The Wavelength of the Cardiac Impulse and Reentrant Arrhythmias in Isolated Rabbit Atrium
The Role of Heart Rate, Autonomic Transmitters, Temperature, and Potassium

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SUMMARY. We measured the wavelength of the cardiac impulse, defined as the distance traveled by the depolarization wave during the functional refractory period, in isolated narrow strips of rabbit atrium. During control, wavelength was 42 mm during pacing with 2 Hz, and was 28 mm at the maximum pacing rate; early premature beats had a wavelength as short as 23 mm. Administration of carbamylcholine (4 × 10⁻⁷ g/ml) shortened the wavelength to 21 mm during 2 Hz, 18 mm at the maximum pacing rate, and 16 mm during an early premature impulse, respectively. The effects of epinephrine (6 × 10⁻⁷ M) were strongly rate dependent. At slow heart rates, epinephrine clearly prolonged the wavelength (58 mm), whereas, during maximum pacing, wavelength remained unchanged (28 mm). Hypokalemia (2 mM) decreased the length of the impulse at all stimulation frequencies. Moderate hyperkalemia (5.6 and 7.0 mM) did not modify wavelength because refractoriness and conduction velocity were affected proportionally. Above 7.0 mM potassium, the wavelength became progressively prolonged because of the development of post-repolarization refractoriness. Cooling to 27°C resulted in a slight lengthening of the impulse. At lower temperatures, however, wavelength prolonged significantly because of a relatively strong prolongation of the refractory period. In separate experiments in 15 × 20 mm segments of atrium, reentrant tachyarrhythmias were induced and the circuit size compared with the wavelength. The size of intraatrial circuits was similar to the magnitude of the measured wavelength during maximum pacing. Carbamylcholine and hypokalemia, both of which shorten the impulse length, also clearly decreased the size of reentrant circuits. Cooling to 27°C, which affects both refractoriness and conduction velocity, only slightly prolonged the wavelength; accordingly, the size of reentrant circuits at 27°C was only slightly longer than at 37°C. These experiments emphasize the importance of the wavelength of the cardiac impulse in relation to the occurrence of intramyocardial reentry. (Circ Res 58: 96–108, 1986)
length of the cardiac impulse is defined as the distance traveled by the depolarization wave during the time the tissue restores its excitability sufficiently to propagate another impulse (wavelength = conduction velocity \times functional refractory period). This implies that conditions which shorten the refractory period or depress conduction will result in a shorter wavelength. Under such conditions, reentrant circuits of smaller dimensions may become possible. On the other hand, interventions which prolong refractoriness or improve conduction will prolong the length of the excitation wave, and only circuits of larger size can exist.

We consider the wavelength of the cardiac impulse of utmost importance for both the induction and perpetuation of tachyarrhythmias based on leading circle reentry. Prerequisites for the initiation of circus movement are: (1) the creation of an arc of unidirectional conduction block, (2) conduction around the area of block, and (3) reexcitation of the tissue proximal to the site of conduction block (Mines, 1913). It seems that these requisites are more easily fulfilled when the wavelength of the impulse is short. Then, already small areas of conduction block may serve as pivoting points for reentry (Allessie et al., 1977). Given a certain degree of inhomogeneity of the myocardium, the chances for the occurrence of small patches of block seem higher than the creation of a single long arc of conduction block. Normally, the length of the excitation wave protects the heart against intramyocardial micro-reentry. However under conditions which shorten the wavelength, this protection may become less effective, and the occurrence of small areas of block may lead to intramyocardial reentry and fibrillation (Moe et al., 1962; Allessie et al., 1985).

In this study, we present a simple biological model to measure directly the length of the excitation wave in atrial muscle. The influences of heart rate, premature beats, autonomic transmitters, extracellular potassium, and changes in temperature are studied and compared with the inductibility and dimensions of intraatrial reentry. Direct measurement of the cardiac excitation wave is a simple method, which expresses the minimal size of an intramyocardial circuit and may be used as an indicator for the risk of leading circle reentry. Since many antiarrhythmic drugs affect both refractory period and conduction velocity, measurement of the wavelength which combines both parameters may help to evaluate and improve our understanding of the mechanisms of action of antiarrhythmic drugs.

**Methods**

Young New Zealand rabbits of both sexes weighing between 1.5 and 2.0 kg were killed with a single blow to the head. The thorax was opened by a mid-sternal incision, and the heart was rapidly excised and transferred to a tissue bath where further dissection was performed. After separation of the atria from the ventricles, a strip of atrial tissue was cut from the roof of the left atrium. The left atrial strip, showing no spontaneous activity, was about 20 mm long and 2–3 mm wide. The thickness of the preparation varied from site to site but never exceeded 0.5 mm. The strip of left atrial myocardium was placed in a tissue bath (content 50 ml) and superfused at a rate of 100 ml/min. The perfusion solution had the following composition (mM): NaCl, 130; KCl, 4.5; CaCl2, 2.2; MgCl2, 0.6; NaHCO3, 24.2; NaH2PO4, 1.2; glucose, 11; and sucrose, 13. The solution was saturated with a mixture of 95% O2 and 5% CO2; pH was 7.35 ± 0.05, and temperature was kept at 37°C unless stated otherwise.

