:** The mean number of wavefronts passing each epicardial site during the 1-s interval (17).
9. **Negative peak dV/dt of VF activations:** The mean rapidity of the downslope of activation, which may be related to the ability of the activation front to excite adjacent tissue.
10. **Propagation speed of the wavefronts:** The mean speed of the centroids of the wavefronts (10).

Algorithms also automatically identified and quantified sequences of wavefronts that formed at least one cycle of re-entry (9). In this analysis wavefronts are grouped into families consisting of wavefronts connected temporally by fragmentation or collision events. If a family contained a sequence of wavefronts that activated tissue more than once, it was deemed re-entrant. From this analysis we computed three addi-

### Table 1. Defibrillation Thresholds (Voltage) in Chronic and Acute Amiodarone Groups

<table>
<thead>
<tr>
<th></th>
<th>Chronic Amiodarone (n = 12)</th>
<th>Acute Amiodarone (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 6)</td>
<td>Amiodarone (n = 6)</td>
</tr>
<tr>
<td>Baseline</td>
<td>365 ± 60</td>
<td>368 ± 38</td>
</tr>
<tr>
<td>Treatment</td>
<td>366 ± 57</td>
<td>389 ± 54</td>
</tr>
</tbody>
</table>

The mean wavelength was approximated by taking the product of the mean propagation speed of the wavefronts and activation interval. The VF activation interval was defined as the reciprocal of the activation rate. The activation interval is thought to be correlated with the VERP during VF (14).

### Statistical analysis.
Results are expressed as mean ± SD. In both groups, VERP and DFT at baseline and after amiodarone or placebo administration were compared by paired t tests. In the chronic group, the 10 VF descriptors computed by use of 1-s data intervals were compared by three-way multivariate analysis of variance. The main independent variable was animal group (chronic amiodarone or control); episode number and time after VF induction were used as blocking variables. In the acute group, we tested for an overall pre-post amiodarone difference in the VF descriptors for every data epoch using doubly multivariate repeated measures analysis of variance. We further tested for pre-post amiodarone differences in each of these individual parameters by computing the 95% Bonferroni confidence intervals. The three re-entry parameters in both groups were compared by unpaired t tests. For all analyses p ≤0.05 was considered statistically significant.

### Results

**DFT.** In the chronic group, the DFTs were not significantly different between the amiodarone and control sub-
Figure 1. Snapshots of re-entrant activation during ventricular fibrillation (VF) episodes in control (A), acute (B) and chronic amiodarone (C) animals. Each colored pixel is an electrode site at which \( \frac{dV}{dt} < 0.5 \) V/s sometime during the 5-ms interval represented by each frame. The black numbers show the time in milliseconds from the onset of the analysis interval for the corresponding frame 15 s after VF induction. Different colored pixels indicate distinct isolated wavefronts with re-entrant circuits shown in red. The arrows indicate the direction of wavefront movements. The re-entrant wavefronts rotate counterclockwise in A and C and clockwise in B. The core perimeter in A is smaller than in B or C. The wavefronts are more fragmented and complex in A than in B or C.
groups either before or after treatment (Table 1). Similarly, in the acute group, the DFT before and after treatment was not significantly different in either the amiodarone or the control animals.

**VERP.** Chronic amiodarone prolonged the VERP by 28% (Table 2). Acute amiodarone, however, did not significantly change the VERP.

**Quantitative analysis of VF activation patterns.** Examples of VF activation sequences in control, acute and chronic amiodarone animals are shown in Figure 1. Quantitative data from all 1-s intervals are pooled in Tables 3 and 4. There were significant overall multivariate differences between the chronic amiodarone and control groups ($p < 0.001$) and between the recordings before and after acute amiodarone ($p < 0.001$).

**NUMBER OF WAVEFRONTS.** Chronic amiodarone reduced the number of wavefronts by 60% compared with the control group (Table 3), and acute amiodarone reduced the number of wavefronts by 42% compared with baseline (Table 4). Chronic amiodarone reduced the number of wavefronts more than acute amiodarone ($p < 0.05$). There was no significant difference in the number of wavefronts for the control animals before and after intravenous DMSO/saline (vehicle) administration (Table 4).

