Importance of Refractoriness Heterogeneity in the Enhanced Vulnerability to Atrial Fibrillation Induction Caused by Tachycardia-Induced Atrial Electrical Remodeling

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Background—Rapid atrial activation causes electrical remodeling that promotes the occurrence and the maintenance of atrial fibrillation (AF). Although remodeling has been shown to alter electrophysiological variables, the spatial uniformity of these changes is unknown.

Methods and Results—Dogs subjected to rapid atrial pacing (400 bpm) for 24 hours (n=12) were compared with sham-operated dogs (instrumented but not paced, n=12). Epicardial mapping (240 bipolar electrodes) and extrastimulation at a large number of sites (mean±SEM, 66±4 per dog) were used to evaluate atrial activation and the heterogeneity of the effective refractory period (ERP), respectively. Rapid pacing increased both the percentage of sites at which AF could be induced by single premature stimuli (from 2.6±0.9% to 11.8±2.8%, \( P=0.007 \)) and AF duration (from 39±28 to 146±49 seconds, \( P=0.03 \)). Atrial tachycardia decreased atrial ERP (from 120±4 to 103±2 ms, \( P=0.003 \)), increased the coefficient of variation of ERP (from 14.9±0.9% to 20.7±0.9%, \( P<0.0001 \)), and accelerated conduction velocity (from 91±2 to 108±3 cm/s, \( P=0.0004 \)), with no change in the wavelength. The increase in ERP heterogeneity was due both to interregional differences in the extent of ERP remodeling and to increased intersite variability within regions. Stepwise multilinear regression indicated that ERP heterogeneity was an independent determinant of the inducibility (\( P<0.0001 \)) and duration (\( P<0.0001 \)) of AF, whereas ERP per se and wavelength were not significant determinants. Combined mapping of AF induction and atrial ERP showed that premature extrastimuli induced AF at sites with short ERP by causing local conduction slowing and/or block in adjacent zones with longer ERP values.

Conclusions—Atrial tachycardia causes nonuniform remodeling of atrial refractoriness that plays an important role in increasing atrial vulnerability to AF induction and the duration of induced AF. (Circulation. 1998;98:2202-2209.)

Key Words: fibrillation ■ remodeling ■ electrophysiology

Atrial fibrillation (AF) is the arrhythmia most frequently encountered in clinical practice and is likely to become more common with the aging of the population.1,2 AF remains a therapeutic challenge, in part because of limitations in our understanding of the pathological and electrophysiological mechanisms underlying AF.3 Over the past few years, rapid atrial activation has been shown to increase the vulnerability to AF induction by premature extrastimuli and to promote sustained AF.4-10 AF models based on tachycardia-induced remodeling are relevant to the process by which AF alters atrial electrophysiology to favor its own maintenance (“AF begets AF”) and produce ultrastructural abnormalities similar to those seen in patients with AF.4,11

Rapid atrial activation increases the spatial variability in AF cycle length,10 which is an index of atrial refractoriness.12 The SD of AF cycle lengths at different sites correlates with AF duration in dogs subjected to rapid atrial pacing,10 suggesting a potential role for refractoriness heterogeneity in contributing to atrial remodeling due to rapid atrial activation. However, the quantitative relations between AF cycle length and effective refractory period (ERP) are complex,13 so that AF cycle length changes are not necessarily an accurate indicator of ERP alterations.

The potential importance of spatial variability in atrial electrophysiology for the induction and maintenance of AF has long been recognized.14 Initial analyses of AF-induced remodeling showed that AF did not alter the difference between ERPs in the left versus right atrium, suggesting that AF may not alter ERP heterogeneity.6 A recent preliminary report points to increased variability in ERP caused by AF on the basis of ERP measurements at an average of 7 atrial sites per dog.15 The present study was designed to evaluate in detail the spatial distribution of changes in atrial electrophysiological properties, particularly the ERP, caused by 24 hours of rapid atrial pacing in dogs and to relate changes in spatial heterogeneity to the substrate for AF.
seconds at a basic cycle length (BCL) of 300 ms. CV was measured with the use of 2 parallel sets (4 bipolar electrodes per set) in each of 5 regions: Bachmann’s bundle (BB, a in Figure 1), the left atrial appendage (LAA, b), the right atrial appendage (RAA, c), the right superior free wall (d), and the right inferior free wall (e). Stimulation for the CV measurement was applied at each of the sites designated by the letters in Figure 1, after it had been ascertained that stimulation at that site resulted in longitudinal conduction at the corresponding series of electrodes. Because of variable contact in the left posterior free wall (LPW), LPW CV could not be measured accurately in all dogs and was therefore not included in the analysis.

