Regional Control of Atrial Fibrillation by Rapid Pacing in Conscious Dogs

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Background. In five chronically instrumented conscious dogs, we studied the effects of rapid pacing on sustained electrically induced atrial fibrillation.

Methods and Results. Twenty-three unipolar atrial electrograms were recorded simultaneously from the bundle of Bachmann and the lateral wall of the right and left atria. During sustained atrial fibrillation, the surface electrocardiogram showed continuous irregularities of the baseline without P or F waves as well as an irregular ventricular rhythm with narrow QRS complexes. The atrial electrograms showed rapid irregular activity with a median cycle length of 85±8 msec and a range (P5–P95) of 33±18 msec. Overdrive pacing of atrial fibrillation was performed using symmetric biphasic rectangular stimuli (2-msec duration, sixfold that of threshold) applied to a pair of stimulating electrodes at the left atrial appendage. Stimulation was started at pacing intervals of about 10 msec longer than the local median fibrillation interval and subsequently shortened in steps of 1 msec. At a critical pacing interval slightly shorter than the median fibrillation interval, the atrium around the pacing site was suddenly captured by the electrical stimuli. The area of local capture had a diameter of 6.1±1.6 cm. The time window of capture was 12±4 msec.

Conclusions. These observations show that during electrically induced atrial fibrillation in chronically instrumented conscious dogs, a short excitable gap is present, permitting regional control of the fibrillatory process by rapid pacing. (Circulation 1991;84:1689–1697)

Programmed electrical stimulation has proven to be a powerful tool in the diagnosis and treatment of various cardiac arrhythmias.1–5 Reentrant arrhythmias like atrial flutter and ventricular tachycardia often can be initiated and terminated by one or more properly timed premature stimuli, whereas rapid pacing at a higher rate than the reentrant tachycardia can entrain and terminate these arrhythmias.6,7 In contrast, attempts to terminate atrial or ventricular fibrillation by local pacing have failed. This has led to the common opinion that fibrillation cannot be influenced by local electrical stimulation.8,9

As proposed by Moe et al10–12 and later experimentally confirmed by Allessie et al,13 atrial fibrillation is based on multiple wandering wavelets that randomly reenter areas soon after they have recovered excitability from previous activation by another wavelet. As a result, the atrium is activated at a very high rate, and local atrial electrograms constantly vary in both configuration and cycle length. The reason for the variation in local fibrillation intervals is not fully understood. On one hand, it might reflect variations in the duration of local refractoriness since the refractory period depends on multiple factors like the direction of impulse propagation (anisotropy),14–16 the length of the previous interval, and electrotropmodulation of the action potential by neighboring wavelets or local intra-atrial conduction block. On the other hand, it is feasible that the variation in cycle length during fibrillation is caused by the fact that after recovery of excitability, the fibers are not always immediately reentered by one of the wandering wavelets. In that case, the local cycle length during fibrillation is determined by the local refractory period plus a variable time that the fibers have to wait before one of the depolarization waves comes close enough to actually activate them again. The latter hypothesis implies that during fibrillation, the atrial fibers are not always activated at their maximal rate and that a short but variable excitable gap might be present.
The aim of the present study was to test the hypothesis that during atrial fibrillation an excitable gap exists and to evaluate to what extent the excitation process during atrial fibrillation can be affected by local electrical pacing. Our results show that in a small time window of 12±4 msec, regular rapid pacing with a cycle length slightly shorter than the average fibrillation interval can capture the atrium over a distance of 3 cm around the site of pacing. This indicates that during atrial fibrillation, a short but significant excitable gap is present that offers the possibility of interfering with the fibrillatory process by local electrical stimulation.

Methods

Five conscious chronically instrumented male mongrel dogs weighing 35–64 kg were used for the present study. To implant a number of epicardial electrodes, the animals were premedicated with Hypnorm® (0.4 ml/kg i.v.) and anesthetized with sodium pentobarbital (15 mg/kg i.v.) followed by positive pressure ventilation with a 2:1 mixture of O₂ and N₂. Through a left intercostal thoracotomy, the pericardium was opened and the heart was exposed. A silicon band (Silastic®) of 10×1.2 cm containing a row of 11 unipolar platinum recording electrodes (diameter, 1.5 mm; interelectrode distance, 6–10 mm) was led through the anterior transverse tunnel between atria and aortic root and sutured to the tips of the left and right atrial appendages. In addition, a row of six electrodes was sutured to the lateral wall of the left and right atria (Figure 1). After closing the pericardium, the electrode leads were tunneled subcutaneously to the neck and exteriorized by a 30-pin connector (outer diameter, 11 mm; Lemos®) through a small cutaneous incision. Three silver plates (diameter, 25 mm) were left subcutaneously to serve as reference and grounding electrodes.

