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A Mechanistically Guided Approach to Treatment of Multi-Wavelet Reentry: Experiments in a Computational Model of Cardiac Propagation

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A Mechanistically Guided Approach to Treatment of Multi-Wavelet Reentry
Experiments in a Computational Model of Cardiac Propagation

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States today. However, treatment options remain limited despite the enormous magnitude of both AF prevalence and the associated economic cost. Of those treatment options that are available, ablation-based interventional methods have demonstrated the highest rates of long-term cure. Unfortunately, these methods have substantially lower efficacy in patients with heavier burdens of disease, thus leaving the most affected individuals with the least hope for successful treatment.

The focus of this research is to develop a mechanistically guided approach towards the treatment of multi-wavelet reentry (MWR), one of the primary drivers of AF. For this purpose, we use a computational model of electrical propagation in cardiac tissue to simulate both episodes of fibrillatory activity and the ablative treatment thereof. We demonstrate that the probability of forming the reentrant circuits necessary for continuous electrical activity is a function of the shape and size of a tissue as well as its underlying cellular properties. Ablation at tissue sites with high probability of circuit formation more efficiently reduces the overall duration of fibrillatory episodes than ablation at sites with low probability. We then propose and validate *in silico* a parameter-based metric for predicting the propensity of an individual tissue to support fibrillation, which we term the fibrillogenicity index. Using this metric, we develop an algorithm for prospectively determining optimized, tissue-specific ablation patterns. Finally, we examine the relationship between multi-wavelet reentry and focal drivers, and demonstrate that MWR and fibrillatory conduction exist along a continuum. We examine the complex interplay between functional and structural substrates within fibrillating tissue and define the mechanisms by which they promote the perpetuation of AF.

These findings present a novel theoretical framework for understanding treatment of multi-wavelet reentry driven AF and provide 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.

Citations

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Chapter 1

Introduction

In the complicated system of pipes and filters that our cardiovascular system represents, the human heart is the engine that keeps everything moving. On one hand, the heart is tasked with the single, relatively straightforward mechanical job of pumping blood throughout the body. However, the simple nature of the heart's occupation belies the elegance and sophistication of its design. Because there is no direct nervous control, each one of the many cardiac cells must work in tandem with its neighbors to produce an organized, regular heart beat. At the same time, these cells are independent operators; there is no clearly defined supervisor that provides instructions to the rest of the heart. Thus, rhythmic contraction is a phenomenon that emerges from the complex interplay between individual cells. As with many complex systems however, alteration of properties at the cellular level may lead to changes in the form of emergent behavior.

Within the heart, one way these changes may manifest is as pathologic forms of contraction known as arrhythmias. Here, inappropriate cardiac function stems from disorganized electrical signaling between cells. While there are many different forms of arrhythmia, perhaps the quintessential example is atrial fibrillation (AF). This disease, characterized by a complete loss of organized contraction in the top chambers of the heart that results in an irregular heartbeat, has long been the subject of med-

ical research. In fact, the first historical mention of atrial fibrillation is commonly attributed to the Chinese physician-emperor Huangdi and his *The Yellow Emperor's Classic of Internal Medicine*, originally published more than 4,500 years ago [1],[2]. While Huangdi made the original connection between irregular pulse and increased morbidity, nearly three millennia passed before British physician and scientist William Harvey made direct observations of disorganized contraction in the atria [3],[4]. Insight into the pathophysiology of this disease would further await the turn of the twentieth century, at which point technical advancements began to make objective clinical measurements possible. In 1904, the Scottish practitioner James Mackenzie used a custom polygraph device to make the first pulse recordings and showed loss of organized atrial contraction during irregular rhythms [5]. Nearly simultaneously, Willem Einthoven made the first electrical recordings of atrial disorganization using his own nascent invention, the electrocardiograph [6]. However, it would be Sir Thomas Lewis, a protégé of both Mackenzie and Einthoven, who would be the first to draw a connection between an irregular heart rate and both electrical and contractile disorganization in the atria [6]. Lewis's hypothesis effectively established the modern clinical definition of atrial fibrillation.

In addition to being a time of rapid progress towards a clinical appreciation of atrial fibrillation, the early nineteen hundreds also marked a time of significant advancement in the understanding of its mechanisms. The renowned physiologist and physician Theodor Engelmann examined disorganized electrical activity in the hearts of frogs [7]. Noting that the individual muscle fibers tended to be out of phase with one another, he proposed that these fibers had become independently excitable; hence the term 'fibrillation'. He therefore hypothesized that AF was the product of multiple ectopic foci firing at different rates [8]. George Mines, a brilliant young scientist working out of McGill University, demonstrated that continuous electrical propaga-

tion could occur as a result of electricity following circular paths known as reentrant circuits [9]. In his experiments in annuli of ex vivo cardiac tissue, he also showed that slowed conduction and unidirectional block were necessary for the formation of these circuits. Another preeminent researcher operating at this time, Walter Garrey, used high frequency electrical pacing to induce episodes of fibrillation in a variety of animal models. He showed that these episodes were independent of the site from which they were initiated, but required a critical mass of tissue for continuation [10]. Based upon his findings, Garrey proposed that fibrillation was the result of multiple simultaneous reentrant circuits.

In the last century since these pioneers laid the groundwork for our understanding of atrial fibrillation, research has continued at a furious pace. A pubmed.gov search for "atrial fibrillation" returns almost 5,000 unique hits from 2015 alone, and the rate of publication has been increasing exponentially since around the 1940s. Nonetheless, despite the massive quantities of energy that have been directed toward its study, AF remains not only the most prevalent arrhythmia, but also one of the arrhythmias most refractory to cure. Of the treatment options that are available, catheter-based ablation of the atria has emerged as one of the most reliable methods for the permanent elimination of AF. However, while anatomically-directed strategies such as pulmonary vein isolation and linear ablation have had demonstrated success in patients with relatively mild AF, there is disagreement over the most appropriate next-step to take in patients with heavier burdens of disease. One approach that seems logical and that has begun to attract significant attention within the AF community is the ablation of atrial sites believed to host drivers of AF. Notably, both complex fractionated atrial electrogram (CFAE) ablation and focal impulse and rotor modulation (FIRM) make use of focal lesions to eliminate electrogram-identified drivers. Unfortunately, follow-up investigations of these strategies have largely failed to replicate the high rates of

cure shown in initial studies.

At least in part, this failure may represent a fundamental mismatch between treatment strategy and mechanism. There are currently multiple hypotheses regarding the primary mechanism of AF, but focal ablation strategies like CFAE and FIRM are only designed for the elimination of localized drivers such as sites of increased automaticity and single-circuit reentry with fibrillatory conduction. Fibrillation may alternatively be perpetuated by more diffuse mechanisms, the exemplar of which is multi-wavelet reentry (MWR). Here, multiple waves of excitation move chaotically about the atria, fusing and dividing as they collide, and forming spatially dynamic reentrant circuits. Focal lesions interrupt only those circuits that, by chance, would have been formed directly beneath the site of ablation. Thus, strategies reliant solely upon focal lesions will have minimal impact on the burden of MWR driven atrial fibrillation. It follows, then, that any comprehensive strategy for the treatment of AF must effectively interrupt both localized and diffuse drivers of fibrillation. However, while localized drivers present obvious targets for interruption once they are identified, there is no readily apparent strategy for eliminating MWR.

Unfortunately, the chaotic nature of multi-wavelet reentry has made it difficult to study within a biological setting. Many of the insights into this conduction pattern have instead been derived from the study of computer models. Gordon Moe, an American computational scientist working during the late nineteen fifties and early sixties, developed a cellular automaton to study electrical propagation within the heart. His experiments within this model were the first to directly demonstrate that MWR could drive self-sustained activity [11]. Nonetheless, the strictly rule-based nature of conduction in Moe's model ignored the electrotonic currents that are necessary for realistic propagation of biological excitement. As computing power increased, more complex mathematical models of excitation and conduction were used to overcome

this hurdle. In particular, differential equation models, largely based upon the earlier work of Alan Hodgkin and Andrew Huxley on the excitation of giant squid nerve axons [12], have been successfully adapted to cardiac tissue. However, these models represent a tradeoff between biological realism and experimental breadth. Differential equation models are substantially more computationally burdensome, and thus their use in the study of tissue-level behavior may be prohibitively time consuming.

The primary goal of this work is to develop an optimized ablation strategy for the treatment of multi-wavelet reentry driven atrial fibrillation. Towards this purpose, I have used a computational model of cardiac propagation that compromises biological realism and low computational burden to explore the intricacies of chaotic conduction patterns within a practical experimental time frame [13]. I propose a mechanistic basis for understanding and predicting the behavior of MWR based upon this exploration. Using this interpretative framework, I then explain an algorithm for titrating the magnitude of ablation-based intervention to the burden of MWR within specific, individualized tissues. Finally, I explore the relationships between MWR and localized drivers of AF in order to develop a more comprehensive treatment strategy.

Figure 1.1: Six pioneers of atrial fibrillation research: A) James Mackenzie, B) Willem Einthoven, C) Thomas Lewis, D) Theodor Engelmann, E) George Mines, and F) Walter Garrey. (Images courtesy of the National Library of Medicine)

Bibliography

[1] Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. *BMJ*. 1995;311(7016):1361-1363

[2] Nattel S, Allessie M, Haissaguerre M. Spotlight on atrial fibrillation-the 'complete arrhythmia'. *Cardiovasc Res*. 2002;54(2):197-203

[3] McMichael J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laënnec. *Br Heart J*. 1982;48(3):193-197

[4] Flegel KM. From delirium cordis to atrial fibrillation: historical development of a disease concept. *Ann Intern Med*. 1995;122(11):867-873

[5] Aronson JK. One hundred years of atrial fibrillation. *Br J Clin Pharmacol*. 2005;60(4):345-346

[6] Silverman ME. From rebellious palpitations to the discovery of auricular fibrillation: contributions of Mackenzie, Lewis and Einthoven. *Am J Cardiol*. 1994;73(5):384-389

[7] Zimmer HG. Profiles in cardiology: Theodor Wilhelm Engelmann. *Clin Cardiol*. 2006;29:518-520

[8] Garrey WE. Auricular Fibrillation. *Phys Reviews*. 1924;4(2):215-250

[9] DeSilva RA. George Ralph Mines, ventricular fibrillation and the discovery of the vulnerable period. *J Am Coll Cardiol*. 1997;29(6):1397-1402

[10] Garrey WE. The nature of fibrillary contraction of the heart — its relation to tissue mass and form. *Am J Physiol*. 1914;33:397–414

[11] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J*. 1964;67:200-220

[12] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117(4):500-544

[13] Spector PS, Habel N, Sobel BE, Bates JH. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol.* 2011;4(4):586-91

Chapter 2

Literature Review

2.1 Basics of Electrophysiology

The human heart is responsible for controlling the distribution of blood throughout the body. In healthy individuals, the heart is divided into four distinct chambers according to electromechanical function. A septum of cardiac tissue prevents direct flow of blood between the right and left sides of the heart and this mechanical division allows the two halves to push blood in different directions. The right side of the heart is responsible for pumping deoxygenated blood from the body's periphery to the lungs, while the left side is responsible for pumping newly oxygenated blood from the lungs back to the rest of the body. Additionally, the top and bottom of the heart, known respectively as the atria and ventricles, are separated by a layer of tough, fibrous tissue. A pair of unidirectional valves embedded within this layer on either side of the septum allows for blood flow from the atria to the ventricles. However, unlike the majority of cardiac muscle, this fibrous tissue cannot transmit waves of electrical excitation, rendering the atria and ventricles electrically insulated from one another.

The electrical and mechanical properties of the heart are intrinsically linked, and the proper function of both is required for physiologic behavior. When a cardiac

muscle cell, or cardiomyocyte, receives ionic current sufficient to perturb its normally negatively charged cell membrane above a particular threshold potential, that cell undergoes a pattern of excitation known as an action potential. The action potential triggers rapid shifts in the cell membrane's ionic permeability, resulting in both a brief positive deflection in membrane potential known as depolarization and the initiation of mechanical contraction. A depolarizing cardiomyocyte transmits current to neighboring cells, altering their membrane potentials and eventually triggering new action potentials in those cells. Importantly, once a cell has triggered an action potential it enters a period of refractoriness during which it cannot be re-excited. Thus, electrical excitement spreads uni-directionally from one cell to the next and is accompanied by an organized wave of contraction.

In typical, healthy human hearts, electrical activity is initiated in the sinoatrial (SA) node, a special section of the right atria that undergoes regular, spontaneous depolarization. From the SA node, waves of excitement spread outward across the two atria in approximately concentric rings, and there is an accompanying organized, downward muscular contraction. Another specialized region of cardiac tissue known as the atrioventricular (AV) node is positioned at the junction between the atria and ventricles. Cardiomyocytes within the AV node have particularly long periods of refractoriness, and limit the rate at which waves of activity can be transmitted from the atria to the ventricles. However, under normal conditions each impulse initiated by the SA node results in a single heart beat, consisting of the sequential, organized contraction of both atria and ventricles. This physiologic pattern of conduction is known as 'sinus' rhythm.

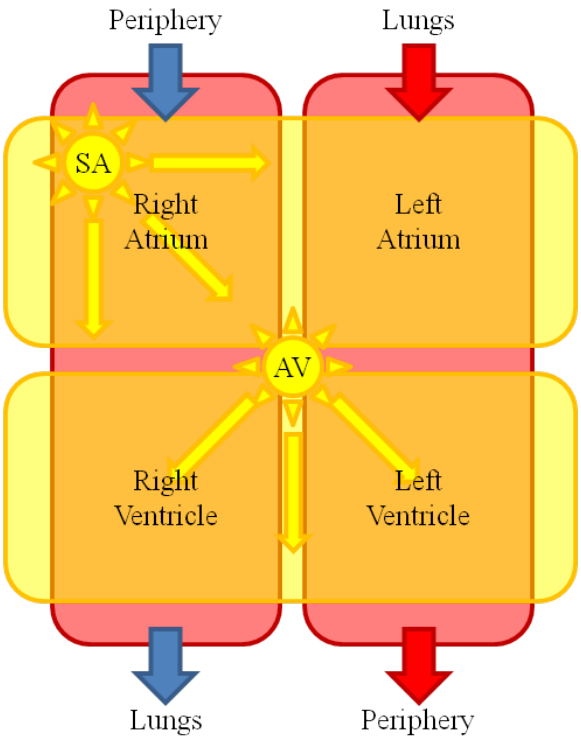

Figure 2.1: A schematic of the four chamber heart showing overlays of mechanical (red and blue coloring) and electrical (orange and yellow coloring) organization. The right side of the heart is responsible for pumping deoxygenated blood from the periphery to the lungs and the left side is responsible for pumping oxygenated blood from the lungs back out to the periphery. Electrical activity is initiated in the atria by the sinoatrial (SA) node and transmitted to the ventricles via the atrioventricular (AV) node.

2.2 Cardiac Action Potentials

As in all mammalian cells, the inside of each cardiomyocyte is separated from its surroundings by a membrane that is largely impermeable to charged molecules. This limited permeability allows energy-intensive protein pumps to maintain ion concentration gradients across the membrane. However, other proteins known as ion channels may, under certain conditions, allow specific ions to diffuse back across the membrane. As the charged ions flow through these channels, the magnitude of the concentration gradient is reduced, and an electric gradient begins to develop in the opposite direc-

Ion	$[ion]_{internal}$(mM)	$[ion]_{external}$(mM)	E_{ion}(mV)
Sodium	8	110	70.0
Potassium	100	4	-86.0
Chloride	45	880	79.4
Calcium	0.0002	1	113.7

Table 2.1: Concentrations in the internal and external cellular environments for a number of relevant ionic species.

tion. For a single ionic species, the potential at which these two opposing gradients equilibrate is described mathematically by the Nernst equation [1] (Eq. 2.1).

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion]_{internal}}{[ion]_{external}} \tag{2.1}$$

Here, E_{ion} is the equilibrium potential for the specific ion of interest, R is the universal gas constant, F is faraday's constant, z is the ionic charge, and $[ion]$ is the ionic concentration. The Nernst equation predicts the electric potential at which the net flow of ions across a cell membrane, permeable to only a single ion, reverses direction. For this reason, it is often referred to as the reversal potential. Table 2.1 presents resting intracellular and extracellular concentrations of biologically relevant ions in mammalian cardiomyocytes, as well as their corresponding reversal potentials. This table is adapted from Katz's Physiology of the Heart[2], in which the author presents chemical activity (a.k.a. effective concentration) values rather than true concentrations.

In practice, cardiomyocytes possess many different ion channels, and the true equilibrium potential results from a balance between all of the individual concentration gradients and the electrical gradient. For the case of monovalent ions, this balance is described mathematically by the Goldman-Hodgkin-Katz (GHK) equation (Eq. 2.2).

$$V_m = \frac{RT}{F} \ln \left(\frac{\sum P_i [ion_i^+]_{external} + \sum P_i [ion_i^-]_{internal}}{\sum P_i [ion_i^+]_{internal} + \sum P_i [ion_i^-]_{external}} \right) \tag{2.2}$$

Here, V_m is the equilibrium membrane potential and P_i is the permeability of either positively charged cations (+) or negatively charged anions (-). Analogous, higher order equations are used to predict the equilibrium potential with consideration of divalent ions such as calcium (Ca^{+2})[3], but the low resting permeability of these ions causes their contribution to be negligible. Solution of the GHK equation using experimental values of concentration and permeability provides an accurate prediction of the membrane potential in resting cardiomyocytes, typically between -80 and -90mV [4]. This highly polarized value is close to the reversal potential of potassium and reflects the significantly higher resting permeability of this ion relative to sodium, chlorine, and calcium.

The differences in permeability are the result of a mechanism known as voltage-gating, in which channels allow for ionic diffusion (i.e., are open) only within certain ranges of membrane potential. At the resting potential, only potassium channels have a high probability of being in the open state. However, any sufficient perturbation of the membrane potential that causes depolarization beyond a threshold of around -65mV (e.g., via current transmitted from neighboring cells) triggers the rapid opening of sodium channels and a corresponding increase in membrane potential towards the reversal potential of sodium as it rushes into the cell [4]. Potassium efflux is simultaneously reduced as the membrane potential becomes more positive. This event marks the beginning of the cardiac action potential (phase 0, Fig. 2.2). There is a nearly simultaneous triggering of sodium channel inactivation that occurs through a parallel, but temporally slower, voltage-gating mechanism (phase 1, Fig. 2.2). The effect of this inactivation is two-fold. First, inactivation prevents sodium channels

from returning directly to the open state, and thus generating a new action potential, for a specific duration of time known as the refractory period. Second, sodium currents are eliminated before the membrane voltage can equilibrate at the sodium reversal potential. Instead, the membrane typically only reaches a peak voltage of around +20mV before it begins to repolarize [4]. However, this peak voltage is sufficient to trigger the opening of voltage-gated calcium channels. The onset of calcium influx counteracts the continuing weak efflux of potassium, and the membrane potential plateaus at around -10 to +10mV (phase 2, Fig. 2.2) [4]. During this period, internal calcium stores are also released adjacent to myofibrils, leading to sustained contraction of the muscle. Gradually, calcium channels begin a time-dependent closure and the membrane voltage begins to slowly repolarize (phase 3, Fig. 2.2). The more negative potential also allows voltage-gated potassium channels to re-open, and the membrane returns to its resting state (phase 4, Fig. 2.2), thus completing the action potential.

2.3 What is Atrial Fibrillation?

Of all the malfunctions that arise within the complex conduction system of the heart, an arrhythmia known as Atrial Fibrillation (AF) is the most common. In this disease, electrical activity in the atria becomes disorganized and unpredictable, preventing coordinated muscular contraction and causing the atria to physically quiver or 'fibrillate'. Fortunately for those that suffer from AF, the atria play a relatively passive role in pumping blood throughout the body. Electromechanical activity in the ventricles remains organized and proceeds at the intermittent rate at which activity propagates across the AV node. Clinically, this presents in patients as episodes of uncontrolled, rapid, and irregular heart rate.

While episodes of atrial fibrillation are not inherently lethal, long term exposure

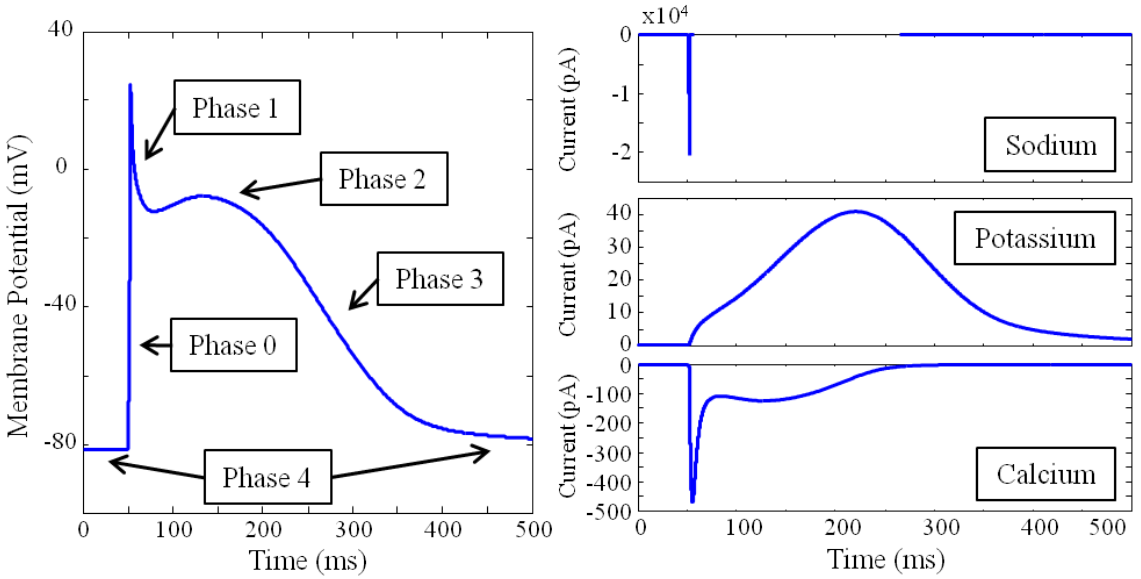

Figure 2.2: Left) A typical, phase-labled atrial action potential (produced with the Courtemanche computational model of atrial cardiomyocytes). Right) Corresponding sodium, potassium, and calcium ionic trans-membrane currents during the atrial action potential.

may lead to a number of serious consequences. In particular, AF is associated with a five-fold increased risk of stroke [5] due to thrombosis of stagnant blood within the atria [6]. Stroke associated with AF is also more severe, and causes higher degrees of lasting debilitation [7]. Additionally, patients frequently experience symptoms such as dizziness, palpitations, syncope, chest pain, dyspnea, and fatigue [8],[9], the combined effect of which leads to a significant decrease in quality of life [10] that is accompanied by a one-and-a-half to two-fold increase in the risk of mortality [11].

Atrial fibrillation is the most prevalent of all cardiac arrhythmias, affecting an estimated 5.2 million individuals within the United States [12] and 33.5 million individuals worldwide as of 2010 [13]. This prevalence is expected to increase substantially over the next twenty years as a result of both increased screening practices and an aging population with higher rates of underlying heart disease [14]. The ubiquity of

this disease is associated with a heavy economic burden. In the United States alone, incremental healthcare costs associated with AF were estimated to be $26 billion dollars per year [15], $6.5 billion of which was AF specific [16]. AF also causes a significant loss in objective productivity, with employed patients taking higher numbers of both sick days and short term disability absence days [17].

Within the most recent guidelines [18],[19], atrial fibrillation is divided into three categories of disease severity: paroxysmal AF, in which episodes of fibrillation last less than seven days, persistent AF, in which episodes are sustained for greater than seven days, and long-standing persistent AF, in which episodes last longer than twelve months. Within the overall population of AF patients, the proportion of paroxysmal cases relative to cases of longer lasting disease is approximately equal [20]-[22]. Greater burdens of AF are associated with a higher degree of resistance to treatment [23],[24]. Thus, differing categories of AF are indication for differing treatment strategies [19]. This categorization is merely a convention however, and the true burdens of disease for individual patients lie along a continuum [25]. What's more, AF appears to be progressive [26],[27]. Changes to the atrial substrate that occur during episodes of fibrillation (a process known as "atrial remodeling") increase the heart's ability to support future episodes [28]-[30], and this feed-forward mechanism leads to the advancement of disease burden over time [31]. In order to prevent this progression (or possibly reverse it [32]), it is therefore of value to provide patients with adequate treatment as early as possible [33].

2.4 Treatments of Atrial Fibrillation

Despite the immense burden that atrial fibrillation places on both patients and the health systems that care for them, treatment options remain limited. Cure rates with

even the most involved treatment strategies rarely exceed 75% [34], and are typically even lower in patients with severe disease [23]. This limitation is especially notable in contrast with the treatment of other cardiac arrhythmias, where cure rates are generally above 90% [35].

Treatment of atrial fibrillation can be divided into two main categories: pharmacologic approaches using anti-arrhythmic drugs (AAD), and interventional strategies [19].

Pharmacologic treatments

The use of anti-arrhythmic drugs in the treatment of atrial fibrillation may be further divided into two primary approaches [36]. In 'rate control' strategies, the goal of treatment is alleviation of symptoms rather than the complete elimination of AF. Here, AADs specifically target cells within the atrioventricular node that are responsible for transmitting excitation from the atria to the ventricles. By increasing the duration of refractoriness in these cells, downward transmission is blocked more frequently, and the rate of ventricular contraction is slowed. Drugs commonly used for this purpose include beta adrenergic blockers (e.g. Metoprolol, Atenolol, and Propranolol) and calcium channel blockers (e.g. Verapamil and Diltiazem) [37]. In contrast, the goal of 'rhythm control' strategies is a return to normal conduction patterns via the total elimination of arrhythmia. Here, AADs alter the properties of atrial cells in order to globally decrease the propensity of tissues to both initiate and support fibrillation. Drugs commonly used for this purpose include sodium channel blockers (e.g. Flecainide and Propafenone) and potassium channel blockers (e.g. Dofetilide and Ibutilide) [38].

Both approaches have been demonstrated as moderately effective, with adequate rate control being achieved in 58% of patients [37] and sinus rhythm being main-

tained in 52% of patients [34], both with single drug trials. Both rate and rhythm control strategies have equivalent survival outcomes, but slightly higher rates of adverse events have been demonstrated in patients undergoing rhythm control [39]. Largely, the choice between these strategies is based upon the degree and form of a patient's symptomaticity, as well as consideration of underlying medical comorbidities and patient preference [40]. Because atrial contraction remains uncoordinated in rate control and because rhythm control may fail, anti-coagulation drugs are prescribed concomitantly in both strategies to reduce the likelihood of stroke [41].

Interventional treatments

The first interventional treatment of atrial fibrillation to demonstrate reliably high rates of cure was the surgical maze operation as pioneered by Cox [42]-[44]. In this approach, surgeons introduce a number of transmural (full tissue thickness) scars to the atria, and, by doing so, restore normal supraventricular function in between 82-100% of patients [45]-[47]. Unfortunately, the length and technical difficulty of this operation, as well as its requirement for cardiopulmonary bypass, confers a number of significant risks including surgery-associated death and AV nodal block requiring the permanent placement of pacemakers [48]. The advent of less invasive interventional treatments has largely relegated this approach to a secondary role in which it is performed only concomitantly with other open-heart operations (e.g. mitral valve repair or replacement), and then only for patients with heavy burdens of disease [49].

