Importance of Geometry and Refractory Period in Sustaining Atrial Fibrillation
Testing the Critical Mass Hypothesis

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Background—The critical mass hypothesis for atrial fibrillation (AF) was proposed in 1914. There has never been a systematic investigation defining the relationship between tissue geometry and AF. The purpose of this study was to determine the association among the probability of maintaining AF and the width, area, weight, effective refractory period (ERP), and wavelength in atrial tissue.

Methods and Results—Isolated canine atria (n=20) were perfused with Krebs-Henseleit solution. Baseline ERPs were obtained with and without acetylcholine (10E-3.5 mol/L) using single extra-stimulus pacing while unipolar electrograms were recorded from 250 sites. The tissue was then partitioned using bipolar radiofrequency ablation, and the ERPs were measured again with and without acetylcholine. Any section of tissue that maintained AF was divided until the arrhythmia was no longer inducible. ERPs and conduction velocities were measured in all of the sections after each ablation, and the wavelengths were calculated. The probability of AF was found to be correlated with increasing tissue areas, widths, and weights (P<0.001). The probability of AF was significantly associated with the length of the ERP and the wavelength (P<0.001). With shorter ERPs and shorter wavelengths, there was an increased probability of sustained AF.

Conclusions—The probability of sustained AF was significantly associated with increasing tissue area, width, and weight and decreasing ERPs and wavelengths. These data may lead to a better understanding of the mechanism of AF and, thus, help to design more-effective interventional procedures in the future. (Circulation. 2005;112[suppl I]:I-7–I-13.)

Key Words: arrhythmia ■ atrial fibrillation ■ maze procedure

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the world. There are thought to be >2.3 million Americans living with AF. In 1914, Garrey hypothesized that a critical mass of tissue was necessary to maintain fibrillation. Garrey theorized that multiple wavelets circulated through the atria around transitory and shifting lines of block, activating the atria in a chaotic manner that sustained AF. Using computer modeling, researchers demonstrated that multiple wavelet reentry theoretically could be a mechanism to sustain AF. Others subsequently confirmed multiple wavelet reentry as a cause of AF in studies in animals and humans. Weiner and Rosenbluth introduced the concept of wavelength, defined as the product of refractory period and conduction velocity (CV), which represents the minimum path length needed for reentry in sustained AF.

The maze procedure divides the atrium into a maze and prevents macro circuit reentry, while still allowing for normal sinus activation of the atrium. Recent long-term follow-up data demonstrated a success rate of >92%. Although a successful procedure, there still remains a subset of patients for which this procedure does not cure of AF.

Kosakai examined their operative experience and found a decreasing success rate with increasing preoperative atrial sizes. When the left atria (LA) diameter was <45 mm, the success rate in conversion to normal sinus rhythm (NSR) after the maze was 100%. When the diameter was >87 mm, there was a 0% success rate for conversion to NSR after the maze. It is hypothesized that the maze procedure does not divide the atria into small enough sections to prevent AF in patients with enlarged atria.

It was the objective of this study to obtain a more quantitative definition of the critical geometry associated with sustained AF. This study evaluated the importance of effective refractory period (ERP), conduction velocities, wavelength, and the geometry of atrial tissue on the maintenance of sustained AF in a canine isolated atrial preparation.

Methods
Normal mongrel dogs (n=20), weighing between 20 and 30 kg, were IV anesthetized with 7.5 mg/kg propofol, intubated, and placed on a positive pressure respirator with 2% to 3% isoflurane for anesthesia throughout the procedure. A median sternotomy was performed, the
The ERP was defined as the shortest S1S2 interval that captured the oxygenated with 95% O2 and 5% CO2 (pH HCO3). In the RA (n=14) preparations, the atrium was dissected from the rest of the heart and divided through the superior venae cava down to the inferior vena cava to facilitate mounting of the tissue on the electrode plaque.13 The right coronary artery was cannulated with a 16-gauge catheter.

In the LA preparations (n=6), the heart lung block was removed, the lungs were cleaned dissected from the heart, and the pulmonary veins were divided ~1 cm from their insertion into the LA. The ventricles and RA were excised. The circumflex artery was dissected up to the aortic root and distally to beyond the last atrial branch, and all of the ventricular branches were ligated. The circumflex artery was cannulated with a 16-gauge catheter.13 The LA was divided through the right and left superior veins, unfolded, and mounted on the electrode plaque.

