Prospective, Tissue-Specific Optimization of Ablation for Multiwavelet Reentry
Predicting the Required Amount, Location, and Configuration of Lesions

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Background—Treatment of multiwavelet reentry (MWR) remains difficult. We previously developed a metric, the fibrilligenicity index, to assess the propensity of homogeneous, 2-dimensional tissues to support MWR. In this study, we demonstrate a method by which fibrilligenicity index can be generalized to heterogeneous tissues and validate an algorithm for prospective, tissue-specific optimization of ablation to reduce MWR burden.

Methods and Results—We used a computational model to simulate and measure the duration of MWR in tissues with heterogeneously distributed action potential durations and then assessed the relative efficacy of a variety of ablation strategies for reducing tissues’ ability to support MWR. We then derived and tested a strategy in which multiple linear lesions partially divided a fibrilligenic tissue into functionally equivalent subsections. The composite action potential duration of heterogeneous tissue was well approximated by an inverse sum of cellular action potential durations ($R^2=0.82$). Linear ablation more efficiently reduced MWR duration than branching ablation patterns and optimally reduced disease burden when positioned at a tissue’s functional (rather than geometric) center. The duration of MWR after application of prospective, individually optimized ablation sets fell within 4.4% (95% confidence interval, 3–5.8) of the predicted target.

Conclusions—We think that this study presents a novel approach for (1) quantifying the extent of a tissue’s electric derangement, (2) prospectively determining the amount of ablation required to minimize the burden of MWR, and (3) predicting the most efficient distribution of these ablation lesions in tissue refractory to standard ablation strategies. (Circ Arrhythm Electrophysiol. 2016;9:e003555. DOI: 10.1161/CIRCEP.115.003555.)

Key Words: action potentials • atrial fibrillation • catheter ablation • electrophysiology • prospective studies

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, affecting an estimated 2.66 million people as of 2010.13 However, despite the high prevalence of this disease and the heavy socioeconomic burden associated with it,1,4 treatment options remain limited,5,6 especially in comparison with other reentrant arrhythmias.7–9 Of the available treatment options, catheter-based ablation has proven to be the most reliable method for the permanent elimination of AF.10–12 Nonetheless, although a standard anatomic basis set of ablation lesions (ie, pulmonary vein encircling/isolation) has been shown to be effective in patients with low disease burden,13–15 there remains dispute over the best next step in treatment of patients with more severe disease.16–18 An approach that seems logical and that has attracted significant attention recently is the delivery of focal lesions to tissue regions thought to host drivers of AF. Indeed, the initial successes of techniques, such as complex-fractionated atrial electrogram ablation20–22 and focal impulse and rotor modulation,23–25 have generated significant excitement in the AF community. Unfortunately, further study of these methods has yielded only mixed results,26–29 and there is reason to suspect that focal lesions may actually increase the incidence of atrial tachycardia by providing the substrate for structural reentry.21 Unlike focal ablation, linear ablation that connects to the nonconducting boundaries of the atria does not produce the substrate for structural reentry.22

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We have previously demonstrated that multiwavelet reentry (MWR; one of the main drivers of AF31–35) terminates only when all circuit cores collide with the tissue boundary30,36 and that the average duration of MWR episodes correlates with the probability of such collisions.37 We also developed a metric, the fibrilligenicity index (Fb),38 to assess the propensity of a tissue to support MWR through the quantification of features that determine the probability of these core–boundary collisions. Lines of ablation provide additional boundary against which circuits can collide and can thus partially reduce a tissue’s fibrillatory burden.37 However, the degree of electric derangement in patients with AF exists along a continuum,38,39 and a given lesion set may not have the same effect in patients having differing burdens of disease. Determining the amount...
WHAT IS KNOWN

- Success rates for ablation of persistent or long-standing persistent atrial fibrillation are low, and there is little consensus about the appropriate ablation strategy for patients in whom pulmonary vein isolation alone is insufficient.
- There are currently no methods for titrating the extent of ablation required for treatment of multiwavelet-driven atrial fibrillation.