Experimental Protocol

The dogs were studied after they had been allowed to recover from surgery for at least 3 days. A multichannel amplifier unit (BurrBrown INA 102 AG; bandwidth, 1–500 Hz) for simultaneous recording of all unipolar electrograms was plugged into the connector in the neck of the dog. A standard surface electrocardiogram (leads I, II, and III) was recorded by external limb electrodes (Schwarzer C3600 cardio graph). A programmable stimulator (SP 3084, Medtronic) delivering symmetric biphasic rectangular pulses of 2-msec duration and six times diastolic threshold (0.3–3.0 mA) was connected to a pair of stimulating electrodes (interelectrode distance, 6 mm) at the left atrial appendage (Figure 1). Biphasic stimulation was used to minimize polarization of the electrodes by alternating anode and cathode. All dogs were studied under unrestrained conditions. Atrial fibrillation was induced by a 2-second burst of stimuli with a cycle length of 20 msec. The duration of the episodes of fibrillation varied from several minutes to more than 3 hours, after which sinus rhythm resumed. After atrial fibrillation had lasted for at least 15 minutes, local electrical stimulation of the left atrial appendage was started. Fixed rate pacing was started at a cycle length of 10 msec longer than the average local fibrillation interval. Subsequently, the pacing interval was gradually shortened in steps of 1 msec up to the shortest fibrillation interval. This procedure was repeated several times at different days to study the variability of the observed phenomena. All electrograms were stored on magnetic tape for off-line analysis. The steepest negative deflection of the electrograms was taken as the moment of local activation.

Results

Characteristics of Electrically Induced Atrial Fibrillation

Long-lasting episodes of sustained atrial fibrillation were induced by a short burst (2 seconds) of stimuli (interval, 20 msec) applied to the left auricle. In Figure 2, a surface electrocardiogram (leads I, II, and III) is given during sinus rhythm and an episode of sustained atrial fibrillation. During sinus rhythm, the P waves were positive in all leads and normal in amplitude and duration. During atrial fibrillation, the ventricular rhythm was totally irregular with narrow QRS complexes of the same morphology as during sinus rhythm. Regular P or F waves were absent, and the electrocardiogram showed continuous irregular fluctuations of the baseline. Thus, all classic electrocardiographic criteria of atrial fibrillation were fulfilled. In Figure 3, a single unipolar electrogram recorded from the left atrium is shown during the induction of atrial fibrillation. In the lower part of the figure, a short time window of the electrogram during atrial fibrillation is shown at a faster time base. During fibrillation, atrial activation was extremely rapid and irregular, and both the amplitude and
configuration of the successive electrical responses varied continuously. In Figure 4, the temporal variation in local fibrillation intervals is shown for a 12-second period of atrial fibrillation. In the upper panel, the intervals between the successive local activations are plotted sequentially. The activation intervals showed a considerable beat-to-beat variation ranging from 56 to 108 msec. The interval histogram (lower panel) showed a distribution with a median cycle length of 78 msec and a 90% variation (P5–95) of 26 msec. In all dogs, the median fibrillation interval of the left atrium was slightly shorter than in the right atrium (right, 88±7 msec; left, 82±6 msec; p<0.05). No differences in stability or rate of fibrillation were found during measurements on several days.