ERP was determined with the extrastimulus technique at as large a number of sites as feasible during each experiment, with sites selected so as to provide representative data from all regions. All basic and premature stimuli were 2-ms square waves with twice-threshold current. The pacing threshold was determined separately at each electrode site, and only sites with a threshold <5 mA were used. The ERP was defined as the longest S1S2 interval that failed to produce a response. A 15-stimulus basic train at a BCL (S1S2) of 300 ms was followed by a premature extrastimulus (S2) at a progressively increasing S1S2 interval and a 1-second pause to observe the response between trains. This method is accurate and reproducible and allows the coupling interval of S2 to be incremented rapidly without altering the basic rhythm.18,19 The coupling interval of S2 was increased by 10-ms increments to obtain an initial estimate of the ERP. The measurement was then repeated with 5-ms increments in the S1S2 interval, and the resulting value was taken as the ERP. In the case of a ≥10-ms difference between the 2 measurements, a third measurement with 5-ms steps was obtained and the mean of all 3 ERP values was used.

After the completion of electrophysiological data acquisition, AF was induced by stimulation of the RAA with 10-Hz, 2-ms stimuli at

Methods

Pacemaker Insertion and Atrial Pacing
Adult mongrel dogs (29.4±0.4 kg, n=24) were anesthetized with sodium pentobarbital (30 mg/kg IV, with additional doses of 4 mg/kg as needed). A pacing lead was inserted into the right atrial appendage with previously described methods,10 and a subcutaneously implanted pacemaker was used to pace the atria for 24 hours at 400 bpm (rapidly paced group, n=12) or left inactivated for 24 hours (sham control group, n=12).

Experimental Protocol
Twenty-four hours after the initial procedure, dogs were reanesthetized with morphine (2 mg/kg SC) and α-chloralose (120 mg/kg IV bolus, followed by a continuous infusion of 29.3 mg/kg h⁻¹). Animals were studied after a median sternotomy, with the same preparation and instrumentation as previously described in detail.10 Five thin silicon plaques containing 240 bipolar electrodes for stimulation and/or recording (Figure 1) were sewn to cover the atrial epicardial surface. The form and location of the arrays were similar to those described previously,10,16,17 but the number of electrodes was increased and their location modified. The hardware configuration permitted pacing at any of the 240 sites in the array. The interpolar distance was 1 mm, and the interelectrode distances were between 3.1 and 4.0 mm for arrays on the right and left atrial free walls and appendages and Bachmann’s bundle and 6 mm for the array between the pulmonary veins.

Signals were filtered (10 to 900 Hz), digitized (12-bit resolution and a 2-kHz sampling rate), and transmitted into a Silicon Graphics computer for data analysis. Activation data were analyzed off-line with computer-determined peak-amplitude criteria for activation, and data for each electrode were reviewed manually. Double potentials indicating local activation block or a pivot point were taken to represent a single local activation at the time of the largest potential. Electrogram timing was compared with QRS complexes to exclude ventricular electrograms.

Electrophysiological Study
In paced dogs, the pacemaker was deactivated. Activation maps for conduction velocity (CV) measurement were obtained after 90
4 times threshold current. AF was defined as a rapid (>450 bpm), irregular atrial rhythm with varying atrial electrogram morphology. To calculate mean AF duration, AF was induced 10 times for AF duration, 10 minutes and twice for AF duration between 10 and 30 minutes. Dogs that developed AF that lasted >30 minutes were eliminated, because such prolonged AF (usually requiring cardioversion for termination) made it impossible to measure ERP at a sufficient number of sites. Two rapidly paced dogs had to be eliminated because of prolonged AF and were replaced by additional animals to maintain the same number of dogs (12) in each group. No control dogs had prolonged AF. The vulnerability to AF induction at each site was determined on the basis of the ability of single S2 stimulus to induce, in a reproducible fashion, AF that lasted >1 second. Overall vulnerability in each dog was defined as the percentage of pacing sites at which AF was inducible.