A programmable stimulator was used to deliver constant current pulses (duration 1–2 msec; strength 2–4 times diastolic threshold) through two platinum plates (2 × 4 mm) embracing one end of the preparation. The distance between the two stimulating electrodes was such that the preparation could move freely between the two plates. Field stimulation was preferred above point stimulation because, in this way, a shorter coupling interval of premature beats and a higher maximum pacing rate could be achieved. In addition, the variability between different experiments was less. To check whether neurotransmitters were released during field stimulation, we measured the effects of a train of strong stimuli applied during the absolute refractory period. This had no effect on either the refractory period or the conduction velocity. Also, the administration of atropine (10–8 m) did not affect the measurements. Impulse propagation along the strip of atrial myocardium was monitored with a multiple-recording electrode, consisting of a row of Teflon-coated silver wires (diameter 0.3 mm) at an interelectrode distance of 2 mm. Unipolar electrograms were recorded, with a large silver plate in the tissue bath as indifferent electrode. After amplification (bandwidth 5–400 Hz), the electrograms were displayed simultaneously on an eight-channel oscilloscope (Tektronix 1503N). Conduction velocity along the strip of atrial myocardium was measured between the first and last electrode on the preparation. The most rapid negative deflection of the electrogram was taken as moment of activation at the recording site. For a reliable measurement of the conduction velocity, it is essential to measure the activation time between two recording sites, rather than using the time difference between the stimulus artefact and a single electrogram. With the latter technique, the latency between the application of an external stimulus and the start of a propagating wavefront is included in the measurement. This may lead to serious underestimation of the conduction velocity. Another reason why one should not use the stimulus artefact is that, because the latency is dependent on the stimulus strength, the measured conduction velocity varies with the amount of current used for stimulation. These problems can easily be avoided by measuring between two recording electrodes. To ascertain that variations in latency and actual origin of the activation wave could not influence our measurements, we positioned the proximal recording electrode at a distance at least 3 mm from the stimulating electrodes.

The wavelength of a cardiac impulse is defined as the distance traveled by the impulse during the time the myocardium restores its excitability to such an extent that a second wave can propagate again. It is determined by the product of conduction velocity and functional refractory period (FRP). To measure the length of the excitation wave, the following stimulation protocols were used. For determination of the wavelength of a regular rhythm, the preparation was paced at a chosen basic rate, and after
every 20th basic stimulus, a premature stimulus was introduced at progressively shorter coupling intervals in steps of 1-5 msec. The functional refractory period of the regular rhythm was defined as the shortest possible interval between the last basic beat and the premature beat (shortest $A_1-A_2$ interval at the electrode closest to the site of stimulation) which was conducted all along the atrial strip. Conduction block of premature impulses usually occurred at the stimulation site. The average conduction velocity along the strip of atrial myocardium during the chosen regular rhythm was calculated from the conduction time and the distance between the first and last recording electrodes along the bundle. The wavelength of premature beats can be measured in a similar manner. The only difference is that now two successive premature stimuli must be given after every 20th basic impulse. The basic rate and the degree of prematurity of the first premature impulse are kept constant, while the coupling interval of the second premature stimulus is progressively shortened to determine the functional refractory period of the premature impulse. To measure the wavelength during maximum pacing ($F_{\text{max}}$), the basic cycle length was gradually shortened until conduction block occurred somewhere along the atrial bundle. The shortest possible pacing interval (interval $F_{\text{nuO}}$) was defined as the pacing interval at which every impulse is conducted all along the strip of atrial myocardium at least 400-500 consecutive beats. The wavelength at $F_{\text{max}}$ can be simply calculated from the shortest pacing interval and the conduction velocity during $F_{\text{max}}$. In a minority of preparations, a slight alternation in conduction velocity ($\pm 5\%$) was observed at the highest driving rate. In that case, the average conduction velocity was used for the calculation of the wavelength.

For mapping studies, we used the isolated roof of the left atrium (measuring about 15 x 20 mm) and a multiplexing system allowing simultaneous registration of 192 signals. Details of the mapping system have been given elsewhere (Allessie et al., 1984). The multiple mapping electrode consisted of a regular matrix of 192 Teflon-coated silver wires (diameter 0.3 mm) with an interelectrode distance of 1.4 mm. This "brush" of recording electrodes was gently positioned on the endocardial surface of the left atrium.

