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ARTICLE

Response of Type I Atrial Fibrillation to Atrial Pacing in Humans

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ABSTRACT: *Background* High-density mapping studies of atrial fibrillation (AF) have suggested the presence of an excitable gap. The purpose of this study was to assess the local and left atrial response to pacing at the high right atrium during type I AF in humans.*Methods and Results* Pacing was performed at the high right atrium during type I AF in 24 patients in the electrophysiology laboratory. The response to pacing was assessed at cycle lengths 10, 20, 30, 40, and 50 ms less than the mean baseline atrial cycle length. Digitized tracings of the baseline tachycardia and the response to pacing were recorded from the high right atrium and from the distal coronary sinus. Computer analysis of these signals was used to calculate a left atrial electrogram density before, during, and after pacing. Two hundred eighty-eight segments of AF with a duration of 3.9±0.5 seconds (mean±SD) were analyzed. Local capture of the right atrium during AF was demonstrated for at least one pacing cycle length in each patient. The left atrial electrogram density was significantly greater than baseline at each pacing cycle length that resulted in local capture, except when pacing at 50 ms less than the mean AF cycle length. There was no significant change in the baseline left atrial electrogram density compared with baseline when pacing did not result in local capture of AF.*Conclusions* Local right atrial capture is often possible by pacing during type I AF and consistently influences the left atrial electrograms recorded in the coronary sinus. These results confirm the presence of excitable tissue in the right and left atria in type I AF.

Key Words: fibrillation ■ pacing ■ excitation

Experimental studies have demonstrated the ability to capture the atrium and to locally entrain atrial fibrillation (AF) within 4 to 6 cm of the pacing site.[1] [2] In humans, one study found no evidence of local capture with right atrial pacing during type I AF,[3] but another study reported that rapid atrial pacing in patients with AF resulted in transient shortening of the AF cycle length at the stimulation site but not at distant recording sites.[4] Therefore, no previous clinical studies have demonstrated that right atrial pacing during AF may influence electrograms recorded at distant sites. The purpose of this study was to assess the effect of endocardial right atrial pacing on the left atrial electrograms recorded within the coronary sinus during type I AF in humans.

METHODS

Characteristics of Subjects

The subjects of this study were 24 patients referred to the University of Michigan Hospital for electrophysiological testing and/or radiofrequency catheter ablation. Exclusion criteria included the inability to cannulate the coronary sinus from the femoral vein approach,[5] a baseline rhythm of AF other than type I, or the inability to induce sustained type I AF by atrial pacing. Of 34 patients screened, 24 patients (15 men, 9 women; mean age, 46±17 years [±SD]) satisfied all criteria and consented to participate in the study. The mean left ventricular ejection fraction was 0.50±0.07. Two patients had an ischemic cardiomyopathy, and two patients had hypertensive heart disease. The electrophysiology study was performed to evaluate supraventricular tachycardia in 17 patients, ventricular arrhythmias in 1 patient, and other arrhythmias or symptoms in 6 patients. Two patients were being treated with a β-adrenergic antagonist, 1 with a calcium channel antagonist, and 2 with digoxin.

Electrophysiological Testing

After informed consent was obtained, three 7F venous sheaths (Daig Corp) were placed in a femoral vein, and three quadripolar electrode catheters (Mansfield EP) with an interelectrode spacing of 2-5-2 mm were positioned as clinically needed. Patients were sedated with intravenous midazolam and fentanyl and received 3000 U heparin IV. Leads V_1, I, II, and III and three intracardiac electrograms were recorded (Mingograph 7; Siemens-Elema AB). Pacing was performed with a programmable stimulator (Bloom Associates, Ltd).

Study Protocol

The study protocol was approved by the Human Research Committee and was performed on completion of the clinically indicated portion of the electrophysiology procedure. Quadripolar electrode catheters were positioned in the high right atrium and the distal coronary sinus. So as to have as much overlap as possible between the pacing and recording sites in the right atrium, electrodes 1 and 3 were used for pacing and electrodes 2 and 4 were used to record the local right atrial electrogram. Type I AF was induced by bursts of rapid pacing at the high right atrium. A sustained rhythm was defined as being >30 seconds in duration. Type I AF was defined as atrial electrograms with discrete complexes with varied morphology and cycle length separated by an isoelectric baseline and with a mean atrial cycle length <180 ms (Fig 1).[3]

Type I AF was induced by pacing in 23 patients and was the baseline rhythm in 1 patient. The mean baseline atrial cycle length and the mean maximum variability in cycle length during AF were 163±22 and 56±23 ms, respectively.

