Regional Entrainment of Atrial Fibrillation Studied by High-Resolution Mapping in Open-Chest Dogs

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Background. It recently has been demonstrated that during atrial fibrillation, a short and variable excitable gap exists, allowing regional control of atrial fibrillation by local stimulation. In the present study, we visualized the process of excitation during regional entrainment of atrial fibrillation by rapid pacing.

Methods and Results. In six open-chest dogs, the excitation of the left atrial free wall was mapped using a spoon-shaped mapping electrode (248 points). Episodes of atrial fibrillation were induced by burst pacing (50 Hz, 2 seconds). During atrial fibrillation, the electrograms showed rapid irregular activity with a median cycle length of 98±16 ms (mean±SD, n=6). Rapid pacing in the center of the mapping electrode at intervals slightly shorter or longer than the median atrial fibrillation interval resulted in regional capture of atrial fibrillation. The window of entrainment was 16±5 ms. Mapping of atrial fibrillation showed that the left atrium was activated by fibrillatory wavelets coming from different directions. During entrainment, a relatively large area with a diameter of about 4 cm was activated by uniform wave fronts propagating away from the site of stimulation. The area of entrainment was limited by intra-atrial conduction block and by collision with fibrillation waves. Regional control of atrial fibrillation was lost by pacing either too slowly or too rapidly. In the first case, retrograde invasion of the area of entrainment by fibrillatory waves resulted in depolarization of the pacing site prior to the stimulus. Pacing too rapidly caused acceleration of atrial fibrillation by induction of local intra-atrial reentry circuits with a revolution time shorter than the pacing interval.

Conclusions. During atrial fibrillation, an area with a diameter of about 4 cm can be entrained by local pacing. The resulting reduction in fibrillating tissue mass was not sufficient to terminate atrial fibrillation. Extension of the area of entrainment was limited by intra-atrial conduction block, whereas entrainment at a too high rate resulted in acceleration of atrial fibrillation by induction of local microreentry.

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KEY WORDS • fibrillation • pacing • mapping

Most reentrant arrhythmias can be terminated by programmed electrical stimulation. In contrast, attempts to interrupt atrial or ventricular fibrillation by local pacing thus far have failed. Theoretically, a volley of perfectly timed and spaced stimuli delivered in resonance with the fibrillatory wavelets should be able to terminate the fibrillatory process. In a recent study in chronically instrumented conscious dogs, we demonstrated that the fibrillating atria can be captured by rapid pacing at cycle lengths slightly longer or shorter than the median fibrillation interval. This implies that during atrial fibrillation, a short excitable gap exists during which local electrical stimuli can interfere with the fibrillatory process.

In the present study, high-resolution mapping around the site of pacing was used to investigate the temporal and spatial effects of local pacing on the excitation process during atrial fibrillation. With this technique, detailed information could be obtained about the mutual interaction between the multiple wandering wavelets during atrial fibrillation and the local electrical stimuli. The spatial phenomena leading to gain and loss of regional control of atrial fibrillation could be visualized. Also, the balance between the regularly paced depolarization waves and the surrounding irregular fibrillatory waves determining the area that could be controlled was studied.

Methods

Six male mongrel dogs weighing between 36 and 51 kg were used; in these animals, the relatively large atrial tissue mass promotes the duration of electrically induced atrial fibrillation. Animal preparation and handling were performed according to the guidelines of the Animal Investigation Committee of the University of Limburg. After premedication with Hypnorm (0.4
mL/kg IV: 10 mg/mL Fluanisone and 0.2 mg/mL Fentanyl), the animals were anesthetized with sodium pentobarbital (15 mg/kg IV) and ventilated with a 2:1 mixture of O₂ and N₂O. Through a midsternal or left intercostal thoracotomy, the pericardium was opened, and the heart was exposed. A standard ECG (leads I, II, and III) was recorded by external limb electrodes (Schwarzer C 3600 cardiograph).