**AREA SWEPT OUT AND REPEATABILITY.** Chronic and acute amiodarone increased the mean epicardial area swept out by each wavefront by 40% and 45%, respectively. Chronic amiodarone increased repeatability by 43%, while acute amiodarone increased it by 54%.

**BLOCK AND BREAKTHROUGH/FOCAL INCIDENCE.** Block incidence was increased 52% by chronic amiodarone but was decreased 22% by acute amiodarone. The breakthrough/focal incidence was increased 50% by chronic amiodarone but was decreased 21% by acute amiodarone.

**ACTIVATION RATE AND CONDUCTION VELOCITY.** Chronic amiodarone decreased the activation rate and conduction velocity by 30% and 22%, respectively (Table 3). However, acute amiodarone did not significantly change either measure (Table 4).

**FRACTIONATION AND COLLISION INCIDENCE.** Chronic amiodarone significantly reduced the incidence of fractionation and collision by 35% and 47%, respectively, while acute amiodarone did not change either measure.

**RE-ENTRY.** Re-entry incidence was significantly reduced by 57% and 44% for chronic and acute amiodarone, respectively. Chronic and acute amiodarone increased the reentrant core perimeter by 39% and 16% and re-entry cycle length by 45% and 22%.

**WAVELENGTH.** Chronic amiodarone increased the estimated wavelength by 12%, while acute amiodarone did not significantly change it.

**SERUM DRUG CONCENTRATIONS.** Six dogs with chronic amiodarone and three dogs with placebo had serum amiodarone concentrations measured. The mean serum amioda-
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Table 3. Ventricular Fibrillation Activation Pattern Descriptors in Chronic Amiodarone Group

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Amiodarone Group</th>
<th>% Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 6)</td>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of wavefronts</td>
<td>102 ± 45</td>
<td>41 ± 21</td>
<td>60%↓</td>
</tr>
<tr>
<td>Area swept out (mm²)</td>
<td>233 ± 47</td>
<td>326 ± 145</td>
<td>40%↓</td>
</tr>
<tr>
<td>Fractionation incidence</td>
<td>0.17 ± 0.07</td>
<td>0.11 ± 0.07</td>
<td>35%↓</td>
</tr>
<tr>
<td>Collision incidence</td>
<td>0.17 ± 0.06</td>
<td>0.09 ± 0.06</td>
<td>47%↓</td>
</tr>
<tr>
<td>Block incidence</td>
<td>0.21 ± 0.12</td>
<td>0.32 ± 0.14</td>
<td>52%↑</td>
</tr>
<tr>
<td>Breakthrough/focal incidence</td>
<td>0.20 ± 0.13</td>
<td>0.30 ± 0.14</td>
<td>50%↓</td>
</tr>
<tr>
<td>Repeatability</td>
<td>5.1 ± 1.3</td>
<td>7.3 ± 1.8</td>
<td>43%↑</td>
</tr>
<tr>
<td>Activation rate (s⁻¹)</td>
<td>8.3 ± 2.2</td>
<td>5.8 ± 1.7</td>
<td>30%↓</td>
</tr>
<tr>
<td>Peak −dV/dt (V/s)</td>
<td>−3.52 ± 1.89</td>
<td>−1.85 ± 0.45</td>
<td>47%↓</td>
</tr>
<tr>
<td>Speed (m/s)</td>
<td>0.54 ± 0.1</td>
<td>0.42 ± 0.18</td>
<td>22%↓</td>
</tr>
<tr>
<td>Reentry incidence</td>
<td>0.076 ± 0.06</td>
<td>0.033 ± 0.05</td>
<td>57%↓</td>
</tr>
<tr>
<td>Number of re-entry cycles</td>
<td>1.88 ± 1.34</td>
<td>1.25 ± 0.56</td>
<td>34%↓</td>
</tr>
<tr>
<td>Reentry perimeter (mm)</td>
<td>44 ± 23</td>
<td>61 ± 31</td>
<td>39%↑</td>
</tr>
<tr>
<td>Wavelength (mm)</td>
<td>65 ± 9</td>
<td>73 ± 10</td>
<td>12%↑</td>
</tr>
</tbody>
</table>

Table 4. Ventricular Fibrillation Activation Pattern Descriptors in Intravenous Amiodarone Group