During sustained type I AF, pacing was performed at a current strength of 10 mA and a pulse width of 2 ms. Local capture was assessed by inspection of the local atrial electrogram and by the presence of a postpacing pause longer than the longest atrial cycle length during AF (Fig 2A and 2B). The initial pacing cycle length was 10 ms less than the mean atrial cycle length. The response to pacing was then assessed at pacing cycle lengths 20, 30, 40, and 50 ms less than the mean atrial cycle length. Bipolar electrograms filtered at 30 to 500 Hz were simultaneously recorded via electrodes 2 and 4 of the right atrial catheter and electrodes 1 and 2 of the coronary sinus catheter at a gain of 20 mV/mm with a TEAC portable data recorder (model R-71, TEAC Corp of America). Recordings were continuous and began with the induction of the sustained arrhythmia.

After completion of the study protocol, 18 patients required cardioversion. Three patients converted to sinus rhythm after infusion of procainamide, and 15 patients required electrical cardioversion. There were no complications related to the study protocol or to cardioversion.

Analysis of Data

The analog recordings of AF were digitized at 1000 Hz with commercially available software (CODAS, Dataq Instruments, Inc). For data analysis, digitized recordings from the right atrium were reviewed and divided into four segments: baseline AF, pacing with local capture, pacing without local capture, and segments recorded after pacing with local capture. Segments recorded after pacing with local capture began 2 seconds after cessation of pacing. For each right atrial segment, the simultaneously recorded digitized atrial signal from the distal coronary sinus catheter was analyzed and a left atrial electrogram density was calculated. The electrogram density was calculated by use of a custom-designed computer program that sampled the digitized signal at 1000 Hz and determined the period of time the atrial signal was isoelectric (SPARCstation, Sun Microsystems, Inc). The time period that the signal was not isoelectric was then divided by the total time of analysis to calculate the left atrial electrogram density (Fig 3). The computer-calculated isoelectric window was defined as any point with a value between zero and one half of the mean of the rectified atrial signal.

Two hundred eighty-eight segments were analyzed. One hundred twenty-seven recordings were of pacing with local capture, 127 were of a segment recorded after pacing with local capture, and 34 were of pacing without local capture. The mean duration of the analyzed segments of AF was 3.9±0.5 seconds.

Statistical Analysis

Continuous variables are expressed as mean±1 SD. Differences between continuous variables were tested by Student's *t* test, and differences between categorical variables were tested by χ^2 analysis. Comparisons of atrial electrogram density were performed by ANOVA with repeated measures. A value of $P<.05$ was considered significant.

RESULTS

Local Capture

Local capture at the high right atrium was demonstrated during pacing at at least one pacing cycle length in each patient with AF. Capture at pacing cycle lengths 10, 20, 30, 40, and 50 ms less than the mean baseline AF cycle length was demonstrated in 21, 23, 18, 10, and 7 patients, respectively.

Left Atrial Electrogram Density

The baseline left atrial electrogram density during type I AF was 39±7%. During pacing with local capture of the high right atrium at cycle lengths 10, 20, 30, and 40 ms less than the mean baseline AF cycle length, the left atrial electrogram density increased to 44±9%, 44±7%, 44±8% (all $P<.001$ versus baseline), and 42±10% ($P<.002$ versus baseline), respectively (Fig 4). During pacing at a cycle length 50 ms less than the mean AF cycle length, the left atrial electrogram density was 40±11% (P=NS versus baseline, Fig 4). An example of the response of the left atrium to pacing with local capture at the high right atrium during type I AF is shown in Fig 5. With local capture of

the right atrium, the left atrial electrogram becomes more disorganized and the electrogram density increases.

The left atrial electrogram density 2 seconds after cessation of pacing that resulted in local capture during pacing at 10, 20, 30, 40, and 50 ms less than the mean baseline AF cycle length was 41±8% (*P*=.1 versus baseline), 41±7% (*P*=.2 versus baseline), 42±6% (*P*=.4 versus baseline), 42±8% (*P*=.1 versus baseline), and 40±13% (*P*=.4 versus baseline), respectively (Fig 6).

During pacing without local capture of the high right atrium at 10 ms less than the mean baseline AF cycle length, the left atrial electrogram density was 40±4% (*P*=.8 versus baseline).

Postpacing Electrograms

There were 127 recordings of a segment of AF after pacing with local capture of the right atrium. Immediately upon cessation of pacing, there was transient fragmentation and disorganization of the right atrial electrogram in 14 cases (11%) and of the left atrial electrograms in 111 cases (87%). The mean duration of transient disorganization after pacing was 33±85 ms in the right atrium and 497±336 ms in the left atrium (*P*<.005). In 112 recordings (88%), the left atrium required more time than the right atrium to reorganize to the original electrogram morphology (Fig 7), and in the remaining 15 recordings (12%), the left and right atria reorganized simultaneously. The left atrial electrograms never became reorganized before the right atrial electrograms.

