Length of Excitation Wave and Susceptibility to Reentrant Atrial Arrhythmias in Normal Conscious Dogs

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We calculated the wavelength of the atrial impulse in chronically instrumented conscious dogs by measuring both conduction velocity and refractory period: wavelength = refractory period x conduction velocity. Implantation of multiple stimulating and recording electrodes allowed wavelength determination at four different areas: the right and left parts of Bachmann's bundle and the free walls of the right and left atria. During programmed electrical stimulation, three types of arrhythmias were observed: rapid repetitive responses, atrial flutter, and atrial fibrillation. During normal rhythm, the wavelength of the atrial impulse varied between 14 and 18 cm. Premature beats had a shorter wavelength, depending on the degree of prematurity. Premature beats that evoked rapid repetitive responses showed a critical shortening of the wavelength below 12.3 cm. Episodes of atrial flutter were induced at a wavelength below 9.7 cm, while fibrillation occurred at wavelengths shorter than 7.8 cm. We correlated the induction of these arrhythmias with the values of refractory period, conduction velocity, and wavelength during control and during administration of several drugs. Intravenous administration of acetylcholine shortened the wavelength by 30–40%, mainly because of refractory period shortening. Both propafenone and lidocaine had strong but opposite effects on refractoriness and conduction and, consequently, little effect on the wavelength. Quinidine markedly prolonged the refractory period, but prolongation of wavelength was less because of a simultaneous decrease in conduction velocity. d-Sotalol also increased refractory period, but because it had no appreciable effect on conduction velocity, this drug was the most effective in prolongation of wavelength. Linear discriminant analysis of the data showed that the refractory period and the conduction velocity each were poor parameters to predict the occurrence of the different arrhythmias (predictive value 48% and 38%, respectively). The combination of both properties, however, as expressed in the wavelength, was a more reliable index that predicted the induction of the different arrhythmias correctly in 75% of the cases. We conclude that the wavelength is a useful parameter for evaluating antiarrhythmic drugs. (Circulation Research 1988;62:395–410)

There is increasing evidence that rapid atrial arrhythmias, like short runs of rapid repetitive responses (RRR), atrial flutter (AFI), and atrial fibrillation (AFib) are based on intra-atrial reentry. However, it is not clear to what extent the anatomical and electrophysiological properties of the atrium contribute to the occurrence of these arrhythmias. Heterogeneity of structural and electrophysiological properties are thought to play a major role in the initiation of reentry because of the increased likelihood of unidirectional block of premature impulse. In canine models, it was found that both artificial and natural atrial lesions clearly favor the induction and perpetuation of AFI. Also, the microarchitecture and anisotropic properties are reported to play an important role by causing inhomogeneous and discontinuous propagation of the impulse. These structural inhomogeneities may, together with spatial dispersion in electrophysiological properties like refractory period, excitability, and stimulating efficacy of the depolarization wave, lead to local conduction block of a premature impulse.

Apart from the occurrence of local conduction block, a second requirement must be fulfilled for the induction of reentry. The conduction time of the impulse traveling around the area of block must be long enough to allow the fibers proximal to the line of block to restore their excitability. Or, as Mines pointed out, "a closed circuit of muscle of considerably greater length than the excitation wave must be available around the area of unidirectional block." The significance of the wavelength for circus movement in the heart has been explicitly discussed by Lewis and later mathematically formulated by Wiener and Rosenblueth as the distance traveled by the depolarization wave during the duration of the refractory period (wavelength = conduction velocity x refractory period). When the wavelength of a premature impulse is long, a large area of conduction block is required. However, when the length of a premature impulse is short — either by depressed conduction or shortened refractoriness — small areas of conduction block may already set up reentrant circuits. Because conduction block is more likely to occur in small areas than in a...
large portion of the myocardium, it is to be expected that the inducibility of reentrant arrhythmias is also dependent on the wavelength of the cardiac impulse.

Not only the chance of induction but also the nature of the resulting arrhythmia seems to be related to the wavelength of the circulating impulse. If the wavelength is long, a stable reentrant rhythm cannot develop in the available myocardium, and only short runs of reentrant responses might occur. At a shorter wavelength, a single and stable reentrant circuit could be established, leading to AF1. When the wavelength is further shortened, multiple reentering wavelets may start to wander through the available tissue, resulting in AFib. Fibrillation is a self-perpetuating rhythm if a critical number of reentering wavelets are present. If the wavelength is relatively long and only a few waves circulate through the heart, fibrillation will be short lasting. If, however, the wavelength is short, fibrillation will not only be easy to induce but, because of the presence of a large number of wavelets, will also tend to be stable and long lasting.