<table>
<thead>
<tr>
<th>Control Group (n = 6)</th>
<th>Amiodarone Group (n = 6)</th>
<th>% Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of wavefronts</td>
<td>101 ± 42</td>
<td>96 ± 42</td>
<td>5%↓</td>
</tr>
<tr>
<td>Area swept out (mm²)</td>
<td>229 ± 47</td>
<td>240 ± 45</td>
<td>5%↑</td>
</tr>
<tr>
<td>Fractionation incidence</td>
<td>0.16 ± 0.06</td>
<td>0.17 ± 0.06</td>
<td>6%↑</td>
</tr>
<tr>
<td>Collision incidence</td>
<td>0.18 ± 0.05</td>
<td>0.17 ± 0.06</td>
<td>6%↓</td>
</tr>
<tr>
<td>Block incidence</td>
<td>0.21 ± 0.11</td>
<td>0.19 ± 0.1</td>
<td>10%↓</td>
</tr>
<tr>
<td>Breakthrough/focal incidence</td>
<td>0.21 ± 0.11</td>
<td>0.21 ± 0.13</td>
<td>0%</td>
</tr>
<tr>
<td>Repeatability</td>
<td>4.8 ± 1.1</td>
<td>5.2 ± 1.4</td>
<td>8%↓</td>
</tr>
<tr>
<td>Activation rate (s⁻¹)</td>
<td>8.1 ± 1.9</td>
<td>8.1 ± 2.4</td>
<td>0%</td>
</tr>
<tr>
<td>Peak −dV/dt (V/s)</td>
<td>−3.47 ± 1.5</td>
<td>−3.29 ± 1.4</td>
<td>5%↓</td>
</tr>
<tr>
<td>Speed (m/s)</td>
<td>0.54 ± 0.07</td>
<td>0.55 ± 0.07</td>
<td>2%↑</td>
</tr>
<tr>
<td>Reentry incidence</td>
<td>0.071 ± 0.05</td>
<td>0.068 ± 0.06</td>
<td>4%↓</td>
</tr>
<tr>
<td>Number of re-entry cycles</td>
<td>1.93 ± 1.36</td>
<td>1.96 ± 1.77</td>
<td>2%↑</td>
</tr>
<tr>
<td>Re-entry perimeter (mm)</td>
<td>41 ± 21</td>
<td>42 ± 18</td>
<td>2%↑</td>
</tr>
<tr>
<td>Wavelength (mm)</td>
<td>67 ± 12</td>
<td>68 ± 13</td>
<td>1%↑</td>
</tr>
</tbody>
</table>

NS = nonsignificant.
lished. Consistent with those studies, we found significant changes in all of the electrophysiologic variables we examined for chronic amiodarone, but significant changes occurred in less than half these variables for acute amiodarone. For example, VERP and VF cycle length were prolonged with chronic amiodarone but not with acute amiodarone.

Both chronic and acute amiodarone administration reduced the number of VF activation wavefronts, increased the area activated by each wavefront and increased the repeatability of the activation sequences. However, chronic amiodarone decreased the incidence of fractionation and collision and increased the incidence of conduction block and of the breakthrough/focus pattern, while acute amiodarone decreased the incidence of conduction block and of the breakthrough/focal pattern without significantly changing the other two variables.

Many of the changes caused by chronic amiodarone may be explained by its prolongation of the refractory period. This includes the decreased activation rate and the decreased number of wavefronts during VF. There are two possible explanations for the increased incidence of epicardial breakthrough after chronic amiodarone: first, increased focal origin of wavefronts and, second, increased transmural orientation of wavefronts arising by re-entry. Amiodarone has been shown to inhibit abnormal automaticity of both Purkinje fibers and ventricular myocardium (26,27). Recent studies demonstrate that chronic amiodarone reduces the dispersion of repolarization both in human and animal hearts by decreasing M cell action potential duration (28,29). The reduction of transmural heterogeneity of repolarization may facilitate transmural wavefront propagation. A wavefront that appears to “block” from epicardial mapping recordings may turn perpendicular to the epicardial surface and propagate deep towards the endocardium. So the second explanation is more likely than the first. If so, the increased incidence of block on the epicardium after chronic amiodarone is also consistent with an increase in transmural orientation of wavefronts.