Before the isolated atrial preparations were mounted to the electrode plaque in the bath, the appendages were ablated using bipolar radiofrequency energy (AtriCure Inc.). The clamp created transmural lesions (~1 mm wide) that prevented electrical conduction across the lesion. The epicardial surface was mounted on a flat electrode platform containing 256 unipolar electrodes with an interelectrode distance of 5 mm. The atrial appendage of each preparation was placed into a slot in the electrode template that allowed the atrium to lie flat.

The preparation was kept in a temperature-controlled bath at 37°C and perfused with a Krebs-Henseleit (KH) solution at a rate of 8 to 10 mL/min (~50 mm Hg). The composition of the KH solution was as follows (mmol/L): Na+, 143; K+, 4.7; Cl−, 128; Ca2+ 1.25, HCO3−, 25; Mg2+, 1.2; and dextrose, 11.1. The solution was oxygenated with 95% O2 and 5% CO2 (pH=7.4). The preparations were continuously superfused with KH (Figure 1).

Pacing sites were marked such that pacing was always performed from the same sites. Pacing was conducted at 1.5 times the pacing threshold. The S1S2 interval used for all of the pacing was 300 ms. The ERP was determined at each pacing site by incrementally decreasing the S1S1 interval used for all of the pacing was 300 ms.

The electrograms recorded during pacing at 300 ms were analyzed to calculate the activation sequence and the CVs.8 The mean, maximum, and minimum CVs and SDs for each section were calculated. Wavelength was calculated as the product of the average CV and the ERP of each section of atrium.8

The results comparing the LA and RA are summarized in Tables 1 and 2. The term “whole section” refers to either the RA or LA before any ablations were performed, that is, the atrium in its entirety. The term “all sections” is used to describe an analysis performed when all of the varying sized sections, including the whole, were combined for that test. This distinction allowed differentiation of innate properties of the native atria from any that could be artifacts from either time in the bath or the ablative procedures.

The RA was significantly larger than the LA. However, the LA was significantly heavier than the RA. The mean maximum widths of the whole RA and LA were not statistically different.

Results

The results comparing the LA and RA are summarized in Tables 1 and 2. The term “whole section” refers to either the RA or LA before any ablations were performed, that is, the atrium in its entirety. The term “all sections” is used to describe an analysis performed when all of the varying sized sections, including the whole, were combined for that test. This distinction allowed differentiation of innate properties of the native atria from any that could be artifacts from either time in the bath or the ablative procedures.

The RA was significantly larger than the LA. However, the LA was significantly heavier than the RA. The mean maximum widths of the whole RA and LA were not statistically different.
There were no differences between the left and right whole atria ERPs in the absence of acetylcholine (Table 2). When acetylcholine was added, the mean ERP in the whole RA was significantly less than in the whole LA. When both RA and LA sections were analyzed in the absence of acetylcholine, the RA was found to have significantly shorter ERPs than the LA. There was no difference in the ERP for all of the sections between the right and the left in the presence of acetylcholine.

The impact of the ablations on the ERP was evaluated. Without acetylcholine, the RA ERPs trended toward decreasing values with each additional ablation ($P=0.077$). This trend was not observed in the LA ($P=0.278$). With the addition of acetylcholine, the ERP in the RA significantly increased over time from the beginning of the study to the end ($25.91 \pm 10.49$ ms to $42.35 \pm 21.58$ ms; $P<0.001$). There was no change in the ERP of the LA preparation over time ($P=0.130$) with the addition of acetylcholine.

All of the CVs were calculated at a paced cycle length of 300 ms. An analysis of all sections combined found no significant difference in mean CVs for those sections that

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**Figure 2.** Electrograms are presented from recordings near the pacing sites. (a) NSR. (b) AF in the entire preparation. (c) NSR in the preparation after first ablation dividing the preparation into halves. (d) AF in one half of the preparation after first ablation.

**Figure 3.** Atrial preparation at the completion of the study after all ablation lesions are complete. Three ablation lesions are noted.
were perfused with acetylcholine and those that were not
\(P=0.476\). Examination of each atrium individually and all
of its CV parameters showed no difference between the
average minimum CV, the average maximum CV, or the
mean CV when comparing the whole RA preparation per-
fused with and without acetylcholine. The average maximum
CV and the overall mean CV were unchanged in the LA
whole preparation with and without acetylcholine present.