DISCUSSION

Main Findings

The results of this study demonstrate that it is often possible to capture the high right atrium during type I AF and that local capture at the high right atrium affects left atrial activity recorded in the coronary sinus. In addition, when there is transient disorganization or increased fragmentation of electrograms in response to pacing, the right atrial electrograms often become reorganized before the left atrial electrograms. The ability to capture the high right atrium and to increase the left atrial electrogram density demonstrates the presence of excitable tissue in the right and left atria during type I AF in humans.

Transient Disorganization of AF After Pacing

Pacing during AF at times resulted in transient disorganization of the right atrial electrograms immediately after cessation of pacing. This observation is consistent with the results of Kirchhof et al,[2] who reported pacing-induced acceleration of AF in dogs attributable to transient, small leading circle reentry circuits induced near the pacing site.

In the present study, pacing during AF often resulted in transient disorganization of the left atrial electrograms without an accompanying disorganization of the right atrial electrograms. Furthermore, when electrograms in both atria became transiently disorganized or more fragmented as a result of pacing, the electrograms recorded in the right atrium often regained their original morphology before the left atrial electrograms. These results demonstrate that the effects of atrial pacing during AF may be more pronounced at sites distant from the pacing site than at the pacing site itself. The explanation for this phenomenon remains unclear, but it is possible that functional or anatomic differences between the two atria result in a greater susceptibility of the left atrium to an acceleration in rate during AF.

Analysis of Pacing Without Capture

When there was not local capture, pacing during AF did not alter left atrial activity. This observation provides validation for the computer-based assessment of left atrial activity used in this study by demonstrating that the computer analysis was not artifactually influenced by the pacing stimuli. To minimize the potential confounding effects of the pacing stimuli, the pacing stimuli were bipolar, the coronary sinus catheter was advanced to the most lateral aspect of the mitral annulus, and coronary sinus recordings were obtained with a bipole distance of 2 mm. The fact that there was no significant increase in the electrogram density when pacing was not accompanied by local capture indicates that the pacing stimuli did not artificially elevate the electrogram density.

Previous Experimental Studies

The presence of an excitable gap during AF has been demonstrated previously in a dog model of AF.[1] [2] The area of local capture had a mean diameter of ≈6 cm in one study,[1] whereas the other study demonstrated entrainment of ≤4 cm of the left atrium by local pacing during AF.[2] Review of the electrogram tracings included in these experimental studies indicates that the pattern of AF was not consistent with type I AF. The results of the present study suggest that pacing from the high right atrium during type I AF affects a larger portion of the atria and extends to the left atrium. This difference in results between the present study and the previous experimental studies may be attributable to a difference in the type of AF induced in these studies or to other differences between AF induced in dogs and humans.

Previous Clinical Studies

One of the earliest clinical studies to assess pacing during type I AF recorded bipole atrial signals from epicardial electrodes ≤1 cm apart in humans after open-heart surgery.[3] During rapid atrial pacing, there was no evidence of atrial capture or of a change in the AF morphology. In contrast to the present study, atrial pacing was epicardial, which may explain the lack of response of the atria to pacing during type I AF.

Two studies in humans have reported the results of high-density mapping during pacing-induced AF.[6] [7] These studies described the presence of broad and uniform wave fronts propagating across the right atrium during type I AF but did not assess the response to pacing. Cox et al[6] described a right atrial reentrant loop around an area of functional block associated with the sulcus terminalis. That study proposed that one type of AF may be due to a large reentrant circuit in the right atrium and that this circuit may have either a stable or a variable cycle length. Konings et al[7] described a similar pattern of a broad uniform wave front activating the right atrium and suggested that the right atrium may be part of a large reentrant circuit. The response to pacing during type I AF in the present study is compatible with a single reentrant circuit arising in the right atrium but does not rule out other possible mechanisms of AF, such as multiple asynchronous sources or multiple wandering reentry wavelets.

In a recent study by Capucci et al,[4] atrial overdrive pacing at cycle lengths of 48 to 80 ms during AF resulted in a postpacing mean decrease in atrial cycle length of ≈9% at the pacing site in 10 patients with idiopathic AF. In contrast to the results of the present study, no changes were observed at other recording sites. This discrepancy between the results of the two studies may be attributable to differences in the techniques used for analysis of electrograms; for example, in the previous study, the only parameter measured during AF was the atrial cycle length, as opposed to electrogram density, which was the parameter measured in the present study. In addition, electrogram analyses in the previous study were performed only after the cessation of overdrive

pacing, whereas in the present study, electrograms were analyzed during overdrive pacing as well as after cessation of overdrive pacing.