### Results

#### The Effects of Rate and Rhythm on the Length of the Excitation Wave

The effects of different pacing rates and premature beats were studied in 30 left atrial preparations. In Figure 1, the effects of heart rate on the functional refractory period, conduction velocity, and wavelength of the atrial impulse are shown. The atrium was paced with frequencies ranging from 2 Hz (interval 500 msec) up to the maximum pacing rate. The shortest possible pacing interval in this tissue was 75 msec ($\pm 9.6$). At pacing intervals between 200 and 500 msec, both refractory period and impulse conduction showed only minor changes, and the length of the excitation wave was constant. There was a slight decrease in refractory period if the pacing interval was prolonged from 200-500 msec. It is likely that this shortening of refractoriness at low pacing rates is particular for the rabbit, since it is absent in most other mammals and has also been found in rabbit ventricular myocardium (Gibbs and Johnson, 1961). At pacing rates above 5 Hz, the length of the excitation wave becomes clearly affected. If the pacing interval is gradually shortened from 200 msec to the shortest possible pacing interval, a progressive shortening of the wavelength up to 40% is seen. This clear rate-dependent shortening of the wavelength is caused both by a shortening of the refractory period and a slowing of conduction at high heart rates.

The effects of single premature beats on refractoriness, conduction velocity, and wavelength are shown in Figure 2. On the abscissa, the degree of prematurity is expressed relative to the functional refractory period during a basic pacing rate of 2 Hz (the shortest $A_1-A_2$ interval is taken as zero). Late and moderately early premature beats do not differ in their wavelength from regular impulses (refractory period and conduction velocity are unaltered). Only closely coupled premature beats show a markedly shortened wavelength, the length of the excitation wave of the earliest premature beat (FRP) being 23 mm compared to 40 mm of a late extrasystole. This shortening of the wavelength of early premature impulses by about 40% is caused mainly by a depression of conduction velocity from 55-33 cm/sec. A slight shortening of the refractory period from 68-61 msec further adds to this effect. It is of interest that, although the amount of shortening of the wavelength by rapid pacing is similar to the shortening brought about by single early premature beats, the range of coupling intervals in which this shortening occurs is different. During single premature beats, the wavelength is abruptly shortened...
REF. PER. ms

COND. VEL. cm/sec

WAVE LENGTH mm

FIGURE 2. The wavelength of premature beats. The mean values (n = 7) and standard deviation of refractory period, conduction velocity, and the wavelength of premature beats are plotted against the degree of prematurity. The shortest possible A1-A2 interval [functional refractory period (FRP)] is taken as zero; the degree of prematurity of all other extrasystoles is related to the FRP. Late premature beats have the same wavelength as the underlying basic rhythm. Only at very early premature beats, in a narrow zone of 40 msec after the FRP, does a sudden and pronounced shortening of the wavelength occur. The short length of early premature beats is caused mainly by their reduced speed of propagation.

FIGURE 3. The wavelength of a regular rhythm (top thick curve), the earliest premature beat (lower thick curve), and premature beats elicited 5, 10, and 20 msec after the functional refractory period, are plotted at different pacing rates. All impulses of both regular and premature beats become shortened if the pacing rate exceeds 5 Hz (interval 200 msec). Note that the wavelength of the earliest premature beat during maximum pacing is only one-third of the impulse length during slow heart rate.

in a narrow zone of only 40 msec directly after the functional refractory period. During rapid pacing, the shortening of the wavelength occurs more gradually over a range of about 125 msec (pacing intervals between 75 and 200 msec). In some experiments, a more elaborate stimulation protocol was applied in which the wavelength of premature beats of varying prematurity were measured at different basic pacing rates. In this way, we could directly compare the respective effects of pacing rate and prematurity. Figure 3 gives the data of such an experiment. The top thick curve shows the changes in wavelength during regular pacing at different cycle lengths. The lower thick curve gives the wavelength of the earliest possible premature beat elicited at those pacing rates. The thinner curves represent the wavelength at different basic pacing rates of premature beats induced respectively 5, 10, and 20 msec after the functional refractory period. From this family of curves, it is clear that an increase in pacing rate above 5 Hz always results in a shortening of the length of the excitation wave. This is true for the regular rhythm itself, the earliest premature beat, and for premature beats coming later in the cycle. At all pacing rates, the length of the earliest premature impulse is about half the wavelength of the regular rhythm. Premature beats arise slightly later in the cardiac cycle (5, 10, and 20 msec after the FRP) and have intermediate values.