The RA and LA preparations were compared for differ-
ences in minimum, maximum, and mean CV values and their
SDs. There was a significant difference in the mean CV for
all of the data points collected in the whole section, with the
LA having a faster mean CV than the RA. The SDs for the
measurement of mean CVs in all of the sections were also
significantly different, with the RA having a greater SD than
the LA. The maximum CV values in the whole atrial
preparations were greater in the right than the left. However,
when the maximum CV values were examined in all of the
sections, there was no significant difference. The minimum
CVs were significantly less in the RA than the LA in the
whole atrial preparations and when all of the sections were
combined. When the CVs were analyzed in relation to
ablations, there was no change in the RA \(P=0.485\) or the
LA \(P=0.320\). The SDs for this evaluation were also not
statistically different (RA, \(P=0.204\); LA, \(P=0.129\)).

Mean wavelength was calculated by multiplying the mean
CV by the ERP. When the mean wavelengths without
acetylcholine were compared among all of the sections, there
was a significant difference between the LA and RA, with the
right having a shorter mean wavelength. Comparison of mean
wavelengths in the presence of acetylcholine showed no
statistical difference. There was no change over time when
the mean wavelengths for all of the sections were pooled and
compared after each ablation \(P=0.508\). There was found to
be no change in the wavelength after each ablation when each
atrium was analyzed individually (RA, \(P=0.595\); LA,
\(P=0.945\)).

The probability of AF was analyzed with a univariable
logistical regression. The impact of ERP, area, maximum
width, minimum width, average width, maximum height,
minimum height, weight, CVs, CV SDs, wavelength, and
atria were evaluated. The results of the univariable logistical
regression are presented in Table 2. McFadden Rho squared
values between 0.2 and 0.4 are considered satisfactory.15

In summary, decreasing ERPs \(P<0.001\), increasing areas
\(P<0.001\) (Figure 4a), increasing maximum and minimum
widths \(P<0.001\), increasing average widths \(P<0.001\),
increasing weights \(P<0.001\), maximum CV \(P<0.001\),
and decreasing wavelengths \(P<0.001\) were all found to be

### TABLE 1. Tissue Geometry of the RA and LA

<table>
<thead>
<tr>
<th>Variables</th>
<th>RA</th>
<th>LA</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area</td>
<td>4068.3±494.7 mm(^2)</td>
<td>3851.9±522.2 mm(^2)</td>
<td>0.027</td>
</tr>
<tr>
<td>Weight</td>
<td>7.61±1.6 g</td>
<td>8.23±0.70 g</td>
<td>0.002</td>
</tr>
<tr>
<td>Maximum widths</td>
<td>91.8±4.4 mm</td>
<td>91.2±4.6 mm</td>
<td>0.518</td>
</tr>
<tr>
<td>Minimum widths</td>
<td>75.7±4.4 mm</td>
<td>78.9±7.1 mm</td>
<td>0.012</td>
</tr>
<tr>
<td>Average widths</td>
<td>83.4±4.3 mm</td>
<td>85.1±4.7 mm</td>
<td>0.057</td>
</tr>
<tr>
<td>Maximum height</td>
<td>56.7±5.9 mm</td>
<td>51.9±2.9 mm</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimum height</td>
<td>38.7±3.9 mm</td>
<td>41.1±7.0 mm</td>
<td>0.044</td>
</tr>
</tbody>
</table>