**Data Analysis**

Regional CV was determined by analyzing activation at each of 2 parallel series of 4 electrodes in each region (Figure 1), with each series of electrodes oriented along the direction of rapid propagation (perpendicular to consecutive isochrones). The CV was determined as previously described for each of the 2 series of parallel electrodes in each region, and the mean of the values obtained was used for analysis. The same sites were used for CV measurements for each experiment. The overall CV for each dog was calculated from the average of each of the 5 regional CV values. An index of CV heterogeneity in each dog was obtained by calculating the coefficient of variation (COV CV = SD/mean × 100%) of the 5 regional CV values. Similar approaches were used to calculate for each dog the overall mean ERP, the mean ERP in each region, and the overall and regional COV in ERP (COV ERP).

Statistical comparisons between only 2 groups were performed by Student’s t test or the Mann-Whitney rank sum test when a normal distribution could not be assumed. ANOVA (for parametric data) or a Kruskal-Wallis rank sum test (when data could not be assumed to be normally distributed) was used for multiple-group comparisons, followed by a Bonferroni-corrected t test or a corrected Mann-Whitney rank sum test. Stepwise multilinear regression was used to assess the dependence of a single dependent variable on multiple independent variables and linear regression to analyze single dependent and independent variables. Average results are given as the mean±SEM unless otherwise indicated, and a 2-tailed P<0.05 was considered statistically significant.

**Results**

**Comparability of Groups and Overall Changes Caused by Rapid Pacing**

Control and paced dogs were similar in size, study duration, and a number of general variables (Table). The number of sites at which ERP was determined and the mean diastolic current threshold were the same for both groups.

Changes in electrophysiological variables and AF susceptibility are illustrated by measurements from 1 dog in each group in Figure 2. ERP was measured at 73 sites in the control dog (A) and averaged 124±16 ms (mean±SD). The ERP tended to be shorter in the posterior left atrium, and COV ERP was 13.5%. AF could not be induced by premature stimuli at any site, and the duration of AF induced by burst pacing averaged 11 seconds. In the paced dog (B), ERP was measured at 94 sites. Mean ERP was 100±22 ms. Large variations in ERP were seen, from values as great as maximum values in the control dog (165 ms) to values as short as 60 ms, much shorter than the shortest ERP (95 ms) in the control dog. ERP heterogeneity was substantial, with a COV ERP of 21.7%. AF could be induced at 19% of sites, indicated by the stars in Figure 2, and mean AF duration was 240 seconds.
Overall, rapid pacing significantly enhanced atrial vulnerability (Table), increasing the percentage of sites per dog at which AF was induced by a single extrastimulus from 2.6±0.9% to 11.8±2.8%. Five control dogs (42%) did not exhibit any AF during premature stimulation, compared with only 1 paced dog (8%). AF duration was also increased significantly in paced dogs. Pacing decreased mean ERP, increased ERP heterogeneity, and increased CV. The offsetting changes in ERP and CV left wavelength unaltered. Rapid pacing had no effect on CV heterogeneity. Wavelength was calculated in each region as the product of local CV and mean ERP and was not altered by pacing in any region. To assess the stability of ERP values in paced dogs, they were measured at the beginning and repeated at the end of the study at a total of 20 sites in 5 dogs. The mean ERP averaged 100.8±3.5 ms at the beginning of the study and 103.0±3.6 ms at the end of the study (P=NS), indicating no significant time-dependent changes.

Regional Changes in Electrophysiological Properties
A quantitative analysis of regional differences in the effect of rapid pacing on ERP is shown in Figure 3. Paced dogs had substantially shorter ERPs in the atrial appendages and the right free wall but little or no change in ERPs in the left posterior wall or Bachmann’s bundle. Thus, ERP remodeling induced by pacing was regionally heterogeneous, accounting (at least in part) for the increased spatial heterogeneity of ERP in paced dogs (Table). The increased heterogeneity caused by rapid pacing was associated with a decrease in the smallest ERP values in each dog, which averaged 62±2 ms in paced dogs, versus 85±4 ms in control dogs (P<0.0001). The largest ERP values were not altered (paced dogs, 162±7 ms; control dogs, 165±7 ms).