The Effects of Carbamylcholine

The effects of carbamylcholine (4 × 10^-7 g/ml) on the atrial impulse were studied in 13 preparations. After a 1-hour control period in which all measured variables were constant, carbamylcholine was added to the perfusate, and the wavelength during slow pacing (2 Hz), the earliest premature impulse, and the highest pacing rate were measured. During wash-out, all variables quickly returned to control values. The effects of carbamylcholine on refractory period, conduction velocity, and wavelength are given in Table 1. As expected, the refractory period was markedly shortened by carbamylcholine. During pacing with 2 Hz, the FRP decreased from 70–38 msec, refractoriness of the earliest possible premature beat shortened from 66–37 msec, whereas the shortest possible pacing interval changed from 80–54 msec. The conduction velocity was not affected by carbamylcholine, with the exception of the earliest premature impulse, which propagated somewhat faster during carbamylcholine administration (42 vs. 35 cm/sec). These changes in refractory period and conduction velocity resulted in a shortening of the length of the excitation wave of 48% during slow pacing, 33% during rapid pacing, and 30% during an early premature beat. This shortening of the wavelength was found at a wide range of pacing rates. This is illustrated in Figure 4 in which the wavelength during regular pacing and the earliest premature beat are plotted at different pacing intervals. Under the influence of carbamylcholine, both curves shift downward and to the left. For early premature beats, the effect of carbamylcholine is the same at all different pacing rates, as can be seen from the parallel shift of the carbamylcholine
The Effects of Carbamylcholine

| Table 1 | The Effects of Carbamylcholine |
|------------------|-----------------|-----------------|------------------|
| Refractory period (msec) | Conduction velocity (cm/sec) | Wavelength (mm) |
| Control | Carbamylcholine | Control | Carbamylcholine | Control | Carbamylcholine |
| Slow regular rhythm | 70 ± 11.0 | 38 ± 6.7* | 60 ± 11.6 | 57 ± 11.0 | 41 ± 8.4 | 21 ± 4.4* |
| Earliest premature beat | 66 ± 9.8 | 37 ± 6.4* | 55 ± 8.6 | 42 ± 7.8* | 25 ± 5.8 | 16 ± 5.0* |
| Shortest pacing interval | 80 ± 8.1 | 54 ± 6.0 | 33 ± 6.1 | 34 ± 6.1 | 27 ± 5.1 | 18 ± 3.0* |

n = 13. * P < 0.001.

curve compared to control. However, during regular pacing, the shortening of the wavelength by carbamylcholine is most marked during slow heart rates. At higher pacing rates (interval shorter than 200 msec), when the wavelength is already significantly shortened by the rapid rhythm itself, there is still additional shortening by carbamylcholine, but less than during slow heart rates.

The Effects of Epinephrine

The action of epinephrine (6 × 10⁻⁷ m) was studied in 12 atrial preparations. Table 2 summarizes the effects on refractory period, conduction velocity, and wavelength during regular pacing and premature stimulation. During slow regular pacing (2 Hz), epinephrine prolonged the refractory period from 66–98 msec; refractoriness of early premature beats increased from 62–93 msec. In contrast, the shortest possible pacing interval increased only slightly (from 80–87 msec). Epinephrine had no significant effect on the conduction velocity in the atrium, nor during slow pacing, rapid pacing or the induction of premature beats. These changes in refractoriness and conduction by epinephrine resulted in a prolongation of the wavelength from 38–58 mm (53%) during slow heart rates and a lengthening of premature impulses from 20–29 mm (45%). At the highest possible pacing rate, however, the wavelength was not significantly altered by epinephrine (27 compared to 28 mm). Thus, the effect of epinephrine on the wavelength of the atrial impulse seems to be strongly rate dependent. In Figure 5, this rate dependency is further investigated by measuring the wavelength during pacing at different basic cycles. In the top panel, the wavelength of regular impulses is plotted as a function of the pacing cycle; the bottom panel gives the wavelength of the earliest premature beats elicited during different heart rates. At pacing cycles between 500 and 300 msec, epinephrine clearly prolonged the wavelength of both basic and premature impulses. However, at heart rates with cycle lengths shorter than 300 msec, the prolongation of the atrial impulses by epinephrine gradually diminished. At the highest possible pacing rate, epinephrine exerted almost no effect on the wavelength of impulses in the atrium.

The Effects of Extracellular Potassium

Changes in extracellular potassium concentration strongly affect the vulnerability of the heart to various arrhythmias (Surawicz, 1980). In particular,
The Effects of Epinephrine

<table>
<thead>
<tr>
<th>Refractory period (msec)</th>
<th>Conduction velocity (cm/sec)</th>
<th>Wavelength</th>
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<tbody>
<tr>
<td>Control</td>
<td>Epinephrine</td>
<td>Control</td>
</tr>
<tr>
<td>Slow regular rhythm (2 Hz)</td>
<td>66 ± 8.1</td>
<td>98 ± 9.9*</td>
</tr>
<tr>
<td>Earliest premature beat</td>
<td>62 ± 7.4</td>
<td>93 ± 13.3*</td>
</tr>
<tr>
<td>Shortest pacing interval</td>
<td>80 ± 8.3</td>
<td>87 ± 12.4</td>
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n = 12.
*P < 0.001.