Recently, a method has been described to measure the wavelength of basic and premature impulses in an in vitro atrial preparation. The aim of the present study was to use this technique in chronically instrumented awake dogs and to directly correlate changes in wavelength to the inducibility of atrial arrhythmias. A number of arrhythmogenic and antiarrhythmic drugs were studied with varying effects on atrial refractory period and conduction velocity. We found that in normal dogs, the induction of RRR, AF1, and AFib was closely related to the wavelength of the initiating premature impulse. Under a wide range of circumstances, the wavelength of the atrial impulse was a consistent electrophysiological index of the susceptibility to atrial arrhythmias (predictive value 75%). We suggest that measurement of the wavelength of the cardiac impulse may be used to evaluate the effects of antiarrhythmic drugs on the susceptibility to reentrant arrhythmias.

Materials and Methods

Nineteen dogs of both sexes, weighing between 30 and 40 kg, were used for this study. After premedication with Hypnorm (0.4 ml/kg i.m.) (1 ml Hypnorm contains 10 mg fluanison and 0.2 mg fentanylbase), the dogs were anesthetized with sodium pentobarbital (15 mg/kg) and ventilated with a 2:1 mixture of oxygen and nitrous oxide. The heart was exposed by a left intercostal incision between the fourth and the fifth ribs, and the pericardium was opened. Two sets of multiple electrodes were placed just proximal to first recording electrodes. Because electrograms recorded at corresponding electrodes occurred almost simultaneously, the impulse propagated parallel to long axis of electrode. Conduction was also uniform because differences in conduction time between neighboring electrodes are similar. Therefore, conduction velocity of impulse may be calculated from conduction time and distance (56 mm) between proximal and distal recording electrodes. Wavelength (given by product of refractory period and conduction velocity) of regular beat was 124 m/sec x 56 mm/46 m/sec = 15 cm. Wavelength of earliest premature beat measured 99 m/sec x 56 mm/68 msec = 8 cm.
Induction of Arrhythmias

After a couple of days, when the dogs had recovered from surgery and were accustomed to the laboratory environment, measurements were made over several hours with the dogs lying quietly on the floor. The amplitude of the recorded electrograms and the thresholds for stimulation allowed measurements to be taken over a period of more than 2 months. During this period, atrial arrhythmias could be frequently induced by the application of single premature stimuli. We distinguished three types of arrhythmias: 1) RRR, a series of no more than five spontaneous premature beats with a cycle length shorter than 150 msec; 2) AFI, a regular rapid rhythm of more than five beats with monomorphic electrograms and a cycle length between 90 and 150 msec; and 3) Afib, an irregular and extremely rapid rhythm with polymorphic electrograms and a totally irregular ventricular response.

Cardiac Drugs

The effects of acetylcholine (Dispersa AG, Mijdrecht, The Netherlands; 0.02 mg/kg/min infused continuously), atropine (ACF Chemiefarma, Amsterdam, The Netherlands; 0.2 mg/kg), isoproterenol (Dispersa AG, 0.5 µg/kg/min), propanolol (ICI Farma, Rotterdam, The Netherlands; 0.3 mg/kg), lidocaine (Xylocaine [Astra, Södertälje, Sweden], bolus injection of 100 mg followed by 0.6 mg/kg/min), ouabain (ACF Chemiefarma, bolus of 20 µg/kg followed by 0.036 µg/kg/min), quinidine sulphate (ACF Chemiefarma, 10 mg/kg), d-sotalol (Bristol-Myers, Zwabenberg, The Netherlands; 8 mg/kg), and propafenone (Rytmonorm [Knoll, Almere, The Netherlands], 4 mg/kg) were studied. All drugs were administered through a catheter in the left atrium. In addition, changes in autonomic tone were studied by comparing measurements while the dogs were asleep and while exercising them on a treadmill (5 km/hr). Although the activity of the vagal nerves was not directly monitored, a high vagal state was assessed qualitatively by a slow irregular sinus rhythm and prolonged atrioventricular conduction.

Immediately after injecting drugs, changes in refractory period and conduction velocity were monitored. The actual measurements were made after the electrophysiological variables had become stable again. The time required to reach a steady state varied for different drugs from less than 1 minute (acetylcholine) to half an hour (quinidine and propafenone). In each dog, the effects of the different drugs were measured several times during the 2-month period. There was no marked variation in the separate tests. For statistical analysis, the average values measured during control and the various interventions were grouped together. Results are given as the mean ± SEM found in the different animals. The statistical significance of differences between groups was determined by Student’s t test. Linear discriminant analysis was used to determine the predictive power, sensitivity, and specificity of refractory period, conduction velocity, and wavelength for the induction of RRR, AFI, and Afib. On the basis of the calculated discriminant functions, critical values of the wavelength for the induction of these arrhythmias could also be determined.