Pace Termination of AF

Although rapid pacing during AF in the present study often resulted in local capture and distant effects, implying the presence of excitable tissue in both the right and left atria, termination of AF by pacing was never observed. In contrast, in a preliminary study by Haffajee et al,[8] right atrial pacing was effective in converting AF to sinus rhythm in three of eight patients with paroxysmal AF. However, a pacing cycle length of 20 ms was used in the previous study, whereas the pacing cycle length in the present study was never <110 ms. It is possible that this difference in pacing cycle lengths explains the different responses to pacing between the two studies.

Study Limitations

The findings of this study are specific to pacing-induced type I AF and may not apply to patients exhibiting spontaneous chronic or paroxysmal AF. Also, only left atrial electrograms recorded from the distal coronary sinus were analyzed, and therefore the response of other areas of the left atrium to right atrial pacing and capture is unknown.

Conclusions

In conclusion, this study demonstrates for the first time that rapid right atrial pacing during AF in humans often results not only in local capture but also in acceleration or increased disorganization of the atrial electrograms at distant left atrial sites recorded from within the coronary sinus. These findings demonstrate that both atria are excitable during type I AF in humans. The ability of right atrial pacing to influence both atria during AF suggests a mechanism by which rapid pacing may terminate AF.

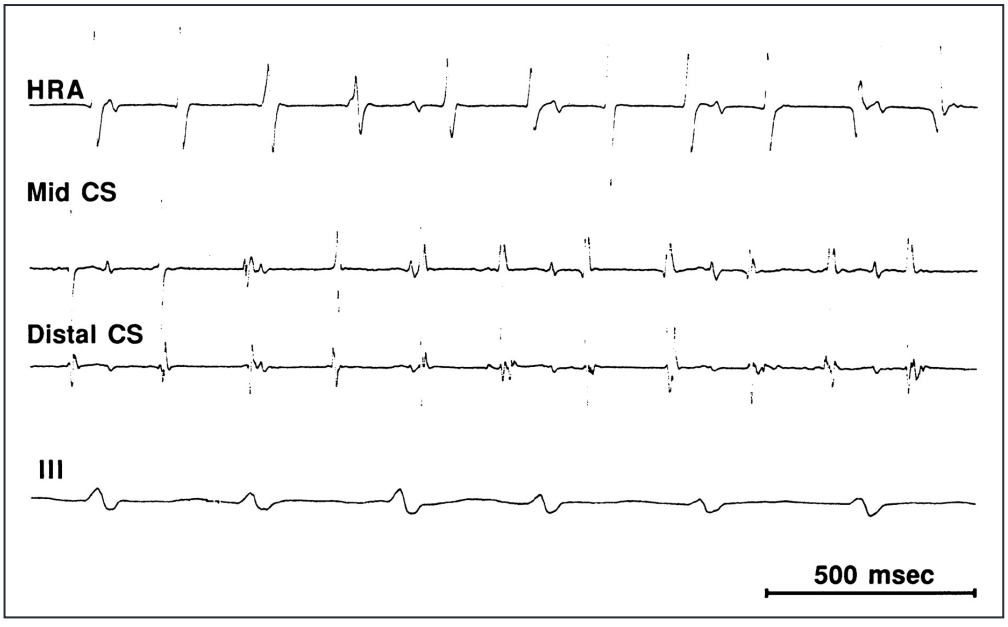

Figure 1. Example of type I atrial fibrillation with a mean cycle length (CL) of 177 ms (range, 160 to 210 ms). Shown are high right atrial (HRA) recording, recordings from mid and distal coronary sinus (CS), and lead III. Note that atrial complexes are discrete electrograms with varied morphology and CL, with an intervening isoelectric period.