### TABLE 2. ERP, CV, and Wavelength in the RA and LA

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA</th>
<th>LA</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole preparation (before ablations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP no ACh</td>
<td>126.9±23.9 ms</td>
<td>139.0±33.7 ms</td>
<td>0.152</td>
</tr>
<tr>
<td>ERP with ACh</td>
<td>23.8±10.7 ms</td>
<td>31.2±8.1 ms</td>
<td>0.003</td>
</tr>
<tr>
<td>All sections combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP no ACh</td>
<td>120.5±27.8 ms</td>
<td>141.2±36.3 ms</td>
<td>0.001</td>
</tr>
<tr>
<td>ERP with ACh</td>
<td>32.7±17.1 ms</td>
<td>33.9±9.1 ms</td>
<td>0.527</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>0.943±0.048 mm/ms</td>
<td>0.99±0.095 mm/ms</td>
<td>0.001</td>
</tr>
<tr>
<td>CV SD</td>
<td>0.279±0.043 mm/ms</td>
<td>0.26±0.036 mm/ms</td>
<td>0.001</td>
</tr>
<tr>
<td>Whole preparation (after ablations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CV</td>
<td>1.486±0.016 mm/ms</td>
<td>1.48±0.03 mm/ms</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimum CV</td>
<td>0.300±0.105 mm/ms</td>
<td>0.41±0.14 mm/ms</td>
<td>0.001</td>
</tr>
<tr>
<td>All sections combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CV</td>
<td>1.457±0.064 mm/ms</td>
<td>1.46±0.09 mm/ms</td>
<td>0.849</td>
</tr>
<tr>
<td>Minimum CV</td>
<td>0.396±0.165 mm/ms</td>
<td>0.48±0.17 mm/ms</td>
<td>0.001</td>
</tr>
<tr>
<td>Wavelength no ACh</td>
<td>112.77±28.9 mm</td>
<td>145.73±46.7 mm</td>
<td>0.001</td>
</tr>
<tr>
<td>Wavelength with ACh</td>
<td>30.4±15.1 mm</td>
<td>33.9±11.6 mm</td>
<td>0.154</td>
</tr>
</tbody>
</table>

\(ACh\) indicates acetylcholine.
significantly associated with an increased probability of sustained AF (Table 3). The factors that did not correlate with an increasing probability of sustained AF were maximum (P = 0.654) and minimum (P = 0.154) heights, mean CVs (P = 0.319) or their SDs (P = 0.516), and minimum CVs (P = 0.299). A multivariable analysis was performed using combinations of ERP, wavelength, weight, area, CV, maximum width, and average width (Table 2 and Figures 4 and 5).

### Discussion

The overall success rate of the maze procedure is reported to be >90%. Patients with enlarged atria and those that have been in sustained AF for an extended period of time preoperatively have a much lower success rate. Garrey hypothesized almost a century ago that there was a critical mass, above which AF was sustained and below which it could be prevented. This study supports this hypothesis, with increasing tissue surface area correlating significantly with the probability of sustaining AF (Figures 4 and 5).

Atrial remodeling, with the increase in atrial fibrosis, can slow CV and can shorten the refractory period in atria with long-standing AF. The duration of preoperative AF is known to be a negative predictor for the success of the maze procedure. The results of this investigation demonstrate the importance of the duration of the ERP, with shorter ERPs more likely to sustain AF. Multivariable logistical regression models demonstrate that increasing tissue size and decreasing ERPs increase the probability of sustained AF (Figure 4b).

When all of the geometric data were analyzed for any correlations with AF, all of the variables correlated well, except for the maximum and minimum heights. This was because the height was not varied during the study.

Two types of logistical regression models were used. Univariable logistical regression models were used to evaluate all of the parameters to determine the probability of inducing sustained AF. ERP and wavelength were the two variables determined to have the best fit and the greatest association with the probability of sustained AF. The variables area, weight, maximum width, minimum width, and average width were all significant but were not determined to have as good of a fit. This demonstrates that the area needed to maintain AF is dependent on functional factors like ERP. The variables of minimum height, maximum height, CV, or CV SD were not significantly associated with predicting the probability of inducing sustained AF. This was in part because of these variables not having been modulated. This does not mean that CV is not important; it was just relatively consistent throughout the duration of the experiment. It is important to note that there was no difference between the probability of inducing sustained AF if the study occurred in the RA or the LA. Whereas, clinically, AF is often associated with the LA, it is also known, clinically, that the refractory periods in the LA are shorter than in the RA. This is

### Table 3: Univariable Logistical Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>McFadden Rho Squared</th>
<th>Constant Coefficient</th>
<th>Variable Coefficient</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP</td>
<td>&lt;0.001</td>
<td>0.513</td>
<td>3.182943</td>
<td>−0.083691</td>
<td>397</td>
</tr>
<tr>
<td>Wavelength</td>
<td>&lt;0.001</td>
<td>0.486</td>
<td>2.851849</td>
<td>−0.082362</td>
<td>397</td>
</tr>
<tr>
<td>Area</td>
<td>&lt;0.001</td>
<td>0.055</td>
<td>−1.837034</td>
<td>4.29E-4</td>
<td>397</td>
</tr>
<tr>
<td>Weight</td>
<td>&lt;0.001</td>
<td>0.048</td>
<td>−1.677815</td>
<td>0.191325</td>
<td>397</td>
</tr>
<tr>
<td>Width max</td>
<td>&lt;0.001</td>
<td>0.060</td>
<td>−1.986520</td>
<td>0.020934</td>
<td>397</td>
</tr>
<tr>
<td>Width min</td>
<td>&lt;0.001</td>
<td>0.058</td>
<td>−1.780872</td>
<td>0.022933</td>
<td>397</td>
</tr>
<tr>
<td>Width avg</td>
<td>&lt;0.001</td>
<td>0.058</td>
<td>−1.891795</td>
<td>0.021654</td>
<td>397</td>
</tr>
</tbody>
</table>