More recently, transcutaneous, catheter-based approaches have moved to the forefront of interventional treatment [49],[50], and are frequently used as first-line therapy for atrial fibrillation [34],[51]. Here, access to the heart is achieved by threading electrode-tipped catheters through the venous system. The atria are then ablated via either radiofrequency (RF) heating [23],[24] or cryothermal cooling [52],[53], result-

ing in electrically unexcitable scars. However, unlike in surgical procedures, ablation may result in temporary stunning of cardiac cells rather than permanent cell death and over time ablated atrial tissue may regain excitability [54],[55]. For this reason, successful cure of AF with catheter based approaches may require follow-up or repeat procedures [56],[57]. The relative rates of scar formation failure in cryo-ablation and RF-ablation appear to be largely equivalent[58]-[60], although there may be slight differences in the rates of peri-operative complications.

Implementation aside, the most significant factor for predicting successful elimination of AF in an individual patient is the strategy selected for ablative scar placement. Of the many possibilities, an anatomic approach in which the pulmonary veins are electrically isolated from the remainder of the atrial substrate has established itself as the baseline standard of care [49],[50]. This strategy, known as pulmonary vein isolation (PVI), is premised upon the fact that the pulmonary veins are frequently sources of ectopic electrical impulses that serve to either initiate or perpetuate AF [61]. Use of PVI by itself has been shown to successfully eliminate fibrillation at one year follow-up in between 62-79% of paroxysmal cases [23],[62]-[67], although one study demonstrated a higher cure rate of 93% [68]. The rates of cure for persistent or long-standing persistent AF are typically lower, at between 20-65% [23],[24],[62],[66],[67],[69]-[71].

A number of supplemental ablation strategies have been proposed for improving the rate of successful AF cure. These approaches generally aim to reduce the propensity of the remaining atrial tissue to support fibrillation. Perhaps the most straightforward method is the extension of PVI using linear ablation to connect anatomic landmarks [72]-[74]. In this case, the most common lesions are connections between the right and left sided pulmonary vein encirclements ("roof line"), between the left vein encirclement and the mitral annulus ("mitral isthmus line"), and between the inferior vena cava and the triscuspid annulus ("cavotricuspid isthmus line"). These

lesions have the advantage of eliminating conduction between large anatomic barriers using a minimal quantity of additional ablation [75]-[77]. While a few studies have shown no significant improvements to AF cure with linear ablation [79],[80], the results are largely favorable. Randomized clinical trials testing this approach demonstrated that the addition of linear ablation increased freedom from AF at one year from 62-69% to 76-87% in paroxysmal cases and from 36-39% to 74-75% in persistent cases [66],[67],[76],[77].

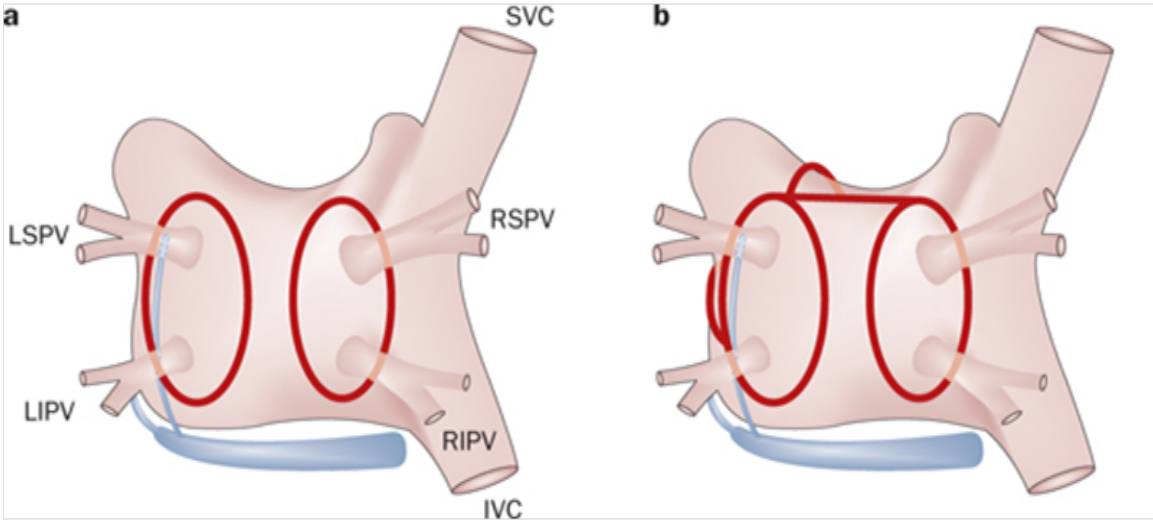

Figure 2.3: The left and right atria (viewed from the posterior) showing locations of common anatomically-guided ablation sites. a) Pulmonary vein isolation. Here, LSPV, LIPV, RSPV, and RIPV refer to the left and right, superior and inferior pulmonary veins, and SVC and IVC refer to the superior and inferior venae cavae. b) A roof line connects the left and right pulmonary vein encirclements. The mitral isthmus line connects the left pulmonary vein encirclement and the mitral valve at the level of the LIPV. Used with permission from Dewire et al. 2010 [78].

Several alternative methods for atrial substrate modification rely on the use of focal ablation rather than linear lesions. Typically, the goal of these strategies is to specifically target and eliminate localized drivers of AF. In one such approach, practitioners rely upon the morphology of electrogram recordings taken at the atrial surface as a surrogate for the underlying electrical behavior. Recordings that show

high frequency disorganized activity are known as complex fractionated atrial electrograms (CFAEs). These CFAEs are assumed to reflect high frequency phenomena such as small regions of rotating propagation (rotors) or sites of rapid spontaneous firing (ectopic foci), both of which have been suspected of driving AF in humans. While an initial investigation into the use of lone CFAE ablation showed freedom from AF in 91% of patients after one year [81], follow up studies demonstrated outcomes as low as 8-38% [63],[82],[83]. Further investigation of CFAE ablation as a supplemental therapy to PVI has also shown unimpressive results [57],[62],[69],[82]. Despite a few studies showing incremental effects of this strategy [63],[84], a recent meta-analyses found there to be no improvement in AF free survival [85]. As a consequence of these findings, CFAE based ablation has started to fall out of favor within the electrophysiology community [86]. One explanation for these disappointing results is that electrogram fractionation stems from mismatches between electrogram resolution and the spatiotemporal variability of the recording region [87]. This implies that CFAEs are a non-specific finding, and therefore ablation of CFAEs does not necessarily equate to elimination of AF drivers. As a final aside on this approach, one group has demonstrated improved freedom from AF using a stepwise ablation strategy that incorporates PVI and both linear and CFAE ablation [88],[89]; early reproduction of this practice seems promising [90].

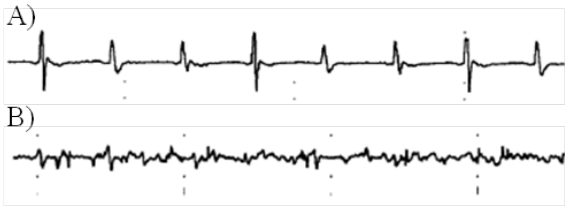

Figure 2.4: Examples of (A) organized and (B) fractionated atrial electrograms. Used with permission from Nademanee et al. 2003 [81].

More recently, another focal ablation strategy has garnered some excitement. This approach, known as focal impulse and rotor modulation (FIRM) [91], relies upon catheters with high numbers of electrodes to make simultaneous recordings of electrical activity throughout the atria [92]. Since the physical locations of these electrodes are known, it is then possible to construct spatial maps of excitation from the electrograms [93]. Sites of rotational activity and outwardly concentric conduction are thought to reflect rotors and focal impulses respectively. Initial investigation into the efficacy of supplemental ablation at these sites demonstrated freedom from AF after nine months to be 82.4%, as compared to 44.9% with standard treatment alone [94]. While independent randomized clinical trials have yet to be performed, preliminary follow-up studies have shown mixed results. While one group was able to replicate the original findings in a small number of patients [95], another group found only 21% of patients to be free of arrhythmia at 18 months [96]. A possible explanation for these discrepant data arises from the mechanical limitations of the procedure. Mismatch between the shape of the multi-electrode catheters and the atria itself may prevent electrodes from being in contact with the tissue surface [97]. This, combined with the use of low resolution electrodes, may result in erroneous or heavily fractionated electrograms [98] that, in turn, contribute to false representations of the electrical activity within the atria [97]. Further study of this approach is required before any concrete conclusions can be drawn.

Closing remarks on treatment of AF

As it stands, the rates of cure for atrial fibrillation remain frustratingly low. Pharmacologic agents are only able to eliminate arrhythmia in around 50% of patients, and, while supplemental ablation strategies such as linear ablation, CFAE ablation, and FIRM have shown glimpses of promise, interventional treatment outcomes have

largely stagnated at around 75% cure since the advent of pulmonary vein isolation. Both pharmacologic and interventional treatments have also shown much poorer outcomes in patients with persistent and long-lasting persistent AF, a group that constitutes nearly half of all AF patients. Since these patients also experience the heaviest symptomatic burdens [21],[99] and have the highest risks of stroke [100],[101] these outcomes are obviously unacceptable. How then might we go about designing more effective treatment strategies? A logical starting point is with a thorough understanding of the pathologic mechanisms responsible for driving atrial fibrillation.

2.5 Mechanisms of Atrial Fibrillation

Possible drivers of AF

Ongoing fibrillation in the atria requires the presence of continuous, disorganized electrical activity. There are several distinct mechanisms by which this activity may be generated. First, spontaneous depolarizations arising from non-pacemakers cells within the atria can generate fresh sources of excitation. As an electrical wave spreads concentrically outward from a site of initiation, the uniform wave-front may encounter cells still refractory from a preceding wave. Excitation failure within these cells leads to breakage along the continuous wave-front and causes a chaotic form of propagation known as fibrillatory conduction. Alternatively, the location of spontaneous firing may change from beat to beat, leading to disorganized activity throughout the atrial tissue via wave-front collisions. Provided that spontaneous firings occur more frequently than existing waves of excitation extinguish, electrical activity will continue indefinitely. Reciprocally, elimination of the cells responsible for focal impulses will ultimately terminate the arrhythmia.

Second, waves of excitation that follow uninterrupted circular paths can propa-

gate continuously. So long as the conduction time around the path is longer than the refractory period of the cells that comprise it, advancing wave fronts encounter a constantly replenishing supply of excitable tissue. This form of continuous propagation, known as reentry, may be further subdivided by the degree to which the position and timing of a completed circuit affects the position and timing of the next. In rotor reentry, waves travel around small, spatially localized paths at regular intervals. Circuits in this form of reentry therefore have a high degree of spatiotemporal autocorrelation. As with AF driven by focal impulses, fibrillatory conduction may lead to unpredictable excitation patterns far from the rotor core. In contrast, multi-wavelet reentry (MWR) is perpetuated by multiple independent waves of excitation rather than a single localized rotor. The population of waves moves chaotically throughout the tissue, fusing and dividing as they bump into one another. Here, circuit formation occurs at seemingly random intervals and is distributed throughout the tissue. Termination of either form of reentrant driver requires the simultaneous interruption of all ongoing circuits, as by the placement of a linear ablation line between a circuit core and the external boundary.

Evidence of AF drivers

While focal impulses, rotors, and multi-wavelet reentry are all theoretically possible, what is the true mechanism responsible for driving atrial fibrillation? This question has been the subject of much consideration due to its implications in the treatment of AF. Largely however, opinions are divided into two camps: those that believe fibrillation is driven by localized sources such as focal impulses or rotors, and those that believe fibrillation is driven by diffuse sources such as multi-wavelet reentry.

Because of the historical difficulties involved with visualizing electrical activity in the atria, much of the early evidence towards the mechanism of AF was inferential. In

a series of experiments within ex vivo cardiac tissue taken from a variety of animals (including loggerhead turtles, notorious in the early 1900's for their predisposition towards AF), Garrey observed that disorganized contraction continued even after removal of the site from which it was induced [102]. Instead, episodes of fibrillation terminated when the size of the tissue was reduced below a critical threshold. This finding formed the basis for his "critical mass hypothesis", in which continuation of AF required sufficient space for self-sustaining reentrant circuits to form. Moe later repeated Garrey's set of experiments in dogs [103] and was the first to formally propose multi-wavelet reentry as the mechanism responsible for AF [104]. He went on to demonstrate the feasibility of MWR within a computer model of cardiac propagation [105]. Further, he suggested that the size of the critical mass required to support MWR was a function of tissue properties determining the size of wavelets (e.g. action potential duration, refractory period). Later groups went on to validate this idea in both animals [106],[107] and humans [108] by demonstrating that fibrillation was more likely to terminate in both smaller tissues and tissues with longer refractory periods. In contrast to both Garrey's and Moe's results, Scherf observed that cooling or isolation of the site of fibrillatory induction caused reversible elimination of AF in dogs [109]. This finding was more compatible with focal sources as the driver for fibrillation. However, Scherf used the chemical aconitine, which induces focal firing, rather than high frequency electrode pacing to induce fibrillation. Atrial activity may thus have been driven by a qualitatively different mechanism.

Gradually, it has become possible to gather more explicit insight into the dynamics of electrical propagation within the atria. By recording simultaneously from ten different electrodes, Allessie was able to demonstrate tachycardia in rabbits driven by stable, stationary reentrant circuits [110]. Unlike electrical circuits around structural obstacles such as scar tissue, the frequency of rotation of these circuits could be in-

creased by pharmacologically reducing the conduction wave-length. Allessie proposed that this form of reentry was therefore the result of a single wave in which the leading edge followed close behind its own receding tail of refractoriness [111]. Here, cells still refractory from a previous rotation cause functional block across the circuit center, thus maintaining the phasic asynchrony of tissue excitation.

The idea of making multiple simultaneous electrogram recordings was extended to fibrillation in the hearts of larger mammals. Now using high density electrode arrays to assess macroscopic patterns of excitability, Allessie and Lee independently repeated the series of canine experiments upon which Moe based his idea of MWR [112]. However, while Allessie was able to verify the presence of multiple wavelets undergoing random reentry, Lee and his group observed focal impulses to be the primary driver of fibrillation [113]. The presence of multiple wavelets in canine models of AF was later corroborated by other groups [114],[115]. In patients undergoing open-heart surgery, Lee mapped electrical excitation in humans and observed multiple wave fronts to be the predominant pattern of activity [116]. Members of the Allessie group went on to use paired high-density electrode arrays on the endocardial and epicardial surfaces and observed significant electrical dissociation between the internal and external layers of musculature [117]. These experiments, performed in both animals [118] and humans [119], demonstrated that random reentry could occur in a direction normal to the tissue surface via wave breakthrough, and that breakthrough was more likely to occur in patients with longer lasting AF. In contrast to these results, Narayan demonstrated the presence of both rotors and focal impulses using activation maps generated from multi-electrode basket catheters [91],[94]. However, these findings may be confounded by a lack of contact between electrodes and the atrial surface [97].

As an alternative to high-density electrode arrays, the dynamics of electrical propagation can also be visualized using a technique known as optical mapping. Here,

cardiac tissue is stained with voltage or calcium sensitive dyes that emit particular wave-lengths of light during cell depolarization. Members of the Jalife group used this technique in conjunction with excitation phase analysis to demonstrate the presence of rotational activity around phase singularities in a variety of animal hearts [120]-[123]. While optical mapping is impossible in humans, the presence of focal drivers is at least circumstantially supported by studies of the spectral characteristics of fibrillation. These studies, in which the dominant frequency of excitation was sequentially measured at sites distributed throughout the atria, demonstrated the presence of distinct domains of high frequency surrounded by lower frequency tissue. The Jalife group proposed that these domains reflected regions of 1:1 conduction around focal sources of rapid activity [124],[125], and that low frequency areas corresponded to regions of fibrillatory conduction [126]. Ablation of high frequency domains caused acute termination of AF in 87% of cases [127], further suggesting the presence of drivers at these sites.

Closing remarks on the mechanisms of AF

There are substantial, and seemingly contradictory, bodies of evidence in support of each of the possible mechanisms of atrial fibrillation. Unfortunately, these data have largely been collected from disparate models of fibrillation (e.g., dogs, sheep, rabbits, pigs, humans, etc), thus rendering direct comparison of experimental results extremely difficult. Even studies in which the electrical activity of the atria was directly visualized have demonstrated the full spectrum of drivers. This said, there are two relatively straightforward explanations for these conflicting results. First, differences in the electrical properties of the various models may actually result in qualitatively different fibrillatory mechanisms. For example, it could be that canine atria, for whatever reason, are more likely to be driven by MWR while sheep atria are

more likely to be driven by rotor reentry. Likewise, patients with differing burdens of disease may be suffering from qualitatively different forms of AF. Alternatively, the different methods of mapping electrical activity could be introducing differing levels of bias towards one mechanism or another. In this case, the activity being recorded in differing models may be identical, but the final observed mechanisms may be distinct from one another. For example, it could be that phase analysis of optically mapped fibrillation is predisposed towards the detection of rotors, while high-density electrode arrays are more likely to demonstrate MWR.

In either case, there is currently no definitive answer to the question of what drives human AF. This fact represents a major stumbling block in the development of effective, mechanistically derived treatment strategies. After all, how can electrophysiologists hope to predict the impact of ablation when they don't actually know the underlying activity they are trying to affect? While the final test of any strategy obviously requires implementation in humans, computer models of cardiac propagation represent an experimental environment in which researchers have exact control over tissue properties and explicit knowledge of the emergent behaviors. For this reason, many scientists have turned toward in silico studies to test the types of theoretical questions necessary for development of improved treatments, but impossible to answer in more ambiguous biological models.

2.6 Computer Models of Excitation

One of the more relevant aphorisms in the world of computer modeling is that "all models are wrong, but some are useful." This saying, generally attributed to the statistician George Box [128], captures both the advantages and potential pitfalls of in silico experiments. While models may provide insight into some otherwise unob-

servable phenomenon, they are only as good as the assumptions on which they are based. In modeling the electrical properties of the heart, there are various levels of biological accuracy with which the excitability of individual cells, the transmission of current between cells, and the spatial distribution of cells can be approximated. There is no true 'right' answer regarding the appropriate degree of realism. Rather, biological accuracy must be selected according to the experimental question being asked. For example, incorporation of individual cellular ion channels may be irrelevant for a researcher interested in macroscopic, tissue-level behavior. Reciprocally, any conclusions regarding intracellular behavior may be worthless if the properties of these channels are ignored. Since these questions of realism must also be balanced against the constraints of computational burden, the least complex model that still provides a meaningful answer is often the most appropriate choice. To quote another maxim (this one attributed to Albert Einstein [129]), "Everything should be made as simple as possible, but not simpler".

The first computational model of cardiac tissue was a rule-based cellular automaton put forth by Moe more than 50 years ago [105]. Partly due to limitations in processing power (Moe was working with an IBM-650, capable of storing up to 2,000 five character words or ten digit numbers), the simulated action potentials within this model were heavily approximated. Cells underwent binary excitation with a refractory period of length proportional to the square of the preceding duration of quiescence. The tail end of each action potential was characterized by a relative refractory period during which activation was possible but occurred more slowly. Cells were arranged within a uniform, hexagonal grid, and excited cells transmitted activation to their unexcited neighbors at a constant rate. Despite the relatively superficial resemblance to real atrial tissue, Moe was able to explicitly demonstrate multi-wavelet reentry as a possible mechanism for AF. Further, his study of this model provided evidence that

fibrillatory burden depended on not only the presence of a critical mass of tissue, but also on the size of wavelets within that tissue.

With the advent of modern computing, it became feasible to employ more sophisticated models of cellular excitation. Most popular among these have been differential equation models based upon work by Hodgkin and Huxley [130]. In their pioneering studies of the giant squid nerve axon, Hodgkin and Huxley proposed that the properties of an excitable cell were akin to those of an electrical circuit. In this analogy, each ion channel capable of producing a trans-membrane current represents a resistor with variable conductance, the impermeable membrane itself represents a capacitor, and the potential differences resulting from ionic concentration gradients across the membrane represent voltage sources (Fig. 2.5). The well established mathematics governing circuit dynamics could hereby be used to model changes in the membrane voltage (Eq. 2.3).

$$\frac{dV_m}{dt} = -\frac{I_{ion}}{C_m} \tag{2.3}$$

In this equation, V_m is the membrane voltage, I_{ion} is the sum of ionic currents, and C_m is the membrane capacitance. As an example, the original study by Hodgkin and Huxley included three trans-membrane currents: sodium, potassium, and a generic leakage current (Eq. 2.4).

$$I_{ion} = I_{Na} + I_K + I_L \tag{2.4}$$

Each of the individual ionic current terms of Eq. 2.4 are in turn calculated according to Eq. 2.5.

$$I_i = g_i \left(V_m - E_i\right) \tag{2.5}$$

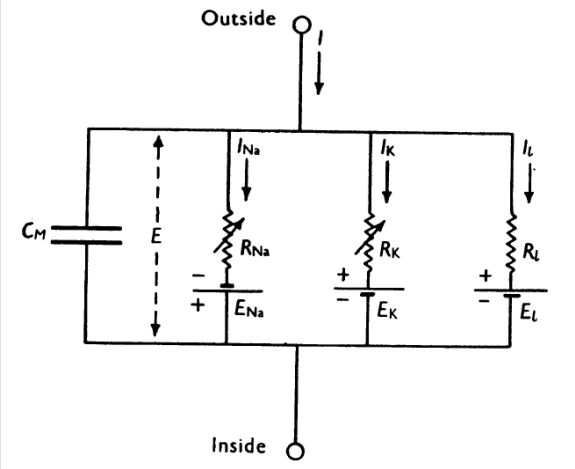

Figure 2.5: The electrical circuit used by Hodgkin and Huxley to model the dynamics of the membranes of excitable cells. Used with permission from Hodgkin et al. 1952 [130].

Here, g_i is the ensemble conductance of a particular ion channel and V_i is that ion's Nernst potential. In essence, this equation states that the flow rate of a particular ion across the membrane is a function of the overall electrostatic driving force scaled by the physical resistance to that flow. In order to capture the voltage-sensitive, open-versus-closed states of ion channels, the ionic conductance factor is itself variable. As an example, Eq. 2.6 presents the conductance of sodium as modeled by Hodgkin and Huxley.

$$g_{Na} = \bar{g}_{Na} m^3 h \tag{2.6}$$

Here, $\bar{g}_{Na}$ is the maximal conductance of sodium across the membrane when all channels are in the open state, and both m and h are 'gating' variables that range between zero, corresponding to the closed state of the channel, and one, corresponding to the open state. In order to capture the temporal aspects of transition between the open and closed states, these gating variables are in turn modeled using differential

equations (e.g., Eq. 2.7.

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \tag{2.7}$$

As described by Hodgkin and Huxley, α_m and β_m are rate constants that vary with voltage but not with time. Each of the ionic current terms is controlled by unique gating variables, the order and number of which are based upon empirical data collected from biological studies.

There are many different models of cardiac excitation based upon this framework, several of which are actively used in the study of fibrillation. These models differ from one another in two important ways. First, models may reflect the behavior of different types of cardiomyocyte (e.g., atrial, ventricular, etc.) or of different species of animal (e.g., human, canine, rabbit, etc.), depending upon from which data set their parameters have been determined. Second, these models vary with respect to their degrees of complexity. Models that incorporate more ion channels require higher numbers of state variables. However, while these increases in complexity theoretically improve the biological realism of the model, they also require larger numbers of calculations per time step and thus increase the overall computational burden.

Working independently from one another, Fitzhugh [131] and Nagumo [132] developed a two-variable, abstracted version of the Hodgkin-Huxley model, as described by the following series of equations.

$$\dot{V} = c \left(V - V^3/3 - W + I \right) \tag{2.8}$$

$$\dot{U} = (a + V - bW) / c \tag{2.9}$$

Here, V is roughly equivalent to the membrane potential, U is roughly equivalent

to a recovery or gating variable, I represents a stimulus current, and a, b, and c are constant parameters that determine the behavioral regime of the model. The simplified nature of the Fitzhugh-Nagumo model not only reduced computational burden, but also allowed for more rigorous mathematical analysis. Fitzhugh demonstrated that the point of intersection between U and V null-clines (Fig. 2.6) determined whether a cell would be resting but excitable, resting but unexcitable, or undergo spontaneous excitation. Further, he showed that rather than a true all-or-nothing form of excitation, cells would enter into either small sub-threshold cycles or large supra-threshold cycles (i.e, production of an action potential) depending on the size of a perturbing current (Fig. 2.6). Differentiation between the two response types followed a 'pseudo-threshold' canard trajectory along the unstable middle section of the V nullcline. While the Fitzhugh-Nagumo model was able to provide a number of insights into general aspects of excitable cells, it lacked a number of biologically relevant properties such as differential time scales for activation and recovery and rate dependence of the action potential duration. Thus, its use in directly studying cardiac properties has been limited.

One of the first examples of an ionic model specific to cardiac tissue was created for ventricular myocytes by Beeler and Reuter [133]. The Beeler-Reuter model included an inward calcium current, thus expanding the Hodgkin-Huxley model to four ionic currents and seven state variables. This ionic model was also the first to be expanded into two dimensions, thereby allowing for the study of tissue-level fibrillatory activity [134]. In this case, the spatial spread of current was modeled by expanding the differential equation of voltage to include a diffusion term (Eq. 2.10).

$$\frac{dV_m}{dt} = -\frac{I_{ion}}{C_m} + D\nabla^2 V \tag{2.10}$$

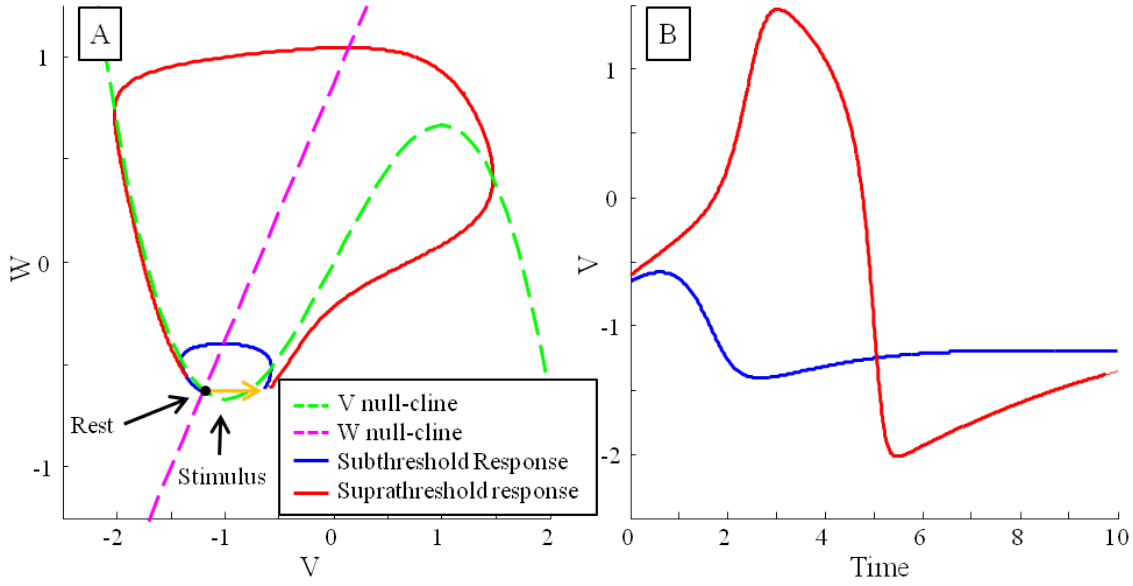

Figure 2.6: A) Phase diagram of the Fitzhugh-Nagumo model for $a = 0.7$, $b = 0.8$, and $c = 3$. Dashed lines show the U and V null-clines and solid lines show the systems responses to stimuli. B) Slight differences in the magnitude of the impulse stimulus produce either subthreshold or suprathreshold type responses.