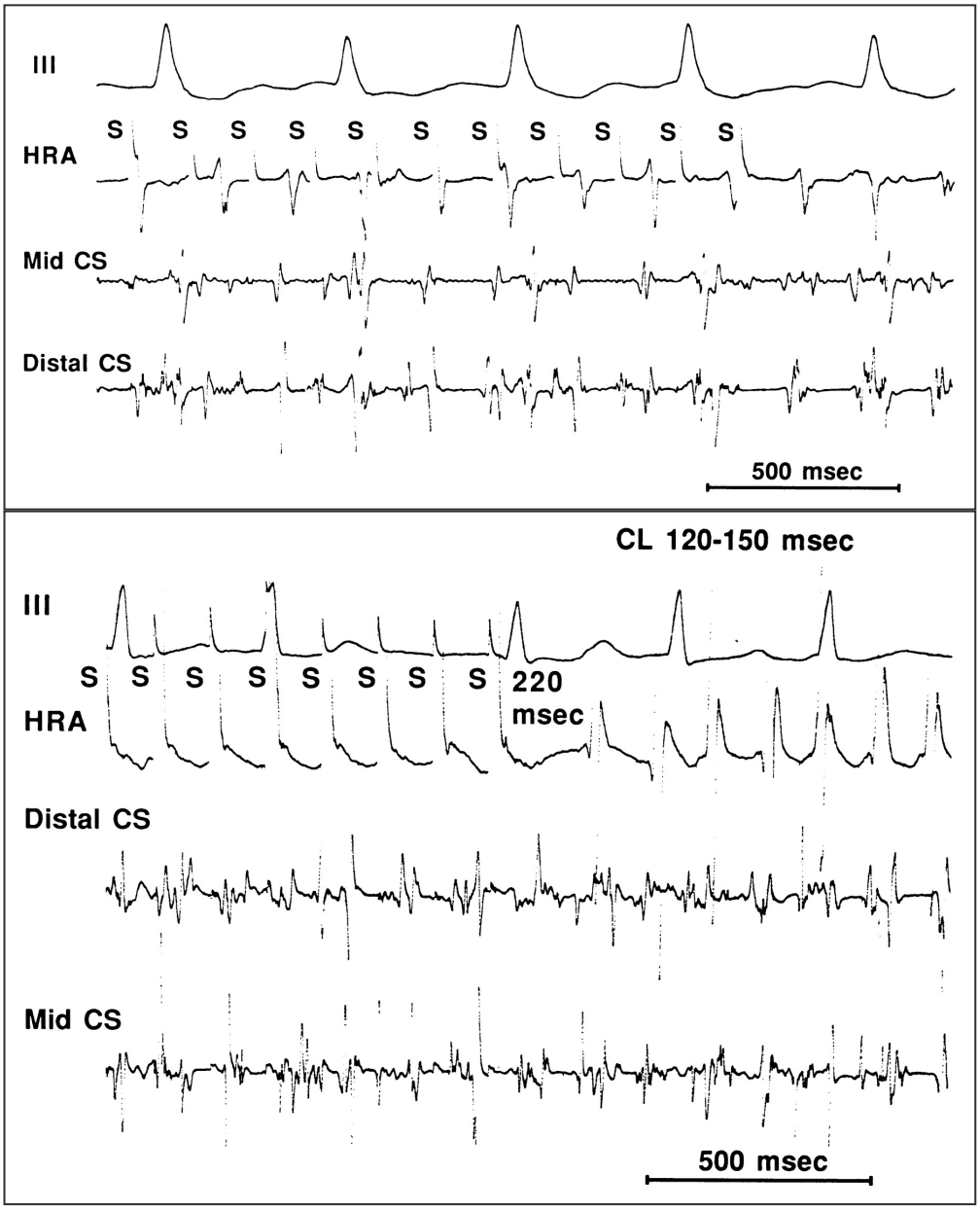

Figure 2. A, HRA pacing and capture during type I atrial fibrillation (AF). Left side of tracing, HRA is being paced at a CL of 130 ms. After each pacing stimulus (S), there is an atrial electrogram, and after last stimulus of pacing train, there is a postpacing interval of 220 ms, which was longer than the AF CL of 120 to 150 ms. This postpacing pause is further evidence that there was local capture. B, Example of HRA pacing without local capture during type I AF. Left side of tracing, pacing stimuli at a CL of 160 ms during type I AF, which has a mean CL of 170 ms. During the pacing train, atrial electrograms recorded from HRA are undisturbed, and no changes in the electrograms are recorded from CS. After last stimulus of pacing train, right and left atrial electrograms are unchanged compared with right atrial pacing without local capture. Abbreviations as in Fig 1.