WHAT THE STUDY ADDS

- The fibrillogenicity index provides a means to quantify the extent of atrial electric derangement and to titrate the amount of ablation required to mitigate this derangement.
- Linear ablation distributed so as to divide the tissue into regions of equal fibrillogenicity maximizes wave–lesion interactions optimizing ablation efficiency.

of ablation required to eliminate MWR in a specific patient is a crucial question because ablation comes at a cost; the benefits of decreased fibrillatory burden must be balanced against the morbidity of increased lesion load. In this study, we demonstrate a method by which the Fb can be generalized to predict the propensity of heterogeneous tissues to support MWR and validate an algorithm for prospective, tissue-specific optimization of ablation to reduce MWR burden.

Methods

Computational Model

In the following experiments, we made use of a previously described computational model of electric propagation in cardiac tissue.30–36,37 This combines a diffusion model of extracellular current spread with a rule-based cellular automaton model of cardiomyocyte excitation. Briefly, cells (each representing ≈1 mm² of cardiac tissue) undergo action potentials when they receive current sufficient to perturb their potential from rest ($V_{\text{rest}}$) to above a defined threshold ($V_{\text{th}}$). Action potentials cause the cell voltage to increase toward peak potential ($V_{\text{peak}}$) after which it gradually returns to $V_{\text{rest}}$ over a period of time, the action potential duration (APD), during which it is refractory to new stimuli. Cells transmit current to their adjacent neighbors, increasing the voltage of each neighbor with a time constant equal to the product of the cell–cell ohmic resistance (R) and the electric charge capacitance of the neighboring cell (C). The number and arrangement of the cells in the model, as well as the parameter values for each cell, can be set so as to allow the simulated tissue to support various patterns of electric excitation. In this study, we designed the simulated tissues such that they were capable of supporting MWR (as opposed to stable focal rotors) by limiting the ratio of RC and APD below a value of 0.18.40 Episodes of MWR were induced by high-frequency (100 Hz) burst pacing from a virtual electrode positioned randomly over the tissue surface. The model simulations were run on the Vermont Advanced Computing Core (http://www.uvm.edu/~vacc/).

Fibrillogenicity Index

The Fb is a parameter-based metric of electric derangement that is highly correlated with MWR episode duration and is calculated according to the following equation:

$$ Fb = \frac{A}{BL \times RC \times APD} \tag{1} $$

Here, A is the tissue area and BL is the length of the unexcitable tissue boundary. Therefore, the Fb quantifies the ratio of area versus boundary length and tissue wave length. In each of 100 simulated rectangular tissues with randomized, homogeneous tissue properties (APD=50–200 ms; RC=8–14 ms; A=2500–10000 mm²; BL=200–400 mm), we measured the mean duration of 500 unique episodes of MWR. We developed a standard curve relating Fb to the mean duration of MWR by fitting these data with a quadratic regression and calculating the coefficient of determination.

Effective Fb

To test the effect of heterogeneous tissue properties on the duration of MWR, we created a series of simulated square tissues (100×100 mm) with distinct regions of long (APDL=125 ms) and short APD (APDS, varied in separate tissues between 85 and 115 ms in increments of 10 ms) and varied the relative areas of these regions. In each tissue, we induced 500 instances of MWR and measured the episode durations. The mean duration and SEM were calculated for each tissue as a function of the percentage of tissue at APDS.

For tissues with multiple patches of differing APD, we calculated an effective APD for the tissue as a whole, APDE. This is calculated as the inverse of the sum of the component durations each weighted by their respective areas on the tissue. That is,

$$ APDE = \frac{N}{\sum_{i=1}^{N} \frac{A_i}{APD_i}} \tag{2} $$

Here, $A_i$ and APDi are the area and APD, respectively, of the ith of N distinct tissue regions. Insertion of Equation 2 into Equation 1 gives the effective Fb, FbE, that we used to predict the duration of MWR episodes in heterogeneous tissues. That is,