A spoon-shaped mapping electrode (diameter, 4 cm) containing 248 regularly spaced silver electrodes (diameter, 0.3 mm; interelectrode distance, 2.5 mm) was used for simultaneous recording of 248 unipolar atrial electrograms from the lateral wall of the left atrium (Fig 1, top). Previous experiments in conscious dogs as well as preliminary experiments in open-chest dogs revealed that constant capture of atrial fibrillation by rapid pacing was more successful in the left than in the right atrium. A silver plate (diameter, 3 cm) fixed to the internal thoracic wall was used as an indifferent electrode.

All electrograms were individually amplified (bandwidth, 1 to 500 Hz; gain, 200 to 300), multiplexed (sampling rate, 1 kHz), AD-converted (resolution, 8 bits), and continuously recorded on videocassette (Sony SL-C9ES). After the experiment, time windows of 4 seconds of data were selected from tape and transferred to a personal computer (Olivetti). The software used for analysis of the signals included an algorithm for automatic detection of the intrinsic negative deflections of the electrograms, generation of color-coded activation maps, and interactive editing of local activation times. In case of fragmented electrograms, the steepest intrinsic deflection was taken as the moment of local activa-
Conduction block was defined as a local conduction velocity of less than 8.25 cm/s associated with an apparent change in direction of impulse propagation distal to the site of conduction block. A detailed description of the mapping system has been given elsewhere. Experimental Protocol

In all experiments (n=6), first the lateral wall of the left atrium was mapped during sinus rhythm and regular pacing (interval, 300 ms). A stimulator was used, delivering symmetric biphasic rectangular pulses of 2-ms duration (Medtronic SP3084) to a pair of stimulating electrodes (platinum; diameter, 0.5 mm; interelectrode distance, 2.5 mm) located in the center of the mapping electrode. Biphasic stimuli were used to minimize polarization of the stimulating electrodes. The diastolic threshold for stimulation was determined during pacing with an interval of 300 ms. To pace the fibrillating atrium within a narrow partially excitable gap, a stimulus strength is required corresponding to the steep slope of the strength-interval relationship. Preliminary experiments revealed an optimal stimulus strength of six times the diastolic threshold. At lower stimulus intensities, entrainment of fibrillation was less successful, whereas further enhancement of the stimulus strength did not increase the likelihood of capture or the area of entrainment. The maps during entrainment of fibrillation showed that a stimulus of six times diastolic threshold still resulted in point stimulation of the atrium. Atrial fibrillation was induced by burst pacing (burst duration, 2 seconds; cycle length, 20 ms). All paroxysms of atrial fibrillation converted spontaneously to sinus rhythm. Only episodes lasting longer than 15 minutes were used in this study. During atrial fibrillation, rapid pacing was started with a cycle length equal to the median fibrillation interval at the site of pacing. Subsequently, the pacing interval was gradually varied in steps of 1 ms until atrial capture occurred. After constant capture was achieved, the time window of capture was determined by gradually shortening or lengthening the pacing interval until capture was lost. This procedure was repeated several times during each experiment.

To characterize the rate of atrial fibrillation, the median cycle length (P50) and the difference between the fifth and 95th percentiles (P5,95) of local fibrillation intervals were used. Other values are given as mean±SD.

Results

Before induction of atrial fibrillation, in each experiment the free wall of the left atrium was mapped both during sinus rhythm and during regular pacing with a cycle length of 300 ms (Fig 1, bottom). During sinus rhythm, the region under the mapping electrode was activated within 30 to 40 ms by a single broad activation wave. During pacing, the impulse propagated radially from the site of stimulation toward the periphery of the mapping electrode. No signs of slow conduction or local intra-atrial conduction block were seen. The electrograms recorded from different parts of the mapping electrode showed single rapid negative deflections of short duration and high amplitude. In all experiments (n=6), the average conduction velocity was 144±26 cm/s during sinus rhythm and 107±13 cm/s during pacing with an interval of 300 ms.

Mapping of Electrically Induced Atrial Fibrillation

In six dogs, atrial fibrillation was induced by a short burst of electrical stimuli applied to the free wall of the left atrium. The episodes of electrically induced atrial fibrillation lasted from 15 to 60 minutes, after which they spontaneously converted to sinus rhythm. In Fig 2, the ECG (leads I, II, and III) recorded during one of these episodes of atrial fibrillation is given together with a unipolar atrial electrogram recorded from the left atrium. The ECG fulfilled all of the classic criteria for atrial fibrillation, showing irregular fluctuations of the baseline without regular P or F waves and a totally irregular ventricular rhythm with narrow QRS complexes. The local atrial electrogram showed rapid and irregular atrial activity with a median cycle length of 91 ms and a variation (P95-P5) of 18 ms. The configuration of the individual electrical complexes changed from beat to beat.