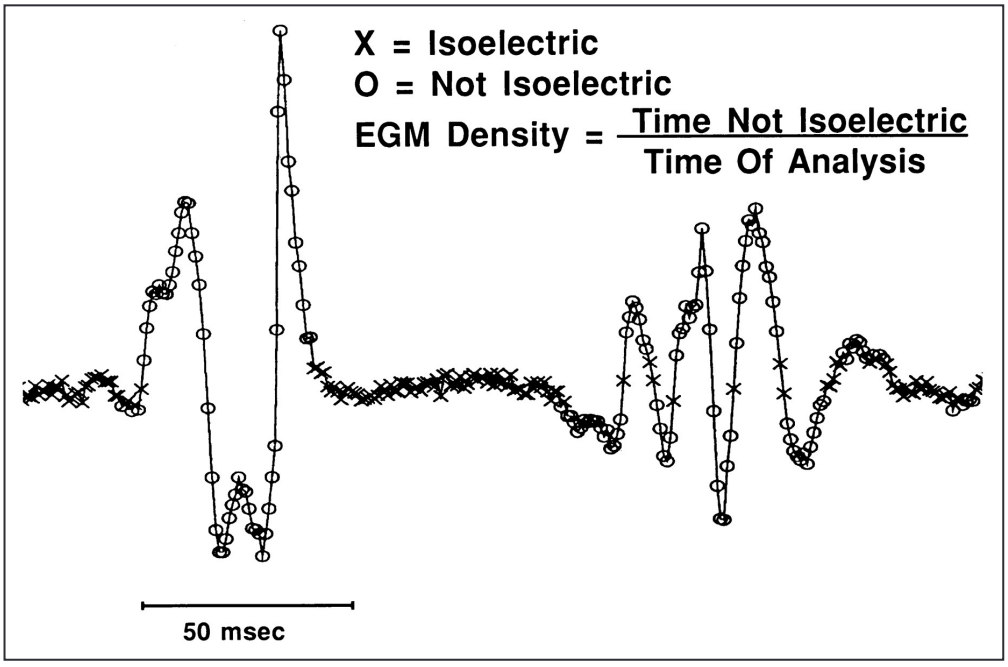

Figure 3. Computer analysis of digitized left atrial electrogram recorded in the distal coronary sinus during type I atrial fibrillation. For each 1-ms interval, the computer assesses whether the atrial signal is within the "isoelectric window." Isoelectric segments are labeled with an "X," and nonisoelectric segments are noted with an "O." Electrogram density was calculated by dividing time not isoelectric by total period of analysis. EGM indicates electrogram.