**Local Pacing of Atrial Fibrillation**

The effects of rapid pacing during atrial fibrillation are demonstrated in Figure 5. In this example, the left atrial appendage was paced with a constant interval of 78 msec (top). The three unipolar electrograms were recorded simultaneously from electrodes on the bundle of Bachmann at distances of 1, 2, and 3 cm from the stimulating electrodes. During atrial fibrillation (left part of tracings), the electrograms varied constantly in morphology and cycle length.
The first eight stimuli did not affect the fibrillatory process because they were falling in the absolute refractory period because the atrium in the vicinity of the pacing site was activated shortly before by one of the fibrillatory impulses. At a certain moment, however (asterisk), the first electrogram recorded at 1 cm from the pacing site suddenly became phase-locked to the stimulus artifact and, simultaneously, the configuration of the electrogram became constant. Two cycles later, the second electrogram recorded 2 cm from the site of stimulation showed the same phenomena, suggesting regional capture of the fibrillating atria. During capture, the difference in activation time between the first and second electrograms was constant (11 msec), indicating regular propagation of a wave front from the site of pacing with a conduction velocity of 91 cm/sec. The third electrogram recorded at a distance of 3 cm from the pacing site showed a different response. During some cycles, the electrogram appeared to be in phase with the stimulus artifact. However, at other moments, it was clearly out of phase, and the configuration of the electrogram varied. Apparently, 3 cm from the site of stimulation, the atrium was not always activated by the wave front originating at the pacing site, but the perturbations in cycle length and morphology of the electrogram indicate occasional activation by fibrillatory wavelets. In other experiments, similar results were obtained. In all dogs, the average distance from the site of pacing that could be captured was 3.1±0.8 cm.

**Time Window of Capture**

Once local capture of atrial fibrillation had been achieved, the pacing rate could be varied within a narrow range without loss of capture. In Figure 6, a single electrogram recorded at a distance of 1 cm from the site of stimulation is shown during constant pacing with a cycle length between 81 and 67 msec. Local capture was maintained at pacing cycles between 80 and 68 msec. Pacing with either longer or
shorter cycles (top and bottom tracings) resulted in loss of capture revealed by the variation in configuration of the electrogram and total dissociation between stimulus artifacts and atrial responses. Thus, in this example, atrial fibrillation could be captured within a time window of 13 msec. In all experiments ($n=16$), the average longest pacing cycle at which capture was maintained was 84±5 msec. This was slightly longer than the median fibrillation interval at the pacing site in the left atrium of 82±6 msec. Apparently, as soon as more than 50% of the fibrillation cycles were shorter than the pacing interval, capture of atrial fibrillation was lost. The time window of capture ranged from 6 to 19 msec with a mean of 12±4 msec. Using stimuli of less than six times diastolic threshold resulted in smaller time windows of capture, whereas higher stimulus intensities did not lengthen the measured excitable gap during fibrillation. Termination of atrial fibrillation by local pacing was never observed.

**Area of Capture**

The area of local capture of fibrillation was dependent on the pacing interval. In Figure 7, six electrograms are shown recorded from the bundle of Bachmann, the left atrial appendage, and the left lateral wall. In the three panels, atrial fibrillation was captured with cycle lengths of 80, 74, and 69 msec, respectively. During pacing with a cycle length of 80 msec (left panel), all electrograms were phase-locked to the stimulus artifact and showed a constant morphology, indicating that almost the entire left atrium was captured. When the pacing interval was shortened to 74 msec (middle panel), the electrodes located far from the site of pacing (bundle of Bachmann and left lateral wall) became dissociated from the stimuli and showed electrograms of varying morphology. When the pacing interval was further shortened to 69 msec (right panel), synchronization close to the pacing site was still maintained, but most electrograms now varied in morphology suggesting beat-to-beat changes in local activation. In other experiments, similar results were obtained. Thus, increase of the pacing rate resulted in a reduction of the area of local capture, the largest portion of the atrium being captured during pacing with the longest possible cycle length.

**Loss of Capture**

Figure 8 shows a single atrial electrogram recorded 1 cm from the site of pacing during sustained atrial fibrillation and loss of atrial capture by pacing either too slowly or too fast. When the pacing interval was gradually lengthened to 81 msec during stable capture, the atrial electrogram suddenly changed in morphology, and capture was lost (arrow). Obviously, pacing at a too slow rate allowed one of the fibrillatory wavelets to penetrate the area of capture and to prematurely activate the tissue under the stimulating electrodes. As a result, the electrical stimuli became ineffective because they were falling in the absolute refractory period of the atrial fibers. Because a fixed pacing rate was used, failure of a single stimulus to excite the atrium led to complete loss of capture because the stimuli and the atrial activation were thrown out of phase. After loss of capture by pacing too slowly, the average fibrillation interval was similar to during control (79 versus 78 msec). Tracing C shows loss of capture after gradual shortening of the pacing interval to 67 msec. Again, the atrial electrogram suddenly became irregular in morphology, and synchronization with the stimulus artifact was lost (arrow). Opposite to what we expected, however, loss of capture during incremental pacing was not due to primary failure of one of the stimuli to excite the atrium at a critical rate. If that were the case, failure of one of the stimuli to excite the atrium should have resulted in a prolonged interval at the moment of loss of capture. However, during loss of capture, a shorter interval was always observed (arrow). In all experiments ($n=16$), loss of capture of atrial fibrillation by
incremental pacing occurred at a minimum mean pacing interval of 72±5 msec and was due to premature activation of the site of stimulation with an interval of 66±6 msec. This unexpected finding can be explained by the observation that immediately after loss of capture, the average local fibrillation interval was shorter than during control (63 versus 78 msec). Obviously, pacing at very high rates locally accelerated the fibrillation process. Local acceleration of atrial fibrillation by rapid pacing usually persisted only for a few seconds, after which the fibrillation rate returned to its original level.