Fig 3 shows a number of activation maps of the free wall of the left atrium during atrial fibrillation. In this example, the median fibrillation interval was 95 ms with a variation (P95-P5) of 38 ms. In the first map, the left atrium was activated by a single broad wavefront propagating at high speed (119 cm/s) toward the atrioventricular groove. The wave also propagated slowly (20 cm/s) into a posterior direction between two lines of functional conduction block (thick lines) leaving the mapping area at t=80 ms (where t is time). One second later (map 2), the atrium was activated in a completely different manner. At t=0 ms, now two waves entered the mapping area, one anteriorly and one posteriorly. The anterior wave was extinguished at t=40 ms when it reached the atrioventricular groove, and conduction into a posterior direction was prevented by a long line of functional conduction block. The posterior wave conducted slowly (35 cm/s) in a zig-zag manner between two lines of conduction block and collided at t=80 ms in the center of the mapping electrode with another wave that had entered at the upper left corner at t=70 ms. Another second later (map 3), the atrium was activated by two opposite waves colliding in the center of the map at t=30 ms. In the right part of the mapping area, a line of functional conduction block separated the two waves. As a result, the inferior part was activated from right to left and the superior part was activated from left to right with a total conduction time of more than 80 ms. Maps 4 through 6 further illustrate the high degree of variation in activation pattern during fibrillation due to multiple wandering wavelets separated by lines of functional conduction block that constantly change in size and localization. Although in map 5 the atrium was activated at high speed by a single broad wavefront, maps 4 and 6 show two examples of a wave front making a 180° turn. Such marked changes in direction of propagation were seen frequently. In contrast, complete intra-atrial reentrant circuits were observed only very rarely. During fibrillation, conduction velocity varied markedly from as high as 139 cm/s in map 5 to as low as 20 cm/s in the upper right corner of map 1. In all dogs (n=6), the conduction time of individual wavelets under the mapping electrode ranged between 30 and 90 ms. Given the average median fibrillation interval of 98±16
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ECG

I

II

III

0.5 s

2 s

200 ms

Left atrium

FIG 2. The ECG (leads I, II, and III) recorded during electrically induced atrial fibrillation together with a single unipolar electrogram recorded from the left atrium. The ECG was characterized by the absence of discrete P or F waves and showed continuous irregular fluctuations of the baseline and irregular RR intervals with narrow QRS complexes. The unipolar electrogram shows rapid irregular atrial activity (dog 6).

In Fig 4, the temporal and spatial variations in electrical activation of the free wall of the left atrium are shown for 4 seconds of fibrillation. In the middle panel, the local fibrillation intervals are plotted sequentially. In the lower panel, the number of electrodes (expressed as percentage of the total mapping area) are plotted that are activated during each period of 10 ms. This figure shows that despite the activation by multiple wavelets, frequently the free wall of the left atrium was free of propagating wave fronts, again emphasizing that complete reentrant circuits were not operative within the mapping area. On the other hand, sometimes electrical activity continued for periods longer than the fibrillation interval (horizontal bars below abscissa). These periods of continuous electrical activity were due to early entry of new fibrillation waves while previous wavelets were still propagating under the mapping electrode or to the presence of long arcs of functional conduction block temporarily dissociating different parts of the mapping area. Only rarely was closed-loop reentry found to be responsible for continuous electrical activity.