Results from univariable analysis are presented above using the equation for the probability of AF: \( P_{AF} = e^{x}/[1 + e^{x}] \), where \( x = \text{constant + coefficient} \times \text{variable} \). Variable units are: ERP (ms), wavelength (mm), area (mm²), weight (g), width and height (mm), velocity and velocity STD (mm/ms), maximum conduction velocity (max CV, mm/ms), minimum conduction velocity (min CV, mm/ms), and atria (left vs right).
TABLE 4. Multivariable Logistical Regression

<table>
<thead>
<tr>
<th>X = constant + $\beta_0$(variable 1) + $\beta_1$(variable 2)</th>
<th>$P$ Value</th>
<th>McFadden Rho Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.209 - 8.219E-2(ERP) + 8.802E-4(area)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.590</td>
</tr>
<tr>
<td>0.701 - 8.801E-2(WL) + 9.12E-4(area)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.569</td>
</tr>
<tr>
<td>1.167 - 8.31E-2(ERP) + 4.38E-2(width avg)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.594</td>
</tr>
<tr>
<td>0.9866 - 8.135E-2(ERP) + 4.112E-2(width max)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.593</td>
</tr>
<tr>
<td>0.3459 - 7.943E-2(WL) + 4.497E-2(width max)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.581</td>
</tr>
<tr>
<td>1.540 - 0.084(ERP) + 0.388(weight)</td>
<td>&lt;0.001, &lt;0.001</td>
<td>0.583</td>
</tr>
<tr>
<td>-20.953 - 7.919E-2(ERP) + 16.292(max CV)</td>
<td>&lt;0.001, 0.003</td>
<td>0.539</td>
</tr>
</tbody>
</table>

Results from the multivariable logistical regression are presented above using the equation for the probability of AF = $e^x/[1 + e^x]$. The value for $x$ is defined in the left column of the table. Variable units are: ERP (ms), wavelength (mm), area (mm$^2$), weight (g), width (mm), mean conduction velocity (mean CV, mm/ms), and maximum conduction velocity(max CV, mm/ms). WL indicates wavelength.

consistent with the findings in this study that show an increased probability of AF with decreasing refractory period.

The multivariable logistic regression combined variables and analyzed both geometric variables and physiological variables to create models for predicting the probability of inducing sustained AF. A series of equations was developed from these models. Table 4 can be used to predict the probability of a section of canine atria fibrillating when particular variables are entered into the equations. The first model presented used the variables of ERP and area. The data in Figure 4 allows for a better appreciation of the impact of ERP and area on the probability of inducing sustained AF. As the area decreased and the ERP increased, the probability of AF decreased. However, with the same ERP, as the tissue area increased, so did the probability of AF. This held true for the graphs that substituted wavelength for ERP, and when the geometric variable was weight, average width, or maximum width instead of area. This has important relevance to the clinical problem of increasing failure rates of the maze in patients with increased atrial size and patients with longstanding AF and decreased ERPs.

The present study represents a first attempt to quantify the relationship between geometric and functional electrophysiological variables and the inducibility of AF in the atrium. In this model, only the width and ERP were modulated. A more complete model will require modifying CV, as well as the height of the tissue. Finally, the model will need to be extended to the entire intact atrium. Although the model was developed in normal tissue, it still has significance for diseased atria. No matter what the underlying pathology, the underlying substrates are still ERP, CV, geometry, and premature impulse formation. As an example, in patients with persistent AF, ERP is decreased. The present model predicts the effects of inducibility with altered ERPs (Figure 6). Nonetheless, the model will have to be tested in diseased tissue. The model is also clinically relevant to those groups of patients with enlarged atria, who, although they have had a complete maze procedure (including PV isolation), still have AF. Using this approach, it may be possible to simulate the effect of different lesion sets on the inducibility of AF.

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