Here, D is the diffusion constant and ∇^2 is the Laplacian operator in space. This form of reaction-diffusion equation is often referred to as a cable equation, particularly when limited to one dimension. Courtemanche used the two dimensional Beeler-Reuter to demonstrate the break-up of rotors into multiple wavelets as a result of conduction block in refractory cells [135].

Another ionic model of non-specific ventricular cardiomyocytes was created by Fenton and Karma [136]. In their model, the number of state variables was reduced to three, thus allowing for more manageable computation of large-scale simulations. However, while the intracellular behavior of each cell followed a simplified set of differential equations, Fenton and Karma modeled the intercellular spread of current using non-uniform, three-dimensional diffusion (Eq. 2.11).

$$\frac{dV_m}{dt} = -\frac{I_{ion}}{C_m} + \nabla \cdot \left(\bar{D}\nabla V\right) \tag{2.11}$$

In this slight variation of Eq. 2.10, $\bar{D}$ is a 3x3 matrix composed of the diffusion rates in each direction. This allowed for the incorporation of both tissue width and anisotropic myocyte orientations into the design of experiments. Using this model, Fenton and Karma demonstrated that anisotropy in the transmural direction could induce twisting of scroll waves (the three dimensional correlate of rotors) and ultimately the breakup of organized reentry into multi-wavelet based fibrillation. Anisotropic diffusion may be further refined to include both intracellular and extracellular compartments in so-called 'bi-domain' models (Eq. 2.12) [137]-[140].

$$M\left(\frac{dV_m}{dt} + \frac{I_{ion}}{C_m}\right) = \nabla \cdot \left(\bar{D}_E\nabla V_E + \bar{D}_I\nabla V_I\right) \tag{2.12}$$

Here, M is the membrane surface area per unit volume, the subscripts E and I correspond to extra- and intra-cellular compartments respectively, and $V_M = V_I - V_E$.

In contrast to the relatively simplistic Fenton-Karma model, a number of ionic models been designed with the goal of incorporating all known aspects of human atrial cardiomyocytes. Two of the most striking examples are models by Courtemanche, who included twelve distinct ionic currents based upon 24 state variables [141], and Nygren, who included eleven ionic currents based upon 29 state variables [142]. Both of these models also incorporate multiple compartments, including intracellular storage compartments from which calcium is released during cellular excitation and contraction. However, while the Courtemanche and Nygren models represent the state-of-the-art in terms of biological realism, their heavy computational requirements render them largely impractical for tissue-level behavioral studies.

Rather than explicitly simulating ionic currents, Spector and Bates proposed a

highly approximated model for studying propagation [143]. In this model, intercellular currents are transmitted according to ohm's law and cells undergo rule-based, piece-wise linear action potentials when they receive current sufficient to increase their potential above the threshold voltage (Fig. 2.7). While this model largely glosses over the specifics of intracellular dynamics, it successively reproduces the effects of electrotonic currents. Thus, even in this simplified model, complex patterns of self-sustaining activity such as rotors and multi-wavelet reentry may emerge spontaneously. Paired with its low computational burden, this model is therefore well suited to the study of fibrillation over relatively long time spans. Using this model, Spector demonstrated that linear ablation extending from the unexcitable tissue boundary to the central core of a reentrant circuit was required for elimination of that circuit [144].

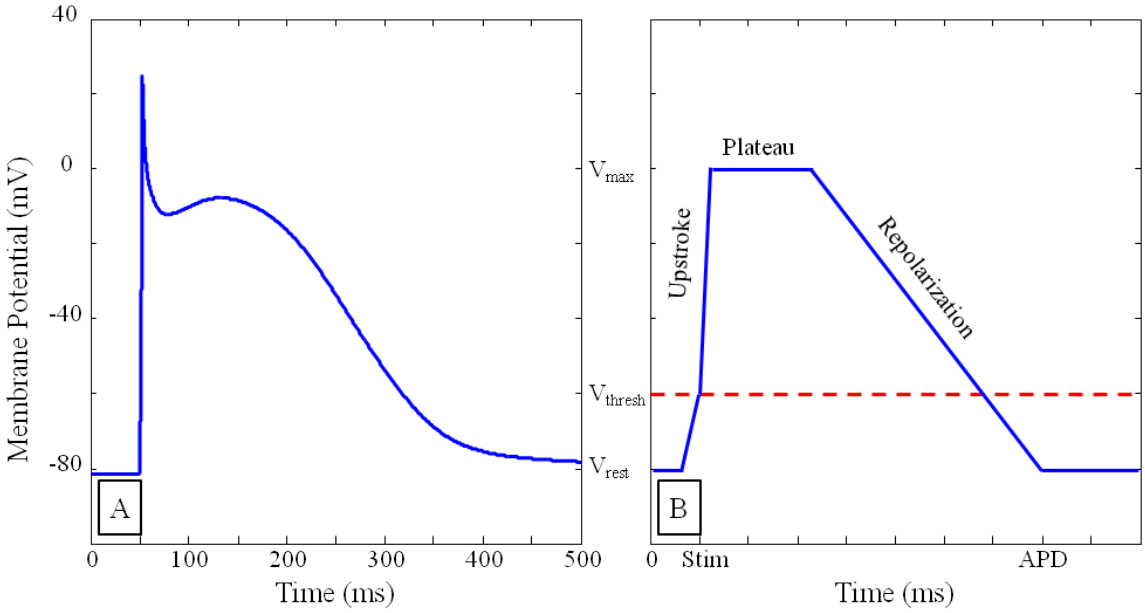

Figure 2.7: Side by side comparison of action potentials produced using the (A) Courtemanche differential-equation model and (B) the Spector linear-piecewise model of cardiomyocyte excitement.

Bibliography

[1] Wright HS. Generation of resting membrane potential *Adv Physiol Educ.* 2004;28:139-142

[2] Katz AM. Physiology of the heart. *Lippincott Williams & Wilkins.* 2001:478-516

[3] Spangler SG. Expansion of the constant field equation to include both divalent and monovalent ions. *Ala J Med Sci.* 1972;9(2):218-223

[4] Jalife J, Delmar M, Anumonwo J, Berenfeld O, Kalifa J. Basic Cardiac Electrophysiology for the Clinician. *Wiley-Blackwell.* 1991;7-71

[5] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-988

[6] Di Minno MN, Ambrosino P, Dello Russo A, Casella M, Tremoli E, Tondo C. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation. A systemic review and meta-analysis of the literature. *Thromb Haemost.* 2015;115(3) [Epub ahead of print]

[7] Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology* 2003;22(2):118-123

[8] Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J.* 2006;152(6):1097-1103

[9] Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN, Kirchhof P, ATRIUM investigators. Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. *Clin Res Cardiol.* 2011;100(10):897-905

[10] Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol.* 2000;36(4):1303-1309

[11] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98(10):946-952

[12] Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112(8):1142-1147

[13] Chugh SS, Havmoeller R, Narayanan J, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129(8):837-847

[14] Wolf PA, Bejamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in the prevalence of atrial fibrillation: The Framingham Study. *Am Heart J.* 1996;131(4)790-795

[15] Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes.* 2011;4(3):313-320

[16] Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health.* 2006;9(5):348-356

[17] Rohrbacker NJ, Kleinman NL, White SA, March JL, Reynolds MR. The burden of atrial fibrillation and other cardiac arrhythmias in an employed population: associated costs, absences, and objective productivity loss. *J Occup Environ Med.* 2010;52(4):383-391

[18] Lévy S, Camm AJ, Saksena S, Aliot E, Breithardt G, Crijns H, Davies W, Kay N, Prystowsky E, Sutton R, Waldo A, Wyse DG; Working Group on Arrhythmias, Working Group on Cardiac Pacing of the European Society of Cardiology, North American Society of Pacing and Electrophysiology. International consensus on nomenclature and classification of atrial fibrillation; a collaborative project of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Europace.* 2003;5(2):119-122

[19] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130(23):2071-2104

[20] Opolski G, Kosior DA, Kurzelewski M, Skrzyńska M, Zagórski A, Janion M, Muzolf M, Wlazłowski R, Pankiewicz B, Łoboz-Grudzień K, Breithardt G; Polish RecordAF. Baseline characteristics of patients from Poland enrolled in the global registry of patients with recently diagnosed atrial fibrillation (RecordAF). *Kardiol Pol*. 2010;68(5):546-554

[21] von Eisenhart Rothe AF, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. *Europace*. 2014;16(6):812-819

[22] Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, Santanna RT, Pires LM, Kruse ML, Lima GG, Leiria TL. Clinical Differences between Subtypes of Atrial Fibrillation and Flutter: Cross-Sectional Registry of 407 Patients. *Arq Bras Cardiol*. 2015;105(1):3-10

[23] Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation*. 2002;105(9):1077-1081

[24] Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol*. 2012;60(19):1921-1929

[25] Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm*. 2006;3(12):1445-1452

[26] Nagarakanti R, Saksena S, Hettrick D, Koehler JL, Grammatico A, Padeletti L. Progression of new onset to established persistent atrial fibrillation: an implantable device-based analysis with implications for clinical classification of persistent atrial fibrillation. *J Interv Card Electrophysiol*. 2011;32(1):7-15

[27] Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. *Am Heart J*. 2007;154(5):884-892

[28] Everett TH 4^{th}, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, Haines DE. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. *Circulation*. 2000;102(12):1454-1460

[29] Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus

formation, systemic embolism, and assessment by transesophageal echocardiography. *Cardiovasc Pathol.* 2000;9(2):95-101

[30] Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Sparks PB, Morton JB, Kalman JM. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *J Cardiovasc Electrophysiol.* 2012;23(3):232-238

[31] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92(7):1954-1968

[32] Reant P, Lafitte S, Jaïs P, Serri K, Weerasooriya R, Hocini M, Pillois X, Clementy J, Haïssaguerre M, Roudaut R. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. *Circulation.* 2005;112(19):28986-2903

[33] Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E, Lewis N, Ng A, Gould P, Lee G, Joseph S, Morton JB, Zentner D, Sanders P, Kistler PM, Kalman JM. Progression of atrial remodeling in patients with high-burden atrial fibrillation: Implications for early ablative intervention. *Heart Rhythm.* 2016;13(2):331-339

[34] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol.* 2009;2(4):349-361

[35] Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol.* 2009;104(5):671-677

[36] Tamargo J, Caballero R, Delpón E. Pharmacological approaches in the treatment of atrial fibrillation. *Curr Med Chem.* 2004;11(1):13-28

[37] Olshansky B, Rosenfeld LE, Warner AL, Solomon AJ, O'Neill G, Sharma A, Platia E, Feld GK, Akiyama T, Brodsky MA, Greene HL; AFFIRM Investigators. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol.* 2004;43(7):1201-1208

[38] AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol.* 2003;42(1):20-29

[39] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347(23):1825-1833

[40] Frankel G, Kamrul R, Kosar L, Jensen B. Rate versus rhythm control in atrial fibrillation. *Can Fam Physician.* 2013;59(2):161-168

[41] You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-e575S

[42] Cox JL, Schuessler RB, D'Agostino HJ Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg.* 1991;101(4):569-583

[43] Cox JL. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J Thorac Cardiovasc Surg.* 1991;101(4):584-592

[44] Cox JL, Jaquiss RD, Schuessler RB, Boineau JP. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. *J Thorac Cardiovasc Surg.* 1995;110(2):485-495

[45] Albåge A, Johansson B, Kennebäck G, Källner G, Scherstén H, Jidéus L; Swedish Arrhythmia Surgery Group. Long-Term Follow-Up of Cardiac Rhythm in 320 Patients After the Cox-Maze III Procedure for Atrial Fibrillation. *Ann Thorac Surg.* 2015;[Epub ahead of print]

[46] Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. *J Thorac Cardiovasc Surg.* 1999;118(5):833-840

[47] Feinberg MS, Waggoner AD, Kater KM, Cox JL, Lindsay BD, Pérez JE. Restoration of atrial function after the maze procedure for patients with atrial fibrillation. Assessment by Doppler echocardiography. *Circulation.* 1994;90(5 pt 2):II285-II292

[48] Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 1/2-year clinical experience with surgery for atrial fibrillation. *Ann Surg.* 1996;224(3):267-273

[49] Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont

JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*. 2007;9(6):335-379

[50] European Heart Rhythm Association; Heart Rhythm Society, Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48(4):854-906

[51] Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005;293(21):2634-2640

[52] Hoyt RH, Wood M, Daoud E, Feld G, Sehra R, Pelkey W, Kay GN, Calkins H; U.S. CryoCor Investigators. Transvenous catheter cryoablation for treatment of atrial fibrillation: results of a feasibility study. *Pacing Clin Electrophysiol*. 2005;28(Suppl 1):S78-S82

[53] Irfan G, de Asmundis C, Mugnai G, Poelaert J, Verborgh C, Umbrain V, Beckers S, Hacioglu E, Hunuk B, Velagic V, Stroker E, Brugada P, Chierchia GB. One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. *Europace*. 2015;[Epub ahead of print]

[54] Kowalski M, Grimes MM, Perez FJ, Kenigsberg DN, Koneru J, Kasirajan V, Wood MA, Ellenbogen KA. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. *J Am Coll Cardiol*. 2012;59(10):930-938

[55] Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation*. 2005;112(5):627-635

[56] Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm*. 2009;6(10):1403-1412

[57] Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol*. 2009;53(9):782-789

[58] Miyazaki S, Kuroi A, Hachiya H, Nakamura H, Taniguchi H, Ichihara N, Takagi T, Iwasawa J, Iesaka Y. Early recurrence after pulmonary vein isolation of paroxysmal atrial fibrillation with different ablation technologies - prospective comparison of radiofrequency vs. second-generation cryoballoon ablation. *Circ J*. 2016;80(2):346-353

[59] Straube F, Dorwarth U, Ammar-Busch S, Peter T, Noelker G, Massa T, Kuniss M, Ewertsen NC, Chun KR, Tebbenjohanns J, Tilz R, Kuck KH, Ouarrak T, Senges J, Hoffmann E; FREEZE Cohort Investigators. First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation. *Europac*. 2015;[Epub ahead of print]

[60] Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G,

Merkel M, Schmitt C. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation*. 2015;132(14):1311-1319

[61] Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339(10):659-666

[62] Atienza F, Almendral J, Ormaetxe JM, Moya A, Martínez-Alday JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MÁ, Tercedor L, Peinado R, Arcocha MF, Ortiz M, Martínez-Alzamora N, Arenal A, Fernández-Avilés F, Jalife J; RADAR-AF Investigators. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol*. 2014;64(23):2455-2467

[63] Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J*. 2010;31(11):1344-1356

[64] Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodriguez LM, Ghaye B, Ayers GM, Crijns HJ, Klein HU, Lau CP. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. *J Am Coll Cardiol*. 2003;42(4):752-758

[65] Hunter RJ, Baker V, Finlay MC, Duncan ER, Lovell MJ, Tayebjee MH, Ullah W, Siddiqui MS, McLEAN A, Richmond L, Kirkby C, Ginks MR, Dhinoja M, Sporton S, Earley MJ, Schilling RJ. Point-by-Point Radiofrequency Ablation Versus the Cryoballoon or a Novel Combined Approach: A Randomized Trial Comparing 3 Methods of Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation (The Cryo Versus RF Trial). *J Cardiovasc Electrophysiol*. 2015;26(12):1307-1314

[66] Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbucicchio C, Maccabelli G, Giraldi F, Bella PD. Left mitral isthmus ablation associated with PV Isolation: long-term results of a prospective randomized study. *J Cardiovasc Electrophysiol*. 2005;16(11):1150-1156

[67] Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, Coin D, Di Donna P, Giustetto C. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2008;1(4):269-275

[68] Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol*. 2006;48(11):2340-2347

[69] Vogler J, Willems S, Sultan A, Schreiber D, Lüker J, Servatius H, Schäffer B, Moser J, Hoffmann BA, Steven D. Pulmonary Vein Isolation Versus Defragmentation: The CHASE-AF Clinical Trial. *J Am Coll Cardiol*. 2015;66(24):2743-2752

[70] Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J*. 2006;27(23):2871-2878

[71] Cheema A, Dong J, Dalal D, Marine JE, Henrikson CA, Spragg D, Cheng A, Nazarian S, Bilchick KC, Almasry I, Sinha S, Scherr D, Halperin H, Berger R, Calkins H. Circumferential ablation with pulmonary vein isolation in permanent atrial fibrillation. *Am J Cardiol*. 2007;99(10):1425-1428

[72] Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367(17):1587-1595

[73] Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation*. 2008;118(24):2498-2505

[74] Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J*. 2006;27(2):216-221

[75] Wong KC, Betts TR. A review of mitral isthmus ablation. *Indian Pacing Electrophysiol J*. 2012;12(4):152-170

[76] Jaïs P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clémenty J, Haïssaguerre M. Technique and results of linear ablation at the mitral isthmus. *Circulation*. 2004;110(19):2996-3002

[77] Hocini M, Jaïs P, Sanders P, Takahashi Y, Rotter M, Rostock T, Hsu LF, Sacher F, Reuter S, Clémenty J, Haïssaguerre M. Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. *Circulation*. 2005;112(24):3688-3696

[78] Dewire J, Calkins H. State-of-the-art and emerging technologies for atrial fibrillation ablation. *Nat Rev Cardiol*. 2010;7(3):129-138

[79] Arbelo E, Guiu E, Ramos P, Bisbal F, Borras R, Andreu D, Tolosana JM, Berruezo A, Brugada J, Mont L. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc*. 2014;3(5):e000877

[80] Tamborero D, Mont L, Berruezo A, Matiello M, Benito B, Sitges M, Vidal B, de Caralt TM, Perea RJ, Vatasescu R, Brugada J. Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ Arrhythm Electrophysiol*. 2009;2(1):35-40

[81] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43(11):2044-2053

[82] Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Wang P, Al-Ahmad A, Arruda M, Themistoclakis S, Bonso A, Rossillo A, Raviele A, Schweikert RA, Burkhardt DJ, Natale A. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol*. 2009;2(2):113-119

[83] Estner HL, Hessling G, Ndrepepa G, Wu J, Reents T, Fichtner S, Schmitt C, Bary CV, Kolb C, Karch M, Zrenner B, Deisenhofer I. Electrogram-guided substrate ablation with or without pulmonary vein isolation in patients with persistent atrial fibrillation. *Europace*. 2008;10(11):1281-1287

[84] Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm*. 2008;5(12):1658-1664

[85] Providência R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ, Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for

Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol.* 2015;8(5):1017-1029

[86] Chugh A. Complex Fractionated Atrial Electrograms in Catheter Ablation of Atrial Fibrillation: Dead and Buried? *Circ Arrhythm Electrophysiol.* 2015;8(5):999-1001

[87] Correa de Sa DD, Thompson N, Stinnett-Donnelly J, Znojkiewicz P, Habel N, Müller JG, Bates JH, Buzas JS, Spector PS. Electrogram fractionation: the relationship between spatiotemporal variation of tissue excitation and electrode spatial resolution. *Circ Arrhythm Electrophysiol.* 2011;4(6):909-916

[88] Haïssaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clémenty J, Jaïs P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol.* 2005;16(11):1138-1147

[89] O'Neill MD, Wright M, Knecht S, Jaïs P, Hocini M, Takahashi Y, Jönsson A, Sacher F, Matsuo S, Lim KT, Arantes L, Derval N, Lellouche N, Nault I, Bordachar P, Clémenty J, Haïssaguerre M. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J.* 2009;30(9):1105-1112

[90] Rostock T, Steven D, Hoffmann B, Servatius H, Drewitz I, Sydow K, Müllerleile K, Ventura R, Wegscheider K, Meinertz T, Willems S. Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach. *Circ Arrhythm Electrophysiol.* 2008;1(5):344-353

[91] Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol.* 2012;23(5):447-454

[92] Schmitt C, Zrenner B, Schneider M, Karch M, Ndrepepa G, Deisenhofer I, Weyerbrock S, Schreieck J, Schömig A. Clinical experience with a novel multielectrode basket catheter in right atrial tachycardias. *Circulation.* 1999;99(18):2414-2422

[93] Barbaro V, Bartolini P, Calcagnini G, Censi F, Morelli S, Michelucci A. Mapping the organization of atrial fibrillation with basket catheters. Part I: Validation of a real-time algorithm. *Pacing Clin Electrophysiol.* 2001;24(7):1082-1088

[94] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM

(Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60(7):628-636

[95] Sommer P, Kircher S, Rolf S, John S, Arya A, Dinov B, Richter S, Bollmann A, Hindricks G. Successful Repeat Catheter Ablation of Recurrent Longstanding Persistent Atrial Fibrillation with Rotor Elimination as the Procedural Endpoint: A Case Series. *J Cardiovasc Electrophysiol*. 2015;[Epub ahead of print]

[96] Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. *Heart Rhythm*. 2015;[Epub ahead of print]

[97] Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2015;8(3):554-561

[98] Lin T, Rillig A, Bucur T, Metzner A, Mathew S, Wissner E, Wohlmuth P, Kuck KH, Ouyang F, Tilz RR. Focal impulse and rotor modulation using the novel 64-electrode basket catheter: electrogram characteristics of human rotors. *Europace*. 2015;17(12):1791-1797

[99] Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation*. 1999;99(23):3028-3035

[100] Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, Iguchi M, Masunaga N, Ogawa H, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GY, Akao M. Incidence of Stroke or Systemic Embolism in Paroxysmal Versus Sustained Atrial Fibrillation: The Fushimi Atrial Fibrillation Registry. *Stroke*. 2015;46(12):3354-3361

[101] Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP; ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J*. 2015;36(5):288-296

[102] Garrey WE. The nature of fibrillary contraction of the heart — its relation to tissue mass and form. *Am J Physiol*. 1914;33:397–414.

[103] Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J*. 1959;58:59-70

[104] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn*. 1962;CXL:183-188

[105] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J*. 1964;67:200-220

[106] Byrd GD, Prasad SM, Ripplinger CM, Cassilly TR, Schuessler RB, Boineau JP, Damiano RJ Jr. Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *Circulation*. 2005;112(9 Suppl):I7–I13

[107] Lee AM, Aziz A, Didesch J, Clark KL, Schuessler RB, Damiano RJ Jr. Importance of atrial surface area and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *J Thorac Cardiovasc Surg*. 2013;146(3):593-598

[108] Kojodjojo P, Peters NS, Davies DW, Kanagaratnam P. Characterization of the Electroanatomical Substrate in Human Atrial Fibrillation: The Relationship between Changes in Atrial Volume, Refractoriness, Wavefront Propagation Velocities, and AF Burden. *J Cardiovasc Electrophysiol*. 2007;18(3):269–275.

[109] Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J*. 1948;36(2):241-251

[110] Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of trachycardia. *Circ Res*. 1973;33(1):54-62

[111] Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ Res*. 1977;41(1):9-18

[112] Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. Cardiac Electrophysiology and Arrhythmias. *Grune and Straton, Inc*. 1985:265–275

[113] Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the Moe hypothesis. *J Cardiovasc Electrophysiol*. 2013;24(3):328-335

[114] Wang J, Bourne GW, Wang Z, Villemaire C, Talajic M, Nattel S. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. *Circulation*. 1993;88(3):1030-1044

[115] Kirchhof C, Chorro F, Scheffer GJ, Brugada J, Konings K, Zetelaki Z, Allessie M. Regional entrainment of atrial fibrillation studied by high-resolution mapping in open-chest dogs. *Circulation*. 1993;88(2):736-749

[116] Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, Goldblatt J, Brown R, Atkinson V, Moten S, Morton JB, Sanders P, Kistler PM, Kalman JM. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J*. 2014;35(2):86-97

[117] Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;3(6):606-615

[118] Eckstein J1, Zeemering S, Linz D, Maesen B, Verheule S, van Hunnik A, Crijns H, Allessie MA, Schotten U. Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: evidence from simultaneous endo-epicardial high-density activation mapping. *Circ Arrhythm Electrophysiol*. 2013;6(2):334-341

[119] de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allessie MA. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation*. 2010;122(17):1674-1682

[120] Davidenko JM, Kent PF, Chialvo DR, Michaels DC, Jalife J. Sustained vortex-like waves in normal isolated ventricular muscle. *Proc Natl Acad Sci USA*. 1990;87(22):8785-8789

[121] Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. *Nature*. 1998;392(6671):75-78

[122] Chen J, Mandapati R, Berenfeld O, Skanes AC, Gray RA, Jalife J. Dynamics of wavelets and their role in atrial fibrillation in the isolated sheep heart. *Cardiovasc Res*. 2000;48(2):220-232

[123] Davidenko JM1, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. *Nature*. 1992;355(6358):349-351

[124] Mansour M1, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. *Circulation*. 2001;103(21):2631-2636

[125] Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M, Jalife J. Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the Langendorff-perfused sheep heart. *J Cardiovasc Electrophysiol*. 2000;11(8):869-879

[126] Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation*. 2006;113(5):626-633

[127] Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavée C, Ploutz-Snyder R, Jalife J, Haïssaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation*. 2005;112(6):789-797

[128] Box EG, Draper NR. Empirical Model-Building and Response Surfaces. *Wiley*. 1987:424

[129] Calaprice A. The Ultimate Quotable Einstein. *Princeton University Press*. 2010:475,384-385

[130] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117(4):500-544

[131] Fitzhugh R. Impulses and Physiological States in Theoretical Models of Nerve Membrane. *Biophys J*. 1961;1(6):445-466

[132] Nagumo J, Animoto S, Yoshizawa S. An active pulse transmission line simulating nerve axon. *Proc. Inst. Radio Engineers*. 1962;50:2061-2070.

[133] Beeler GW, Reuter H. Reconstruction of the action potential of ventricular myocardial fibres. *J Physiol*. 1977;268(1):177-210

[134] Courtemanche M. Re-entrant rotating waves in a beeler-reuter model of two-dimensional cardiac electrical activity. *International Journal of Bifurcation and Chaos*. 1991;1(2):431-444

[135] Courtemanche M. Complex spiral wave dynamics in a spatially distributed ionic model of cardiac electrical activity. *Chaos*. 1996;6(4):579-600

[136] Fenton F, Karma A. Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation. *Chaos*. 1998;8(1):20-47

[137] Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. I. Distribution of the electrotonic potential. *Biofizika*. 1977;22(2):307-312

[138] Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. II. Distribution of a flat front of excitation. *Biofizika*. 1977;22(3):518-522

[139] Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. III. Steady state of the front of excitation. *Biofizika*. 1977;22(4):671-675

[140] Tung L. A bi-domain model for describing ischemic myocardial d-c potentials. *Massachusetts Institute of Technology Ph.D. Dissertation*. 1978

[141] Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *Am J Physiol*. 1998;275(1 Pt 2):H301-H321

[142] Nygren A, Fiset C, Firek L, Clark JW, Lindblad DS, Clark RB, Giles WR. Mathematical model of an adult human atrial cell: the role of K+ currents in repolarization. *Circ Res*. 1998;82(1):63-81.

[143] Spector PS, Habel N, Sobel BE, Bates JH. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol*. 2011;4(4):586-91

[144] Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, Benson BE, Bielau P, Bates JH. Ablation of multi-wavelet re-entry: general principles and in silico analyses. *Europace*. 2012;14(Suppl 5):v106-v111

Chapter 3

Ablation of Multi-Wavelet Reentry Guided by Circuit-Density and Distribution: Maximizing the Probability of Circuit Annihilation

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3.1 Abstract

Background: A key mechanism responsible for Atrial Fibrillation is multi-wavelet reentry (MWR). We have previously demonstrated improved efficiency of ablation when lesions were placed in regions of high circuit-density. In this study we undertook a quantitative assessment of the relative impact of ablation on the probability of MWR termination and the inducibility of MWR, as a function of lesion length and

circuit-density overlap.