To determine whether increased spatial ERP heterogeneity in paced dogs was due entirely to interregional differences in the extent of ERP remodeling or whether intraregional differences might also contribute, we performed the analysis illustrated in Figure 4. The COV in refractoriness was calculated within each region and was found to be increased significantly by rapid pacing in 3 regions: the right and left atrial appendages and the right free wall. These are the same regions in which the greatest absolute change in ERP occurred (Figure 3), implying that within the regions of greatest ERP remodeling, there was considerable intersite variability in the extent of remodeling. Consequently, atrial tachycardia caused nonuniform shortening in ERP both within and among various atrial regions.

Relation Between Electrophysiological Properties and Atrial Vulnerability
Having examined changes in ERP heterogeneity in paced dogs, we turned our attention to the factors potentially accounting for their enhanced vulnerability to AF induction. Figure 5 shows an analysis of the relations between vulnerability to AF induction in each dog (expressed as a percentage of sites at which AF could be induced by extrastimuli) and ERP, ERP heterogeneity (as measured by COV ERP), and wavelength. There was a strong correlation between vulnerability and ERP heterogeneity, whereas the relationship with ERP was weak and that with wavelength was nonsignificant. When stepwise multilinear regression was applied to select a model relating AF vulnerability (dependent variable) to ERP, COV ERP, and CV (independent variables that changed with pacing) in all dogs, the model selected had a correlation coefficient of 0.82, and the only independent variable that provided statistically significant predictive value to the model was COV ERP (P<0.0001).

We next examined in detail the activation sequences for premature stimuli at S1S2 intervals 5 ms greater than the ERP, at sites at which AF could be induced (n=20) or at sites without AF inducibility (n=10). Figure 6 shows an example
Panels A and B show atrial activation induced by stimulation in the right atrial free wall for the last complex of the basic train (A1) and the atrial premature complex elicited by an S2 delivered with a coupling interval (90 ms) 5 ms greater than the ERP. Panels C and D are enlarged representations of activation in the right atrial array overlying the stimulation site. The extrastimulus captured the region around the stimulation site (star), with a latency of about 20 ms. The impulse was blocked in the superior direction, and conduction was greatly slowed in the inferior direction, leading to marked slowing of atrial activation. The next cycle (panel E) began close to the stimulation site, 90 ms after initial activation. Panel F shows ERP values in the region of the stimulation site. The ERP at the site at which reentry was induced was 85 ms, and a corridor through which the S2 was propagated had ERP values of 80 to 90 ms, similar to the activation-reactivation interval of 90 ms and permitting reexcitation. At the line of block above the stimulation site, ERPs were all larger, ranging from 95 to 125 ms.

Figure 7 shows data from a different dog, with examples of extrastimulation at adjacent sites, at 1 of which (top) AF could not be induced and at another of which (bottom) AF was induced by premature stimulation. The last S1 of the basic train was propagated rapidly and uniformly during stimulation at either site (left, top and bottom). The S2 with the shortest S1S2 interval (110 ms) that permitted capture at the noninducible site (top, middle) was associated with an increased latency and some conduction slowing, but conduction remained relatively uniform. In contrast, the earliest S2 capturing the inducible site (S1S2=70 ms) was followed by substantial local conduction delay and an arc of conduction block below the site of stimulation (bottom, middle). Slow conduction around the arc of block led to reactivation in the region of extrastimulation, as shown in the lower right panel. The distribution of ERPs in the region of the 2 stimulation sites is shown in the upper right panel, along with the isochrones of the A2 causing reentry reproduced from the lower middle panel. The line of block corresponds to areas with refractory periods between 100 and 105 ms, substantially greater than the ERP of 65 ms at the site at which reentry was induced and accounting for the line of block in response to the extrastimulus. In contrast, the ERP at the site at which reentry could not be induced was 105 ms, longer than the ERP at almost all other sites in the area and permitting continuous, if somewhat slowed, conduction of the complex resulting from the extrastimulus.
In all 20 cases of AF induction for which activation data were available, reentry was induced at a site of relatively short refractoriness, with 1 or more zones of conduction block corresponding to an adjacent series of sites of greater refractoriness. The conduction block and slowing are reflected by the overall conduction times of A2 complexes at S1S2 intervals 5 ms greater than the ERP, which averaged 128 ± 6 ms (P = 0.0005) for stimulation at sites at which AF could be induced, compared with 93 ± 6 ms for stimulation at noninducible sites. In contrast, conduction times of the last A1 complex of the basic train were similar for inducible and noninducible sites (76 ± 2 versus 73 ± 3 ms, respectively). These results indicate that the heterogeneous ERP remodeling caused by rapid pacing established the substrate that permitted single extrastimuli to induce AF at many more sites in paced dogs than in control dogs.