Regional Entrainment of Atrial Fibrillation

In Fig 5, an example is shown of overdrive pacing of atrial fibrillation. The atrium was paced at the center of the mapping electrode with a regular interval of 86 ms. At the site of pacing, the median fibrillation cycle length was 91 ms (P<0.05, 32 ms). The electrogram shown at the top was recorded close to the site of stimulation. In the first part of the tracing, the stimuli did not capture the atrium as can be seen from the variation in configuration and cycle length of the electrogram and from the dissociation between stimulus artifacts and atrial responses. However, at the moment indicated by the arrow, the electrogram suddenly became phase-locked to the stimulus and the atrial responses became constant in configuration. Before regional capture of atrial fibrillation occurred, the atrium under the mapping electrode was activated in an irregular manner by multiple wavelets from various directions (maps 1
Fig 3. Activation of the lateral wall of the left atrium during electrically induced atrial fibrillation. Top, The ECG (lead II) and an electrogram recorded from the center of the mapping electrode (asterisk in map 1) are shown. The maps, taken at about 1-second intervals, correspond to the beats indicated by the encircled numbers on the electrogram. The lower edge of the mapping electrode was positioned over the atrioventricular groove (hatched area). Isochrones were drawn every 10 ms. During fibrillation, the left atrium was activated by multiple wavelets (arrows) entering the mapping area from different directions. Frequently, arcs of intra-atrial conduction block occurred (thick lines) (dog 3).

through 3). During the first map, a single fibrillation wave entered the mapping area at the left side at t = -58 ms, and the site of pacing at the center of the mapping electrode was activated at t = -10 ms. Thus, at the moment the stimulus was given (t = 0 ms), the fibers under the stimulating electrodes were in their refractory period and the stimulus was not effective. During the next beat (map 2), the site of pacing was activated 6 ms before the moment of stimulation, and the stimulus fell again in the absolute refractory period. During the third beat, the stimulus was given simultaneously with activation of the site of pacing by a broad fibrillation wave (propagating from the upper left to the lower right part of the electrode) that did not appear to be affected by the stimulus. During the fourth beat, however (map 4), the area under the pacing electrode was clearly captured by the stimulus, and the lower right quadrant of the mapping area was activated by a paced wave front. The stimulus was given 86 ms after the previous beat, and capture was obtained because a next fibrillation wave did not enter the mapping area until only 10 ms before the stimulus. Because the conduction time toward the center of the electrode was longer than 10 ms, the pacing site could be excited by the stimulus before it was reached by the fibrillation wave. Because the estimated fibrillation interval at the site of pacing between beats 3 and 4 would have been 102 ms if the stimulus had not been given, a local excitable gap of at least 16 ms would have been present. During the subsequent beats (maps 5 and 6), almost the entire mapping area was activated by a single wave front propagating radially from the site of stimulation. Only a small segment of the upper part of the electrode remained activated by incoming fibrillation waves.

In the Table, the entrainment intervals in five dogs are compared with the local fibrillation intervals measured in the center of the mapping electrode during a period of 10 seconds. Due to technical difficulties in one
dog (dog 6), the experimental protocol could not be completed (data excluded from the table). Although in these five dogs the average median fibrillation interval was 95±14 ms, the shortest cycle of stable entrainment was 89±16 ms. The shortest pacing interval of 89 ms coincided with the P_{95} of the fibrillation interval histogram. This implies that during at least 70% of all fibrillation intervals an excitable gap must exist. Because the average P_{95} of the fibrillation intervals was 110±15 ms, during the longer fibrillation intervals the excitable gap can be as long as 20 ms.

During sustained capture of atrial fibrillation, the area of entrainment varied from case to case. In Fig 6, an example is given in which the entire area under the mapping electrode was entrained by rapid pacing (interval, 102 ms). Although the surface ECG and the right atrial electrogram still showed all of the characteristics of atrial fibrillation, almost the entire free wall of the left atrium was entrained. The four consecutive maps show that the entire mapping area was activated by the stimulus without any sign of intra-atrial conduction block or entering of fibrillation waves. In Fig 7, another example is given in which the area of entrainment was more limited. In this case, during sustained capture of atrial fibrillation with a pacing interval of 98 ms, marked beat-to-beat differences in activation pattern were found. Only the right part of the mapping area was activated in a regular 1:1 fashion, whereas the left part was activated irregularly. The electrogram recorded from the right part of the mapping electrode (asterisk)
FiguRe 5. Epicardial mapping of the free wall of the left atrium during capture of atrial fibrillation by rapid pacing with a constant interval of 86 ms. The six consecutive maps show the transition between atrial fibrillation and regional capture by local stimulation at the center of the mapping electrode. The unipolar electrogram (top) was recorded close to the pacing site (asterisk in map 1). During the first three beats, the stimuli were given shortly (10, 6, and 1 ms, respectively) after the pacing site was activated by a fibrillation wave and thus were not effective. During beats 4 through 6, the atrium was captured by the stimuli, resulting in entrainment of most of the atrium under the mapping electrode. In each map, t=0 corresponds to the moment of stimulation. Thick lines indicate arcs of conduction block. The dashed area of the mapping electrode was positioned over the atrioventricular groove (dog 6).