$$ FbE = \frac{A}{BL \times RC \times APDE} \tag{3} $$

Effect of Ablation

Lesion Distribution

To assess the relative efficacy of various lesion distributions (Figure 1), we measured the effect on MWR duration of a fixed total lesion length distributed as 1 line, 2 lines, a square lesion that reduced tissue area, or a branched lesion. The tested tissue had homogeneous distributions of properties (150×60 mm; APD=75 ms; RC=11 ms). We studied total lesion lengths from 0 to 100 mm (in increments of 2 mm). In each case, lesions were connected to the external boundary. The mean duration and SEM of 500 unique episodes of MWR were determined as a function of the quantity of ablation (ie, the total number of cells ablated).

Wave Versus Lesion Interactions

We hypothesized that the spatial configuration of ablation affected the potential for collisions between circuit cores and lesions. To test
this, we examined the number of waves (mean and SEM) that passed over each cell in the tissue (150x60 mm; APD=70 ms; RC=10 ms) during 10 s of MWR (n=3). Cells with electric potential >40% of the difference between $V_{max}$ and $V_{min}$ were considered to be part of a wave, and the number of times each cell hosted a new wave was counted. To quantify wave–lesion interactions, we counted the number of waves that excited each cell adjacent to the ablation lesions. We then compared the rate of wave–lesion interactions as a function of lesion distribution.

**Effect of Tissue Transection**

We next examined the effect of transecting rectangular tissues (150x60 mm) at different positions along their long axes with linear lesions. Transection was tested in 3 tissue series: (1) tissues in which APD was uniform (mean APD varied in separate tissues between 85 and 115 ms in increments of 10 ms), (2) tissues composed of 2 distinct regions with different APD values (20% area with APD=60 ms; 80% area with APD varied in separate tissues between 85 and 115 ms in increments of 10 ms), and (3) tissues in which APD varied smoothly but randomly between values of 65 and 115 ms (Figure 2).

**Partial Transection**

In the third of the above tissue series, we additionally examined the effect of partial tissue transection by applying an ablation line that reached 3 quarters of the way across the tissue from the bottom boundary at different positions along the tissue’s long axis. In a single rectangular tissue capable of supporting long episodes of MWR (150x60 mm; APD=85 ms; RC=10 ms), we incrementally applied ablation (2-mm increments per line) that ultimately divided that tissue into halves, thirds, fourths, and fifths. The durations of 500 unique episodes of MWR were determined after the application of each new ablation extension, and the mean duration was calculated.

**Ablation Delivered to Left Atrial Geometry**

We examined the effect of tissue transection in a more realistic left atrial geometry (Figure 3). Computed tomographic images of the heart were used to generate a curved, 2-dimensional (2D) surface mesh composed of 6810 triangular units of area each representing an average of 1.8 mm² and corresponding to the endocardial surface of the atrium. This mesh was created using open-source MeshLab software (meshlab.sourceforge.net). First, a standard lesion set (pulmonary vein isolation plus a mitral isthmus line) were considered to be part of a wave, and the number of times each cell hosted a new wave was counted. To quantify wave–lesion interactions, we counted the number of waves that excited each cell adjacent to the ablation lesions. We then compared the rate of wave–lesion interactions as a function of lesion distribution.

**Effect of Tissue Transection (Partial and Complete)**

For any fixed total amount of ablation, delivery of a smaller number of longer lines was more effective than that of a larger number of shorter lines (compare points along a vertical line in Figure 5B). The degree to which any single line

**Effect of Tissue Transection (Partial and Complete)**

For any fixed total amount of ablation, delivery of a smaller number of longer lines was more effective than that of a larger number of shorter lines (compare points along a vertical line in Figure 5B). The degree to which any single line
could reduce fibrillatory burden was limited by tissue width (eg, if the tissue was 60-mm wide, further linear ablation must be at least partially distributed across additional lines). Duration of MWR could be further decreased through delivery of more lines, increasing the total number of ablated cells (Figure 5B).