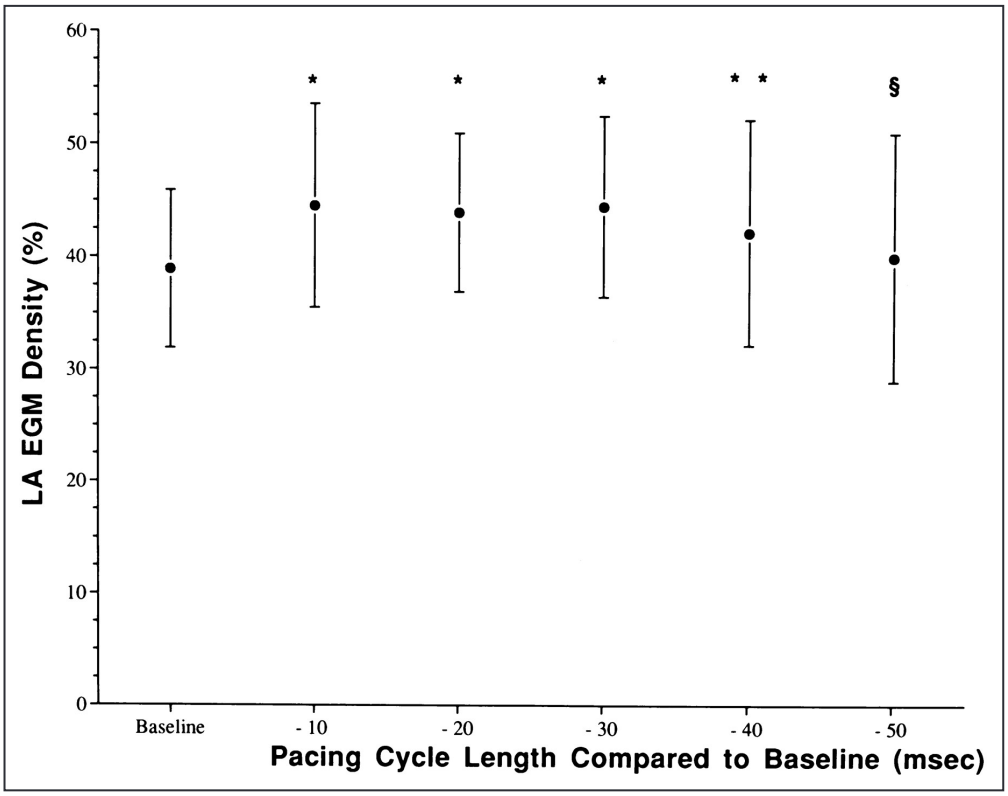

Figure 4. Changes in left atrial electrogram (LA EGM) density calculated from atrial recordings from distal CS during pacing with local capture of the HRA during type I AF. Solid circles represent mean values of electrogram density, and bars represent ±1 SD. Numbers −10, −20, −30, −40, and −50 refer to results during pacing at 10, 20, 30, 40, and 50 ms less than mean baseline atrial CL. At all pacing CLs except for 50 ms less than baseline mean atrial CL (−50), the LA EGM density was significantly greater during pacing than at baseline. *P<.001 vs baseline; **P<.002 vs baseline; §P>.05 vs baseline. Abbreviations as in previous figures.

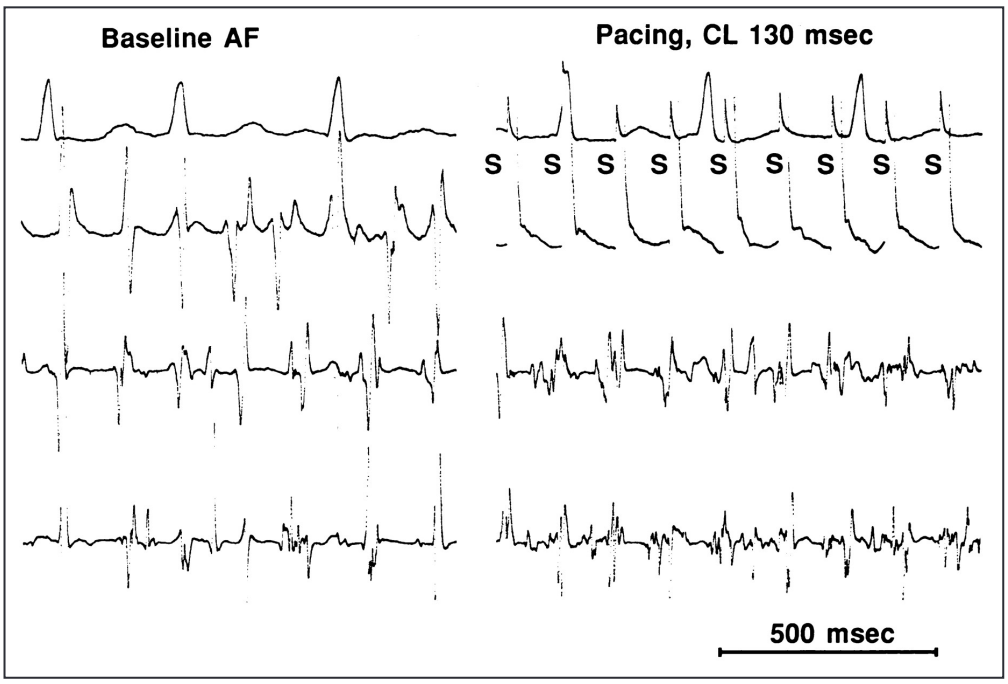

Figure 5. Response of left atrium to right atrial pacing and local capture during type I AF. Tracings on left are of baseline type I AF (mean CL, 140 ms; range, 110 to 150 ms). Right, there is pacing (S) at 130 ms and right atrial capture. In response to right atrial capture, there is an increase in LA EGM density recorded from the distal CS compared with baseline, and LA EGMs become more disorganized. Abbreviations as in previous figures.