showed a constant configuration and was phase-locked to the stimuli. In contrast, the electrogram recorded from the left part of the electrode (triangle) varied both in configuration and in time relation to the stimulus artifacts. The extent to which the left part of the mapping area was activated by the stimulus varied from beat to beat. During some beats, it was almost completely activated by the paced wave front (ie, maps 2, 3, and 6), whereas during other beats, the entire left margin of the mapping electrode was activated by fibrillatory wavelets (maps 1, 5, and 8). Complete capture of the mapping area was prevented for two reasons. First, when the fibrillation interval was shorter than the pacing interval, a fibrillatory wave invaded the area of entrainment to collide with the paced wave front. Examples of this can be seen in maps 2, 3, and 7. Second, due to the high rate of pacing, intra-atrial conduction block of the paced wave front occurred. Good examples of this can be seen in maps 5 and 8, in which a long line of functional conduction block prevented the stimulus to activate the left part of the mapping area, which then was consecutively activated retrogradely by a fibrillation wave. Note that in map 7 only a couple of milliseconds before the stimulus was delivered, an area close to the site of stimulation was depolarized. Although the possibility of abnormal impulse formation cannot be excluded, the most likely explanation of this phenomenon is epicardial breakthrough of a fibrillatory wavelet propagating in one of the atrial trabeculae. Although the occurrence of intra-
Loss of Capture by Pacing Too Slowly or Too Rapidly

When the pacing interval was made either longer or shorter, at a given moment regional control of atrial fibrillation was lost. In Fig 8, an example is shown in which capture was lost because pacing was too slow (pacing interval, 104 ms). As can be seen from the electrogram at the top, from the moment indicated by the arrow the atrial responses started to precede the stimuli, and thus capture of fibrillation was lost. Maps 1 through 6 show the sequence of events leading to loss of capture. In map 1, the mapping area was still completely captured by the stimulus, resulting in a wave front spreading radially from the site of stimulation to the borders of the electrode. No signs of slow conduction or intra-atrial conduction block were present. During beats 2 through 6, the upper part of the mapping area was progressively invaded by a single small fibrillatory wavelet. Because the fibrillation interval was slightly shorter than the pacing interval, during each beat this wavelet penetrated further into the area of entrainment, finally resulting in activation of the site of pacing slightly before the stimulus (map 5). As a result, the stimulus was no longer effective, and maps 5 and 6 show complete activation by fibrillation waves. When pacing too slowly, in all cases progressive retrograde penetration of fibrillatory wavelets into the mapping area was the reason for loss of capture.

In Fig 9, the sequence of events leading to loss of capture by pacing too rapidly are shown. In this example, 1:1 capture was maintained up to a pacing interval of 71 ms. During pacing at 70 ms interval capture was suddenly lost (arrow). During beats 1 through 4, capture was still maintained, and a radially propagating wavefront activated the area around the pacing site. Due to the high pacing rate, arcs of antegrade intra-atrial conduction block were present (thick lines). In map 4, the paced impulse turned slowly in a counterclockwise direction around one of these lines of conduction block.

<table>
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<th>Dog</th>
<th>( P_{50} )</th>
<th>( P_5 )</th>
<th>( P_{95} )</th>
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\( P_{50} \) indicates the median cycle length; \( P_5 \), fifth percentile; and \( P_{95} \), 95th percentile.