**Relation Between Electrophysiological Properties and AF Duration**

Figure 8 shows the results of an analysis of the relationship between AF duration and ERP, ERP heterogeneity, and wavelength. Only ERP heterogeneity shows a significant correlation with AF duration. We also analyzed the relations between minimum or maximum ERP in each dog and AF duration and found no significant correlation. When multilinear regression was applied to the relation between AF duration and ERP, COV ERP, and CV, the best predictive model (r = 0.78) included only 1 independent variable that contributed significantly: the heterogeneity in ERP (P < 0.0001).

**Discussion**

In the present study, we evaluated in detail the spatial distribution of changes in ERP caused by rapid atrial pacing. The results show that tachycardia-induced ERP remodeling is spatially nonuniform, with increased ERP variability both within and among various atrial regions in rapidly paced dogs. Whereas AF duration and vulnerability were not significantly related to ERP per se or to wavelength, they were strongly correlated with ERP heterogeneity. Furthermore, detailed activation mapping showed that local heterogeneities in ERP were central to the ability of premature extrastimuli to induce AF. Reentry was generally initiated at sites with shorter ERP, as a result of the presence of adjacent regions with longer ERP that created arcs of conduction block and other adjacent regions of shorter refractoriness through which conduction occurred. Thus, the spatial nonuniformity of tachycardia-induced ERP remodeling is important in generating a substrate that promotes the occurrence of AF.

**Comparison With Previous Studies of Tachycardia-Induced Atrial Electrical Remodeling**

Like previous investigators, we found that electrically induced atrial tachycardia increases the duration and inducibility of AF and reduces the ERP. Investigators have observed varying alterations in conduction. Wijffels et al noted an increase in CV after 6 to 24 hours of sustained AF in the...
goat, which they attributed to a decrease in refractory period. In contrast, several groups have reported an increase in atrial conduction time and/or a decrease in conduction speed after longer periods of tachycardia.\textsuperscript{4,7,10,20} In the present study, we noted an increase in CV after 24 hours of atrial tachycardia, consistent with the findings of Wijffels et al.\textsuperscript{7} The varying results regarding CV changes may point to the existence of multiple changes that can affect CV, with the observed effect depending on the balance. Changes reported to date that can have opposite effects on CV include decreased ERP and increased connexin 43 expression,\textsuperscript{21} which would tend to increase CV, and decreased $I_{Na}$,\textsuperscript{20} which would have the opposite effect.

Relatively little information is available about the distribution of atrial ERP remodeling. Wijffels et al\textsuperscript{7} found that the difference between right and left atrial ERP was not altered during atrial remodeling and that the variability of AF cycle length at 12 sites was the same after 1 and 14 days of AF. We have noted an increase in the variability of AF cycle length in dogs subjected to rapid pacing for periods of up to 6 weeks.\textsuperscript{10} Preliminary results from Tieleman et al\textsuperscript{15} point to an increase in ERP heterogeneity as measured at an average of 7 sites in the goat, due largely to smaller changes in Bachmann’s bundle, consistent with our observations.