Results

Effects of Rate and Rhythm

It is known from clinical programmed electrical stimulation that both early premature beats and a high heart rate enhance the chances of induction of atrial arrhythmias. We determined the effects of different...
pacing rates on the electrophysiological properties of the atria in 19 dogs. The relation between the pacing interval and the refractory period, conduction velocity, and wavelength as measured in Bachmann's bundle is plotted in Figure 2, left panel. At a moderate pacing rate (interval 350 msec), refractory period was 114 ± 7 msec, conduction velocity was 127 ± 10 cm/sec, and wavelength was 14.5 ± 1.7 cm. When the pacing interval was shortened from 350 to 200 msec, there was no appreciable change in any of the three parameters. Further decrease of the pacing interval resulted in a gradual and progressive decrease in refractory period, conduction velocity, and wavelength. At the shortest possible pacing interval (110 msec), refractory period had shortened to 89 ± 5 msec and conduction velocity to 89 ± 14 cm/sec. As a result, the wavelength was shortened by 46% to 7.9 ± 1.2 cm.

The effects of single premature beats during regular pacing with a cycle length of 350 msec are shown in the right panel of Figure 2. Late premature beats did not affect any of the parameters. At coupling intervals shorter than 250 msec, the refractory period decreased progressively from 114 ± 7 to 80 ± 4 msec (30%). Also, the conduction velocity showed a progressive decrease from 127 ± 10 to 82 ± 6 cm/sec (35%). Because of this combined decrease in refractoriness and conduction velocity, the wavelength of the earliest coupled impulse shortened gradually to 6.6 ± 0.5 cm (55%). It should be noted that the average values obtained from 19 dogs do not show supernormal conduction of premature impulses. The phenomenon of supernormal conduction, which has been observed in both human and canine atrium,25-27 was absent in the majority of our cases. In only four dogs was some degree of supernormal conduction seen in either Bachmann's bundle or the free wall of the right or left atrium. In these cases, conduction velocity of premature impulses with a coupling interval of about 200 msec was slightly (5-10%) faster than propagation of the regular impulses; this did not lead to a statistically significant increase in conduction velocity of late premature beats for the whole population of dogs.

Spatial Dispersion in Wavelength

The value of the wavelength cannot be expected to be uniform throughout the atrium. Local differences in refractoriness and conduction velocity will also lead to spatial dispersion in the wavelength. In Figure 3, the effects of premature beats in four major regions of the atria are plotted. Table 1 gives the local differences in electrophysiological properties during regular pacing (350-msec cycle length), the earliest premature beats, and pacing at a maximal pacing rate (110-130-msec interval). The refractory period in the left atrium was always shorter than in the right atrium. During regular rhythm, refractory period varied from 111 msec in the

![Figure 2](http://circres.ahajournals.org/)

**FIGURE 2.** Left panel: Mean and standard deviation (n = 13) of refractory period, conduction velocity, and wavelength as function of pacing interval as measured in left part of Bachmann's bundle. Shortening of pacing interval from 350 to 200 msec had no significant effect on the three variables. A further decrease of pacing interval led to progressive shortening of both refractory period and conduction velocity, resulting in wavelength shortening from 14.5 to 7.9 cm. Right panel: Effect of degree of prematurity of extrasystoles on refractory period, conduction velocity, and wavelength (left part of Bachmann's bundle, n = 18) is plotted. Premature beats with coupling intervals longer than 250 msec did not alter these variables. Further shortening of coupling interval resulted in progressive shortening of wavelength from 14.5 to 6.6 cm due to a combined decrease in refractoriness and conduction velocity.
free wall of the left atrium to 133 msec in the right part of Bachmann’s bundle \( (p<0.001) \). During the earliest premature beat, refractoriness of the left part of Bachmann’s bundle averaged 80 msec as opposed to 99 msec in the right part of Bachmann’s bundle \( (p<0.001) \). Also during rapid pacing, a statistically significant difference in refractory period was found \( (p<0.001) \) between these different parts of the atrium. During slow regular rhythm, conduction velocity did not show significant differences between any of the four locations. However, during premature beats and maximal pacing, spatial differences in conduction velocity became apparent. Spatial differences in conduction velocity were greatest between the left and right parts of Bachmann’s bundle \( (p<0.001) \). Figure 4 shows electrograms recorded along the bundle of Bachmann during a basic and an early premature beat. In the upper panel, the bundle was activated from right to left (stimulating electrodes at the tip of the right appendage). In the lower panel, the activation was from left to right (pacing of left appendage). Conduction of the basic impulse was uniform and similar in either direction (conduction velocity 138 and 133 cm/sec). However, during the propagation of premature impulses, conduction was considerably slower in a left-to-right than a right-to-left direction \( (79 versus 109 \text{ cm/sec}) \).