**Effect of Ablation Location**

In tissues with uniform APD, a complete linear transection through the center of the tissue proved the most effective at reducing episode duration (Figure 6A). As the ablation line was moved away from the geometric center of the tissue, its effect on MWR duration was progressively reduced. In heterogeneous tissues, the optimal transection position was shifted away from the geometric center toward the side with the shorter APD (Figure 6B). The magnitude of this shift was directly proportional to the relative values of $APD_L$ and $APD_S$.

In both homogeneous and heterogeneous tissues, the optimal transection position was accurately predicted as the point at which the 2 resulting tissue segments (either side of the line) had the same values of $Fb_c$. Limiting lesion length to 75% of the tissue width did not affect the optimal transection position but reduced the overall effect of ablation.

The presence of localized APD shortening also affected the optimal transection position in the more realistic left atrial geometry (Figure 7). When APD was uniformly distributed across the atrial surface, the transection of the atrium into equal halves (50% of the area on each side of the line) resulted in the maximum reduction in MWR episode duration. In tissue with a discrete patch of shorter APD, the optimal transection position was shifted 1.4 cm in the direction of the patch (69% of the atrial area on the $APD_L$ side of the line and 31% on the $APD_S$ side).

**Prospective Ablation Optimization**

We prospectively assessed the minimum ablation required to reduce MWR burden below a target threshold of 3 s (Figure 8). Before ablation, the magnitude of disease burden in the 60 randomized tissues spanned 2 orders of magnitude (5–500 s). Optimal lesion sets reduced MWR duration below the target threshold in all cases. Durations were lower than the target by an average of 0.83±0.03 s (4.4±0.7% of total intervention).

**Discussion**

Ablation of MWR is qualitatively different from the ablation of other reentrant arrhythmias because the circuits that comprise MWR are functional, multiple, and mobile.\(^{11,12}\) As a result, the treatment of MWR is not aimed at eliminating the possibility of its existence but at maximizing the probability of its spontaneous termination through collisions between circuit cores and unexcitable boundaries.\(^{37}\) In this study, we found that this probability could be altered through the application of ablation, the effect of which depended on the configuration, location, and extent of its delivery. The mechanism of this dependence was via the effect of these 3 factors on the probability of wave–lesion interactions.

**Quantifying Atrial Electric Derangement**

A shift in perspective from a deterministic to a probabilistic view point offers many advantages. For example, it is possible to prospectively assess the propensity of a tissue to support MWR by viewing its electric activity as a population of interacting waves that fuse, divide, and annihilate.\(^{12,28}\) Tissues that support only small numbers of waves are much more likely to reach quiescence (ie, a wave population equal to 0) than those that support large numbers of waves. The $Fb$ provides an empirical method for predicting the mean wave population, and therefore, the duration of MWR episodes, through the tissue parameters that determine both wave...
size (APD, $R$, and $C$) and tissue size ($A$ and $BL$; Figure I in the Data Supplement). It follows that we can control the duration of MWR through the direct manipulation of these parameters. The delivery of ablation, for example, increases the total boundary length and therefore the probability that waves will collide with that boundary and annihilate. By maximizing the rates of wave–lesion interactions for each ablated cell, we can minimize both the average wave population and the duration of MWR.

**Effect of Ablation Configuration and Location**

We demonstrated that geometrically complex patterns, such as branching lesions, reduce MWR duration less effectively than simple, linear lesions (Figure 5A). This is because the protruding segments of branching lesions act like breakwaters, shielding their more central surfaces from exposure to incoming waves (Data Supplement). On average, these lesions have fewer wave–lesion interactions per ablated cell and are therefore less efficient. Linear lesions minimize this shielding effect by maximizing the distance between all ablated cells. In homogeneous tissues, placement of perpendicular lesions at the geometric center maximizes the distance between all points along the contiguous boundary surface (including the ablation points), thus maximizing the number of wave–lesion interactions. Bisection at this location produces 2 new independent tissues with the minimum net Fb and maximally reduced MWR episode duration (Figure 6A). Interestingly, waves in close proximity to a lesion display an attenuated version of the shielding effect, screening the boundary surface from more distant waves. This implies that boundary surfaces have basins of influence, the steepness of which is proportional to the surrounding wave size. When basins of influence overlap one another (as in smaller tissues with larger waves), the importance of optimizing lesion placement becomes more apparent (Figure 6A).