The Effects of Temperature

Since hypothermia clearly affects the vulnerability of the heart to various arrhythmias (Holland and Klein, 1958; Covino and Damato, 1962; Nielsen and Owman, 1968), it is of interest to know the influence of changes in temperature on the length of the excitation wave. It is well known that cooling prolongs the refractory period and depresses conduction of the cardiac impulse. However, because the effects on refractoriness and conduction velocity are opposite, it is difficult, if not impossible, to predict...
how the wavelength of the impulse will be modified without simultaneous measurement of both electrophysiological properties. We studied the wavelength at several temperatures in 13 experiments; only the wavelength during maximum pacing (F_max) was measured. Temperature was varied in steps of 2°C between 38°C and 26°C in all experiments; in two experiments the temperature was further lowered to 23°C and 21°C. In Figure 6, the average values of the minimum pacing interval, the conduction velocity at F_max, and the wavelength during maximum pacing are plotted for different temperatures. It is clear that changes in temperature have pronounced effects on both conduction velocity and the maximum pacing rate. Cooling the heart from 37°C to 27°C almost doubled the shortest possible pacing interval (prolongation of interval F_max from 86–167 msec). The speed of propagation at F_max was decreased from 34–21 cm/sec. Since the length of the excitation wave is determined by the balance between refractoriness and conduction velocity, this resulted in only a moderate shortening of the atrial impulse from 28 mm at 37°C, to 33 mm at 27°C.

Further cooling caused a steeper prolongation of the wavelength, because below 27°C the prolongation of the shortest possible pacing interval clearly outweighs the concomitant depression in conduction velocity. Thus, lowering temperature from 37°C to 27°C resulted in a strong reduction of the maximum pacing frequency, whereas the wavelength of the impulses is only slightly affected. Only when the temperature falls below 27°C, is there prolongation of the wavelength until complete inexcitability occurs.

Wavelength and the Size of Intramyocardial Circuits

To test our hypothesis that the size of intramyocardial circuits is governed by the wavelength of the cardiac impulse, we mapped reentrant circuits in the same type of tissue in which the wavelength was measured. For these mapping experiments (n = 5), instead of a narrow strip of left atrial muscle, a 15 × 20 mm sheet cut from the roof of the left atrium was used. Figure 7 shows the effects of carbamylcholine on rate and dimensions of an intratrial circuit. During a long-lasting episode of regular reentrant rhythm, evoked by a critically timed premature beat, carbamylcholine was added to the perfusate. This resulted in an immediate gradual shortening of the cycle length of the arrhythmia from 90–60 msec (middle panel, Fig. 7). At the bottom of this figure, activation maps of the rapid reentrant rhythm are shown before and after the administration of carbamylcholine. During control (left map), the impulse circulated in a clockwise direction with a revolution time of 90 msec. From the length of the central arc of functional conduction block (indicated by a thick line), the size of the intraatrial circuit can be estimated to be about 30 mm. Under the influence of carbamylcholine, the revolution time of the circulating impulse shortened to 60 msec (right map). This acceleration of the reentrant rhythm was not brought about by an increase in speed of conduction, but by a shortening of the circular pathway. As can clearly be seen by comparing both maps, the central arc of block has considerably "shrunken" and now is no longer than 5 mm. Obviously, because of the shortening of the refractory period by carbamylcholine, the impulse was able to short-cut part of the circuit, resulting in an intramyocardial circuit as small as 17 mm.

Intraatrial reentry during low potassium was mapped in four experiments. At normal potassium levels, it is difficult to induce reentry within the atrium. However, when the potassium level is lowered, runs of rapid repetitive activity can be induced easily by the induction of a single early premature beat. In Figure 8, two experiments are shown in which runs of 10 and 20 rapid repetitive responses were induced by a single premature stimulus. In panel A, the maps of the second and fifth cycle are
FIGURE 6. The influence of temperature on the shortest possible pacing interval (top panel), the conduction velocity (middle panel), and the wavelength during maximum pacing (lower panel). Lowering temperature from 37°C to 27°C caused a marked prolongation of the minimum pacing interval from 86-167 msec. At the same time, conduction velocity decreased from 34-21 cm/sec. Since prolongation of refractory period and depression of conduction velocity have opposite effects on the wavelength, the effect of cooling on the wavelength was limited. Lowering the control temperature by 10 degrees resulted in only a slight lengthening of the activation wave from 28-33 mm. If the heart is further cooled below 27°C, the minimum pacing interval becomes greatly prolonged, leading to a marked prolongation of the wavelength at very low temperature.