Methods and Results: We used a computational model to simulate MWR in tissues with (and without) localized regions of decreased action potential duration and increased intercellular resistance. We measured baseline circuit-density and distribution. We then assessed the impact of various ablation lesion sets on the inducibility and duration of MWR as a function of ablation lesion length and overlap with circuit-density. Higher circuit-density reproducibly localized to regions of shorter wavelength. Ablation lines with high circuit-density overlap showed maximum decreases in duration of MWR at lengths equal to the distance from the tissue boundary to the far side of the high circuit-density region (high overlap: -43.5% [CI, -22.0% to -65.1%] vs. low overlap: -4.4% [CI, 7.3% to -16.0%]). Further ablation (beyond the length required to cross the high circuit-density region) provided minimal further reductions in duration and increased inducibility.

Conclusion: Ablation at sites of high circuit-density most efficiently decreased reentrant duration while minimally increasing inducibility. Ablation lines delivered at sites of low circuit-density minimally decreased duration yet increased inducibility of MWR.

3.2 Introduction

Atrial fibrillation (AF), despite its prevalence and clinical and financial impact [1], has remained difficult to treat either pharmacologically or interventionally [2]. Catheter ablation is potentially curative, but has demonstrated only modest success in paroxysmal AF and yields relatively poor results when applied to more advanced AF [3],[4]. The reason for this poor performance likely stems from our current lack of knowledge about how lesions should be placed to maximize their antiarrhythmic effects. Sug-

gested ablation strategies have been aimed at both the triggers that initiate episodes of AF [5],[6] and at the substrate responsible for its perpetuation [7]. However, without a detailed mechanistic understanding of how ablation actually terminates AF, these strategies remain largely guesswork.

While there are many potential mechanisms by which the atria can fibrillate, there is much data to support a prominent role for multi-wavelet reentry (MWR) [8]-[11]. We have previously demonstrated that MWR is comprised of multiple coexisting, temporally and spatially dynamic circuits [12]. Termination of MWR requires interruption of each of these circuits, but because they are constantly changing in space and time, there is no immediately obvious location for an ablation lesion that would achieve circuit interruption. For this reason, circuit interruption must be viewed as a probabilistic phenomenon that occurs whenever a wavelet happens to impinge upon a line of non-conducting tissue, be it an anatomical boundary of the atrium or a lesion created by catheter ablation. Seen in this way, the goal of ablation then becomes the placement of lesions so as to maximize the probability of circuit collision.

We have previously demonstrated that the extension of atrial boundaries via ablation can increase the probability of collision, circuit interruption and MWR termination [12]. We have also shown that the efficacy of ablation can be enhanced by delivering lesions to areas of tissue having high circuit-density [12]. These represent powerful principles upon which to build an ablation strategy, but they must be constrained by the need to minimize total lesion burden so as to minimize the associated morbidity. The optimized placement of lesions to treat MWR thus requires a detailed understanding of how MWR initiation and termination are affected by total lesion length, and by the placement of lesions relative to the regional circuit-density distribution across the atrial tissue. Gaining this understanding was the goal of the present study, which we undertook in the precisely controlled virtual environment of

a computation model of electrophysiology.

3.3 Methods

Computational model of cardiac propagation

In order to explore the interplay between ablation length, overlap with circuit-density, inducibility and reentrant duration, we required a model of cardiac tissue detailed enough to exhibit MWR but computationally inexpensive enough to simulate thousands of unique scenarios in a reasonable timeframe. For this purpose, we used a physics-based cellular automaton which has been described previously [13]. Our model consists of a two dimensional array of electrically excitable cells (each representing a large group of myocytes) connected via resistive pathways. Each cell generates an action potential (AP) when it receives sufficient current from neighboring cells and subsequently undergoes a period of refractoriness. The exact characteristics of each cell's AP are determined by 1) its programmed baseline parameters (e.g. upstroke velocity, repolarization duration, restitution) and 2) electrotonic current shifts. Intercellular resistance (ICΩ) is user defined. Action potential duration (APD) was heterogeneous throughout the tissue; each cell's value was randomly chosen from a programmed mean and range. In some experiments we created a tissue patch in which APD varied about a shorter mean value and inter-cellular resistance was higher than the remainder of the tissue.

Tissue designs

We created a series of seven tissues (80$\times$80 cells), baseline APD 130$\pm$5ms and ICΩ 9 ohms. Some tissues contained a short wavelength patch (created by shortening APD

and increasing inter-cellular resistance). Patch size, shape, location and APD/ICΩ were varied (see table 1). Tissues 1-3 varied the minimum distance of the patch from the outer tissue boundaries while maintaining the same overall patch size, shape and APD/ICΩ parameters. In tissues 4 and 5 the patch had the same characteristics as in tissue-1, except the width was increased 2-fold and 3-fold respectively. In tissue-6 the patch was the same as in tissue-1, except with a reduced gradient of APD/ICΩ relative to the remainder of the tissue (patch: APD 105$\pm$5ms, ICΩ 11ohms). Tissue-7 had no patch.

Circuit-density mapping

In each tissue we attempted to induce MWR using high frequency stimulation (0.1kHz for 1000ms). During successive simulations, stimulation was performed at each of 64 sites (8$\times$8 grid). The cell voltages of the entire tissue were recorded for 10,000ms. We created a custom algorithm for identifying the density and distribution of circuit cores during each episode of MWR. At each time step we used an edge finding algorithm based on the Sobel approximation of spatial derivatives to identify the leading edge of activation wave-fronts ('edge' function, MathWorks, Natick MA). The ends of each leading edge were tracked through time; if the path of a wave-end returned to a previous position (after at least 50ms) it was considered to have formed the core of a reentrant circuit. All cells circumscribed by this closed wave-end path were considered to be within the circuit core. For each cell, the number of times that it was contained within a circuit core (normalized to the maximum circuit-density in that tissue, summed over all episodes of MWR) was considered to be that location's circuit-density.

We examined the reproducibility of circuit-density distributions by repeating the above experiment in tissue-1 (heterogeneous tissue parameters) and tissue-7 (homoge-

neous tissue parameters) using two additional sets of starting positions (similar to the original 8×8 grid of starting positions, but shifted by a single cell). Two dimensional correlations between resulting distributions for the respective tissues were calculated using the MATLAB function 'corr2':

$$r = \frac{\sum_m \sum_n \left(A_{mn} - \bar{A}\right)\left(B_{mn} - \bar{B}\right)}{\sqrt{\left(\sum_m \sum_n \left(A_{mn} - \bar{A}\right)^2\right)\left(\sum_m \sum_n \left(B_{mn} - \bar{B}\right)^2\right)}} \tag{3.1}$$

Ninety five percent confidence intervals for both tissues were then determined.

Ablation algorithm

Ablations consisted of branching trees of linear scar (unexcitable, electrically disconnected). Lesion sets were generated with a custom randomization algorithm. All lesions were connected to an outer tissue edge. Lesions were encoded as nodes connected by lines. The first node was positioned adjacent to the tissue (such that all lines were peninsulas, no structural reentrant circuits could be formed). Subsequent nodes were positioned at random sites within the tissue. Each node had a "pointer" that determined which node it was connected to. Nodes had a hierarchy; each node's order was determined by the number of line segments that separated that node from the tissue edge. Lower order nodes could be attached to any higher order node. Multiple lower order nodes could be attached to the same higher order node, but each node had only one higher order attachment. Nodes (and lines) were added until some predefined length was reached. Ablation trees that enclosed regions of tissue were re-randomized to preclude creation of quarantined cells. Figure 3.1 shows an example of an ablation tree encoding and translation.

(A)

Node #	1	2	3	4
Pointer	0	1	2	2
X Position	1	25	11	31
Y Position	8	24	40	48

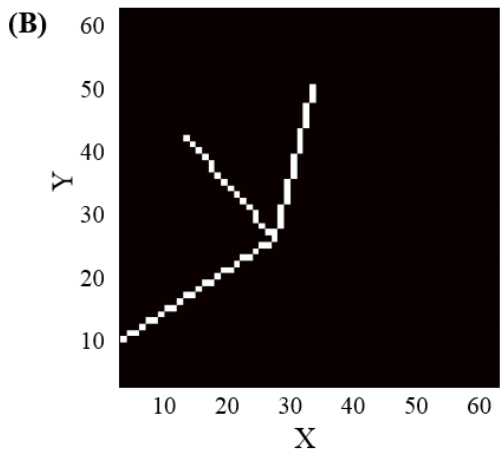

Figure 3.1: Examples of (A) an ablation line encoding and (B) the resulting ablation pattern. In the encoding, each node is comprised of 1) a pointer describing which higher-order node it is connected to (a pointer of 0 indicates that a node is attached to the tissue boundary) and 2) an x, y coordinate describing its position within the tissue.

Experimental protocols

For each of the seven tissues, we assessed 1) circuit-density and distribution, 2) percent inducibility of MWR, and 3) average time-to-termination of MWR. Each assessment was made at baseline (no ablation) and then repeated in the presence of ablation. We randomly generated 375,000 different ablation trees, from 10 to 150 cells in total length (in 10 cell increments) with 25,000 trees at each length. Ablation trees were laid over the baseline circuit-density maps of each tissue and then sorted according to their average circuit-density overlap (defined as the sum of the normalized circuit-density values of each cell that was covered by the ablation lesion set divided by the

total number of ablated cells). All 25,000 ablation trees were sorted according to their circuit-density overlap and these values were then sorted into deciles. From the 25,000 ablation trees the 10 trees whose circuit-density overlap was closest to each decile were selected and then applied to each of the tissues.

We evaluated the effect of these ablation trees on the tissue's ability to support MWR by burst pacing (0.1kHz for 1000ms) from 20 randomly selected pacing sites. Percent inducibility of MWR and average time-to-termination (up to 100,000ms, for all episodes that lasted at least 2,000ms) were assessed. The percentages of successful induction attempts and the durations of successful reentrant runs were averaged for each ablation length and for each overlap percentile.

In order to test the impact of ablation position relative to the high circuit-density patch on time-to-termination we created two homogeneous tissues of 80x80 cells, one with and one without a high circuit-density patch. In both tissues, a linear ablation was placed perpendicular to the tissue boundary either close to or remote from the patch (Fig. 3.2). Burst pacing from a random position (0.1kHz, 1,000ms) was then carried out to attempt induction of MWR. This was repeated 1,000 times and the mean duration and inducibility were recorded. Times to termination resulting from near and far ablation lines were compared using a Student's t-test for both tissues.

Error bars were based on standard errors of the mean. All of our computations were performed on the Vermont Advanced Computing Core (University of Vermont).

3.4 Results

Circuit-density distribution

We generated maps of the baseline (pre-ablation) circuit-density/distribution for each of the seven tissues. In each case, circuits were heterogeneously distributed across

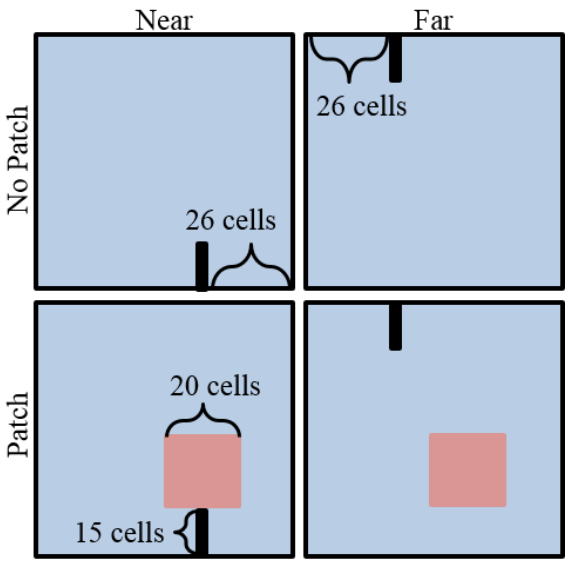

Figure 3.2: Experimental design for examining the effect of an ablation line's proximity to a high circuit-density patch on the duration of MWR.

the tissue (Fig. 3.3). In tissue with a short wavelength patch, circuit-density was always higher in the region of the patch, regardless of the site of induction, and there was a large gradient in circuit-density between the minimum and maximum sites. In contrast, in tissues without a short wavelength patch the distribution of circuits varied, depending upon the site from which pacing/induction occurred, and the gradient in circuit-density was minimal. We quantified the reproducibility of circuit distribution by calculating the 2D correlation between repeated maps of the same tissue when MWR was induced from different pacing sites. In tissue without a patch the 2D correlation was 0.209 [CI, 0.0550 to 0.3639], while in tissue with a patch 2D the correlation was 0.851 [CI, 0.7830 to 0.9197].

Inducibility of MWR

In the tissue without a short wavelength patch (#7) and the tissue with a low wavelength gradient between the patch and surrounding tissue (#6), there was a steady

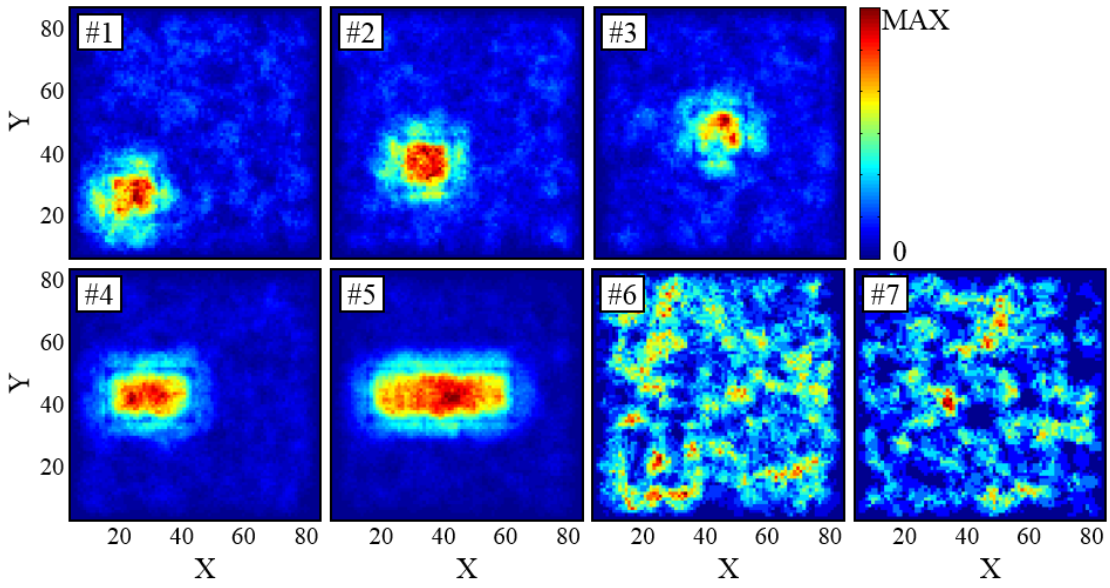

Figure 3.3: Circuit-density maps. Color-bar indicates normalized circuit-density. Because inducibility and time-to-termination varied between tissues not all maps are based upon the same total duration of MWR.

increase in MWR inducibility as ablation length increased (Fig. 3.4). By contrast, in the tissues containing a markedly aberrant patch (#1-5), there was a tri-phasic impact of ablation length on inducibility of MWR. First, inducibility markedly increased during Phase-1 when the ablation line had not become long enough to reach the high circuit-density region. Inducibility then decreased slightly during Phase-2 when the ablation line made its way across the high circuit-density region. Finally, inducibility increased again in Phase-3 as the ablation line moved beyond the high circuit-density region. Furthermore, there was no significant difference in inducibility between an ablation in Phase-3 and an equivalent length ablation that did not intersect with the high circuit-density patch.

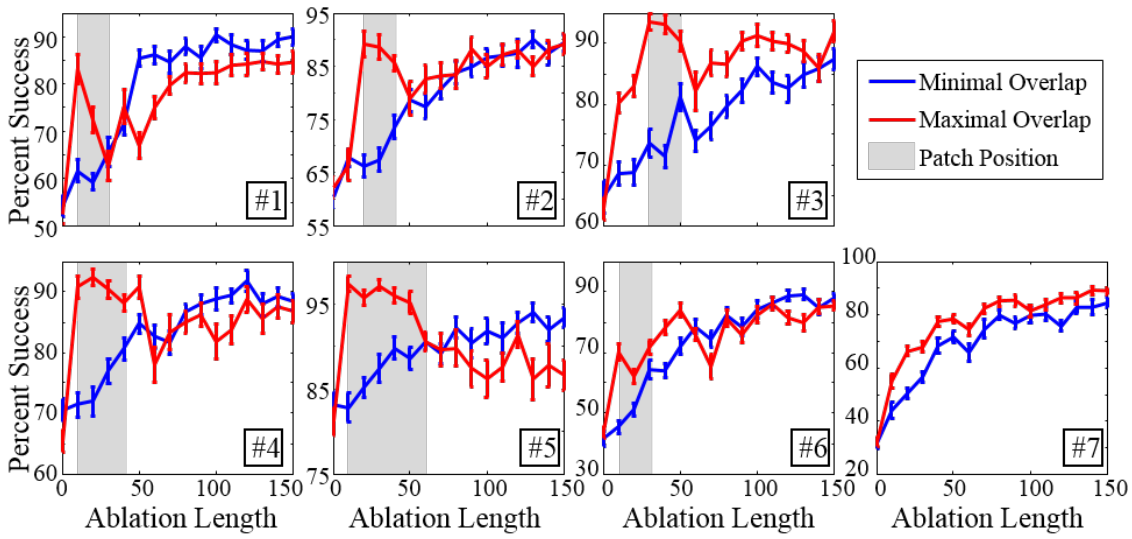

Figure 3.4: Percentages of successful induction attempts as a function of ablation length. Blue indicates low circuit-density overlap ablation lines; red indicates high circuit-density overlap ablation lines. Gray bar indicates distance to-and-through patch (from the tissue edge). Note tri-phasic changes in inducibility for high overlap lines placed in heterogeneous tissues (1-6).

Ablation efficiency

We define ablation efficiency as the amount by which mean time-to-termination decreases when an additional ablation point is added to an existing ablation line. In the tissue without a short wavelength patch (#7) and the tissue with a low wavelength gradient between the patch and surrounding tissue (#6), the duration of MWR decreased approximately linearly with increasing ablation length (Fig. 3.5), and this relationship was independent of whether or not the ablation lines overlapped with high circuit densities areas of the tissue. In other words, ablation efficiency was constant. In contrast, in the tissues that had a short wavelength patch (#1-5), MWR termination time was strongly affected by the degree to which the ablation lines overlapped with the short wavelength patch. Also, the ablation efficiency varied substantially with ablation length, exhibiting the same 3 phases as seen in Figure 3.4

with MWR inducibility. Thus, Phase-1 had negative ablation efficiency, Phase-2 had very high positive efficiency, and Phase-3 had slight positive efficiency (Fig. 3.5). The end of Phase-2 marked the point of maximum decrease in time-to-termination (high-overlap: -43.5% [CI, -22.0% to -65.1%] vs. low-overlap: -4.4% [CI, 7.3% to -16.0%] – percentages are relative to time-to-termination of respective tissue without ablation).

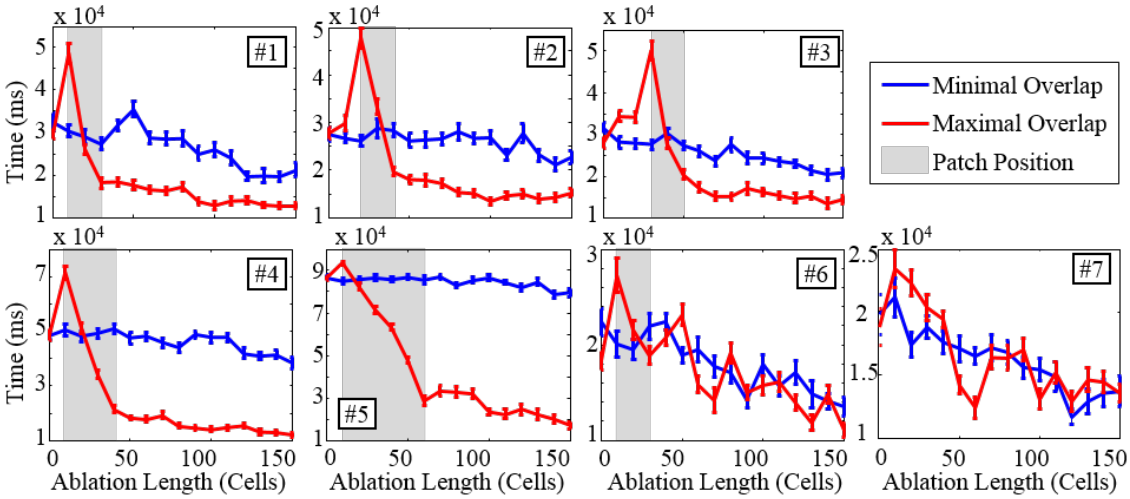

Figure 3.5: Times to termination of induced episodes of MWR as a function of ablation length. Blue indicates low circuit-density overlap ablation lines and red indicates high circuit-density overlap ablation lines. Gray bar indicates distance to-and-through patch (from the tissue edge). Note the tri-phasic changes in time-to-termination for high overlap lines placed in heterogeneous tissues (1-6).

Proximity to high circuit-density patch

Finally, we examined the impact of ablation line proximity to a high density patch prior to the line becoming long enough to impinge on the patch itself. Short ablation lines were placed either at the bottom right or top left of the squares of tissue shown in Figure 3.2. In the tissue without a short wavelength patch, line location had no significant impact on time-to-termination (2.23×10^4ms vs. 2.03×10^4ms, $p = 0.07$).

In contrast, in the tissue that had a short wavelength patch, the line closer to the patch caused time to MWR termination to increase substantially more than the more distant line (6.99×10^4ms vs. 3.45×10^4ms, $p < 0.001$).

3.5 Discussion

Successful ablation of atrial fibrillation requires alteration of a tissue's propensity to support the initiation and perpetuation of MWR. We found that inducibility, measured as the ability of rapid pacing to produce MWR, varied with tissue properties and with the presence, extent and location of ablation lines (Figures 3.2-3.5). Perpetuation, measured as mean time-to-termination of MWR, varied depending upon whether ablation lines predominantly caused wave-annihilation or new wave-formation.

Initiation: ablation lesion placement and inducibility of MWR

In order for pacing to result in MWR, wave-break must occur (otherwise contiguous concentric activation wave-fronts propagate until they reach a tissue boundary and then extinguish) [14],[15]. There must also be rotation of the wave's leading edge and propagation in a closed continuous path to create a circuit [16]. Any tissue property that increases the probability of wave-break (and wave-rotation) will increase the inducibility of MWR.

Source-sink mismatch (where excited tissue has insufficient charge to bring neighboring unexcited tissue to its activation threshold) can provide the conditions for wave-break and reentry [17]. Source-sink balance is a dynamic feature of tissue, varying with wave-shape, diastolic intervals and many other emergent physiologic parameters. The probability that source-sink mismatch (and hence wave-break) will develop is increased in the presence of regional tissue heterogeneity [10].

Wave-break itself can produce the necessary conditions for rotation [15],[17]. Once wave-break has occurred there is a gradient of source-sink balance along the wave's leading edge. In the middle of a wave's leading edge each cell acts as the source for the tissue directly in front of it. The excited cells at the broken end of the leading edge (site of wave-break) are the source for the sink cells which lie in front and to their side (Fig 3.6). This results in slower conduction at the broken end and more rapid conduction along the leading edge [16].

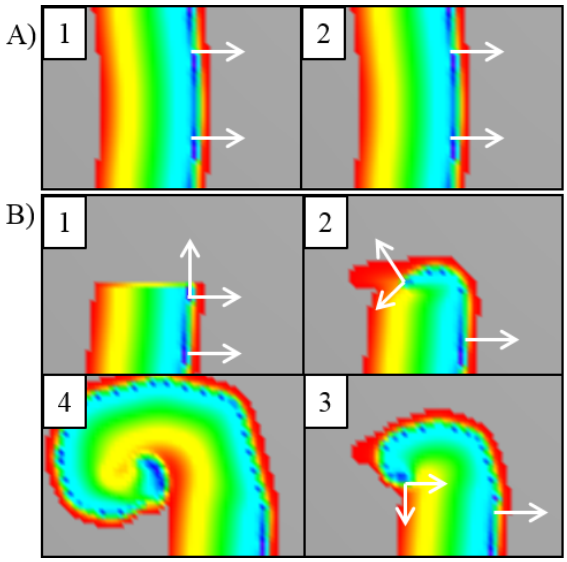

Figure 3.6: Wave propagation (A) unbroken and (B) broken wave-fronts. White arrows represent the direction of current flow from source to sink. Unbroken wave-fronts have the same conduction velocity at all points (in homogeneous tissue) and proceed in a straight line. In the event of wave-break, slower conduction velocity at the wave-end (due to increased sink size) produces rotation and can lead to reentry.

Ablation lines can decrease sink size. As a wave-front travels along an ablation line, current cannot flow into the ablated cells (which are electrically disconnected), thus the sink is comprised of the unexcited cells directly in front of the wave's leading edge. As a wave, propagating along an ablation line, reaches the end of that line, there are suddenly cells in front of and to the side of the wave-front where it meets

the ablation line. The result is an abrupt increase in sink size. Whether or not this increased sink is sufficient to create wave-break depends upon the source-sink balance of the un-ablated tissue. Our data suggest that ablation lesions in tissue regions that have a low propensity for wave-break (pre-ablation) can increase the likelihood of wave-break and therefore increase inducibility. On the other hand in tissue regions that, due to their electrophysiologic properties, have a high propensity for wave-break, delivery of an ablation line can diminish the likelihood of wave-break/circuit formation and reduce inducibility.

Perpetuation: termination of MWR is a probabilistic phenomenon

Unlike in arrhythmias with fixed anatomic circuits, termination of MWR is a probabilistic phenomenon [12]. MWR is comprised of multiple coexisting circuits; when all waves are extinguished MWR terminates. The total wave population is determined by 1) the number of new waves formed (e.g. through wave-break) and 2) the number of waves annihilated (e.g. via core collision with an outer boundary). When the core of a circuit collides with an outer boundary its circuit is interrupted and that wave's reentry ceases [12]. When wave-break occurs in the leading edge of a wave, new circuits can be formed. Circuits are spatially dynamic in MWR therefore the likelihood of a collision (and termination/wave-number reduction) is dependent upon the probability of a core meandering into an outer boundary. If one can increase wave-annihilation without increasing new wave-formation than the probability of termination can be increased.

We hypothesized that by increasing the total length of the tissue boundary through the addition of ablation lines contiguous with the outer boundary; we would increase

the probability of collision events and thus increase the likelihood of MWR termination. We further hypothesized that placing ablation lines in areas of high circuit-density would increase the probability of core collision and wave-annihilation, and therefore of MWR termination. Interestingly, while we did find shorter times to termination when ablation lines were placed in high circuit-density regions (Fig 3.5); we also found that ablation in areas of low circuit-density increased time-to-termination. This indicates that increasing wave-annihilation is not the only effect that an ablation line can have on MWR.

As discussed above, ablation lines can increase the propensity for wave-break and thus new circuit formation, as may occur when the leading edge of a wave-front interacts with the end of an ablation line. The impact of an ablation line on the probability of MWR termination is thus dependent upon whether the line is more likely to interact with the leading edge of an existing wave to produce a new wave, or to interrupt the core of a circuit and annihilate an existing wave. In heterogeneous tissue, cores are, by definition, more likely to be found in the high circuit-density areas. Accordingly, ablation lesions placed in high circuit-density areas are more likely to meet moving cores and thus terminate their corresponding waves, which explains the increased efficiency of lesions placed in high circuit-density areas (Fig 3.5). However, the leading edges of the waves that rotate around these cores move outward, and thus tend to propagate away from the high circuit-density areas, and so may interact with ablation lines placed in low circuit-density areas to generate new waves. This explains the negative ablation efficiency of lines placed in low circuit-density regions of tissue.