Discussion

Mechanism of Atrial Fibrillation

During sustained atrial fibrillation, regular P or F waves are absent, and the electrical activity of the atria is represented in the surface electrocardiogram by continuous irregular fluctuations of the baseline. Electrograms recorded directly from the surface of the atria show rapid local activations that vary in both configuration and cycle length. On the basis of animal experiments and computer simulations, Moe et al.10–12 developed a "multiple wavelet" hypothesis to explain the electrophysiological mechanism of fibrillation: "... the grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. It may become extinguished as it encounters refractory tissue; it may divide again or combine with a neighbor; it may be expected to fluctuate in size and change in direction. Its course, though determined by the excitability or refractoriness of surrounding tissue, would appear to be as random as Brownian motion. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist."10

Using high-resolution mapping of the atria, Allessie et al.13,17 confirmed this hypothesis experimen-
tally, both in the isolated canine heart and during intraoperative mapping in humans. In the dog, the critical average number of wandering wavelets for sustained atrial fibrillation was estimated to be between four and six.\textsuperscript{13} Interestingly, in both humans and dogs, complete intra-atrial reentrant circuits were only rarely observed. More frequently, rather than reexciting their own wake of refractoriness, the wandering impulses reentered areas that had been activated shortly before by another wavelet. Hoffman and Rosen\textsuperscript{18} designated this type of reentry as “random reentry.”

Excitable Gap During Atrial Fibrillation

In our present series of electrically induced atrial fibrillation in awake chronically instrumented dogs, long-lasting episodes of atrial fibrillation were induced by rapid pacing. Stable atrial flutter and fibrillation have been reported in a canine model of sterile pericarditis.\textsuperscript{19–21} Although in the present chronic animal model, it has been shown that the refractory period and conduction velocity of the atria remained normal during a period of 2 months,\textsuperscript{22} it cannot be excluded that pathological changes due to the epicardial electrodes might have affected the vulnerability of the atria to atrial fibrillation. The average median fibrillation interval was 88±7 msec in the right and 82±6 msec in the left atrium ($p<0.05$). The histograms of local fibrillation intervals showed a variation (P$_{5-95}$) of 33±18 msec. This variation in cycle length can be explained by two different mechanisms. First, it might reflect temporal fluctuations in the functional refractory period of the atrium. Because of the complex and fragmented excitation during fibrillation, the duration of the action potential can be expected to vary because of electrotonic modulation by the passage of neighboring wavelets or local intra-atrial conduction block.\textsuperscript{23} In addition, early excitation might be prevented if the amount of excitatory current generated by a small approaching fibrillation wave is insufficient or is dissipated over a large area (impedance mismatch).\textsuperscript{24} Finally, if during atrial fibrillation the local cycle length varies, this will cause cycle length–dependent variations in the duration of the action potential.

An alternative explanation for the temporal variation in local fibrillation interval is the assumption of a variable excitable gap. If the cells are not always immediately activated by one of the wandering wavelets after they have regained a minimum level of excitability, the local cycle length will be determined by the local refractory period plus the time the cells have to wait until an excitation wave has come close enough to excite them. In that case, the shortest cycle length during fibrillation represents the local refractory period, whereas the longer cycles contain a partially excitable gap. Our present observations that in a time window of 12±4 msec local electrical stimulation (stimulus strength, six times threshold) during fibrillation resulted in regular wave fronts propagating away from the site of pacing demonstrate that such an excitable gap actually exists. This implies that the temporal variation in local fibrillation intervals is at least in part