reconstructed. They show intraatrial reentry with a cycle length of 50 msec and a circular pathway of about 15 mm. It is also interesting to see that the position of the vortex is shifted from the upper right corner of the atrium during the second cycle to a mid-lower position during the fifth cycle of the tachyaryrhythmia. In panel B, two beats of a longer period of rapid repetitive responses are shown. In this case, two separate areas of block were present. The reentrant circuit had a "figure 8" configuration, where two wavefronts circulated around two arcs of block, one in a clockwise and the other in a counterclockwise direction. However these two circulating impulses cannot be regarded as two independent circuits, since the isthmus between the two zones of block served as a common reentrant pathway for both circulating wavefronts. At one side of the isthmus (the "entrance" of the common pathway), the two wavefronts coalesced. At the other end (the "exit" of the isthmus) the impulse diverged again in a clockwise and a counter-clockwise rotating wave. In this example, also, the position of the vortices changed between the first and the 12th cycle. In addition, the direction in which the common wavefront travels through the isthmus between the two arcs of block is reversed. In the map of the first cycle, the common wave propagates through the isthmus from left to right, whereas, during the 12th beat, the isthmus is traversed in a right-to-left direction. The size of the two circuits during the first reentrant beat can be estimated to be 15-16 mm. During the 12th beat, the circuits seem a little larger, and measure 17 and 21 mm, respectively. These mapping studies seem to confirm that the shortening of the refractory period caused by low potassium leads to reentrant rhythms which are faster than

FIGURE 7. The effects of administration of carbamykholine (10^-6 g/ml) on cycle length (middle panel) and dimension of intraatrial reentry (lower panel). Carbamykholine caused a dramatic acceleration of the already very fast reentrant rhythm: the cycle length decreased from 90-60 msec. The two maps at the bottom show the spread of excitation before and after the administration of carbamykholine. Both maps are reconstructed from multiple unipolar electrograms recorded 1.4 mm apart. Using such high spatial resolution, it was not necessary to calculate isochrones by interpolation. As shown by the maps, the rapid rhythm is based on a clockwise circulating wavefront. The solid line in the center of the vortex represents the central arc of block where the impulse turns around. Comparing the two maps, it is evident that, under the influence of carbamykholine, the reentrant loop has become considerably smaller. We estimate the perimeter of the intraatrial circuit, before and after carbamykholine, to be 30 and 17 mm.
FIGURE 8. Two examples of paroxysms of rapid repetitive reentry in isolated pieces of rabbit atrium induced by a single early premature beat. The extracellular potassium concentration was lowered to 2 mM. In panel A, the second and fifth cycles of a short run of reentrant activity are mapped. A small reentrant loop with a circular pathway of about 15 mm around a 5-mm central arc of block (thick solid line) is seen. The functional and dynamic nature of this kind of intramyocardial reentry is illustrated by the clear shift in position of the vortex between the second and fifth cycle of the arrhythmia. In panel B, another example of a longer run of reentrant activity in low K⁺ is shown. In this case, two arcs of conduction block were present, and the reentrant activity had a "figure of 8" configuration. Again, the position of the reentrant activity is not fixed, but "wanders" around the myocardium. Circuit size varies between 15 and 21 mm.

normal and are based on intramyocardial circuits which are smaller in size because of the concomitant shortening of the wavelength of the impulse.

The effects of cooling on intratral reentry was studied in three preparations. At 37°C, a long-lasting reentrant arrhythmia was induced in the isolated left atrium by the induction of early premature beats and continuous administration of carbachol (10⁻⁷ M). When the cycle length of the circus movement had become constant, the temperature of the perfusate was gradually lowered until the intratral circuit was interrupted. Figure 9 is an example. At 37°C, the impulse was found to circulate in a clockwise direction with a cycle length of 98 msec. The S-shaped thick line in the center of the vortex indicates the arc of functional conduction block around which the impulse circulates; the size of this intramural loop can be estimated to be about 27 mm. A gradual decrease of the temperature to 29°C resulted in a progressive increase of the revolution time from 98–159 msec. It is noteworthy that despite this strong reduction in rate, the reentrant rhythm remained regular and did not terminate. The number of isochrones increased and are closer together, indicating that the speed of propagation has slowed down uniformly along the circuitous pathway. The central S-shaped arc of functional block is somewhat enlarged, resulting in some increase in size of the circuit from 27 to about 31 mm. In the lower panels of Figure 9, four electrograms were selected to show the pathway of the circulating impulse around the upper pivoting point. The exact position of the four electrograms is indicated on the maps.
moved upward. Instead of traveling directly from site A to D, the impulse now reaches site D after making a detour along the upper part of the preparation (note the shift in position of the intervening electrograms B and C).

Moderate cooling strongly reduced both the maximum rate of pacing and the cycle length of intraatrial reentry. At the same time, the length of the excitation wave and the size of a leading circuit are only slightly prolonged. At temperatures below 27°C, the wavelength is markedly prolonged and intraatrial circuits are interrupted.