Tissue properties, circuit distribution and map utility

As described above, tissue properties determine (in a probabilistic fashion) the distribution of circuit cores. If tissue properties are homogeneous, then over time any tissue location has an equal probability of containing a core. This has two consequences 1) the circuit distribution over one time period may not be the same as the distribution over some future time period and 2) there is no site at which one can expect that an ablation line is more likely (on average) to interact with a core than any other site. In contrast, if there is regional heterogeneity of tissue physiology, circuit cores have a higher probability of existing in certain regions (e.g. short wavelength patches). Under these circumstances 1) there is a higher likelihood that the circuit distribution will remain the same over time and 2) one can therefore place an ablation lesion in a site that has a higher probability of resulting in core collisions. Thus circuit-density mapping can usefully be employed for determining optimal lesion placement when there is regional heterogeneity of tissue physiology. As regional heterogeneity is reduced circuit distribution becomes less reproducible. This means that a circuit-density map will be less predictive of future circuit distribution and therefore be of less value as a guide to ablation placement.

In the clinical setting it is not easy to directly measure many of the tissue properties that influence wavelength (e.g. action potential duration, source-sink mismatch). However, the distribution of tissue properties determines where circuit cores tend to be, therefore by measuring circuit distribution we are indirectly identifying tissue properties. The identification of high circuit-density regions allows us to determine where to place ablation lines so as to 1) maximize wave-annihilation and 2) minimize wave-break thereby minimizing inducibility and maximizing the probability of termination.

Clinical correlation

In this and prior studies we have proposed that termination of MWR requires circuit interruption via core collision with an outer boundary [12]. Linear ablation connected to a tissue edge increases the probability of such a collision; focal ablation does not directly cause circuit transection and does create the substrate for a new structural circuit. Despite this focal ablation has been successfully employed to target reentry (rotors) in clinical practice [18],[19]. These seemingly incompatible perspectives may both be correct. A study from Trayanova demonstrated that rotors within a patch containing distributed discontinuities can generate fractionated electrograms [20]. When focal ablation was delivered to this region rotors were not directly terminated but rather they were more likely to meander out of the patch and annihilate when colliding with a tissue boundary [20].

Limitations

The work described in this study was performed entirely in a computational model of electrical propagation. Ultimate biological confirmation is essential, of course, and remains pending. Nevertheless, it would be practically impossible to address the questions of the present study in the detail we have achieved using anything other than a computational model because of the thousands of iterations required to obtain statistically reliable estimates of quantities such as ablation efficiency and probability of termination as a function of ablation line length. Our results thus establish the principles upon which optimal ablation strategies can be designed. With a map of circuit distribution in a given patient, one can predict the impact of a particular lesion set on the inducibility and sustainability of MWR before delivering a single lesion.

Tissue geometry significantly influences source-sink balance and the specific be-

havior of the human atria will be intimately related to its geometry (size, shape, boundary locations, and discontinuities). Our studies were performed in a very abstract domain: flat 2-dimensional sheets of tissue. As such they demonstrate the general principles of wave dynamics and their response to ablation but do not reveal specific details that can be anticipated in human atria.

Our study focused exclusively on MWR, thus our results do not apply to AF that results from focal drivers with fibrillatory conduction.

3.6 Conclusions

We have shown that short wavelength tissue patches reproducibly give rise to increased circuit-density during MWR. We have further shown that ablation at sites of high circuit-density is most effective at decreasing the time-to-termination while minimally increasing the inducibility of MWR. Importantly, ablation lines delivered at sites of low circuit-density do little to decrease time-to-termination and increase inducibility of MWR. We conclude that circuit-density maps provide a means to determine the most effective and efficient distribution of ablation lesions for treatment of AF.

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Conflict of interest disclosures

None

Bibliography

[1] Sanoski CA. Clinical, economic, and quality of life impact of atrial fibrillation. *Journal of managed care pharmacy*. 2009;15:S4-S9

[2] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analyses. *Circ Arrhythmia Electrophysiol*. 2009;2:349-361

[3] Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F, Jr., Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation*. 2002;105:1077-1081

[4] Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the hamburg sequential ablation strategy. *J Am Coll Cardiol*. 2012;60:1921-1929

[5] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659-666

[6] Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation*. 2000;102:2619-2628

[7] Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and trigger ablation for reduction of atrial fibrillation (STAR AF): A randomized, multicentre, international trial. *Eur Heart J*. 2010;31:1344-1356

[8] Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: Longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;3:606-615

[9] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch. Int. Pharmacodyn.* 1962;CXL:183-188

[10] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J.* 1964;67:200-220

[11] Nattel S. Atrial electrophysiology and mechanisms of atrial fibrillation. *J Cardiovasc Pharmacol Ther.* 2003;8 Suppl 1:S5-11

[12] Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, Benson BE, Bielau P, Bates JH. Ablation of multi-wavelet re-entry: General principles and in silico analyses. *Europace.* 2012;14 Suppl 5:v106-v111

[13] Spector PS, Habel N, Sobel BE, Bates JH. Emergence of complex behavior: An interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circulation: Arrhythmia and Electrophysiology.* 2011;4:586-591

[14] Chen J, Mandapati R, Berenfeld O, Skanes AC, Gray RA, Jalife J. Dynamics of wavelets and their role in atrial fibrillation in the isolated sheep heart. *Cardiovasc Res.* 2000;48:220-232

[15] Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J.* 1959;58:59-70

[16] Fast VG, Kleber AG. Role of wavefront curvature in propagation of cardiac impulse. *Cardiovasc Res.* 1997;33:258-271

[17] Weiss JN, Qu Z, Chen PS, Lin SF, Karagueuzian HS, Hayashi H, Garfinkel A, Karma A. The dynamics of cardiac fibrillation. *Circulation.* 2005;112:1232-1240

[18] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol.* 2012;60(7):628-636

[19] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. *J Am Coll Cardiol.* 2004;43:2044-2053

[20] Ashihara T, Haraguchi R, Nakazawa K, Namba T, Ikeda T, Nakazawa Y, Ozawa T, Ito M, Horie M, Trayanova NA. The role of fibroblasts in complex fractionated electrograms during persistent/permanent atrial fibrillation: Implications for electrogram-based catheter ablation. *Circ Res.* 2012;110:275-284

Chapter 4

Prospectively Quantifying the Propensity for Atrial Fibrillation: A Mechanistic Formulation

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4.1 Abstract

The goal of this study was to determine quantitative relationships between electrophysiologic parameters and the propensity of cardiac tissue to undergo atrial fibrillation. We used a computational model to simulate episodes of fibrillation, which we then characterized in terms of both their duration and the population dynamics of

the electrical waves which drove them. Monte Carlo sampling revealed that episode durations followed an exponential decay distribution and wave population sizes followed a normal distribution. Half-lives of reentrant episodes increased exponentially with either increasing tissue area to boundary length ratio (A/BL) or decreasing action potential duration (APD), resistance (R) or capacitance (C). We found that the qualitative form of fibrillatory activity (e.g., multi-wavelet reentry (MWR) vs. rotors) was dependent on the ratio of resistance and capacitance to APD; MWR was reliably produced below a ratio of 0.18. We found that a composite of these electrophysiologic parameters, which we term the fibrillogenicity index ($Fb=A/(BL*APD*R*C)$), reliably predicted the duration of MWR episodes ($r^2 = 0.93$). Given that some of the quantities comprising Fb are amenable to manipulation (via either pharmacologic treatment or catheter ablation), these findings provide a theoretical basis for the development of titrated therapies of atrial fibrillation.

4.2 Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in the United States, affecting an estimated 2.66 million adults as of 2010 [1],[2]. Unfortunately, despite the magnitude of its impact on the healthcare system [3], current treatments have proven inadequate, particularly in patients with longer lasting AF [4]-[6]. At least in part, this is due to our inability to tailor therapies to the specific electrical abnormalities of individual patients' hearts. Instead, the severity of AF is categorized in a binary fashion based upon whether episodes of AF last less than or greater than 7 days [7], and ablation strategy is selected based upon this classification (i.e. pulmonary vein encircling alone vs. encircling plus additional atrial ablation) [4],[8]. Because the duration of AF episodes reflects the degree of electrical derangement in the heart, and

this property exists along a continuum [9], it is therefore not surprising that basing therapy on a binary system often leads to unsatisfactory results.

It seems reasonable to suppose that better outcomes could be achieved by basing therapy on a more comprehensive assessment of atrial electrophysiology which accounts for the unique characteristics of individual patients' hearts. Indeed, the relationship between atrial properties and the propensity to fibrillate has long been a subject of intense investigation. As early as 1912, investigators recognized that a "critical mass" of tissue is required to support fibrillation [10]-[12]. In addition, it has long been appreciated that shortened refractory period and slowed conduction velocity are pro-fibrillatory [13]-[15]. Nevertheless, the precise manner in which these factors determine the atria's propensity to fibrillate remains poorly understood, and thus the degree to which they should be manipulated in the treatment of AF is unclear.

Accordingly, the purpose of this study was to quantify how electrophysiologic parameters determine the propensity of atrial tissue to support fibrillation. We pursued this goal with the aid of a previously described computational model which allowed us to study the behavior of multi-wavelet reentry (MWR), a chaotic propagation pattern which has long been considered one of the key mechanisms of AF [16]-[18]. In a previous paper, we introduced the idea of viewing MWR from a population dynamics perspective [19]. The wave population varies as a function of wave births and deaths and MWR terminates when the population reaches zero. We hypothesized that while the destinies of individual waves cannot be easily anticipated, the effect of parameter changes (e.g., changes in area, boundary length and wavelength) on average wave behavior (i.e. AF duration) can be quantitatively predicted. Further, we propose that changes to these parameters are pro- or anti-fibrillatory based upon their relative impact on the probabilities of wave births and deaths.

4.3 Methods

We performed a series of numerical experiments with a previously described computational model of cardiac electrical propagation [12],[19],[20]. Model code was written in C++ and simulations were run on the Vermont Advanced Computing Core (see www.uvm.edu/ vacc/ for specifications). The model consists of a rectangular grid of excitable "cells" (each representing a roughly 1 mm^2 group of cells) having a combined area of A and an outside boundary length of BL. The cells are connected to each other by electrically conducting pathways of resistance R via von Neumann neighborhoods (up, down, right and left). Because relative rather than absolute voltages guide the model's behavior, each cell had a voltage which varied on a continuous scale between a minimum, $V_{min} = 0$, representing the resting or polarized state, and a maximum, $V_{max} = 1$, representing the fully depolarized state. Pairs of connected cells exchange charge at a rate determined by their voltage differences and R. The accumulated charge in a cell determines its voltage in inverse proportion to its capacitance C. When the voltage of a cell reaches a set threshold $V_{min} < V_{thresh} < V_{max}$ that cell's voltage ascends rapidly to V_{max}, and is then refractory for the duration of the action potential, APD. In this way, the depolarization of one cell spreads to its neighbors to generate a propagating action potential. The model time step was scaled relative to the length of typical action potentials such that it represented approximately 1ms. A degree of heterogeneity was also introduced by randomizing cellular APDs around mean values using a uniform distribution of $\pm$10ms.

Reentrant activity was initiated in the model via high-frequency burst pacing (100Hz for 1s) from a virtual electrode placed over a randomly chosen cell. Due to the chaotic nature of MWR, even small changes in the position from which reentry was induced could result in large differences in the state of the model's activity at a given

time step; thus, induction from each electrode location produced a unique episode of MWR. The qualitative nature of reentry depended on the values of the model parameters. Reentrant patterns were visually categorized by an observer blinded to the model parameters into four distinct groups: pure MWR, MWR with occasional rotor formation, rotors with occasional bouts of MWR, or rotors only (see Video S4.1 for representative examples of these reentrant phenotypes).

At each time step, we located all those cells which had become depolarized within the previous 10ms and defined the individual waves existing at that point in time to be the distinct groups of contiguous depolarized cells (Fig. 4.1); this allowed us to track the wave population through time. Figure 4.2 shows two representative examples of wave population versus time.

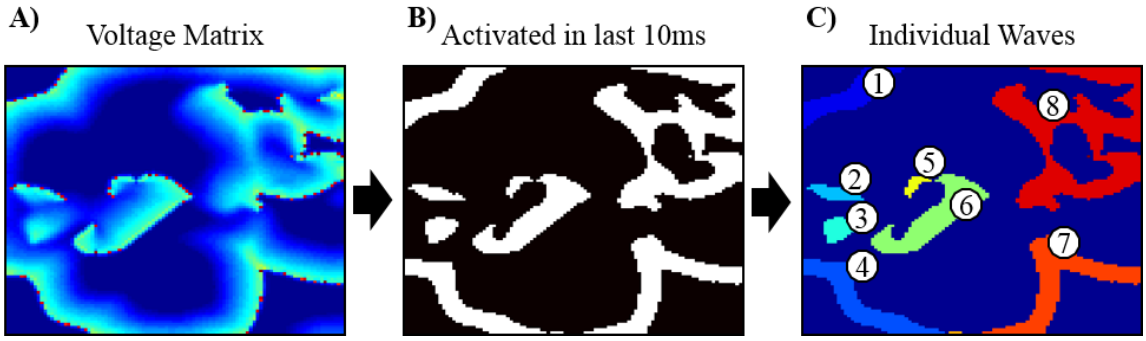

Figure 4.1: Wave Identification Algorithm. A) An example of MWR in the computational model, B) The cells that became depolarized within the previous 10ms (shown in white), C) The eight distinct groups of contiguous depolarized cells which constitute the individual waves.

We generated three series of rectangular virtual tissues in each of which a single parameter was varied (A/BL, APD and RC as shown in Table 4.1). Tissue sizes in our model typically ranged between 2,500 and 10,000 cells. This range allows for between 5 and 50 waves to coexist on a tissue depending on that tissue's properties. This range of wave to chamber size ratios encompasses that found in mapping studies

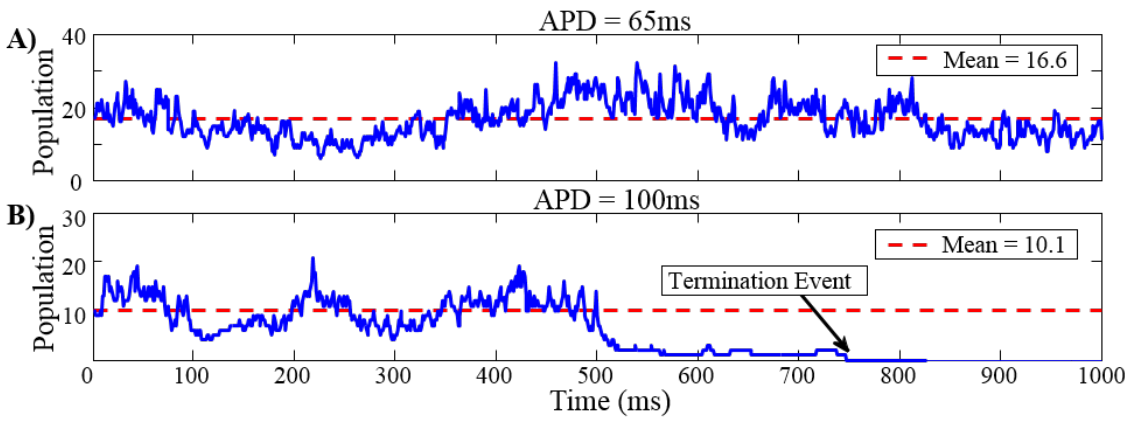

Figure 4.2: Wave Population Time Series. Examples of wave population time series for short (A) and long (B) wavelength tissues. The mean wave population for the short wavelength tissue (16.6 waves) was substantially lower than that of the long wavelength tissue (10.1 waves). At approximately 750ms, the wave population in the long wavelength tissue drops to zero and reentry terminates.

of multi-wavelet reentry in humans [21],[22].

We used a Monte-Carlo approach to determine how both the duration and population dynamics of MWR were affected by the values of these key parameters. In each tissue, we initiated 500 unique episodes of MWR and recorded the durations of each episode up to a maximum of 10,000s or until spontaneous termination occurred. We generated histograms by binning episodes according to their duration to produce

Tissue Series	A/BL	APD	RC
#1 (Varying A/BL)	12.5 to 25mm	80ms	10ms
#2 (Varying APD)	20mm	50 to 100ms	10ms
#3 (Varying RC)	20mm	880ms	8 to 16ms
#4 (Randomized)	12.5 to 25mm	30 to 150ms	8 to 16ms

Table 4.1: Tissue Parameter Ranges. Ranges of model parameter values used in the virtual tissue experiments.

probability distributions of episode length. Runs which failed to initiate reentry or lasted the maximum duration were excluded. In those same tissues, we initiated an additional 10 episodes of reentry in which we recorded the activation patterns of each cell for up to a maximum of 10s or until spontaneous termination occurred; these activation patterns were used to calculate the wave population at each time step. Since approximately 2s worth of model time could be produced in 1s of real computing time, individual simulation durations ranged between 1s and 1.5hrs depending on the tissue's propensity to fibrillate. We generated histograms by binning time steps according to their population level.

We also tested the interaction between multiple simultaneous parameter changes. We generated one hundred additional virtual tissues with randomized properties (Table 4.1). In each of these tissues we initiated 500 unique episodes of MWR, and recorded the duration of each episode for up to 10,000s or until spontaneous termination occurred.

4.4 Results

Semi-logarithmic histograms of the number of MWR episodes as a function of duration were well fit by linear regression (Fig. 4.3), indicating that the number of episodes to last a given duration followed an exponentially decaying distribution. It was therefore possible to calculate the half-life of reentry ($t_{1/2}$, the amount of time required for half of initiated episodes to terminate) from the slope of these regressions, λ, (Eq. 4.1).

$$t_{1/2} = \frac{\ln(2)}{\lambda} \tag{4.1}$$

Normalized histograms of the amount of time spent at a given population level (expressed as relative probability) revealed that the probability of a given number of

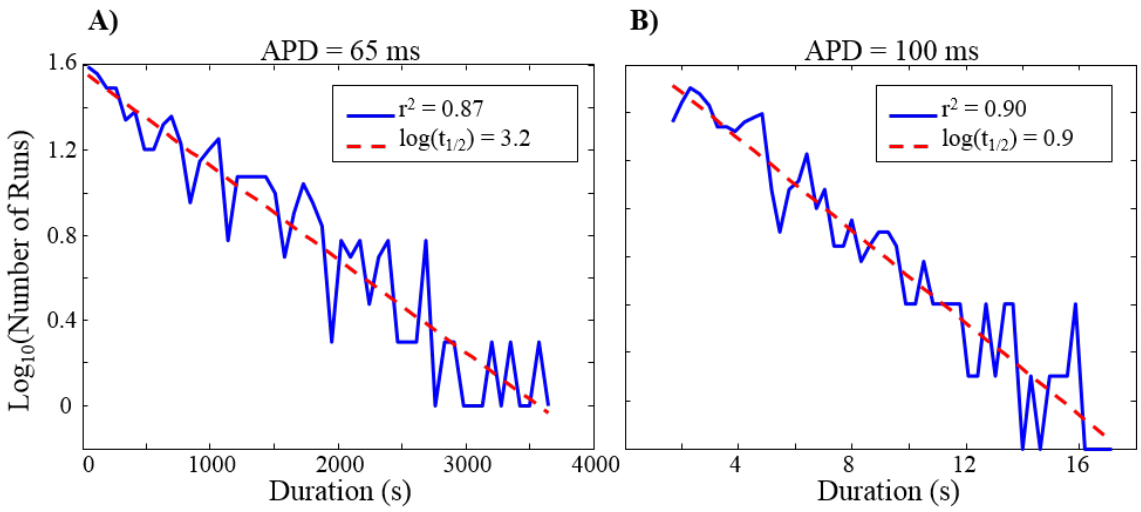

Figure 4.3: Episode Duration Distributions. Example semi-logarithmic plots demonstrating the exponentially decaying number of MWR episodes to last a given duration. Short wavelength tissue (A) had a shallow slope and resulted in a longer half-life (approximately 26 minutes). Long wavelength tissue (B) had a steep slope and resulted in a shorter half-life (approximately 7 seconds).

waves was normally distributed around the mean wave population (mean $r^2 = 0.94$ over $\pm 2\sigma$ from the mean population - Fig. 4.4).

The probability that a population of waves will increase (red) or decrease (blue) in number at the next time step is a function of population size (Fig. 4.5). When the current population number falls below the mean, the probability that the number of waves will increase at the next time step is increased, and visa-versa. When the population number equals the mean there is an equal probability of having an increase and a decrease in the number of waves at the next time step. The population variance is inversely related to the rate at which these probabilities diverge from one another. The jaggedness of the plots near the highest and lowest populations is due to smaller sample sizes at the population extremes (i.e. fewer naturally occurring instances of these numbers of waves).

Half-life increased exponentially with either increasing A/BL or decreasing APD

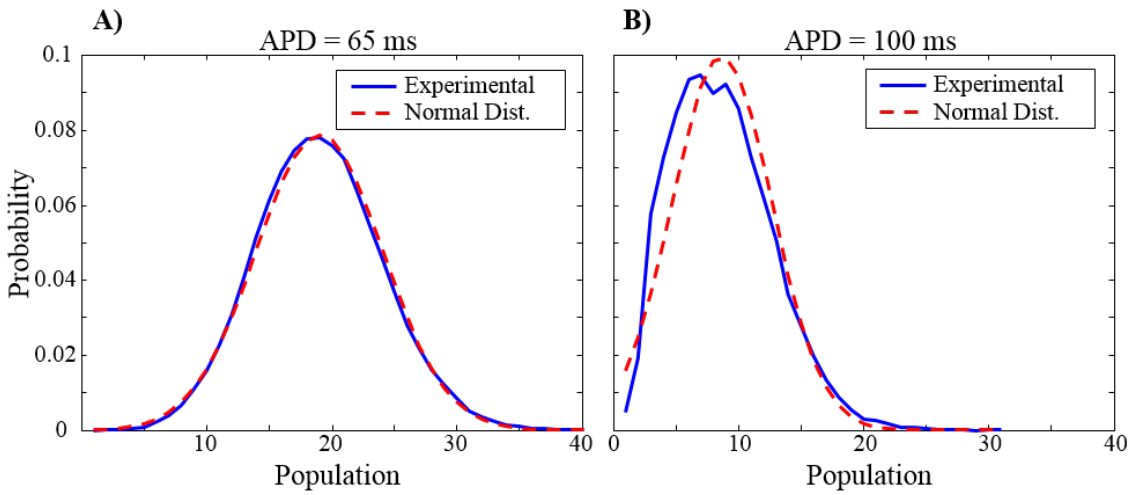

Figure 4.4: Wave Population Distributions. Probability distributions of the percentage of time spent at each individual wave population for short (A) and long (B) wavelength tissues (red line - normal distribution).

or RC (Fig. 4.6, A-C). These exponential relationships broke down when the ratio of RC/APD reached approximately 0.15-0.20. We were unable to generate values of $t_{1/2}$ for APD values below 60ms due to computational limitations (all episodes lasted until the maximum allowed time, 10,000s).

Mean wave population increased linearly with increasing A/BL and decreased linearly with increasing APD and RC (Fig. 4.6, D-F). Changes in variance ran largely parallel to changes in population mean for both A/BL and APD but had a positive dependence on RC, increasing until RC/APD reached approximately 0.15-0.2 and decreasing at higher values. We were unable to generate meaningful data for A/BL values below 13.75 due to the short durations of MWR. We calculated the probability of reaching a zero wave population according to Equation 4.2 (the cumulative probability below zero of a normal distribution function).

$$P_{(\text{population}\leq 0)} = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{0} e^{-(x-\mu)^2\left(2\sigma^2\right)} dx \tag{4.2}$$

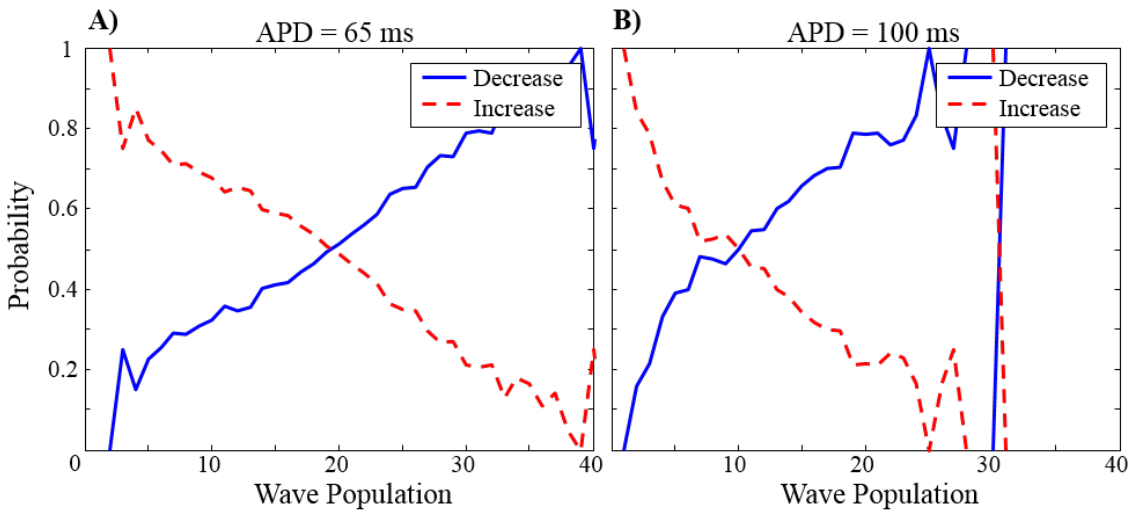

Figure 4.5: Population Dynamics Probabilities. Representative examples: probabilities of increases or decreases in population as a function of current number of waves. (A) short and (B) long wavelength tissues.

Here, μ is the population mean and σ is the standard deviation of the population's variability. We approximated the expected duration of reentry as the inverse of these cumulative probabilities. For example, if there is a twenty percent chance of termination per second, on average we expect reentry to last 5 seconds. Just as with the dependency of $t_{1/2}$ on these parameters, increases in expected duration were found with increasing A/BL, decreasing APD, and decreasing RC (Fig. 4.6, G-I). Similar breakdowns in the linearity of these dependencies were seen at ratios of RC/APD of 0.15-0.20. We composed a metric for a tissue's propensity to fibrillate that incorporates the effects of what we considered to be the three most relevant parameters (A/BL, APD, and RC) on MWR episode duration. We term this metric the fibrillogenicity index and define it as

$$Fb = \frac{A}{BL * APD * RC} \tag{4.3}$$

There was a clear exponential relationship between $t_{1/2}$ and Fb, but an r^2 correlation value of only 0.42 (Fig. 4.7A). We noticed that the majority of outlying points were exhibiting non-MWR type of behavior. After limiting our plot to tissues displaying only MWR the correlation between $\log\left(t_{1/2}\right)$ and Fb was much greater ($r^2 = 0.82$, Fig. 4.7B). We calculated the ratio of RC/APD for tissues in each of the four behavior categories (Fig. 4.8). An analysis-of-variance revealed a statistically significant ($p \ll 0.001$) difference in this value between groups, suggesting a method for predicting the behavior-type of a tissue based solely on the ratio of RC/APD. A receiver-operator curve analysis showed that a RC/APD cutoff of 0.18 resulted in a sensitivity of 91.4% with a false positive rate of only 5.7%. Using this cutoff value, we re-plotted $\log\left(t_{1/2}\right)$ as a function of Fb and found that the r^2 correlation coefficient improved to 0.93 (Fig. 4.7C).