**Effect of Tissue Heterogeneity on Optimal Lesion Location**

In tissues with heterogeneously distributed cell properties, the density of waves is spatially varied (higher in regions of shortened APD) and different regions contribute nonuniformly to the maintenance of MWR. Maximizing the number of wave–lesion interactions is no longer achieved with ablation at the tissue’s geometric center. We demonstrated that the effect of a heterogeneous APD distribution on Fb is well approximated by an area-weighted inverse sum of APDs of the individual cells comprising the tissue (Figure 4). Thus, although the variations in APD cause wave size to be altered locally, APD$_{e}$ provides an estimate of the average number of waves per unit area and allows an effective Fb, Fb$_{e}$, to be calculated (Equation 3). Performing a topological mapping to normalize wave sizes throughout the tissue shows that the transection point at which the Fb$_{e}$ values on either side of the dividing lesion are equivalent is the same point at which their effective areas, and thus supported wave populations, are equal. This position also maximizes the functional distance between points along the contiguous boundary, thereby maximizing the rates of wave–lesion interactions per ablated cell. We demonstrated experimentally that transection at this functional midpoint maximally reduces the duration of MWR episodes (Figure 6B) and that this midpoint is shifted in the direction of the lowest APD (Figure 7).

**Partial Tissue Transection**

Clinical considerations, such as the need for continuous conduction between the sinus node and all atrial cells, preclude the practical use of lesions that fully transect the atria. Fortunately, the mechanistic basis for full transection applies to partially transecting lesions as well. The goal of ablation is still to maximize the rates of wave–lesion interactions (and therefore wave annihilation) per ablated cell, and this is still achieved by applying lesions perpendicular to the outer boundary in positions that expose both of its surfaces to equal populations of reentrant waves. We demonstrated that the optimal positions for both fully and partially transecting lesions were the same...
Prospective Ablation Optimization

It is our contention that the severity of AF exists along a spectrum, and hence, the magnitude of the treatment effect required for its alleviation must also exist along a spectrum. In other words, a patient with more advanced AF is likely to require more extensive ablation than a patient with paroxysmal AF. Seen in this light, it is not surprising that uniform ablative strategies may result in comparably efficient reductions in MWR duration, its overall efficacy is lower because of the smaller total amount of added boundary length. Greater efficacy may be achieved via the delivery of additional partially transecting linear lesions distributed evenly across the tissue’s functional area (Figure 5B).

Limitations

Our goal in this study was to establish the theoretical underpinnings of the FB and to test its performance in a controlled setting, something that can only be done exhaustively and with complete precision in a computational model. Nevertheless, the concepts we present here cannot be considered confirmed in any practical sense until they have been demonstrated in a biological setting, something that goes beyond the scope of this study. The contribution we have made here, therefore, is to produce a set of testable predictions that can serve to guide the design of future experimental studies aimed at advancing the rational design of patient-specific ablation sets for treating AF.

Although our studies are motivated by the need to design lesion sets tailored to individual cases of AF, we are still some distance away from this goal. Several key challenges must first be overcome. For example, FB makes the use of tissue properties (A/BL, APD, and RC) to quantify average AF duration. Although area and boundary length are easily obtained, it is difficult to directly measure APD and RC in the clinical setting. We have previously demonstrated that these same properties determine local tissue activation frequency and that electrogram frequency correlates with tissue frequency when measured with electrodes of adequate spatial resolution. Thus, it should be possible to calculate FB using electrogram mapping to indirectly measure tissue properties. Ultimately, biological validation will be required before FB can be applied clinically. Nevertheless, FB provides a theoretical foundation on which patient-specific ablation strategies may eventually be based.