Again these temperature experiments show a good agreement between: (1) the maximum pacing frequency \( F_{\max} \) and the rate of intraatrial reentry, and (2) the wavelength of the impulse and the dimensions of intramyocardial circuits.

**Discussion**

We propose to use the wavelength of the cardiac impulse as an index for the vulnerability of the heart to fibrillation. Together with the mass of cardiac tissue and the degree of inhomogeneity of conduction properties, the length of the excitation wave seems a key factor in the inducibility and stability of fibrillation. In this study, we developed a simple in vitro model in which the wavelength can be directly measured under a wide variety of circumstances. The wavelength of the atrial impulse as found in this model was compared with the actual dimensions of intraatrial reentry determined by high resolution mapping in a small sheet of the same tissue. A number of important physiological variables were investigated, including cardiac rate and rhythm, autonomic nervous transmitters, extracellular potassium, and changes in temperature. Under all those different conditions, there was good agreement between the length of the excitation wave and the size of intra-myocardial circuits.

**Autonomic Transmitters**

Under normal conditions, the wavelength of the impulse in the isolated rabbit atrium is longer than 4 cm. Compared to the small size of a rabbit heart, it is unlikely that a circuit of that size can exist. However, during rapid heart rate or the occurrence of early premature beats, the wavelength is considerably shortened to about 2.5 cm. Normally, this wavelength is still long enough to protect the rabbit atrium against initiation of intraatrial reentry, and in only a minority of cases can short runs of rapid repetitive activity be induced in the isolated left atrium of the rabbit by programmed stimulation alone. In contrast, atrial fibrillation and intraatrial reentry can easily be induced in combination with vagal stimulation or the administration of acetylcholine (Burn et al., 1955; Allessie et al., 1977, 1984, 1985). Also, in man, paroxysms of atrial fibrillation may be related to a high parasympathetic tone (Coumel et al., 1978). In the present study, we measured a strong reduction of the length of the excitation wave under the influence of carbamylcholine. During slow rhythm, this drug shortened the impulse from 41–21 mm. Induction of premature beats further reduced the wavelength up to 16 mm. During regular pacing at the highest possible frequency, the wavelength was 18 mm. Mapping of intraatrial reentry confirmed that the length of the circuit was similar to the wavelength of the impulse as measured during maximum pacing. During carbamylcholine administration, circuits as small as 15–20 mm were identified. Not only do circuits of this size easily fit in the available tissue mass, but the reduction in wavelength also strongly facilitates the initiation of circus movement. For the successful induction of reentry, an area of unidirectional conduction block of at least half the wavelength is a condition "sine qua non." It is obvious that the chances to fulfill this criterion are higher when the required area of conduction block is smaller. For the isolated left atrium of the rabbit, the critical wavelength for easy induction of intramyocardial reentry is in the order of 20 mm.

In the intact canine heart, and also in man, atrial fibrillation induced by programmed stimulation in healthy individuals usually terminates spontaneously within seconds or minutes. However, during vagal stimulation or administration of acetylcholine, fibrillation becomes self-sustained and spontaneous reversion to sinus rhythm no longer occurs (Burn et al., 1955; Allessie et al., 1985). The data presented in this study strongly suggest that the fibrillatory action of parasympathetic transmitters is based on an overall shortening of the wavelength in the atria. Because of the smaller dimensions of intraatrial circuits, more circulating wavelets can be present simultaneously in the available cardiac tissue mass (Moe, 1962; Allessie et al., 1985). During rapid pacing, carbamylcholine shortened the wavelength of the impulse about 30%, suggesting that this amount of shortening is sufficient to prevent resumption of sinus rhythm and may be responsible for perpetuation of atrial fibrillation. On the other hand, this value gives a clue that drugs which prolong the activation wave about 30% may be effective in preventing paroxysms of atrial fibrillation.

The role of the sympathetic nervous system in the initiation and perpetuation of intraatrial reentry is uncertain. Clinical evidence that catecholamines play a role in the occurrence of paroxysmal atrial fibrillation is scarce (Coumel et al., 1982). In animal studies, the effects of administration of (nor)epinephrine on the electrophysiological properties differ from species to species (Webb and Hollander, 1956; Hoffman and Cranefield, 1960). Reentry within segments of isolated left atrium of the rabbit is not affected by the addition of epinephrine to the tissue bath; the only effect observed was a very slight prolongation in cycle length of the reentrant rhythm (Allessie et al., 1977). In the present studies,
we found that epinephrine prolonged the refractory period and the wavelength only at slow driving rates. At higher heart rates, this effect disappears and no effect of epinephrine on refractoriness or conduction was found when the atrium was paced at its maximum driving rate. From these measurements, one might expect that, because of prolongation of the refractory period and the wavelength of premature beats, the induction of intraatrial circuits is less likely when epinephrine is present. However, perpetuation of intraatrial reentry, once established, seems to be unaffected by adrenergic compounds.