4.5 Discussion

Multi-wavelet reentry can at times appear to be an incomprehensible writhing mass of waves that fuse, divide, and annihilate across the atria in an apparently random fashion. Due to the complex, non-linear dynamics of propagation, it is extremely difficult to predict the long-term destiny of individual waves. However, by analyzing the system's bulk characteristics rather than the evolving states of each specific wave, we have demonstrated that the ensemble behavior (i.e. MWR duration) can be predicted with a remarkable degree of accuracy. Knowledge of the statistics of wave population dynamics provides the link between atrial properties (size, shape and wavelength) and the duration of MWR episodes. By understanding how and why changes in parameters affect statistical metrics such as population mean and variance, we can predict how those same changes will ultimately alter episode duration.

Population dynamics

Changes in wave population result from transient imbalances between wave formation events such as division, and wave reduction events such as fusion or annihilation. These life cycle events are the consequence of specific interactions between waves and their environment: division results from wave-front/wave-tail interactions, fusion results from wave-front/wave-front interactions, and annihilation results from wave-front/boundary interactions. The balance of these processes determines the population mean. The extent to which deviations in the number of waves alter this balance determines how avidly the population returns to the mean. While a reduction in the wave population increases the probability of wave division there is a non-zero probability that the population will continue to decrease and ultimately result in a zero wave population (MWR termination). Lower mean number of waves (which requires fewer sequential reduction events) and higher variance (which reduces the tendency to return to the mean) both result in a higher probability of reaching zero population and termination.

Tissue properties, wave population and MWR duration

By influencing the relative probabilities of wave division, fusion and annihilation, tissue properties determine the duration of MWR episodes. Increasing the ratio of tissue area to boundary length (A/BL) decreases the rate of wave annihilation relative to wave fusion and division and thus increases both mean number of waves and MWR duration. Increasing APD increases wavelength and therefore the area encompassed by individual waves. This preferentially increases the likelihood of annihilation and fusion and leads to a decrease in both the mean number of waves and MWR duration. As RC increases wavelength decreases but there is a concomitant increase

in the excitable gap between waves. The combined effect is to gradually decrease mean number of waves and increase population variance, and ultimately leads to a decrease in MWR duration. Sufficient increase in the excitable gap reduces wave-wave interactions and allows for the formation of stable rotors.

The qualitative relationship between a tissue's properties (area, boundary length and wavelength) and its capacity to maintain fibrillation has been studied in both animal models and humans. Garrey was the first to formulate the 'mass hypothesis', demonstrating that the duration of fibrillation correlated with tissue area and width (no measurements of wavelength or refractoriness were performed) [11]. Subsequently the role of wavelength (as well as tissue size) was shown to correlate with AF duration in animal models [23],[24] and in humans [25]. While it has long been recognized that increases in A/BL or decreases in APD will result in increased duration of multi-wavelet reentry [17],[24],[25], this study presents the first quantitative analysis of these dependencies (e.g., linear vs. exponential, etc.).

The fibrillogenicity index captures the balance between the two major forces which affect wave population dynamics: the size and shape of the tissue in which MWR exists (as determined by A/BL), and the size and shape of the waves themselves (as determined by APD and RC). So long as these opposing forces are scaled together, the absolute values of individual parameters are inconsequential. As an important caveat, our probabilistic formulation for predicting the duration of MWR is dependent upon individual waves having a non-zero probability of interacting with other waves or with tissue boundaries. Accordingly, we found that as pure MWR transitions to include spatially stable rotors, the fibrillogenicity index becomes less predictive of episode duration.

Application of the fibrillogenicity index to therapy

Perhaps the most promising aspect of the fibrillogenicity index is its potential application in treatment strategies. A common approach in deciding which lesion set to apply is to classify patients as having either paroxysmal (< 7 days) or persistent (≥ 7 days) AF [7]. Ablation is typically limited to pulmonary vein encirclement and isolation in paroxysmal AF, whereas patients with persistent AF are felt to require further atrial substrate modification (such as roof and isthmus lines or ablation of complex fractionated atrial electrograms (CFAE) [4],[8]). While this binary approach can be effective in patients whose AF durations are less than a few months, cure rates are 50% or lower in patients with longer lasting AF [6]. Obviously, standard treatment protocols are inadequate within this population. Regardless of which strategy one chooses for deciding where to ablate, a method is required for determining how much to ablate. In other words, if more extensive ablation is called for, by what degree should it be increased?

Optimization of any approach to targeted ablation will require a titration method for determining the extent of lesions necessary at driver sites. The fibrillogenicity index has been designed to provide just such guidance, and thus offers a potentially useful compliment to any map-guided ablation strategy.

Limitations

As in any purely in silico experiment, the generalizability of our results remains limited and these findings will require validation in a biologic system, ultimately humans. None the less, computational modeling does offer some unique and powerful advantages over biologic experimental preparations. Only through the use of a computational model was it possible to explicitly isolate and manipulate each variable

independently. Furthermore, the Monte-Carlo approach we made use of in characterizing probability distributions of MWR episode durations relied on collecting data from a large number of reentrant episodes. This type of high volume data collection is not possible in the clinical arena. Even within the computational arena however, we restricted our analysis to highly idealized instances of atrial substrate (two dimensional rectangular tissues with homogeneously distributed cell properties). Future extension of the fibrillogenicity index must account for the complex geometries, regional heterogeneities and anisotropy found in human hearts.

Our probabilistic formulation of wave population dynamics applies only to situations in which the positions of reentrant circuits change chaotically. However, as intercellular resistance and action potential duration are altered to produce a shortened propagation wavelength and a smaller radius of curvature, multi-wavelet reentry resolves gradually into a more spatially stable, rotor-driven, form of reentry. The phenotype of reentrant behavior is dependent on the ratio of RC/APD. As with the magnitudes of other parameters presented in this study, a direct mapping to the biological realm would be inappropriate. Instead, it is the way in which a relative change in these parameters affects the ultimate behavior of the tissue which is of interest. For example, any decrease in APD increases not only the duration of reentry, but also the likelihood of rotor-driven reentrant forms.

We have not explicitly addressed the impact of remodeling in our simulations. It has been demonstrated that progressive changes to ion channel expression and development of interstitial fibrosis can increase AF burden [26]. For example, coupling between myocytes and fibroblasts/myofibroblasts has been shown to alter APD, resting membrane potential, and conduction velocity [27],[28], and can ultimately lead to an increase in tissue's propensity to fibrillate [29]. Remodeling effectively describes the movement through parameter space that results from feedback between behaviors

(AF itself) and parameters (e.g. resistance, capacitance, APD). By focusing only on the steady state situation we have defined the mapping between model parameters and behavior (i.e. Fb). Thus with the fibrillogenicity index we can predict the impact, though not the dynamics, of remodeling.

The fibrillogenicity index is calculated from parameters that we have complete knowledge of in the computational environment but which are difficult to measure in the clinical setting. Though it is relatively straightforward to gather information regarding the size and shape of a patient's atria (e.g. via CT scan or electro-anatomic mapping), measurements of APD, resistance and capacitance cannot easily be obtained. We have previously demonstrated that electrogram frequency (when acquired using electrodes with high spatial resolution) correlates well with tissue wavelength and may therefore offer a practical, measurable alternative for calculating the fibrillogenicity index.

4.6 Conclusions

We report a mechanistic, population dynamics based framework for understanding multi-wavelet reentry using a computational model of propagation. During MWR, the number of waves which coexist on a given tissue follows a normal distribution, the mean and variance of which can be used to calculate the probability of spontaneous termination. Three key parameters influence the duration of reentrant episodes: tissue size and shape, action potential duration, and resistance and capacitance. Increases in the tissue-area to boundary-length ratio, or decreases in APD or RC resulted in exponential increases in the duration of MWR episodes. We demonstrated that the phenotype of reentrant behavior (MWR vs. spatially stable rotors) is dependent upon the ratio of RC/APD; below a ratio of 0.18 reentry reliably fits into the

category of pure MWR. Finally, we have defined a metric for quantifying a tissue's propensity to fibrillate. The fibrillogenicity index is derived from a tissue's properties and accurately predicted MWR half-life over a wide range or durations (1s to 6hrs, $r^2 = 0.93$). We believe that the fibrillogenicity index provides a foundation upon which patient-specific treatment protocols for AF can be built.

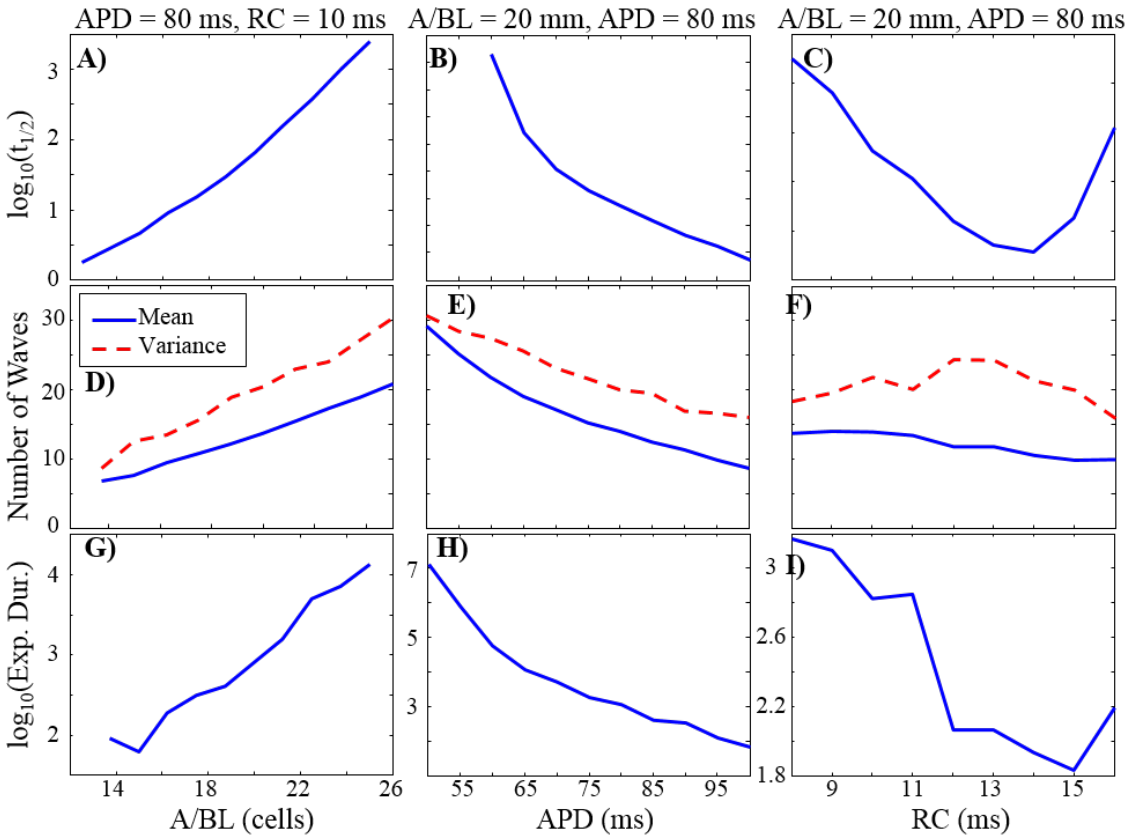

Figure 4.6: Parameter Dependencies of MWR Behavior. A-C: Semi-log plots of MWR half-life as a function of A/BL (A), APD (B), and RC (C). D-F: The mean number of waves per time step (shown in blue) and population variance (shown in red) as functions of A/BL (D), APD (E), and RC (F). G-I: Semi-log plots of the expected duration of reentry (calculated from the population mean and variance) as a function of A/BL (G), APD (H), and RC (I). Note the similar parameter dependencies of MWR half-life and expected duration.

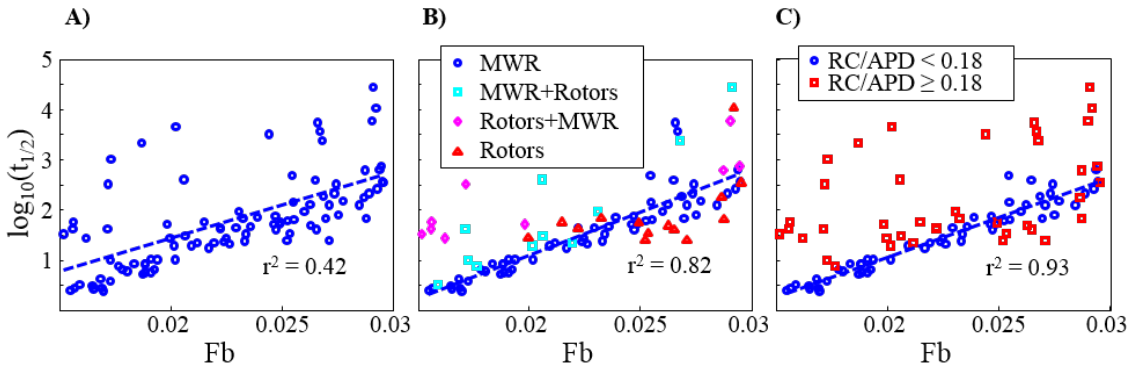

Figure 4.7: Utility of the Fibrillogenicity Index. The logarithm of the MWR half-lives as a function of the fibrillogenicity index. For all randomly generated tissues, the fit is poor (A). Limiting the analysis to tissues displaying only MWR results in a substantially improved correlation coefficient (B). Using an RC/APD cutoff of 0.18 to identify likely MWR episodes further improves correlation coefficient (C).

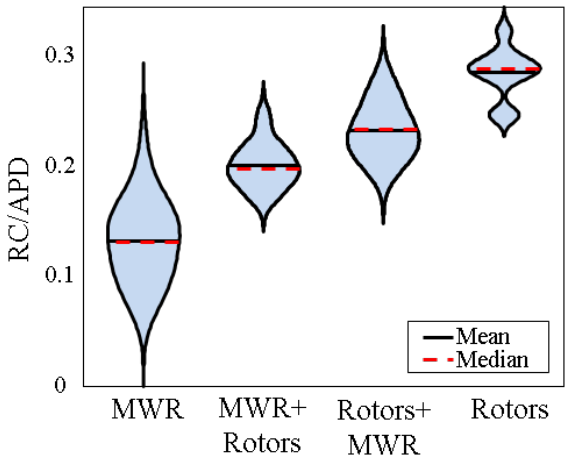

Figure 4.8: Parameter Dependency of Reentrant Behavior. Violin plot showing the distribution of RC/APD ratios for the four different categories of reentrant behavior. Violin width corresponds to relative sample density.

Bibliography

[1] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby J V, et al. Prevalence of Diagnosed Atrial Fibrillation in Adults. *J Am Med Assoc*. 2014;285: 2370–2375.

[2] Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110: 1042–1046.

[3] Sanoski CA. Clinical, economic, and quality of life impact of atrial fibrillation. *J Manag Care Pharm*. 2009;15: S4–S9.

[4] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009;2: 349–361.

[5] Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, et al. Pulmonary Vein Isolation for Paroxysmal and Persistent Atrial Fibrillation. *Circulation*. 2002;105: 1077–1081.

[6] Tilz RR, Rillig A, Thum A-M, Arya A, Wohlmuth P, Metzner A, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol*. 2012;60: 1921–1929.

[7] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa, JE, Cleveland JC, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014; 64(21): 2246-2280.

[8] Wright M, Haïssaguerre M, Knecht S, Matsuo S, O'Neill MD, Nault I, et al. State of the art: catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2008;19: 583–592.

[9] Charitos EI, Pürerfellner H, Glotzer TV, Ziegler PD. Clinical Classifications of Atrial Fibrillation Poorly Reflect its Temporal Persistence: Insights From 1195

Patients Continuously Monitored with Implantable Devices. *J Am Coll Cardiol*. 2014;63: 2840-2848

[10] Cox JL. The Surgical Treatment of Atrial Fibrillation. *J Thorac Cardiovasc Surg*. 1991;101: 584–592.

[11] Garrey WE. The nature of fibrillary contraction of the heart—its relation to tissue mass and form. *Am J Physiol*. 1914;33: 397–414.

[12] Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, et al. Ablation of multi-wavelet re-entry: general principles and in silico analyses. *Europace*. 2012;14(5): v106–v111.

[13] Jacquemet V, Virag N, Kappenberger L. Wavelength and vulnerability to atrial fibrillation: Insights from a computer model of human atria. *Europace*. 2005;7(2): 83–92.

[14] Rensma PL, Allessie MA., Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res*. 1988;62: 395–410.

[15] Wang J, Bourne GW, Wang Z, Villemaire C, Talajic M, Nattel S. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. *Circulation*. 1993;88: 1030–1044.

[16] De Groot MS, Houben RPM, Smeets JL, Boersma E, Schotten U, Schalij MJ, et al. Electropathological Substrate of Longstanding Persistent Atrial Fibrillation in Patients With Structural Heart Disease Epicardial Breakthrough. *Circulation*. 2010;3: 1674–1682.

[17] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J*. 1964;67: 200–220.

[18] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther*. 1962;140: 183–188.

[19] Carrick RT, Benson B, Habel N, Bates ORJ, Bates JHT, Spector PS. Ablation of multiwavelet re-entry guided by circuit-density and distribution: maximizing the probability of circuit annihilation. *Circ Arrhythm Electrophysiol*. 2013;6: 1229–1235.

[20] Spector PS, Habel N, Sobel BE, Bates JHT. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol*. 2011;4: 586–591.

[21] Allessie M, Lammers W, Bonke F, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J. Cardiac Arrhythmias. *Grune & Stratton Orlando*, FL. 1985. pp. 265–276.

[22] Allessie MA, de Groot NMS, Houben RPM, Schotten U, Boersma E, Smeets JL, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3: 606–615.

[23] Byrd GD, Prasad SM, Ripplinger CM, Cassilly TR, Schuessler RB, Boineau JP, et al. Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *Circulation.* 2005;112: I7–I13.

[24] Lee AM, Aziz A, Didesch J, Clark KL, Schuessler RB, Damiano Jr. RJ. Importance of atrial surface area and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *J Thorac Cardiovasc Surg.* 2013;146: 593–598.

[25] Kojodjojo P, Peters NS, Davies DW, Kanagaratnam P. Characterization of the Electroanatomical Substrate in Human Atrial Fibrillation: The Relationship between Changes in Atrial Volume, Refractoriness, Wavefront Propagation Velocities, and AF Burden. *J Cardiovasc Electrophysiol.* 2007;18: 269–275.

[26] Wijffels MCEF, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation.* 1995;92: 1954–1968.

[27] Jacquemet V, Henriquez CS. Modelling cardiac fibroblasts: interactions with myocytes and their impact on impulse propagation. *Europace.* 2007;9(6): vi29–vi37.

[28] Jacquemet V, Henriquez CS. Loading effect of fibroblast-myocyte coupling on resting potential, impulse propagation, and repolarization: insights from a microstructure model. *Am J Physiol Heart Circ Physiol.* 2008;294: H2040–H2052.

[29] McDowell KS, Arevalo HJ, Maleckar MM, Trayanova N. Susceptibility to arrhythmia in the infarcted heart depends on myofibroblast density. *Biophys J.* 2011;101: 1307–1315.

4.7 Supplemental Materials

Supplemental Video S4.1: Categories of Reentry. In this video, we present examples from four different positions along the spectrum of reentrant behavior: 1) pure MWR, 2) MWR with occasional rotor formation, 3) rotors with occasional bouts of MWR, and 4) stable rotors.

Chapter 5

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

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5.1 Abstract

Background: Treatment of multi-wavelet reentry (MWR) remains difficult. We previously developed a metric, the fibrillogenicity index (Fb), to assess the propensity of homogeneous, two dimensional tissues to support MWR. In the present study we demonstrate a method by which Fb can be generalized to heterogeneous tissues, and validate an algorithm for prospective, tissue-specific optimization of ablation to re-

duce 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 (APD) 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 fibrillogenic tissue into functionally equivalent subsections. The composite APD 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% CI, 3% to 5.8%] of the predicted target.

Conclusion: We believe that this study presents a novel approach for 1) quantifying the extent of a tissue's electrical 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 tissues refractory to standard ablation strategies.

5.2 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, affecting an estimated 2.66 million people as of 2010 [1],[2]. However, despite the high prevalence of this disease and the heavy socio-economic burden associated with it [3],[4], treatment options remain limited [5],[6], especially in comparison with other reentrant arrhythmias [7]-[9]. Of the available treatment options, catheter-based ab-

lation has proven to be the most reliable method for the permanent elimination of AF [10]-[12]. Nonetheless, while a standard anatomically-based set of ablation lesions (i.e. 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]-[19]. An approach that seems logical and that has attracted significant attention recently is the delivery of focal lesions to tissue regions believed to host drivers of AF. Indeed, the initial successes of techniques such as complex fractionated atrial electrogram (CFAE) ablation [20]-[22] and focal impulse and rotor modulation (FIRM) [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 non-conducting boundaries of the atria does not produce the substrate for structural reentry[30].

We have previously demonstrated that MWR (one of the main drivers of AF [31]-[35]) terminates only when all circuit cores collide with the tissue boundary [30],[36] and that the average duration of MWR episodes correlates with the probability of such collisions [37]. We also developed a metric, the fibrillogenicity 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 electrical derangement in patients with AF exists along a continuum [38],[39], and a given lesion set may not have the same effect in patients suffering from differing burdens of disease. Determining the amount 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 the present study we demonstrate a method by which the fibrillogenicity index 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.

5.3 Methods

Computational model

In the following experiments we made use of a previously described computational model of electrical propagation in cardiac tissue [30],[36],[37]. This combines a diffusion model of electrotonic current spread with a rule based cellular automaton model of cardiomyocyte excitation. Briefly, cells (each representing approximately $1mm^2$ of cardiac tissue) undergo action potentials when they receive current sufficient to perturb their potential from rest (V_{rest}) to above a defined threshold (V_{thresh}). Action potentials cause the cell voltage to increase towards peak potential (V_{peak}) after which it gradually returns to Vrest 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 electrical 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 0.1838.

Episodes of MWR were induced by high frequency (100Hz) burst pacing from a virtual electrode positioned randomly over the tissue surface. The model simulations were run on the Vermont Advanced Computing Core (www.uvm.edu/ vacc/).

Fibrillogenicity index

The fibrillogenicity index is a parameter-based metric of electrical derangement that is highly correlated with MWR episode duration and is calculated according to the equation

$$Fb = \frac{A}{BL * RC * APD} \tag{5.1}$$

Here, A is the tissue area and BL is the length of the unexcitable tissue boundary. The fibrillogenicity index therefore quantifies the ratio of area vs. boundary length and tissue wave length. In each of one hundred simulated rectangular tissues with randomized, homogeneous tissue properties (APD = 50-200ms, RC = 8-14ms, A = 2,500-10,000mm^2, BL = 200-400mm) 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 this data with a quadratic regression and calculating the coefficient of determination.

Effective fibrillogenicity index

To test the impact of heterogeneous tissue properties on the duration of MWR, we created a series of simulated square tissues (100 × 100mm) with distinct regions of long (APD_L = 125ms) and short APD (APD_S, varied in separate tissues between 85ms to 115ms in increments of 10ms), and varied the relative areas of these regions. In each tissue we induced 500 instances of MWR and measured the episode durations.

Mean duration and standard error of the mean (SEM) were calculated for each tissue as a function of the percentage of tissue at APD_S.

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

$$APD_E = \sum_{i=1}^{N} A_i \left[\sum_{i=1}^{N} \frac{A_i}{APD_i} \right]^{-1} \tag{5.2}$$

Here, A_i and APD_i are the area and APD, respectively, of the i^{th} of N distinct tissue regions. Insertion of Eq. 5.2 into Eq. 5.1 gives the effective fibrillogenicity index, Fb_E, that we used to predict the duration of MWR episodes in heterogeneous tissues. That is,

$$Fb_E = \frac{A}{BL * RC * APD_E} \tag{5.3}$$

Impact of ablation lesion distribution

In order to assess the relative efficacy of various lesion distributions (Fig. 5.1), we measured the impact on MWR duration of a fixed total lesion length distributed as one line, two lines, a square lesion that reduced tissue area or a branched lesion. The tested tissue had a homogeneous distributions of properties (150×60mm , $APD =$ 75ms, $RC = 11$ms). We studied total lesion lengths from 0 to 100mm (in increments of 2mm). In each case lesions were connected to the external boundary. The mean duration and SEM of 500 unique episodes of MWR was determined as a function of the quantity of ablation (i.e. the total number of cells ablated).

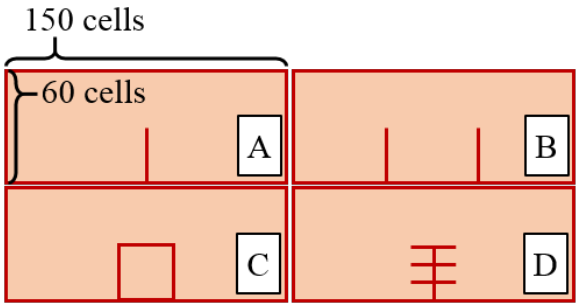

Figure 5.1: Examples of the four lesion patterns tested: A) a single linear lesion at the center of the tissue's long axis, B) two linear lesions positioned at one third and two thirds along the tissue's long axis, C) a square lesion set, and D) a branching lesion set. Direct comparison was only made between lesion patterns of equal total ablation quantity.

Wave vs. lesion interactions

We hypothesized that the spatial configuration of ablation impacted 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 (150×60mm, $APD =$ 70ms, $RC = 10$ms) during 10 seconds of MWR ($n = 3$). Cells with electric potential greater than 40% of the difference between V_{max} and V_{rest} 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.

Impact of tissue transection

We next examined the impact of transecting rectangular tissues (150×60mm) at different positions along their long axes with linear lesions. Transection was tested in three tissue series: 1) tissues in which APD was uniform (mean APD varied in

separate tissues between 85ms to 115ms in increments of 10ms), 2) tissues composed of two distinct regions with different APD values (20% area with $APD_S = 60$ms, 80% area with APD_L varied in separate tissues between 85ms to 115ms in increments of 10ms), and 3) tissues in which APD varied smoothly but randomly between values of 65ms and 115ms (Fig. 5.2).

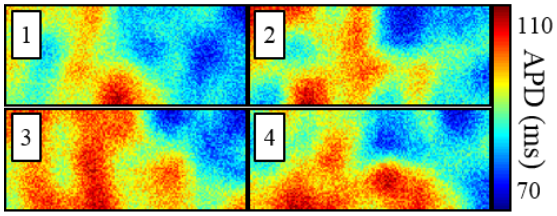

Figure 5.2: The third tissue series described in the text consisted of four randomly generated tissues with smoothly varying APD heterogeneity. During randomization, tissues with a high degree of asymmetry were preferentially selected.

Partial transection

In the third of the above tissue series, we additionally examined the impact of partial tissue transection by applying an ablation line that reached three 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 (150×60mm, $APD = 85$ms, $RC = 10$ms), we incrementally applied ablation (2mm 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 impact of tissue transection in a more realistic left atrial geometry (Fig. 5.3). Computed tomography images of the heart were used to generate a curved, two-dimensional surface mesh composed of 6,810 triangular units of area each representing an average of 1.8mm^2 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 that included pulmonary vein isolation and a mitral isthmus line was applied, rendering the mesh topologically equivalent to an uninterrupted 2D sheet with an area of 98.3cm^2 . Next, the impact of transecting the tissue by applying a single lesion between the mitral annulus and pulmonary vein isolation ring was tested with both homogeneous (APD = 90ms, RC = 12ms) and heterogeneous (RC = 12ms, 19% area at APD_S = 70ms, 81% area at APD_L = 90ms) tissue properties. In the tissue with heterogeneous properties, APD_S was localized to a region adjacent to the mitral isthmus line that contained the left atrial appendage.