**FIG 6.** Four consecutive maps during entrainment of the free wall of the left atrium with a pacing interval of 102 ms. The left atrial electrogram was recorded close to the pacing site (see asterisk in map 1). While the ECG (lead II) and the electrogram from the right atrial appendage (RA) show the continuation of atrial fibrillation, the entire area under the mapping electrode was captured by the stimulus. In each map, the moment of stimulation has been taken as \( t=0 \) ms (dog 3).
and reentered the area under the pacing electrodes. As a result, during beats 5 and 6, the site of stimulation was activated by local intra-atrial reentry with a revolution time of 60 ms. Consequently, because the pacing interval was 70 ms, capture was lost.

**Local Acceleration of Atrial Fibrillation by Rapid Pacing**

The phenomenon of local acceleration of atrial fibrillation by rapid pacing is further illustrated in Figs 10 and 11. In Fig 10, the local fibrillation intervals recorded at 2.5 mm from the site of stimulation are plotted sequentially. Before and after pacing, the fibrillation interval varied between 82 and 116 ms, with a median interval of 96 ms. During 10 seconds, the atrium was paced with a constant interval of 96 ms. Shortly after pacing was started, atrial fibrillation accelerated, and the fibrillation intervals varied between 45 and 90 ms (P50, 63 ms). After about 7 seconds of pacing, the fibrillation intervals gradually became longer again until 1:1 capture occurred. When the pacemaker was turned off, atrial fibrillation continued at the same rate as before. In all dogs, such episodes of transient acceleration of atrial fibrillation by rapid pacing were found. The average median interval of accelerated atrial fibrillation was 55±30 ms (n=6).

In Fig 11, eight consecutive activation maps are shown representing the events during the initial phase of acceleration of fibrillation as indicated by the open box in Fig 10. During the first three beats, the left atrium was activated by fibrillation waves entering the mapping area with a cycle length of 80 to 90 ms. The stimuli applied at the center of the mapping electrode were not effective because they fell in the refractory period of these fibrillatory wavelets. In map 4, the stimulus applied at t=263 ms was given 66 ms after the pacing site had been activated by the previous fibrillatory wave. Obviously, this time was sufficient for the fibers to restore their excitability, and the stimulus evoked a propagated wave front colliding with a fibrillation wavelet entering the mapping area at the top. Propagation into the direction of the atrioventricular groove was blocked (double bars). The stimulated wave front turned counterclockwise around the left end of this line of block and reentered the site of pacing 64 ms after the stimulus. This resulted in a small intra-atrial
FIG 8. Loss of capture is shown as a result of pacing too slowly. In this experiment, stable capture was maintained at pacing intervals between 89 and 104 ms. During pacing at 104 ms, capture suddenly was lost at the moment indicated by the arrow. Bottom, The activation patterns during loss of capture are given. During beats 1 through 3, capture was maintained. In map 4, the pacing site was activated simultaneously by an incoming fibrillation wave and the stimulus. During beats 5 and 6, the pacing site was prematurely activated by fibrillation waves, and capture was lost. All isochrones are related to the moment of stimulation (t=0). The electrogram was recorded at the asterisk (map 1). The dashed area represents the atrioventricular groove (dog 3).

Discussion

Spread of Excitation During Electrically Induced Atrial Fibrillation

During atrial fibrillation, the electrical activity of the atria is represented by a continuous irregular undulation of the ECG baseline without P or F waves. Unipolar electrograms recorded directly from the surface of the atria show rapid local activations varying in both configuration and cycle length. Based on animal experiments and computer simulations, Moe and colleagues hypothesized that atrial fibrillation was maintained by multiple independent wavelets activating the atria irregularly and at a very high rate. Hoffman
Lossof capture

* I

(70 ms)

1 2 3 4 5 6

100 me

3

4

6C

3

4

FIG 9. Loss of capture is shown as the result of pacing too rapidly. In this experiment, stable capture was maintained at pacing intervals between 89 and 71 ms. During pacing at 70 ms, capture was lost due to local acceleration of fibrillation (arrow). Bottom, The activation maps during loss of capture are given. During beats 1 through 4, capture was maintained despite the presence of various arcs of antegrade conduction block (thick lines). During beat 4, local intra-atrial reentry occurred, and the pacing site was activated simultaneously with the next stimulus (map 5). In map 6, the mapping area was completely activated by the local reentrant circuit (revolution time, 60 ms), and capture was lost. All isochrones are related to the moment of stimulation (t=0). The electrogram was recorded at the asterisk (map 1). The dashed area represents the atrioventricular groove (dog 2).