As a consequence of local differences in refractoriness and conduction velocity, the wavelength varied in different parts of the atria. During a normal rhythm, wavelength ranged from 14.5 cm \( (\text{the left part of Bachmann’s bundle}) \) to 17.7 cm \( (\text{the right part of Bachmann’s bundle}) \) \( (p<0.001) \). During early premature beats, spatial differences in wavelength were more pronounced. The shortest wavelength again was found at the left part of Bachmann’s bundle \( (6.6 \text{ cm}) \). In the free wall of the right atrium, the wavelength of a premature beat was 7.6 cm; in the free wall of the left atrium, it was 7.7 cm. The longest wavelength \( (10.7 \text{ cm}) \) was found in the right part of the bundle of Bachmann \( (p<0.001) \). During rapid pacing, the wavelength varied between 7.9 cm at the left part of Bachmann’s bundle to 12.3 cm at the right part of Bachmann’s bundle \( (p<0.001) \).

**Effects of Autonomic Transmitters**

The autonomic nervous system is known to modulate the electrophysiological status of the atria. To measure the effects of changes in autonomic tone on the wavelength of the atrial impulses, we studied the influence of acetylcholine, atropine, isoproterenol, propranolol, and treadmill exercise. In Figure 5 and Table 2, the action of acetylcholine and atropine on the wavelength of premature beats in the left part of Bachmann’s bundle is given. Administration of acetylcholine \( (0.02 \text{ mg/kg/min}) \) substantially reduced the refractory period during regular pacing without affecting conduction velocity, resulting in a shortening of the wavelength from 14.5 to 10.2 cm. Vagal blockade by administration of atropine \( (0.2 \text{ mg/kg}) \) had an opposite effect.

![Figure 3. Effects of premature beats on wavelength in four different areas of the atrium: •, right part of Bachmann’s bundle \( (n = 15 \text{ dogs}) \); ●, left part of Bachmann’s bundle \( (n = 18) \); ▽, free wall of the right atrium \( (n = 15) \); ★, free wall of the left atrium \( (n = 4) \). At all sites, increasing prematurity of extrasystoles caused progressive shortening of wavelength. Local differences in wavelength during normal rhythm (350-msec interval) varied from 14.5 to 17.7 cm. During early premature impulses, wavelength ranged from 6.6 to 10.7 cm.](image-url)

**Table 1. Effects of Variations in Rate and Rhythm on Refractory Period, Conduction Velocity, and Wavelength at Four Different Atrial Areas**

<table>
<thead>
<tr>
<th>Atrial Areas</th>
<th>Regular rhythm</th>
<th></th>
<th>Earliest premature beat</th>
<th></th>
<th>Maximal pacing rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>( \text{RP} ) (msec)</td>
<td>( \text{CV} ) (cm/sec)</td>
<td>( \text{WL} ) (cm)</td>
<td>( \text{RP} ) (msec)</td>
<td>( \text{CV} ) (cm/sec)</td>
</tr>
<tr>
<td>BB Left</td>
<td>18</td>
<td>114±7</td>
<td>127±10</td>
<td>14.5±1.7</td>
<td>80±7</td>
<td>82±6</td>
</tr>
<tr>
<td>BB Right</td>
<td>15</td>
<td>133±7*</td>
<td>133±12</td>
<td>17.7±1.7*</td>
<td>99±7*</td>
<td>107±13*</td>
</tr>
<tr>
<td>FW Right</td>
<td>15</td>
<td>124±9‡</td>
<td>123±13</td>
<td>15.2±1.5</td>
<td>92±7*</td>
<td>83±8</td>
</tr>
<tr>
<td>FW Left</td>
<td>4</td>
<td>111±7</td>
<td>132±9</td>
<td>14.7±1.9</td>
<td>81±6</td>
<td>95±7‡</td>
</tr>
</tbody>
</table>

\*\( p<0.001 \) compared to BB Left values; †\( p<0.01 \); ‡\( p<0.05 \).
Figure 4. Conduction of regular and early premature beats (EPB) along Bachmann’s bundle during pacing at right (upper panel) or left auricle (lower panel). Recordings of one of two rows of electrodes on bundle are shown (interelectrode distance 12 mm). In both directions, basic impulse is propagated uniformly and at the same speed. Conduction of earliest premature beat, although still uniform, is much slower in left-to-right (79 cm/sec) than in right-to-left direction (109 cm/sec).