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**Figure 8.** Three tracings of a single electrogram recorded at a distance of 1 cm from site of stimulation. Panel A: Atrial fibrillation without pacing. Panels B and C: Loss of capture because of pacing either too slowly (81 msec; panel B) or too fast (67 msec; panel C). Local fibrillation intervals during control and directly after loss of capture are indicated at right. Pacing at very short intervals (panel C) caused local acceleration of atrial fibrillation (average fibrillation interval, 63 vs. 78 msec).
due to variation in the duration of a short partially excitable gap, caused by continuous changes in the course of randomly reentering wavelets. In studies on type II atrial flutter in a canine sterile pericarditis model, mean excitable gaps of 18 and 25 msec were found.\textsuperscript{20,21} Thus, the excitable gap of 12±4 msec during atrial fibrillation is still shorter than the excitable gap during rapid atrial flutter.

**Mechanisms of Local Capture During Atrial Fibrillation**

In the present study, we used fixed-rate pacing to capture atrial fibrillation. The window of pacing intervals resulting in local capture was narrow and varied from 6 to 19 msec. When the pacing interval became longer than the average fibrillation interval, capture was lost, probably because the area around the stimulus electrode was invaded by one or more shortly coupled fibrillatory wavelets resulting in activation of the site of stimulation before the moment of the next scheduled stimulus.

We had expected gradual shortening of the pacing interval during capture to result in loss of capture because at a critical rate one of the stimuli would fail to excite the underlying tissue. The resulting doubling of the effective pacing interval would give ample opportunity to the fibrillatory waves to enter the area of capture and activate the tissue under the stimulating electrode. Consequently, at the moment of loss of capture, the cycle length under the stimulating electrode should be longer than the pacing interval. In contrast to what was expected, however, loss of capture during incremental pacing was always associated with a cycle length that was actually shorter than the pacing interval. This unexpected finding was found to be due to local acceleration of fibrillation by rapid pacing. The most likely explanation for this phenomenon is that pacing at rates higher than the average fibrillation rate further shortens the refractory period in the area of capture, thus facilitating the induction of small, closed reentrant circuits in the area around the pacing site. Because the cycle length of functional atrial reentry is primarily determined by the refractory period of the fibers,\textsuperscript{22} the initiation of such local reentrant circuits should result in acceleration of fibrillation. Spontaneous interruption of local leading circle reentry suddenly restores the original rate of fibrillation where multiple waves are reentering each other rather than themselves.

The observation that the area of local capture was limited to a distance of about 3 cm from the site of pacing might be due to spatial dispersion in the duration of the refractory period.\textsuperscript{26,27} The slightly lower rate of fibrillation in the right atrium can be explained by a somewhat longer refractory period in the right atrium.\textsuperscript{22} At the site of stimulation (left atrium), the longest pacing interval with which capture could be maintained was limited by the median fibrillation interval. Because of the somewhat longer refractory period in the right atrium, the slowest rate of capture of the left atrium was presumably too fast for the right atrium to follow in a 1:1 fashion. In this way, further extension of the area of capture toward the right atrium is limited by the occurrence of local intra-atrial conduction block of the propagating stimulated wave front.

**Future Implications**

Although we never succeeded in terminating atrial fibrillation by pacing, the possibility of controlling a considerable part of the atria by local electrical stimulation may provide a clue for alternative forms of electrical treatment of atrial fibrillation. In the present study, the atrium was captured over a distance of approximately 3 cm from the site of stimulation. Obviously, the area of capture was too small to terminate fibrillation because sufficient tissue mass was still involved in the fibrillatory process. If, however, the area of capture could be enlarged, the remaining fibrillating part of the atria might become so small that it can no longer sustain the fibrillatory process and atrial fibrillation might be terminated by local pacing. Although it is clear that we are still far from this option, there are several possible ways of improving the present pacing protocol. First, instead of using an independent fixed-rate pacemaker, sensed pacing might be used. A major limitation of fixed-rate pacing is that as soon as one of the applied stimuli fails to excite the atrium, capture of atrial fibrillation is completely lost. However, if failure of a single stimulus could be sensed, complete loss of capture might be prevented by resetting the moment of the next stimuli. This might enable capture of atrial fibrillation at slower pacing rates than during fixed-rate pacing. Because we have found that the area of capture is larger at slower pacing rates, in this way the area of capture might be effectively increased. Another obvious way to try to control a larger portion of the fibrillating atria is to pace at multiple sites. Whether local pacing of atrial fibrillation will become of clinical consequence will in large part depend on the effects of these changes in pacing technique.

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