and Rosen designated this process as random reentry. Recently, high-resolution mapping studies of atrial fibrillation both in canine hearts and during cardiac surgery in humans confirmed this hypothesis. It was estimated that an average of four to six independent wandering wavelets must be present to maintain the fibrillatory process. Therefore, in the present experiments, big dogs with a relatively large atrial tissue mass were used in which episodes of sustained atrial fibrillation could be induced easily. The present mapping results closely agree with earlier findings in showing that during atrial fibrillation, the free wall of the left atrium was activated by single or multiple wavelets entering from different directions. Frequently, multiple wavelets fused into a single wave front, or new waves were formed after interference with a local arc of conduction block. Although the fibrillatory wavelets frequently changed the direction of propagation and often made a 180° turn, a full 360° reentrant loop rarely was observed in the free wall of the left atrium. In a recent mapping

FIG 10. Local acceleration of atrial fibrillation by rapid pacing. The local fibrillation intervals recorded 2.5 mm from the site of pacing are plotted sequentially. During atrial fibrillation (AF), the atrium was paced with a constant cycle length of 96 ms for 10 seconds. The horizontal dotted line indicates the pacing interval. The activation maps given in Fig 11 were recorded during the initial phase of acceleration of atrial fibrillation as indicated by the open box (dog 3).
study in both dogs and patients, Cox and colleagues described a wide spectrum of activation patterns during atrial fibrillation, ranging from a single localized or shifting reentrant circuit irregularly activating the rest of the atria to more complex and continuously changing activation patterns as found in the present experiments and caused by multiple independent wavelets. Because we mapped only the left atrial wall, the presence of a single localized reentry circuit in the right atrium could not be excluded but appears to be unlikely because the electrogram recorded from the right atrium was irregular in both configuration and cycle length. In a study by Konings and colleagues, three types of atrial fibrillation were distinguished: type I, characterized by single broad wave fronts activating the right atrium without significant areas of slow conduction or conduction block; type II, characterized by the presence of two or three wavelets propagating into different directions and frequently changing speed and direction of propagation; and type III, in which the excitation of the atria was highly complex due to a high degree of fragmentation into numerous different wavelets that frequently fused and collided or reentered areas shortly after they had been activated by another wavelet. According to these criteria, fibrillation in the present study should be classified as type II.

**Regional Entrainment of Atrial Fibrillation**

In patients with atrial flutter (type I), Waldo and colleagues were the first to demonstrate that rapid pacing could entrain atrial flutter. They further showed that increasing the rate of entrainment frequently resulted in termination of atrial flutter. Recent mapping studies demonstrated that during entrainment, the paced wave front enters the excitable gap of the reentry circuit to propagate both in antidromic direction to collide with the orthodromic wave front of the preceding beat and in orthodromic direction to reset the tachycardia. Termination of the reentrant circuit occurs when the paced orthodromic wave front is blocked. Successful entrainment of a reentrant tachycardia depends not only on the existence of an excitable gap but also on a proper site of stimulation. If the site of pacing is located far away from the reentry circuit, entrainment may fail due to conduction disturbances of the stimulated wave fronts between the pacing site and the reentry circuit.

In the present study, high-resolution mapping of atrial fibrillation revealed that the mechanisms of regional control of fibrillation by rapid pacing are not essentially different from entrainment of atrial flutter. Pacing during fibrillation with a cycle length slightly shorter than the median fibrillation interval led to penetration of paced wave fronts into the excitable gap between the wandering fibrillation waves (Fig 5). The resulting radially propagating stimulated wave fronts partly collided with incoming fibrillation waves (comparable with the antidromic wave during entrainment of flutter) and partly acted as new wave fronts participating in the fibrillatory process (orthodromic wave during entrainment of flutter). Analogous to entrainment of atrial flutter, during the onset of entrainment of atrial fibrillation the site of collision between the paced wave front and incoming fibrillatory waves gradually shifted away from the site of pacing. Prolongation of the pacing interval allowed the entering fibrillatory waves to approach the pacing site and resulted in loss of capture. Shortening of the pacing interval during entrainment reduced the number of fibrillation waves that could enter the area of entrainment. In contrast to entrainment of atrial flutter, increasing the pacing rate did not result in termination of atrial fibrillation. Instead, local
acceleration of fibrillation occurred, which led to loss of entrainment.