Effect and resulted in an increase of the refractory period and a concomitant lengthening of the basic excitation wave. The shortest possible wavelength that could be attained by premature impulses was also greatly influenced by the parasympathetic nervous system. During control, the wavelength of the earliest premature beat was 6.6 cm. Under the influence of acetylcholine, a wavelength of 5.3 cm was the shortest measured; during administration of atropine, the wavelength was not shorter than 7.7 cm.

Treadmill exercise (5 km/hr) prolonged atrial refractoriness resulting in a shortest wavelength of 7.3 cm. In contrast to the important influence of parasympathetic activity on the electrophysiological properties of the atrium, variations in sympathetic tone had much less effect. As shown in Table 2, isoproterenol caused only a slight reduction of the shortest wavelength from 6.6 to 6.3 cm due to some shortening of the refractory period. Blockade of sympathetic activity by propranolol (0.3 mg/kg) had no effect on any of the measured electrophysiological variables.

To test whether the influence of the autonomic nervous system on inducibility of atrial arrhythmias was related to changes in spatial dispersion of refractory periods, we measured the refractory period at 22 different sites located at the free wall of the right and left atria and along Bachmann’s bundle. Figure 6 shows the effects of various autonomic states on the distribution of refractory periods in the atria. In the absence of any autonomic activity after blockade by atropine and propranolol (Figure 6A), there were marked differences in refractory period in different parts of the atria. This intrinsic refractoriness showed only slight variations in the free wall of the right atrium; the difference between the shortest and longest refractory period was no more than 6 msec (156-162 msec). However, in all dogs, a consistent shortening of the local refractory period was found along the bundle of

Table 2. Effects of Autonomic Nervous System on Refractory Period, Conduction Velocity, and Wavelength at Left Part of Bachmann’s Bundle

<table>
<thead>
<tr>
<th>Condition</th>
<th>Regular rhythm</th>
<th>Earlyest premature beat</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>RP (msec)</td>
<td>CV (cm/sec)</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>114±7</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>18</td>
<td>80±11*</td>
</tr>
<tr>
<td>Atropine</td>
<td>11</td>
<td>129±11*</td>
</tr>
<tr>
<td>Treadmill</td>
<td>8</td>
<td>119±12</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>5</td>
<td>110±10</td>
</tr>
<tr>
<td>Propranolol</td>
<td>6</td>
<td>113±8</td>
</tr>
</tbody>
</table>

RP, refractory period; CV, conduction velocity; WL, wavelength.

*p<0.001; †p<0.01; ‡p<0.05.
The fact that refractory period shortened more in areas with a long intrinsic refractory period (right atrium) than in parts with an already short intrinsic refractory period (left atrium). This is clearly reflected by the histograms in the right side of Figure 6. Increasing vagal activity or administration of acetylcholine not only shifted the histograms to the left but also narrowed their range. In Table 3, the values of the refractory period during total autonomic blockade are listed from high to low values, and the absolute and relative degree of refractory period shortening by vagal activity and administration of acetylcholine are given. It is clear that a high vagal tone decreases the refractory period in the right atrial free wall by 20–24% and in Bachmann’s bundle by only 11–15% (p<0.001), while the free wall of the left atrium exhibits a refractory period shortening of only 4–11% (p<0.001). In contrast, the effect of direct administration of acetylcholine did not vary in different parts of the atria, and the refractory period was uniformly shortened by 41–50% (p>0.05).

Effects of Propafenone, Lidocaine, Quinidine, d-Sotalol, and Ouabain

In Figure 7 and Table 4, the effects of propafenone, lidocaine, quinidine, and d-sotalol on the left part of Bachmann’s bundle are given. All drugs significantly prolonged atrial refractoriness (29–41%) for regular atrial free wall. During treadmill exercise (Figure 6B), the maximal difference in refractory period between the right and left atria was less than during autonomic blockade and amounted to 26 msec (119–145 msec). When the dogs were asleep and under the influence of a high vagal tone (Figure 6C), a maximal difference of 26 msec (107–133 msec) was found during regular pacing. Administration of acetylcholine (Figure 6D) resulted in a strong overall decrease in refractory period, the greatest difference between the right and the left atria being 33 msec (60–93 msec). This decrease in spatial dispersion in refractory periods by autonomic activity is caused by the fact that refractory period shortened more in areas with a long intrinsic refractory period (right atrium) than in parts with an already short intrinsic refractory period (left atrium). This is clearly reflected by the histograms in the right side of Figure 6. Increasing
correlated with the induction of the various arrhythmias. In total, 549 episodes of atrial arrhythmias were induced in 19 dogs (RRR, n = 223; AF1, n = 118; AFib, n = 208). In Figure 10, cumulative histograms of the induction of arrhythmias during control and the administration of seven different drugs (acetylcholine, propafenone, lidocaine, ouabain, quinidine, and d-sotalol) are plotted in relation to the refractory period (upper panel), conduction velocity (middle panel), and wavelength (lower panel). Although at shorter refractory periods a relatively higher incidence of AFib was observed (upper panel), prolongation of the refractory period did not prevent the induction of arrhythmias. AFib, AF1, and RRR were inducible at a wide range of wavelength values, and at a certain refractory period, any type of atrial response to the test stimulus could be expected. Also, the predictive power of the conduction velocity for induction of arrhythmias was low (middle panel). Again, at most values of conduction velocity, any of the four types of responses could be found.