**Potassium**

During low potassium, intraatrial reentry can be readily induced, but is generally self-terminating (Lammers et al., 1981). One of the interesting findings of the present study is that during hypokalemia (2 mM), the wavelength of early premature beats is markedly shortened (by 40%), whereas, during rapid pacing, the impulse is only slightly shorter than normal. This observation offers a good explanation for the arrhythmogenic profile of low potassium. The easy induction of rapid repetitive responses by a single premature beat fits with the extremely short wavelength of premature impulses. The self-terminating character of the arrhythmias is based on the gradual prolongation of the length of the rapid impulses leading to a gradual increase of circuit size and, finally, to interruption of the circulating impulse.

Increased extracellular potassium depresses conduction and prolongs refractoriness in cardiac tissue. When the potassium level is moderately elevated (up to 7 mM), these two electrophysiological properties are affected to the same extent. Since they exert opposite effects on the wavelength of the impulse (slow conduction shortens the wavelength, whereas prolonged refractoriness lengthens it), the length of the excitation wave was not altered by moderate hyperkalemia. However, at extracellular potassium levels exceeding 7 mM, the time course of recovery of excitability becomes more affected than the speed of conduction. As a result, the length of the cardiac impulse is dramatically prolonged at severe hyperkalemia. This may well be the underlying mechanism of the long-known defibrillatory action of potassium infusion (Wiggers, 1953). To terminate atrial or ventricular fibrillation, it is not necessary that potassium be raised to such a high level that cardiac conduction is completely blocked. Fibrillation can be stopped with the myocardium still able to conduct normal impulses (Grunbach et al., 1954). At about 10 mM [K+]o, prolongation of the wavelength of the fibrillatory impulses may be expected to be sufficient to terminate the fibrillatory process.

**Cooling and Arrhythmias**

The concept that the rate of intramyocardial reentry is similar to the maximum pacing rate and that its size is equal to the wavelength of the impulse was tested further by changing the temperature of the heart. Cooling exerted different quantitative effects on the maximum pacing rate and the length of the impulse, the maximum pacing rate being more sensitive to temperature changes than the wavelength (Q10 = 1.94 and 1.17, respectively). Intraatrial reentry showed the same behavior. The rate of a reentrant rhythm slowed down markedly when the atrium was cooled. At the same time, the circuit length increased only slightly until—at very low temperatures—the circulating impulse was blocked and the reentrant rhythm suddenly terminated. This observation is in agreement with the studies of Holland and Klein (1958) who found that isolated but intact rabbit atria did not fibrillate at temperatures below 24°C. In man, also, temperature plays an important role in the occurrence of cardiac arrhythmias. In patients in whom, during normothermia, ventricular tachycardia can be readily induced by programmed electrical stimulation, it is much more difficult, or even impossible, to produce ventricular tachycardia during intraoperative mapping performed under hypothermia (Josephson and Wellens, 1984). If these tachycardias are based on reentry within a relatively small diseased part of the ventricles, the prolongation of the wavelength by cooling might have disturbed the delicate balance between the functional size of the circuit and the available mass of diseased tissue, resulting in disappearance of the arrhythmia.

**Inhomogeneity and Anisotropy**

By stressing the significance of the wavelength of the impulse in reentrant arrhythmias, we do not mean to say that other factors are not involved. It is quite well understood that structural inhomogeneities or local differences in electrophysiological or ultrastructural properties might be equally important. The relative importance of wavelength and inhomogeneity may well differ from case to case; some arrhythmias are caused by too short a wavelength, whereas other arrhythmias predominantly arise on the basis of overtly increased inhomogeneity. In addition, we want to emphasize that anisotropy of the heart may also play an important role. Conduction velocity in the myocardium is dependent on the direction of propagation relative to the fiber orientation (Spach et al., 1982). Therefore, even at the same site, the wavelength of the impulse may vary, depending on the direction of the propagating wavefront. When a bundle of muscle fibers is activated by an impulse running parallel to the long fiber axis, the wavelength will be long, whereas, when the same bundle is activated perpendicular to the fiber direction, the wavelength will be shorter. Since the strips of atrial muscle used in our studies did not consist of a single bundle of parallel fibers (like the crista terminalis or Bachmann’s bundle), the measured wavelength of the atrial impulse should be considered as some intermediate value.
between a maximum wavelength for parallel conduction and a minimum wavelength for an impulse propagating perpendicular to the fiber orientation.

So far, it has been difficult to quantify the degree of spatial inhomogeneity and anisotropy, which together determine the propagation of the impulse. Before wavelength and heterogeneity can be used together as indices for the vulnerability to fibrillation, we need a method to quantify the spatial dispersion in the ability of atrial or ventricular myocardium to propagate an impulse, and to determine the role of anisotropy in the occurrence and stability of intramyocardial reentry.

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