**Role of Refractoriness Heterogeneity in AF**

Variable refractoriness was essential for the generation of AF in the classic computer model of Moe et al.\textsuperscript{24} Dogs with AF induced by single extrastimuli after cardiopulmonary bypass have increased refractoriness dispersion.\textsuperscript{22} Dogs with idiopathic AF have increased ERP dispersion,\textsuperscript{23} and the ability of flecainide to terminate idiopathic and vagal AF in dogs is associated with reductions in ERP dispersion.\textsuperscript{16,23} Increased ERP dispersion appears to play a central role in vagally induced experimental AF.\textsuperscript{17,24} Patients with AF have an increased spatial variability in AF cycle length,\textsuperscript{13} and atrial tissues from patients with AF show an increase in ERP heterogeneity.\textsuperscript{25} The leading-circle model and a variety of experimental observations suggest an important role for the reentry wavelength in determining susceptibility to reentrant atrial arrhythmias,\textsuperscript{26,27} including AF.\textsuperscript{16,23,28} Conversely, in some studies, AF duration was not correlated with wavelength but appeared to be related to ERP dispersion.\textsuperscript{17,24} In the present study, rapid atrial activation did not alter the wavelength but increased ERP dispersion, and ERP dispersion was a predictor of both AF duration and inducibility. Recent observations suggest that functional reentry during AF may correspond to spiral-wave reentry.\textsuperscript{29} Further application of the spiral wave concept may help to explain how interventions that increase refractoriness dispersion can promote AF maintenance without altering the reentrant wavelength.

**Novel Findings and Potential Significance**

The major novel contributions of the present study are (1) the demonstration that tachycardia-induced remodeling increases ERP dispersion both within and among atrial regions, implying spatial variability in the degree of remodeling; (2) the finding that increased ERP dispersion contributes to the AF-promoting effects of atrial tachycardia; and (3) the analysis by epicardial mapping of the relationship between ERP dispersion and the activation of extrasystoles that cause atrial reentry leading to AF.

The induction of atrial reentry by premature beats is an important clinical mechanism of AF initiation.\textsuperscript{30} The ability of single extrastimuli to initiate atrial reentry and AF has been associated with inhomogeneities in conduction\textsuperscript{2} and refractoriness.\textsuperscript{31} The present study is the first of which we are aware to relate activation maps of AF induction to detailed maps of ERP. The results suggest that local inhomogeneities in refractoriness can play a significant role in the ability of premature extrastimuli to induce AF and may contribute to the ability of sustained atrial tachycardia to increase atrial vulnerability. Given the probable clinical significance of atrial tachycardia-induced remodeling,\textsuperscript{2,33} an appreciation of the potential role of spatial heterogeneity in remodeling is important.

**Limitations of Our Findings**

Electrophysiological variables were measured at only 1 atrial cycle length. The use of several cycle lengths would have greatly increased the duration of experiments, introducing potentially important time-dependent confounding factors and making the study practically infeasible. We did not analyze ERP heterogeneity during AF or at the minimum 1:1 cycle length, which would have been interesting and relevant but technically difficult. We cannot exclude the possibility that wavelength during AF might have been related to AF duration; however, wavelength was not decreased at a BCL of 300 ms in paced dogs, and ERP rate adaptation is reduced in tachycardia-remodeled atria.\textsuperscript{6,7,10} suggesting that wavelength would not be reduced at rapid rates in our dogs.

We chose 24 hours of rapid pacing for study because this interval is sufficient for significant atrial remodeling\textsuperscript{6,8} but is not associated with an excessive prevalence of prolonged AF (>30 minutes). In our experience, prolonged AF due to tachycardia-induced remodeling makes detailed ERP mapping impossible because of the frequent induction of AF, requiring subsequent cardioversion, during ERP determination. Our results are pertinent to the mechanisms of remodeling and AF promotion resulting from recent-onset AF (within 24 hours). Similar mechanisms may be operative during AF of longer duration, but it would be inappropriate to assume that our observations necessarily apply to AF that lasts several days or weeks.

Our mapping system samples the atrial epicardial surfaces extensively but does not provide information about septal activation or the activation of subendocardial structures, such as the pectinate muscles. Such regions may play an important role in atrial reentry, including AF.\textsuperscript{34–36} and were almost certainly involved in reentrant excitations (like those shown in Figure 6), for which our mapping revealed only part of the reentry circuit.

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