The histograms correlating induction of atrial arrhythmias to the wavelength of the atrial impulse (lower panel) showed a clearly different picture. Although the different arrhythmias were still not completely separated by wavelength into four individual subpopulations, the degree of overlap of the subgroups was far less compared with the histograms of refractory period and conduction velocity. When the wavelength of the atrial impulse was long, no arrhythmias occurred. When the wavelength got progressively shorter, first RRR, then AF1, and finally AFib was observed. By linear discriminant analysis, optimal cutoff points between the four subpopulations were calculated, which can be regarded as critical wavelength values for the inducibility of the three different types of arrhythmias. These critical values are indicated by arrows. For the induction of RRR, a critical wavelength of 12.3 cm was found. For AF1, the critical wavelength was 9.7 cm, and AFib was induced at wavelengths shorter than 7.8 cm.

In Table 5, the predictive power, sensitivity, and specificity of refractory period, conduction velocity, and wavelength for the induction of the different arrhythmias are given. The results clearly show that the wavelength is the best predictor for the induction of arrhythmias (correct classification 65–82%). Both conduction velocity and refractory period had a much lower predictive value (15–79% and 9–57%, respectively). In a total of 750 responses observed in 19 dogs, during both control and the administration of seven different drugs, the overall correct prediction of the wavelength was 75%, compared with 48% and 38% for refractory period and conduction velocity, respectively. Wavelength was also the most sensitive (88–100%) and most specific (80–96%) index for the inducibility of arrhythmias. In Figure 11, the critical values of refractory period, conduction velocity, and wavelength for the induction of the three different arrhythmias are plotted during control and the administration of various drugs. The critical values of both refractory period and conduction velocity varied widely under these different circumstances. In contrast, the critical value of wavelength (lower panel) was markedly constant despite the strong

changes in electrophysiological properties exerted by the different drugs. Administration of quinidine (10 mg/kg) prolonged the shortest possible wavelength of premature beats to 9.1 cm. At this wavelength, AFib could no longer be induced. d-Sotalol (8 mg/kg) prolonged the shortest wavelength to 9.6 cm; this drug completely prevented the induction of both AFI and AFib.

Figure 12 directly illustrates the correlation between the electrophysiological properties of the atrium and the induction of arrhythmias. Refractory period is plotted on the x-axis and conduction velocity on the y-axis. Since wavelength is given by the product of refractory period and conduction velocity, isowavelength curves can also be drawn (Figure 12A). In Figure 12B, all individual responses (no arrhythmias, RRR, AFI, and AFib; n = 750) as observed during control and the administration of several drugs are plotted. In Figures 12C–F, the different responses are plotted separately. Figure 12C gives the cases in which no arrhythmias were induced together with the calculated critical wavelength for the induction of RRR (12.3 cm). In Figure 12D, RRR is plotted; the critical wavelength zone for induction of RRR lies between 12.3 and 9.7 cm. Similarly, for AFI (Figure 12E), there was a narrow wavelength range in which this arrhythmia occurred (9.7–7.8 cm). AFib almost invariably was induced when the wavelength of the provoking impulse became shorter than 7.8 cm. This figure shows that in the awake dog, under a wide variety of circumstances and a wide range of refractory period and conduction velocity values, there exists a specific bandwidth of the length of the atrial impulse at which specific atrial arrhythmias are induced.