Acute amiodarone, which is also antiarrhythmic (24), did not lengthen the refractory period nor change many of the measured variables as did chronic amiodarone. Yet, acute amiodarone increased the organization of VF by several measures including a decreased number of wavefronts, an increased area of epicardium activated by each wavefront, an increased repeatability of activation sequences and a decreased incidence of conduction block. Acute amiodarone has been shown to flatten the slope of the restitution curve (30), which may explain these findings during VF. The restitution hypothesis of VF states that the slope of the action potential duration (APD) restitution curve, in which APD is plotted against the preceding diastolic interval (DI), is the main determinant of wave break (31). When the slope of this curve is steep (>1) over a sufficient range of DIs, small perturbations in DI will be amplified into larger differences in APD. These APD differences create larger differences in the following DI. If this oscillation in APD grows large enough, action potential failure occurs, causing wave break (32). No data are available about how chronic amiodarone, which increased the incidence of conduction block, affects the restitution properties of myocardium. However, other electrophysiologic properties, which are likely to be affected by drugs such as conduction velocity or cell coupling, also contribute to the development and maintenance of VF (32,33).

The effects of acute and chronic amiodarone on re-entry during VF. While VF is almost universally thought to be maintained by re-entry (34), only 2% to 8% of wavefronts have been identified as parts of re-entry circuits (9,35,36). Whether VF is maintained by multiple wavelets (37,38) or a single “mother” rotor (35), wavelength prolongation (39) or prevention of conduction block (40) may explain the mechanisms of most drugs’ antifibrillatory actions. The number of wavefronts is thought to decrease as the wavelength increases, making it more likely that VF will not be maintained (39). However, some drugs with marked antiarrhythmic effects do not prolong wavelength (40). For example, one of these drugs, procainamide, has been shown to prevent conduction block and reduce the number of VF wavefronts (40), which is assumed to inhibit VF maintenance. This assumption is supported by clinical data (41) demonstrating that procainamide converts polymorphic ventricular tachycardia or VF to monomorphic ventricular tachycardia. Recently, widening of the excitable gap has been proposed to explain the mechanism of antifibrillation drugs for atrial fibrillation (42). Widening of the excitable gap will lower the chance that fibrillation wavefronts encounter areas of partially refractory tissue. As a result, slowing of conduction and fractionation of wavefronts will occur less frequently, and fibrillation may not be maintained.

We found that both acute intravenous and chronic oral amiodarone markedly decreased the incidence of re-entry during VF, but by different mechanisms. With chronic amiodarone, the increased VERP and decreased VF activation rate suggest that wavelength was prolonged. The increased wavelength also may be responsible for the increased perimeter of the core of the re-entrant circuits after chronic amiodarone.

After acute amiodarone administration, the absence of significant changes in VERP, VF rate and conduction velocity suggests that the wavelength was unchanged. Thus, an increased wavelength is not always needed for VF to show an increased organization by several measures including decreased incidence of re-entry, increased perimeter of re-entry cores, decreased re-entry cycle length, decreased number of wavefronts, increased area activated by each wavefront, repeatability of activation sequences, decreased incidence of conduction block and decreased incidence of a breakthrough/focal activation pattern. It is possible that these changes were caused by an increased excitable gap (42) and/or a decrease in the slope of the restitution curve (32).
Study limitations. One limitation of the study is that only normal healthy dogs were studied. Most patients with arrhythmias have organic heart disease, which can affect the patterns of activation during VF (12). It is unclear whether the different effects of acute and chronic amiodarone are directly applicable to VF in patients with heart disease. A second limitation is that we studied only one dosage of amiodarone in each group and only one treatment duration in the chronic group. Because the action of amiodarone is concentration- and time-dependent (43,44), studies with different drug concentrations and different time periods are needed. A third limitation is that transmural recordings were not made. Such recordings are needed to determine if the findings on the epicardium are similar to those of the endocardium and midwall. A fourth limitation is that we used indirect methods to estimate the refractory period and wavelength during VF (VERP during pacing and activation rate during VF) that do not account for differences in the restitution curve or the excitable gap with and without amiodarone. Optical or mean atrial pressure recordings can provide more direct information.

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