Atrial remodeling causes progressive dilation, changes in ion channel expression and interstitial fibrosis. These combine to increase AF duration via their effect on the atria’s architecture, refractory period, and conduction velocity. In this study, we have examined tissues with a wide range of area, boundary length, APD, and intercellular resistance, and we demonstrate that these parameter changes correspond to a progressive increase in the duration of MWR. Although we have not modeled dynamic changes to FB, we have examined a substantial range of properties over which remodeling occurs. Thus, the FB serves as a measure of a tissue’s electrical derangement at a specific moment in time. As an important caveat, our model of interstitial fibrosis does not include alterations to cellular excitability that may result from either fibroblast/myocyte coupling or discontinuities in tissue thickness. In addition, although the range of disease burden we have examined spans over 4 orders of magnitude (3 s to 6 hours of episodes of MWR), computational burden limited our ability to quantify episode durations in more severely deranged tissues. Application of our ablation strategy to patients with highly diseased atria, therefore, assumes that FB can be accurately extrapolated to tissues with more advanced disease.

Although debate continues as to the mechanisms responsible for AF, there is evidence to suggest that reentrant drivers exist along a spectrum that includes MWR and focal drivers with fibrillatory conduction. The ablation strategy we propose in this study is aimed at interrupting the spatially dynamic circuit formation of MWR. However, AF may involve microanatomic reentry that is characterized by stable circuits. Such forms of AF are only terminated by ablation that directly targets these drivers. Both fibrillatory conduction and MWR require tissue properties conducive to dynamic wavebreak; FB quantifies the extent to which fibrillatory conduction can be self-sustaining. Even in the presence of focal drivers, FB provides a metric of functional substrate and thereby defines the burden of disease remaining after their elimination. Thus, we propose FB as part of a comprehensive cure for AF, which may require more than a single strategic approach.

A practical issue concerns the efficacy of ablation itself because ablated tissue may heal and lead to the development...
of gaps in linear lesions over time.47 The actual implementation of a patient-specific ablation protocol may, thus, require more >1 visit to the ablation laboratory to be fully effective. This is, however, a limitation of all ablation-based treatment strategies and does not reflect the theoretical framework we have presented here.

Conclusions
In this study, we used a computational model to explore the effects of both heterogeneity and ablation on cardiac tissue's propensity to support MWR. An inverse sum of APD2 weighted by area served as a useful approximation of the composite APD in heterogeneous tissues and could be used to accurately predict their burden of MWR (R²=0.82). Linear ablation reduced the duration of MWR more efficiently than lesion patterns with higher geometric complexity because they produced higher rates of wave–lesion interactions. We also found that partial transection dividing fibrillating tissue into regions that supported equivalent wave populations has presented here.

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Disclosures
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References


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Figure S1: A standard curve demonstrating the functional dependence of mean MWR duration on $Fb$ (in square, two dimensional tissues with uniformly distributed $APD$) was developed using quadratic regression.

Quadratic Regression:
\[
\log_{10}(MD) = 5.689 Fb^2 - 121 Fb + 1
\]

Coefficient of Determination:
\[
r^2 = 0.95
\]
Figure S2: Density maps showing the number of times each cell was excited by a propagating wave in tissues with linear or branching lesion distributions. Ablated cells were never excited (blue) and cells adjacent to boundaries (tissue edge and ablation lesions) were excited less frequently than cells farther from boundaries.

With a branching lesion distribution (top) there is a distinct decrease in the number of excitations in the region between lesion branches, reducing the number of possible wave-lesion interactions. Linear lesions are exposed to a greater number of waves (middle and bottom) than branching lesions. When the ablation line is placed close to the tissue edge (bottom) fewer waves reach the “protected” region between the tissue edge and the left side of the line, reducing wave-lesion interactions and hence ablation efficacy.
Figure S3: MWR episode duration as a function of the position of either complete (solid blue line) or partial (solid red line) transection in four heterogeneous tissues with smoothly varying, randomized APD distributions. The dashed vertical red lines show theoretically predicted point of minimum duration. The dashed vertical green lines show the geometric center of the tissue.