Discussion
Wavelength as Index for Reentrant Arrhythmias

This study shows that the length of the atrial excitation wave is an important determinant for the induction of atrial arrhythmias. In 19 chronically instrumented awake dogs studied during a period of more than two months, more than 500 episodes of atrial tachyarrhythmias (RRR, AFI, and AFib) were induced. The influence of the autonomic nervous system and several cardiac drugs (quinidine, lidocaine, ouabain, d-sotalol, and propafenone) were studied regarding both basic electrophysiological properties and the inducibility of atrial arrhythmias. The duration of the refractory period of the myocardium is widely recognized to be an important parameter for the vulnerability to AFib. This has led to the common opinion that agents that prolong refractoriness have antiarrhythmic properties. In our studies, we showed that under some circumstances, such as the administration of acetylcholine or the presence of a high vagal tone, shortening of refractoriness clearly favored the induction of atrial tachyarrhythmias. Similarly, some drugs that prolonged the refractory period, such as quinidine and d-sotalol, exhibited a definite antiarrhythmic ef-

FIGURE 10. Cumulative histograms of occurrence of no arrhythmias (No Arr), rapid repetitive responses (RRR), atrial flutter (AFI), and atrial fibrillation (AFib) in relation to refractory period, conduction velocity, and wavelength of early premature beats during control and administration of various drugs (see text). Height of each bar represents total number of observations; different shadings indicate different types of responses. Optimal cutoff points of wavelength as computed by discriminant analysis are indicated by arrows. See text for further description.
Table 5. Predictive Value, Sensitivity, and Specificity of Refractory Period, Conduction Velocity, and Wavelength for Induction of Different Atrial Arrhythmias

<table>
<thead>
<tr>
<th>Number of arrhythmias</th>
<th>Refractory period</th>
<th>Conduction velocity</th>
<th>Wavelength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PV (%)</td>
<td>Sens (%)</td>
<td>Spec (%)</td>
</tr>
<tr>
<td>201</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>223</td>
<td>17</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>118</td>
<td>15</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>208</td>
<td>79</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Overall predictive value</td>
<td>750</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

PV, predictive value; Sens, sensitivity; Spec, specificity.

flect. However, on other occasions (administration of lidocaine or propafenone), a clear prolongation of the refractory period did not result in a diminishment of episodes of atrial arrhythmias. In all of our experiments, the overall predictive power of the refractory period for the induction of atrial arrhythmias by early premature impulses was 48%

Compared with the extensive literature on the relation between the refractory period and cardiac arrhythmias, studies about the role of conduction velocity are relatively scarce. These papers agree that abnormalities in P-wave morphology or prolongation in intra-atrial conduction time are major predisposing factors for the development of AF and AFib. In our series of normal dogs, a poor correlation between conduction velocity and atrial arrhythmias (predictive power 38%) was found. As for the refractory period, under some conditions slowing of conduction did correlate with the occurrence of arrhythmias, but under other circumstances either the vulnerability to atrial arrhythmias was unchanged (lidocaine and propafenone) or actually decreased (quinidine). It is noteworthy that supernormal conduction of moderately premature impulses, which has been repeatedly described for both human and canine atrium, was found in our series in only about 25% of the cases. If present, conduction velocity of late premature impulses was less than 10% faster than regular impulses. This brief and slight phase of supernormal conduction might occur either in the free wall of the right or left atrium or in Bachmann's bundle. We could not confirm that supernormal excitability was preferentially present in Bachmann's bundle. Because the premature impulses showing local supernormal conduction were not associated with the induction of atrial arrhythmias, the significance of this phenomenon in relation to arrhythmias must be low.

In contrast to the invalidity of either the refractory period or the conduction velocity alone, the combination of both parameters as given by the wavelength (wavelength = refractory period × conduction velocity) turned out to be a good index for the inducibility of arrhythmias (predictive value = 75%).

There is abundant evidence in the literature that atrial arrhythmias such as RRR, AF, and AFib that are induced by the application of a single early premature impulse...
stimulus are based on a reentrant mechanism. In the present study, no attempt was made to collect direct evidence of the reentrant nature of the various tachyarrhythmias. This would have required chronic implantation of several hundreds of recording electrodes, which would have complicated the experiment considerably. However, we assume that the atrial arrhythmias induced in our studies were based on intra-atrial reentry.

During a slow rhythm, the length of the excitation wave varied between 14–18 cm in various parts of the atria. Such a long wavelength offers a highly effective protection against the possibility of the impulse becoming trapped in a circuitous pathway. To start a circuit under these circumstances, a unidirectional conduction block of at least 7–9 cm would be required. The occurrence of such a large area of conduction block is rather unlikely. In addition, the dimensions of normal atria can hardly accommodate a sustained circuit of that size. However, gradual shortening of the wavelength by the induction of premature beats with increasing prematurity was accompanied by the occurrence of increasingly serious arrhythmias. Critical wavelength zones were identified in which certain types of atrial arrhythmias were readily induced. In 80% of the cases, no arrhythmias were induced at a wavelength longer than 12.3 cm. At a wavelength between 12.3 and 9.7 cm, 65% of early premature beats induced short series of spontaneous repetitive responses. At a wavelength between 9.7 and 7.8 cm, AFI was induced in 73% of the cases, and at wavelengths shorter than 7.8 cm, AFib occurred in 82% of the cases.