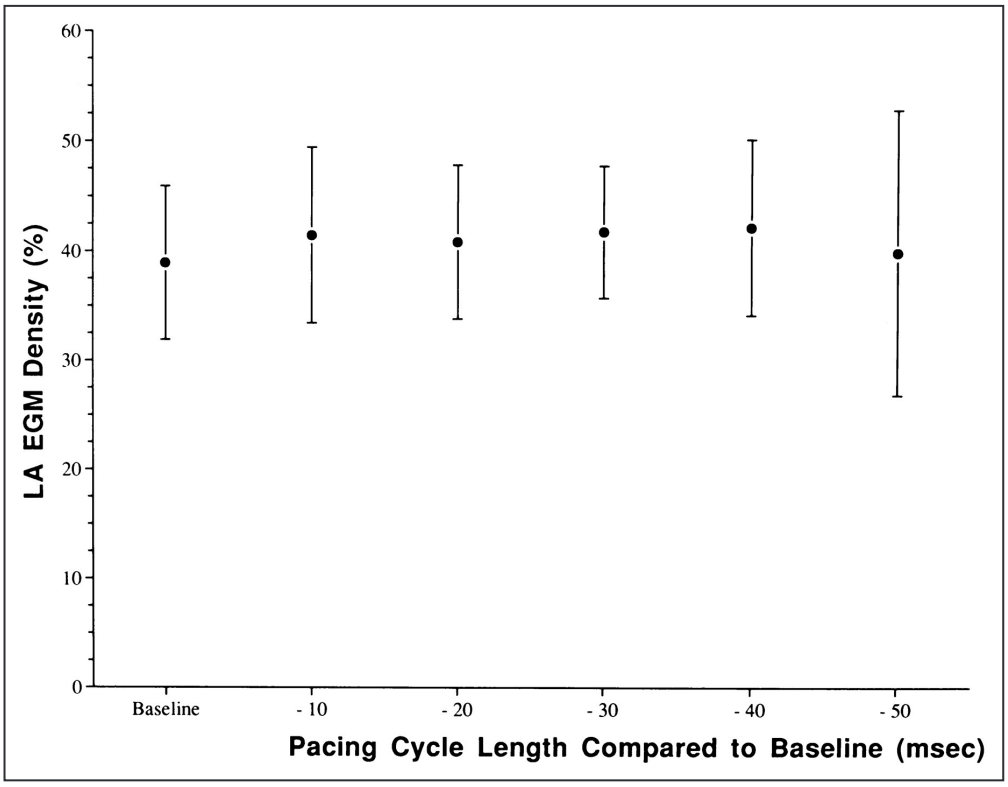

Figure 6. LA EGM density calculated from atrial recordings from the distal CS 2 seconds after cessation of right atrial pacing and local capture during type I AF. Solid circles represent mean values of ECG density, and bars represent ±1 SD. Numbers −10, −20, −30, −40, and −50 refer to results 2 seconds after pacing with local capture at 10, 20, 30, 40, and 50 ms less than mean baseline atrial CL. There were no significant changes in the LA EGM density compared with baseline after any pacing CL. Abbreviations as in previous figures.

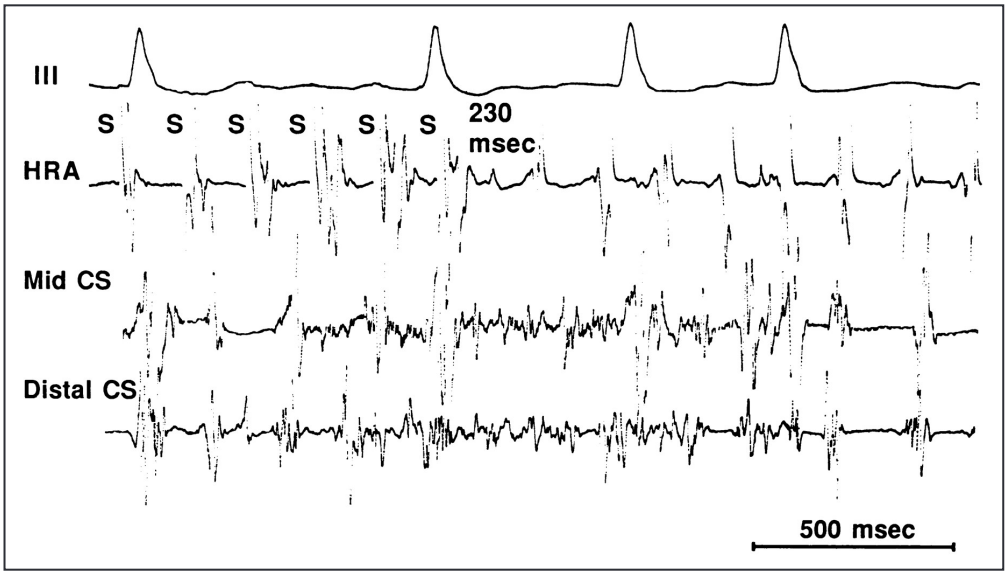

Figure 7. Pacing and local capture at the HRA with delayed reorganization of type I AF recorded from the CS. Left side of tracing, HRA is being paced at a CL of 150 ms. After each pacing stimulus (S), there is an atrial electrogram, and after last stimulus of pacing train, there is a postpacing interval of 230 ms, which was longer than the AF CL of 130 to 150 ms. After cessation of pacing, right atrial electrogram immediately organizes to type I AF; however, there is transient fragmentation and disorganization of LA EGM recorded from the CS. LA EGMs reorganize to type I AF ≈900 ms after cessation of right atrial pacing. Abbreviations as in previous figures.

ARTICLE INFORMATION

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