Prospective titration of ablation quantity to electrical derangement

Finally, we developed and tested an algorithm for prospectively determining the minimum ablation required to reduce MWR burden by an arbitrary degree in 60 rectangular tissues with randomly selected dimensions, APD, and RC. We used Fb_E to predict MWR episode duration both prior to ablation and after complete tissue transection. Linear interpolation between these points in the Fb-$\log_{10}$(Mean Duration) plane was used to predict the impact of partial transection. The optimal ablation set was defined as the smallest amount of lesion and the smallest degree of partial tissue

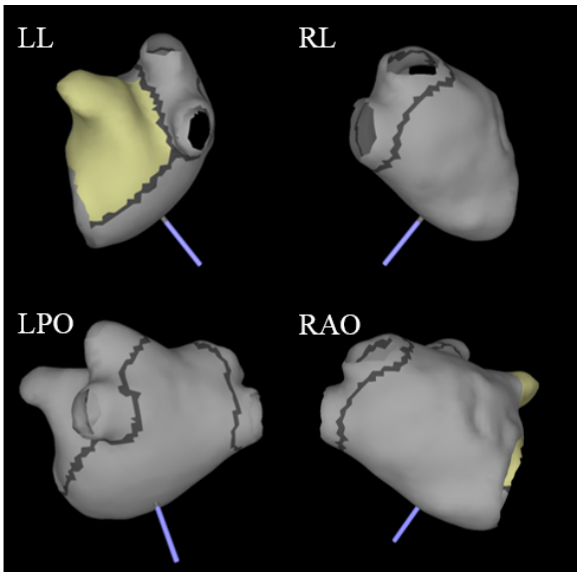

Figure 5.3: Left lateral (LL), Right lateral (RL), Left posterior oblique (LPO), and Right anterior oblique (RAO) views of the curved, two dimensional left atrial surface mesh. Ablated cells of the standard lesion set (pulmonary vein isolation plus a mitral isthmus line) are shown in dark grey and the region of shortened APD is shown in yellow.

transection that reduced mean MWR duration below an arbitrary threshold of 3s. We then measured the mean duration of 500 unique MWR episodes both before and after application of this optimal, partially transecting, ablation lesion set.

5.4 Results

Effective fibrillogenicity index and MWR duration before ablation

In homogeneous, unablated tissue, there was a direct relationship between Fb and the duration of MWR episodes that was well described by a quadratic regression (R^2=0.95, supplemental Fig. S5.9). In heterogeneous tissues MWR episode duration increased as the number of cells with APD_S increased (Fig. 5.4). This relationship

was well predicted (mean R^2=0.82) by Fb_E (Eq. 5.3).

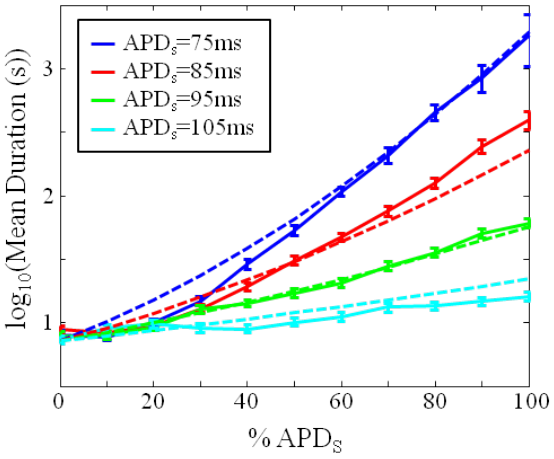

Figure 5.4: A semi-logarithmic plot demonstrating the functional dependence of mean MWR episode duration on the fraction of tissue possessing APD_S. The solid lines represent experimentally determined values and the dashed lines represent values predicted by Fb_E. Error bars represent 95% confidence intervals.

Ablation efficiency and lesion distribution

Ablation decreased the duration of MWR. Increasing the number of ablated cells resulted in an approximately linear reduction in the ability of a homogeneous tissue to support MWR (Fig. 5.5A). Of the several lesion patterns we investigated, a single linear lesion extending perpendicularly from the center of the long axis of the tissue proved to be the most efficient at reducing episode duration. More complex patterns such as the square lesion set and the branching lesion set resulted in decreased ablation efficiency. Linear lesions resulted in significantly more wave-lesion interactions per ablated cell than branched lesions (14.3±0.3 vs. 12.4±0.2 interactions per second, $p < 0.05$; see supplemental Fig. S5.10).

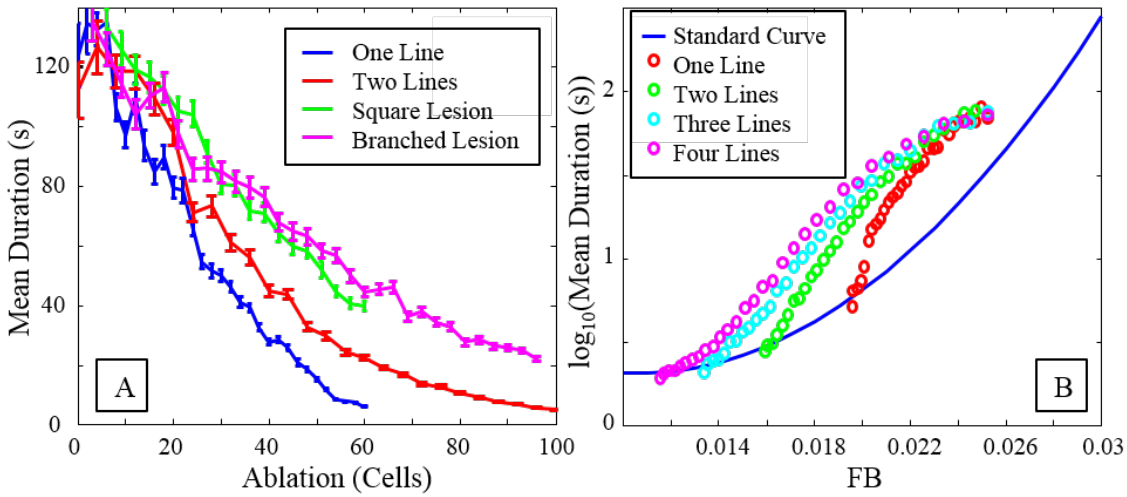

Figure 5.5: A) MWR episode duration as a function of the number of ablated cells, shown here for a variety of lesion patterns (single lesion, dual lesions, square lesion, and branching lesion). Error bars represent 95% confidence intervals. B) A semi-logarithmic plot demonstrating the reduction of MWR episode duration with both increasing degree of tissue transection (top right to bottom left within specific color) and increasing number of divisions (right to left across colors). Notice that both un-ablated (top right) and fully transected (bottom left) tissues, fall close to the standard curve relating Fb and MWR episode duration (solid blue line).

Impact 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 a larger number of shorter lines (compare points along a vertical line in Fig. 5.5B). The degree to which any single line could reduce fibrillatory burden was limited by tissue width (e.g., if the tissue was 60mm 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 (Fig. 5.5B).

Impact 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 (Fig. 5.6A). As the ablation line was moved away from the geometric center of the tissue, its impact on MWR duration was progressively reduced. In heterogeneous tissues, the optimal transection position was shifted away from the geometric center towards the side with the shorter APD (Fig. 5.6B). 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 two resulting tissue segments (either side of the line) had the same values of Fb_E.

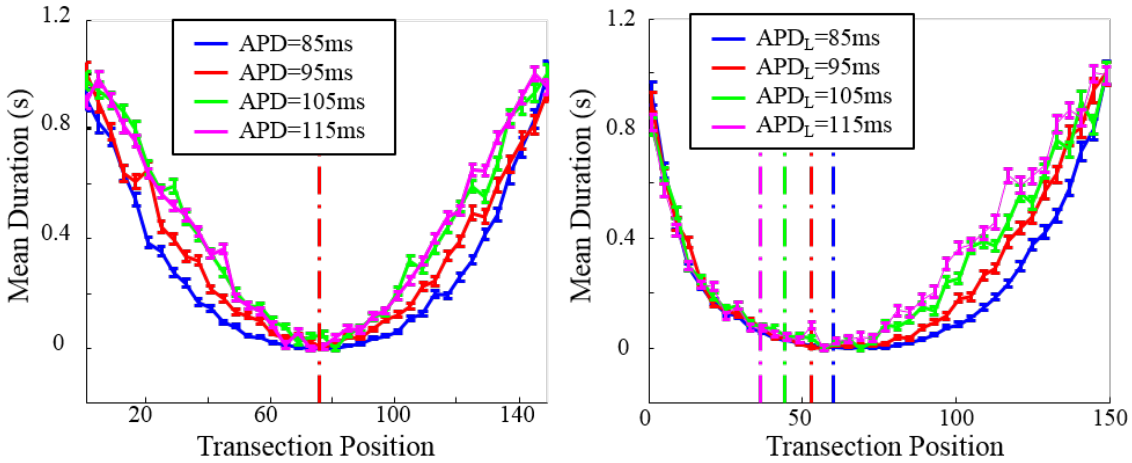

Figure 5.6: MWR episode duration as a function of transection position in: A) Homogenous tissues. The dashed vertical red line shows the theoretically predicted point of minimum duration at the middle of the tissue long axis. B) Heterogeneous tissues. Here, the left 20% of each tissue had $APD_S = 60$ms. The dashed vertical lines show ablation positions at which the values of Fb_E for the left and right tissue segments are equal. This position shifts leftward as the difference between APD_L and APD_S increases. Error bars represent 95% confidence intervals.

In diffusely heterogeneous tissues, the optimal transection position was similarly

shifted towards the side with shorter average APD (supplemental Fig. S5.11) and was accurately predicted as being located at the point where the two resulting segments of the transected tissue had equal values of Fb_E Limiting lesion length to 75% of the tissue width did not impact the optimal transection position, but did reduce the overall impact of ablation.

The presence of localized APD shortening also impacted the optimal transection position in the more realistic left atrial geometry (Fig. 5.7). 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).

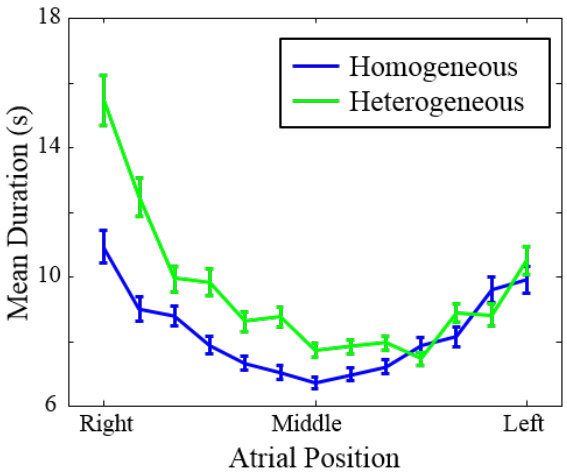

Figure 5.7: MWR episode duration as a function of transection position on the curved, two dimensional left atrial mesh. Ablation was performed both with (green) and without (blue) the presence of an APD_S region on left side of the atrium. The point of minimum duration occurs at the geometric center when APD is uniformly distributed across the tissue, but is shifted towards the side of shortened average APD in the presence of heterogeneity. Error bars represent 95% confidence intervals.

Prospective ablation optimization

We prospectively assessed the minimum ablation required to reduce MWR burden below a target threshold of 3s (Fig. 5.8). Prior to ablation, the magnitude of disease burden in the 60 randomized tissues spanned two orders of magnitude (5-500s). 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±0.03s (4.4±0.7% of total intervention).

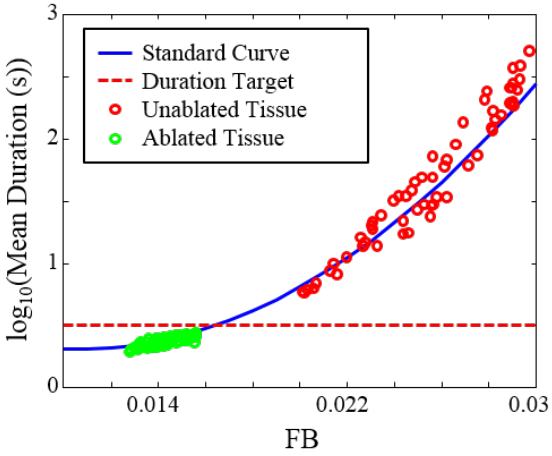

Figure 5.8: A semi-logarithmic plot demonstrating the use of our ablation optimization algorithm for reduction of MWR episode duration by an arbitrary degree. Here, fibrillogenic tissues with randomly generated properties (red circles) were partially transected by a prospective, algorithmically determined number of lesions (green circles) to reduce their fibrillatory burden below an arbitrary threshold (horizontal red line). For reference the blue line indicates the "standard curve" relating Fb to mean duration of MWR.

5.5 Discussion

Ablation of multi-wavelet reentry is qualitatively different from the ablation of other reentrant arrhythmias because the circuits that comprise MWR are functional, mul-

tiple and mobile [31],[32]. 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 the present study, we found that this probability could be altered through the application of ablation, the effect of which depended upon the configuration, location and extent of its delivery. The mechanism of this dependence was via the impact of these three factors on the probability of wave-lesion interactions.

Quantifying atrial electrical derangement

A shift in perspective from a deterministic to a probabilistic view point offers a number of advantages. For example, it is possible to prospectively assess the propensity of a tissue to support MWR by viewing its electrical activity as a population of interacting waves that fuse, divide, and annihilate [32],[38]. Tissues that support only small numbers of waves are much more likely to reach quiescence (i.e., a wave population equal to zero) than those that support large numbers of waves. The fibrillogenicity index provides an empiric 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) (Supplemental Fig. S5.9). 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.

Impact of ablation configuration and location

We demonstrated that geometrically complex patterns such as branching lesions reduce MWR duration less effectively than simple, linear lesions (Fig. 5.5A). This is because the protruding segments of branching lesions act like breakwaters, shielding their more central surfaces from exposure to incoming waves (supplemental Fig. S5.2). 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 two new independent tissues with the minimum net Fb and maximally reduced MWR episode duration (Fig. 5.6A). 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 (Fig. 5.6A).

Impact 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 non-uniformly 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 impact 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 (Fig. 5.4). Thus, even though 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 fibrillogenicity index, Fb_E, to be calculated (Eq. 5.3). 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 (Fig. 5.6B) and that this midpoint is shifted in the direction of lowest APD (Fig. 5.7).

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 (supplemental Fig. S5.11). However, while partial transection may result in comparably efficient reductions in MWR duration, its overall efficacy is lower due to 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 (Fig. 5.5B).

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 application of a specific lesion set (e.g. pulmonary vein isolation plus roof and left mitral isthmus lines) does not have the same efficacy in all patients [6],[14],[15],[40]. In the present study we sought an approach for both quantifying the extent of electrical derangement in individual tissues and for prospectively determining the optimal ablation set required to treat that derangement. Towards this purpose, we developed and validated an algorithm that prospectively titrated the number and extent of linear lesions required to reduce a tissue's preexisting propensity to support MWR by a desired amount. In all cases, the optimized ablation set was sufficient to achieve the desired reduction in fibrillatory burden (Fig. 5.8).

Limitations

Our goal in the present study was to establish the theoretical underpinnings of the fibrillogenicity index 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 the present 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.

While 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 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 [41] and that electrogram frequency correlates with tissue frequency when measured with electrodes of adequate spatial resolution [42],[43]. Thus it should be possible to calculate Fb using electrogram mapping to indirectly measure tissue properties. Ultimately, biologic validation will be required before Fb can be applied clinically. Nevertheless, Fb provides a theoretical foundation upon which patient-specific ablation strategies may eventually be based.

Atrial remodeling causes progressive dilation, changes in ion channel expression and interstitial fibrosis [44],[45]. These combine to increase AF duration via their impact on the atria's architecture [46], refractory period [44], and conduction velocity [45]. In the present 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 with a progressive increase in the duration of MWR. While we have not modeled dynamic changes to Fb, we have examined a substantial range of properties over which remodeling occurs. Thus, the fibrillogenicity index 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. Additionally, while the range of disease burden we have examined spans over four orders of magnitude (3s-6hrs 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.

While debate continues as to the mechanisms responsible for AF [18],[19], there is evidence to suggest that reentrant drivers exist along a spectrum that includes MWR as well as focal drivers with fibrillatory conduction [39]. The ablation strategy we propose in the current study is aimed at interrupting the spatially dynamic circuit formation of MWR. However, AF may involve micro-anatomic 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 wave break; 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, since 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 than one visit to the ablation laboratory in order 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.

5.6 Conclusion

In this study, we used a computational model to explore the effects of both heterogeneity and ablation on cardiac tissue's propensity to support multi-wavelet reentry. An inverse sum of APDs 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 ($R^2 = 0.82$). 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 caused the greatest reductions in MWR per ablated cell. Based on these findings, we developed an algorithm for prospectively determining tissue-specific optimized ablation patterns, and successfully reduced MWR duration below a target threshold of 3s in 100% of tested tissues ($n = 60$). We believe that this study presents a novel approach for 1) quantifying the extent of a tissue's electrical derangement, 2) prospectively determining the amount of ablation required to minimize the burden of AF and 3) predicting the most efficient distribution of these ablation lesions in tissues refractory to standard ablation strategies.

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Disclosures

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Bibliography

[1] Go AS, Hylek EM, Phillips KA, Henault LE, Selby J V, Singer DE. Prevalence of Diagnosed Atrial Fibrillation in Adults. *J Am Med Assoc*. 2014;285:2370–2375.

[2] Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.

[3] Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4:313–320.

[4] Sanoski CA. Clinical, economic, and quality of life impact of atrial fibrillation. *J Manag Care Pharm*. 2009;15:S4–S9.

[5] January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;130:e199-e267

[6] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009;2:349–361.

[7] Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol*. 2009;104:671–677.

[8] Tai C-T, Chen S-A, Chiang C-E, Lee S-H, Wen Z-C, Huang J-L, Chen Y-J, Yu W-C, Feng A-N, Lin Y-J, Ding Y-A, Chang M-S. Long-Term Outcome of Radiofrequency Catheter Ablation for Topical Atrial Flutter: Risk Prediction of Recurrent Arrhythmias. *J Cardiovasc Electrophysiol*. 1998;9:118–121.

[9] Kay GN, Epstein A, Dailey S, Plumb V. Role of radiofrequency ablation in the management of supraventricular arrhythmias: experience in 760 consecutive patients. *J Cardiovasc Electrophysiol*. 1993;4:371–392.

[10] Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: The A4 study. *Circulation*. 2008;118:2498–2505.

[11] Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, Arribas F, Fernández-Lozano I, Bodegas A, Cobos A, Matía R, Pérez-Villacastín J, Guerra JM, Ávila P, López-Gil M, Castro V, Arana JI, Brugada J. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501–507.

[12] Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A Randomized Trial of Circumferential Pulmonary Vein Ablation Versus Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation. The APAF Study. *J Am Coll Cardiol*. 2006;48:2340–2347.

[13] Haïssaguerre M, Jaïs P, Shah DC, Takahashi a, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666.

[14] Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A., Dicandia C, Calabro MP, Mazzone P, Ficarra E, Di Gioia C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial Electroanatomic Remodeling After Circumferential Radiofrequency Pulmonary Vein Ablation: Efficacy of an Anatomic Approach in a Large Cohort of Patients With Atrial Fibrillation. *Circulation*. 2001;104:2539–2544.

[15] Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SWK, Greenstein R, Pelosi Jr. F, Strickberger SA, Morady F. Pulmonary Vein Isolation for Paroxysmal and Persistent Atrial Fibrillation. Circulation. 2002;105:1077–1081.

[16] Lalani GG, Trikha R, Krummen DE, Narayan SM. Rotors and Focal Sources for Human Atrial Fibrillation. *Circ J*. 2014;78:2357–2366.

[17] Tung R, Buch E, Shivkumar K. Catheter Ablation of Atrial Fibrillation. *Circulation*. 2012;126:223–229.

[18] Narayan SM, Jalife J. CrossTalk proposal: Rotors have been demonstrated to drive human atrial fibrillation. *J Physiol*. 2014;592:3163–3166.

[19] Allessie M, de Groot N. CrossTalk opposing view: Rotors have not been demonstrated to be the drivers of atrial fibrillation. *J Physiol*. 2014;592:3167–3170.

[20] Narayan SM, Wright M, Derval N, Jadidi A, Forclaz A, Nault I, Miyazaki S, Sacher F, Bordachar P, Clémenty J, Jaïs P, Haïssaguerre M, Hocini M. Classifying fractionated electrograms in human atrial fibrillation using monophasic action potentials and activation mapping: evidence for localized drivers, rate acceleration, and nonlocal signal etiologies. *Heart Rhythm*. 2011;8:244–253.

[21] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43:2044–2053.

[22] Verma A, Lakkireddy D, Wulffhart Z, Pillarisetti J, Farina D, Beardsall M, Whaley B, Giewercer D, Tsang B, Khaykin Y. Relationship between complex fractionated electrograms (CFE) and dominant frequency (DF) sites and prospective assessment of adding DF-guided ablation to pulmonary vein isolation in persistent atrial fibrillation (AF). *J Cardiovasc Electrophysiol*. 2011;22:1309–1316.

[23] Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23:447–454.

[24] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation with or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60:628–636.

[25] Shivkumar K, Ellenbogen KA., Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: First multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J Cardiovasc Electrophysiol*. 2012;23:1277–1285.

[26] Atienza F, Almendral J, Ormaetxe JM, Moya Á, Martínez-Alday JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MÁ, Tercedor L, Peinado R, Arcocha MF, Ortiz M, Martínez-Alzamora N, Arenal Á, Fernández-Avilés F, Jalife J. Comparison of Radiofrequency Catheter Ablation of Drivers and Circumferential Pulmonary Vein Isolation in Atrial Fibrillation. *J Am Coll Cardiol*. 2014;64:2455–2467.

[27] Verma A, Jiang C, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo C a., Haverkamp W, Weerasooriya R, Albenque J-P, Nardi S, Menardi

E, Novak P, Sanders P. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. *N Engl J Med*. 2015;372:1812–1822.

[28] Providencia R, Lambiase PD, Srinivasan N, Ganesha Babu G, Bronis K, Ahsan S, Khan FZ, Chow A. WC, Rowland E, Lowe M, Segal OR. Is There Still a Role for CFAE Ablation in Addition to Pulmonary Vein Isolation in Patients with Paroxysmal and Persistent Atrial Fibrillation? A Meta-Analysis of 1,415 Patients. *Circ Arrhythmia Electrophysiol*. 2015;8:1017-1029

[29] Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R. Quantitative Analysis of Localized Sources Identified by Focal Impulse and Roter Modulation Mapping in Atrial Fibrillation. Circ Arrhythmia Electrophysiol. 2015;554–562.

[30] Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, Benson BE, Bielau P, Bates JHT. Ablation of multi-wavelet re-entry: general principles and in silico analyses. *Europace*. 2012;14 Suppl 5:v106–v111.

[31] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther*. 1962;140:183–188.

[32] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J*. 1964;67:200–220.

[33] Allessie M, Lammers W, Bonke F, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. *Cardiac Electrophysiology and Arrhythmias*. 1985;265–276.

[34] Allessie M a, de Groot NMS, Houben RPM, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;3:606–615.

[35] Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation*. 1994;89:1665–1680.

[36] Spector PS, Habel N, Sobel BE, Bates JHT. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol*. 2011;4:586–591.

[37] Carrick RT, Benson B, Habel N, Bates ORJ, Bates JHT, Spector PS. Ablation of multiwavelet re-entry guided by circuit-density and distribution: maximizing the probability of circuit annihilation. *Circ Arrhythm Electrophysiol*. 2013;6:1229–1235.

[38] Carrick RT, Bates ORJ, Benson BE, Habel N, Bates JHT, Spector PS. Prospectively Quantifying the Propensity for Atrial Fibrillation: A Mechanistic Formulation. *PLoS:One*. 2015;10:e0118746.

[39] Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, Goldblatt J, Brown R, Atkinson V, Moten S, Morton JB, Sanders P, Kistler PM, Kalman JM. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J*. 2014;35:86–97.

[40] Tilz RR, Rillig A, Thum A-M, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck K-H, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol*. 2012;60:1921–1929.

[41] Benson BE, Carrick RT, Habel N, Bates ORJ, Bates JHT, Bielau P, Spector PS. Mapping Multi-Wavelet Reentry without Isochrones: An Electrogram-Guided Approach to Define Substrate Distribution. *Europace*. 2014;16 Suppl 4:iv102-iv109

[42] Correa de Sa DD, Thompson N, Stinnett-Donnelly J, Znojkiewicz P, Habel N, Müller JG, Bates JHT, Buzas JS, Spector PS. Electrogram fractionation: the relationship between spatiotemporal variation of tissue excitation and electrode spatial resolution. *Circ Arrhythm Electrophysiol*. 2011;4:909–916.

[43] Stinnett-Donnelly JM, Thompson N, Habel N, Petrov-Kondratov V, Correa de Sa DD, Bates JHT, Spector PS. Effects of electrode size and spacing on the resolution of intracardiac electrograms. *Coron Artery Dis*. 2012;23:126–132.

[44] Wijffels MCEF, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.

[45] Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic Rapid Atrial Pacing: Structural, Functional, and Electrophysiological Characteristics of a New Model of Sustained Atrial Fibrillation. *Circulation*. 1995;91:1588–1595.

[46] Gaspo R, Bosch R, Talajic M, Nattel S. Functional Mechanisms Underlying Tachycardia-Induced Sustained Atrial Fibrillation in a Chronic Dog Model. *Circulation*. 1997;96:4027–4035.

[47] Kowalski M, Grimes MM, Perez FJ, Kenigsberg DN, Koneru J, Kasirajan V, Wood MA, Ellenbogen KA. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. *J Am Coll Cardiol*. 2012;59:930–938.

5.7 Supplemental Materials

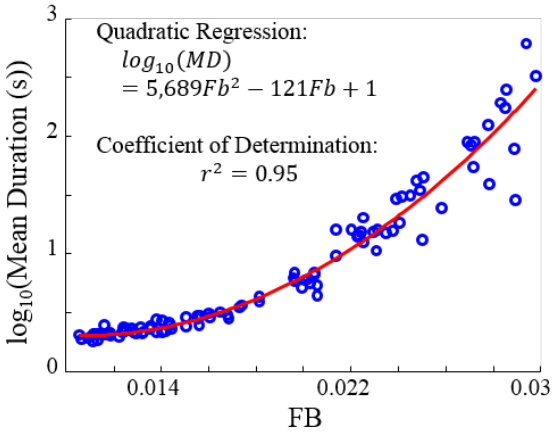

Figure 5.9: A standard curve demonstrating the functional dependence of mean MWR duration on Fb (in square, two dimensional tissues with uniformly distributed APD) was developed using quadratic regression.

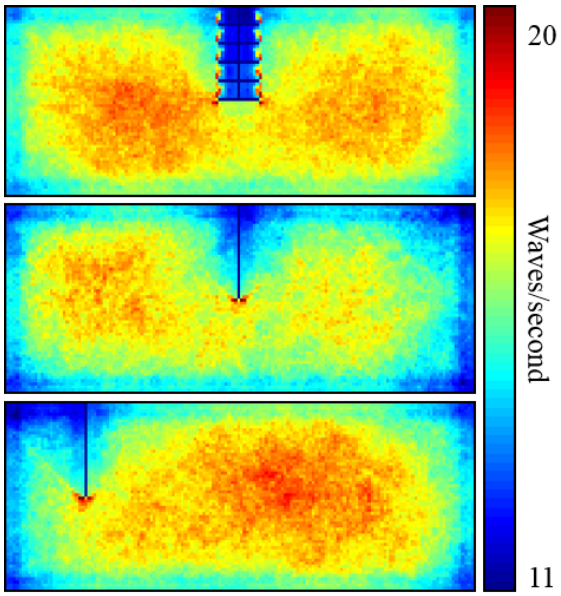

Figure 5.10: Density maps showing the number of times each cell was excited by a propagating wave in tissues with linear or branching lesion distributions. Ablated cells were never excited (blue) and cells adjacent to boundaries (tissue edge and ablation lesions) were excited less frequently than cells 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.