This concept of a critical wavelength for reentrant arrhythmias suggests that it might be useful to describe the effects of cardioactive drugs in terms of their influence on the wavelength. Drugs that shorten the
wavelength must be regarded as potentially arrhythmogenic, while agents that prolong the wavelength can be expected to possess antifibrillatory properties.

Spatial Dispersion in Refractory Period

We measured local refractory periods at 22 different sites in conscious dogs during both treadmill exercise (low vagal state) and sleep (high vagal activity) as well as during direct intravenous infusion of acetylcholine. Under all circumstances, there were marked regional differences in local atrial refractoriness. In the absence of vagal activity, either by administration of atropine or during treadmill exercise, the differences in refractoriness between the right (162 msec) and left (117 msec) atrium were maximal. When the dog was asleep, atrial refractory periods were shorter and local differences were less (133 and 107 msec, respectively). This decreased spatial dispersion in atrial refractory periods by physiologically high vagal activity was caused by a relatively strong shortening of refractory period in the right atrium (22%) compared with only 8% in the left atrium. In contrast with increased vagal activity, direct administration of acetylcholine caused a uniform shortening of the refractory period in both atria by 41–49%, resulting in a longest refractory period of 93 msec (right atrium) and a shortest refractory period of 60 msec (left atrium). These data differ from the studies by Zipes et al, who found that in anesthetized dogs with cut vagi, artificial vagal stimulation increased the spatial dispersion in refractory periods. An increase in local differences in refractory period by vagal stimulation was also reported by Alessi et al. A possible explanation for this difference between our observations and the studies of Spach et al is the distance of the recording points. While we measured the overall conduction time over a long distance (4–6 cm), Spach recorded conduction times over a total distance between 200 μm and 1–2 mm. Although at a microscopic scale (200 μm) clear differences in conduction velocity in different directions may exist, the complex geometry of the atria, consisting of many bundles running in different directions, may diminish the effect of anisotropy on a macroscopic scale. In such a situation, small areas of slow anisotropic conduction will not delay the propagation of a wide depolarization wave because the areas of slow conduction are bypassed by alternative fast conducting routes.

Regional Differences in Wavelength

During normal rhythm, the local wavelength was 14.5 cm in the left part of Bachmann's bundle, 14.7 cm in the lower free wall of the left atrium, 15.2 cm in the right atrial free wall, and 17.7 cm in the right part of Bachmann's bundle. During early premature beats, the local wavelength was 6.6, 7.7, 7.6, and 10.7 cm, respectively. During rapid pacing, the wavelength varied between 7.9 and 12.3 cm (Table 1). Under all circumstances, the shortest wavelength was found in the left part of Bachmann's bundle. This part of the atria was also the most favorable site to induce AFib and AFib. This is in agreement with the studies of Pastelin et al, who showed that rapid pacing at the left entrance of the interatrial bundle was a reliable way to produce AFib. They used this observation to support their view that preferential internodal and interatrial pathways play an important role in providing a reentrant pathway for AFib. The higher arrhythmogenic nature of the left part of Bachmann's bundle can, however, also be explained on the basis of the relatively short wavelength of that region. Ogawa et al showed that premature impulses elicited at the high left atrium caused prolonged interatrial conduction, fragmentation of electrograms, longitudinal dis-
sociation, and reentry in the region of Bachmann's bundle.

The shortest wavelength (6–7 cm, as measured in normal canine atria) would require a surface area of 3–4 cm² for reentry. The high degree of uniform anisotropy in the bundle of Bachmann may, however, reduce the minimal dimensions for reentry. If, in some parts of the circuit, the impulse propagates transverse to the fiber rotation, the conduction velocity of the impulse will slow down in these segments. This will lead to a shorter average wavelength and a shorter possible intra-atrial circuit. Age-related progressive electrical uncoupling of side-to-side connections between atrial fibers may lead to local transverse conduction velocity as slow as 0.07 m/sec. Also, areas of poorly coupled fibers may be present in diseased atria with progressive fibrotic changes and abnormal electrophysiological characteristics. A human atrial refractory period of 150 msec and a depressed conduction velocity of 0.07 m/sec would result in a wavelength of only 1 cm. Such a short wavelength would enable the occurrence of a reentrant circuit within an area of only 8 mm²; this may implicate that with increasing age and atrial disease, reentry may occur in progressively smaller regions of the atria. The frequent occurrence of AFib in diseased or older hearts may be explained by a shortening in wavelength of the atrial impulse, enabling the presence of more circulating wavelets in the available tissue mass.

References

Key Words • atrial arrhythmias • reentry • wavelength • dispersion of refractoriness
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