Acceleration of Atrial Fibrillation by Rapid Pacing

Acceleration of reentrant tachycardia by overdrive pacing is well documented and is thought to be due either to the induction of a new (faster) reentry circuit or to the creation of “double-wave” reentry. The present study shows that pacing-induced acceleration of atrial fibrillation is due to the induction of small leading circle reentrant circuits (diameter, approximately 3.5 cm) near the site of pacing. These small reentrant circuits were not stationary but rather changed in both size and position (wandering leading circle). They always terminated spontaneously, which was promptly followed by resolution of the original fibrillation rate. Because leading circle reentry is thought to have no excitability gap, acceleration of atrial fibrillation can simply be explained by the induction of temporary leading circle reentry. In addition, rapid pacing during atrial fibrillation might cause further rate-dependent shortening of the refractory period, facilitating induction of leading circle reentry of small dimensions and cycle length.

What Limits the Area of Capture?

Theoretically, in a homogeneous medium, regional entrainment of atrial fibrillation with a pacing interval slightly shorter than the median fibrillation interval should result in progressive enlargement of the area of entrainment until the boundaries of the atria are reached and all fibrillatory wavelets are extinguished. In reality, however, atrial fibrillation could not be terminated by local pacing from a single site because the area of capture remained limited to a region with a diameter of about 5 cm. Mapping of regional entrainment of atrial fibrillation showed that a progressive shift of the collision point between paced and fibrillatory wavelets further away from the site of pacing was prevented by conduction block of the paced wave fronts (see Fig 8). It is known that the atria are far from homogenous and show a considerable degree of spatial dispersion in refractory period, excitability, and conduction velocity. and colleagues demonstrated that in the dog, the refractory periods in the left atrium are shorter than those in the right atrium. This probably also accounts for the differences in fibrillation rate between the left and right atria. We believe that spatial inhomogeneities in refractory period are responsible for failure to entrain both atria during fibrillation. If not all parts of the atria can follow the high pacing rate in a 1:1 manner, intratrial conduction block of the paced depolarization waves will occur in areas with longer refractory periods. In these parts, atrial fibrillation will proceed at a slower average rate than the rate of entrainment, thus maintaining the asynchrony in activation that is responsible for perpetuation of fibrillation.

Study Limitations

A limitation of the present study is that only part of the atria could be mapped. Complete mapping of both atria with the available number of electrodes would have lowered the spatial resolution to such an extent that reliable reconstruction of the complex activation patterns during fibrillation would not have been possible. Total atrial mapping is required to provide more insight in the effects of regional entrainment of fibrillation on the fibrillatory process in the remaining part of the atria.

Although the present mapping study demonstrated that the phenomena of transient entrainment are not restricted to single reentrant circuits but also may occur in case of random reentry by multiple wavelets, regional control of fibrillation by rapid pacing did not result in termination of atrial fibrillation. Apparently, the average number of fibrillation waves in the remaining part of the atria still exceed the critical number of wavelets required for perpetuation of fibrillation. Obviously, further enlargement of the total area of entrainment would be necessary to terminate the arrhythmia. This may be achieved either by optimization of the pacing protocol or by pacing at multiple sites. Instead of using a fixed pacing interval as we did in the present study, one might vary the interval of entrainment depending on the interval between the surrounding fibrillation waves. In this way, the average rate of entrainment might be decreased without losing control at the site of pacing. It may be expected that pacing at an average rate that is slower will lead to entrainment of a larger part of the atrium. Pacing at multiple sites and synchronizing the different areas of entrainment could be another approach to enlarge the tissue mass that is being defibrillated by local pacing. Whether entrainment of atrial fibrillation will have future implications for the management of atrial fibrillation will depend in large part on the degree of success of these changes.

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