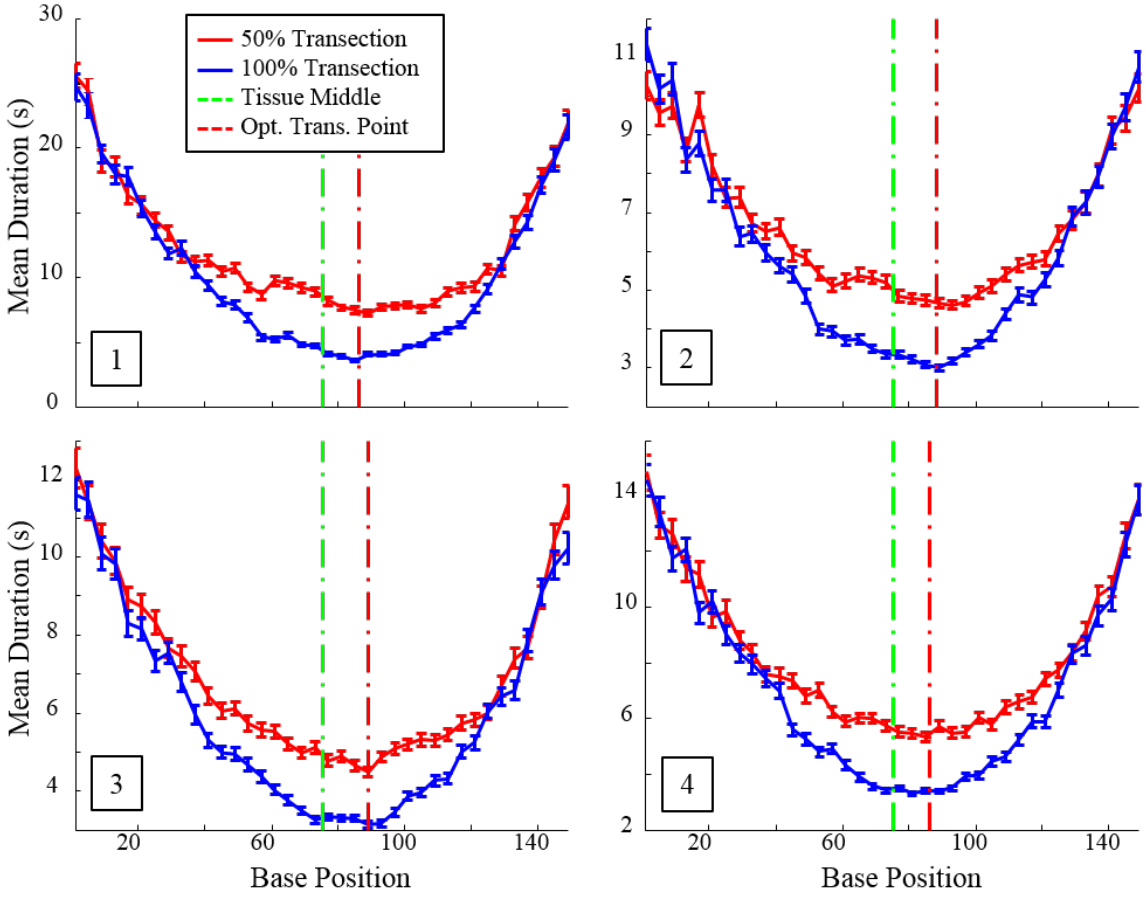

Figure 5.11: MWR episode duration as a function of the position of either complete (solid blue line) or partial (solid red line) transection in four heterogeneous tissues with smoothly varying, randomized APD distributions. The dashed vertical red lines show theoretically predicted point of minimum duration. The dashed vertical green lines show the geometric center of the tissue.

Chapter 6

The Relationship Between Multi-Wavelet Reentry and Focal Drivers With Fibrillatory Conduction: The Interplay of Structural and Functional Reentrant Substrates

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6.1 Abstract

Background: Two of the most widely accepted hypotheses regarding the mechanism of atrial fibrillation are multi-wavelet reentry and focal drivers with fibrillatory conduction. In the present study, we explore the interplay between the structural and

functional substrates that these mechanisms require, as well as their respective roles in driving atrial fibrillation.

Methods and Results: We used a computational model to simulate fibrillation and measure its duration either in the presence or absence of a substrate for structural micro-reentry. The probability of spontaneous micro-reentry was measured as a function of the propensity of the surrounding functional substrates to fibrillate, as well as both the excitable gap and degree of protection of the structural circuit. Finally, we examined the likelihood of atrial tachycardia upon termination of fibrillation. We found that the presence of a structural substrate had little impact on the overall duration of fibrillatory episodes except in tissues with an otherwise low propensity to fibrillate. Micro-reentry was repeatedly initiated and terminated by multi-wavelet reentry but was more likely to occur if the structural substrate was well protected from the surrounding functional substrate. Fibrillation was more likely to end in atrial tachycardia when the structural substrate was large and in close proximity to the unexcitable external boundary of the tissue.

Conclusion: Multi-wavelet reentry and fibrillatory conduction represent two points along a single continuous spectrum. The impact of a structural substrate on the overall duration of fibrillation depends upon where the surrounding functional substrate falls on this spectrum.

6.2 Introduction

Since research of atrial fibrillation (AF) first began more than 100 years ago [1]-[3] there has been much debate over the mechanisms responsible for its persistence [4]-[6]. Largely, however, opinions have been divided between two apparently competing hypotheses: multi-wavelet reentry (MWR) and focal drivers with fibrillatory

conduction (FDFC). In the MWR hypothesis, fibrillation results from spatially dynamic, self-perpetuating functional reentry [7]-[9]. In contrast, the FDFC hypothesis proposes that changing conduction patterns are driven by stationary sources of excitation [10]-[12]. While these hypotheses are often considered mutually exclusive, there is an important parallel between them. In both MWR and FDFC, it is the presence of diffuse functional heterogeneity that leads to variable propagation [13]-[15]. We propose that fibrillatory conduction (FC) and MWR differ only in the magnitude of this functional heterogeneity, and thus represent two different points along a continuum. In atria with relatively low propensity to fibrillate, changing propagation is passive and dependent upon the presence of active drivers. In the presence of more extreme electrical derangement, variable conduction is self-sustaining and therefore perpetuates even in the absence of a driver.

One type of focal driver that has been recently demonstrated in animal models [16],[17] and *ex vivo* human hearts [36] is structural micro-reentry . Here, reentrant circuits are formed around small unexcitable obstacles and emit waves of excitation that undergo fibrillatory conduction. This is typically viewed as a one sided relationship in which the focal driver acts upon the surrounding functional substrate. However, in order for reentry around a structural obstacle to be initiated, a wave must undergo unidirectional conduction block and anchor to that obstacle. Micro-reentry may subsequently be terminated by an appropriately timed collision with an external wave that causes bidirectional block. Both FC and MWR provide a continual source of external waves with varied timing and direction and can thus act as the means of both initiation and termination of structural micro-reentry. We propose that a thorough understanding of fibrillation therefore requires not only an appreciation of how focal drivers cause FC, but also of how FC affects focal drivers. In the present study, we use a computational model of propagation to study the interactions between

functional and structural substrates and examine the impact that these interactions have on the overall duration of fibrillation.

6.3 Methods

Computational model

In the following experiments, we made use of a previously described computational model of electrical propagation in cardiac tissue [18],[19]. This combines a diffusion model of electrotonic current spread with a rule based cellular automaton model of cardiomyoctye excitation. Briefly, cells (each representing approximately 1mm^2 of cardiac tissue) undergo action potentials when they receive current sufficient to perturb their potential from rest (V_{rest}) to above a defined threshold (V_{Thresh}). Action potentials cause the cell voltage to increase towards peak potential (V_{peak}) after which it gradually returns to V_{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 adjusted so as to allow the simulated tissue to support various patterns of electrical excitation. In order to test the relationships between functional and structural substrate, we generated simulated two-dimensional sheets of tissue with centralized, circular regions of unexcitable scar tissue. The model simulations were run on the Vermont Advance Computing Core (www.uvm.edu/ vacc/).

Fibrillation with and without a structural substrate

To test whether fibrillatory conduction would perpetuate in the absence of localized drivers, we created a series of simulated tissues, each with a central obstacle (radius = 2mm) that was partially protected by ring of unexcitable scar (radius = 7mm, angle of exposure = 60°). Each tissue had dimensions equal to 80 × 80mm and had uniform RC equal to 8ms. The mean APD of individual tissues ranged between 50ms and 200ms in 5ms increments, and had ±10ms of random variation. In each tissue, we initiated structural reentry around the central obstacle. One second after its initiation, structural reentry was eliminated by ablation of the entire central region (radius ≤ 7mm). We then calculated the mean duration and standard error of the mean (SEM) of the remaining fibrillatory conduction for up to a maximum of 10,000s. These values were compared to predictions made using the fibrillogenicity index (Fb, Eq. 6.1), a previously described metric of tissue's propensity to support multi-wavelet reentry [20],[21].

$$Fb = \frac{\text{Area}}{\text{Boundary Length} * APD * RC} \tag{6.1}$$

Additionally, we examined the impact of structural reentry on ongoing MWR. In each tissue of the series described above, we initiated 500 unique episodes of MWR by high frequency (100Hz) burst pacing from a virtual electrode. The duration of the resulting MWR episodes were then measured for up to a maximum of 10,000s for one of three ablation set-ups: no micro-reentrant substrate, protected micro-reentrant substrate, and focally ablated micro-reentrant substrate (Fig. 6.1). We calculated the mean duration and SEM of the mean.

Figure 6.1: Close ups of the three ablation setups. Here, white cells represent sites of ablation and black cells represent excitable tissue. From left to right: 1) no substrate for micro-reentry, 2) protected micro-reentrant substrate, and 3) focally ablated micro-reentrant substrate (allows for macro-reentrant reentry).

Lifespan of structural reentry during coexistant MWR

In order to assess the dynamics of structural reentry in coexistence with multi-wavelet reentry, we created a series of simulated tissues with a central obstacle partially protected by a ring of unexcitable scar (radius = 7mm). In separate tissues, the APD for the central region (radius $\leq$ 7mm) and the surrounding area were varied independently, from 30 ms to 100ms and from 50ms to 130ms, both in 10ms increments and with $\pm$10ms of random variation. The radius of the central obstacle was varied from 1mm to 4.5mm in increments of 0.5mm, thus altering the frequency of potential structural reentry around that obstacle. The obstacle's angle of exposure to the surrounding tissue was varied between 0° and 360° in 15° increments. In each tissue, we induced 50 ten second episodes of fibrillation by high frequency (100Hz) burst pacing from a virtual electrode positioned far from the central lesion. Structural reentry was declared when all cells directly adjacent to the central obstacle were found to be simultaneously undergoing periodic excitation, as defined by Equation 6.2. In this case, a threshold for periodic behavior (t_{thresh}) of 5ms was used.

$$t_{thresh} \geq (APD_1 + APD_3) - 2APD_2 \tag{6.2}$$

The mean and SEM were calculated for both the number and duration of struc-

tural reentrant episodes in each tissue.

Probability of atrial tachycardia with focal obstacles

Lastly, we tested the likelihood that fibrillatory conduction would end in atrial tachycardia as a function of both the distance between, and the relative sizes of, a focal obstacle and the external boundary. To do this, we created two series of simulated tissues. The first was composed of cylindrical tissues with circumference of 80mm and height ranging from 10mm to 80mm in increments of 5mm. The second was composed of annuli of excitable tissue with a constant width of 10mm but a variable internal radius that ranged from 1mm to 20mm in increments of 1mm. Both sets of tissues had APD values equal to 70ms. In each tissue, we initiated 500 unique episodes of multi-wavelet reentry by high frequency (100Hz) burst pacing for 1s from a randomly positioned virtual electrode. Periodic behavior was declared when all cells were found to be simultaneously undergoing periodic excitation (Eq. 6.2), and the proportion and standard error of the proportion (SEP) of episodes in each tissue that ended in periodic behavior versus quiescence was recorded.

6.4 Results

Duration of FC after elimination of focal drivers

The duration of fibrillatory conduction after elimination of the focal driver increased with decreasing APD. This increase was well predicted by the fibrillogenicity index (Fig. 6.2A). The driver produced fibrillatory conduction except when the value of APD the surrounding functional substrate was between 90ms and 110ms in. Over this range, there was 2:1 conduction block of emitted waves and no wave break occurred.

Quiescence was reached immediately following elimination of the micro-reentrant circuit.

There was no difference between the duration of MWR episodes in the absence of a structural obstacle (and therefore no potential for a micro-reentrant circuit) and with focal ablation of the structural circuit (thus allowing for macro-reentry but not micro-reentry; Fig. 6.2B). The presence of a substrate for structural micro-reentry increased the duration of MWR episodes for tissues with APD longer than 100ms.

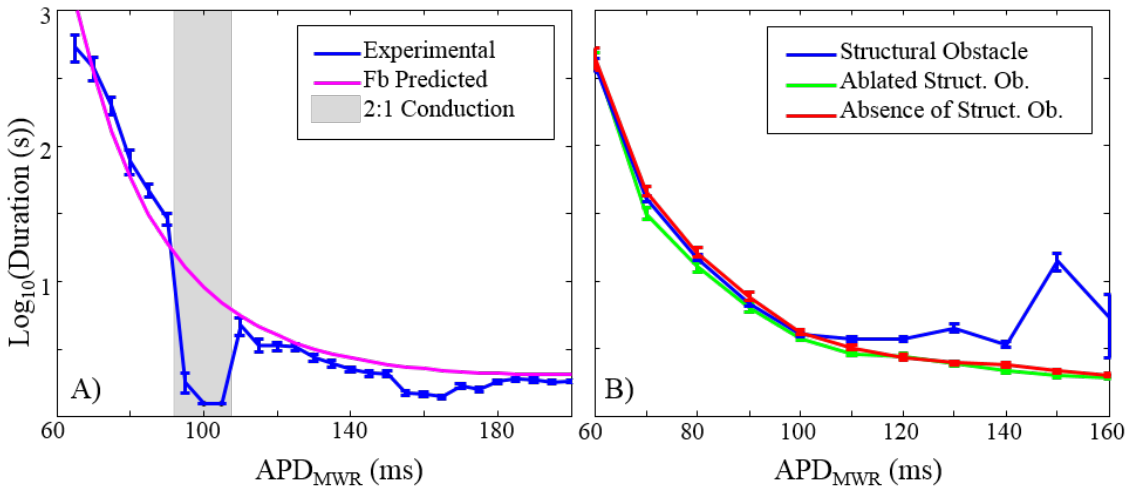

Figure 6.2: The effect of structural reentry on the duration of MWR. *Left*: Duration of fibrillation after elimination of the substrate for structural reentry. The grey box indicates APD_{MWR} values over which 2:1 conduction block occurred and fibrillatory conduction was not initiated. *Right*: Duration of fibrillation in the presence (blue), absence (red), and after ablation of (green) the substrate for structural reentry. Error bars show 95% confidence intervals.

Dynamics of structural reentry

The percentage of time that the protected structural obstacle hosted periodic reentrant waves varied as a function of the frequency of MWR in the surrounding tissue as well as the excitable gap and degree of protection of the structural circuit. As the

frequency of MWR in the surrounding tissue decreased, the probability of structural reentry rapidly increased until the point at which MWR and structural reentrant frequencies were the same, and then began to decrease (Fig. 6.3A). As the excitable gap of the structural circuit increased, the probability of fixed reentry was gradually increased (Fig. 6.3B). Increasing exposure of the structural obstacle led to decreasing probability of structural reentry (Fig. 6.3C). The average durations of both anchoring and non-anchoring episodes, as well as the frequency of anchoring are shown in Supplemental Figure 6.5.

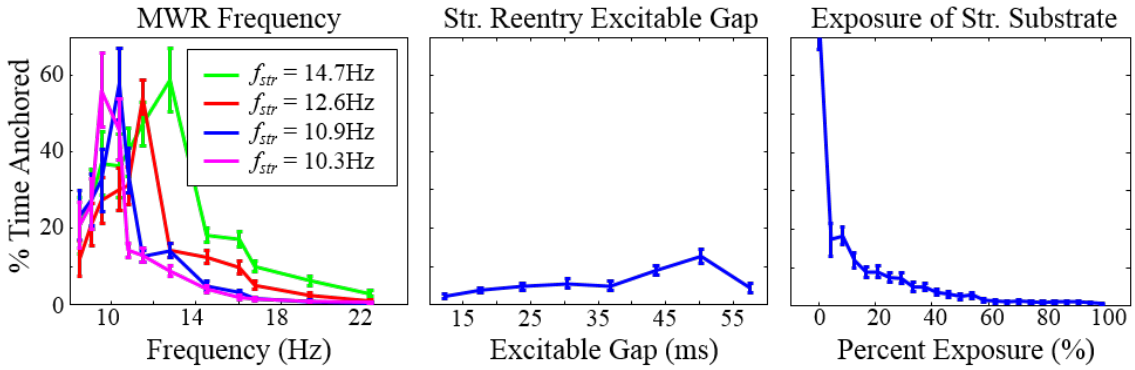

Figure 6.3: The percentage of time during which structural reentry existed as a function of the (left) frequency of MWR, (middle) the excitable gap, and (right) the exposure to the surrounding tissue of the unexcitable obstacle. Error bars show 95% confidence intervals.

Atrial tachycardia after termination of MWR

The probability of episodes of MWR ending in macroscopic structural reentry decreased linearly with increasing distance and disparity of size between the internal and external boundaries (Fig. 6.4).

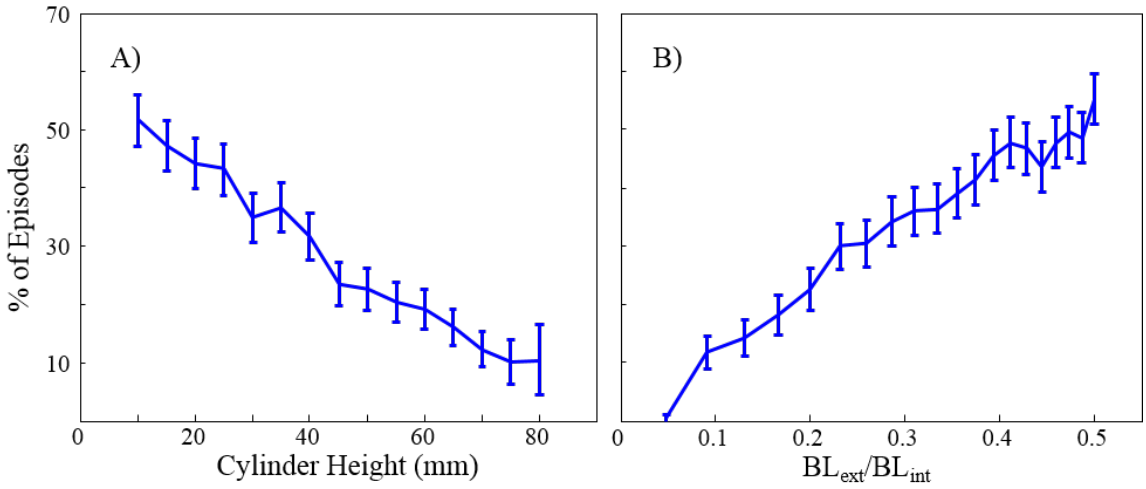

Figure 6.4: The percentage of MWR episodes that end in atrial tachycardia (rather than quiescence) as a function of the (A) distance between and (B) the ratio of size of internal and external unexcitable boundaries. Error bars show 95% confidence intervals.

6.5 Discussion

Multi-wavelet reentry and focal drivers with fibrillatory conductionare often considered mutually exclusive mechanisms for the maintenance of fibrillation [5],[6]. However, the characteristics of a tissue that facilitate MWR are the same as those that promote FC. In both cases, irregular activation patterns require breakage of wavefronts by the non-uniform refractory tails of preceding waves. In the present study we demonstrate that the duration of fibrillation following the elimination of a structural driver depends upon the properties of the underlying functional substrate. Thus, MWR and FC may be considered two points along a continuum of propensity to fibrillation.

Characterizing functional substrate

We have previously proposed that a thorough understanding of MWR and its treatment requires shifting to a probabilistic view point [20],[21]. This perspective offers a number of advantages. For example, it is possible to prospectively assess the propensity of a tissue to support MWR by viewing its electrical activity as a population of interacting waves that fuse, divide, and annihilate. Tissues that support only small numbers of waves are much more likely to reach quiescence (i.e., a wave population equal to zero) than those that support large numbers of waves. The fibrillogenicity index provides an empiric method for predicting the mean wave population, and therefore the duration of MWR, through the tissue parameters that determine both wave size (APD, R, and C) and tissue size (A and BL).

In MWR, the formation of reentrant circuits is chaotic and occurs with a low degree of spatiotemporal autocorrelation [7],[22]. As a result, prospective identification of where circuits will be formed at a specific moment in time is extremely difficult. Furthermore, the diffuse distribution of circuits means that there is no obvious ablation strategy that completely eliminates the possibility of MWR. However, by mapping the aggregate positions of many circuits, it is instead possible to develop probability distributions of where circuit formation is likely to occur. Thus, the most effective ablation strategies for treatment of MWR are those that maximize the probability of circuit interruption. We previously proposed the delivery of linear lesions distributed evenly across the circuit-formation probability-distribution as the optimal approach to ablation of MWR.

Structural obstacles with fibrillatory conduction

In contrast to diffusely distributed MWR, structural reentry is spatially fixed. Ablation of focal drivers is conceptually straightforward but identifying driver sites in the presence of fibrillatory conduction is challenging. Provided that their positions can be identified, structural reentry therefore provides a straightforward target for ablative elimination. Not surprisingly, a number of strategies have been designed with this type of focal driver in mind, including the ablation of high dominant frequency sites, complex fractionated atrial electrogram (CFAE) ablation [23], and focal impulse and rotor modulation (FIRM) [12]. However, while these approaches showed promising initial results, the outcomes of follow up studies have shown minimal improvements over standard interventional treatments [24],[25]. Successful treatment of atrial fibrillation may require both elimination of focal drivers and modification of the functional substrate. Since exclusive targeting of focal drivers has relatively little impact on the remaining functional substrate, it is possible for underlying MWR to persist after ablation. We demonstrated that the fibrillogenicity index accurately predicts the duration of persistent MWR (Fig. 6.2A).

Interactions between functional and structural reentry

In the presence of both a structural obstacle and a sufficiently fibrillogenic functional substrate, MWR and structural reentry may cohabitate and together drive fibrillation[26]. These mechanisms do not exist independently. Rather, there is consistent interaction between the two. Structural reentry is repetitively initiated and terminated by MWR. Through an ongoing series of chaotic wave collisions, MWR produces many random instances of unidirectional conduction block. When conduction block occurs adjacent to an unoccupied structural obstacle, the wave may anchor

to that obstacle and induce structural reentry. If instead this conduction block occurs nearby preexisting structural reentry, the circuit may be either terminated or temporarily accelerated depending upon whether the block occurred parallel or anti-parallel to the direction of circuit rotation. Alternatively, MWR may be induced by structural reentry. Here, structural circuits emit waves more quickly than cells of the surrounding tissue recover their excitability. Wave-fronts encounter refractory tissue, leading to localized conduction block and breakage of the wave-front. These breakages provide a replenishing source of wavelets for the continuation of MWR.

The probabilities of these events depend upon the relative properties of the functional and structural substrates. Both initiation and termination of structural reentry require access of MWR waves to the structural obstacle. As the APD of the functional substrate decreases, the frequency of MWR increases. Thus, the numbers of waves, and therefore instances of conduction block , in close proximity to the structural substrate increase as well. This leads to a corresponding decrease in the percentage of time that the structural obstacle supports reentry since the substrate is under constant bombardment by incoming waves (Fig. 6.3A). Likewise, increasing the exposure of the obstacle to the surrounding functional substrate allows waves to approach the structural circuit from more directions, and therefore also causes a decrease in the likelihood of stable wave anchoring (Fig. 6.3B). When the frequency of MWR and structural reentry are the same, the percentage of time during which waves are anchored to the obstacle peaks. Neither driver is able to entrain the other and, once initiated, structural reentry is able to continue largely unmolested. Counter-intuitively, functional substrate with long APD (low frequency) also causes a drop in the likelihood of structural reentry (Fig. 6.3C). In this case, waves emitted by the relatively fast reentrant circuit collide with refractory tissue in the directly adjacent functional substrate. This leads to conduction block in the immediate proximity

of the structural substrate and subsequent interruption of reentry. Finally, increasing excitable gap leads to an increase in the incidence of structural reentry. More space between an anchored wave's front and refractory tail make it more robust to perturbations form the functional substrate.

Reciprocally, structural reentry may also affect the dynamics of MWR. We demonstrated that high frequency structural reentry may induce wave break, and potentially MWR, by sending out waves at a rate faster than the surrounding functional substrate can uniformly recover its excitability (figure 1a). If the functional substrate is able to recover rapidly, or if the tissue is entirely refractory, uninterrupted 1:1 or 2:1 conduction (respectively) of the emitted waves may occur. In this way, wave break is prevented and there is no initiation of MWR. For functional substrate with long APD, the presence of structural substrate may increase the duration of MWR (Fig. 6.2B). In this case, structural reentry provides a source for new waves when MWR in the surrounding tissue would otherwise terminate spontaneously.

Atrial tachycardia after termination of MWR

One of the well known complications associated with focal ablation of AF is the induction of atrial tachycardia [27]-[29]. However, while focal ablation provides a substrate for macroscopic structural circuits to form, structural reentry does not occur in every instance. To understand why and when atrial tachycardia is likely to be induced, it is helpful to once again consider MWR as a randomly fluctuating population of waves. Each of these waves has an excitation front, a refractory tail, and two wave ends. Wave ends may be either free-floating, in which case they are phase singularities at the point where wave front and tail meet, or anchored to boundaries. If both of a wave's ends are anchored to the same boundary, the wave front is presented with a diminishing supply of excitable cells and will extinguish against the boundary

when its supply is exhausted. If instead the two wave ends are on opposite boundaries, the wave front encounters a replenishing supply of excitable cells and will propagate indefinitely as a structural circuit. In the absence of ongoing MWR, this reentrant circuit becomes organized macroscopic reentry or, in other words, atrial tachycardia.

From the probabilistic viewpoint, MWR continues until all wave ends are anchored to structural boundaries. In the case of uninterrupted sheets of excitable tissue, there is only one boundary for wave ends to anchor to, and the rhythm will terminate once all waves are extinguished. However, in tissues with a focal obstacle (e.g., vein orifice or focal ablation), waves may also anchor to separate boundaries. Though anchored waves rotating in opposite directions around the obstacle will extinguish against one another as they collide, an odd number of dual-boundary anchored waves will lead to macroscopic structural reentry. Thus, properties which affect the likelihood of dual-boundary wave-end anchoring affect the likelihood of atrial tachycardia. Boundaries that are further apart from one another or are more disproportionate in size reduce the probability of a single wave having wave ends anchored on opposite boundaries (Fig. 6.4).

Limitations

Our goal in this series of experiments was to establish the theoretical principles that define interaction between functional and structural substrates during cardiac fibrillation. In particular, we were interested in defining quantitative relationships between emergent behaviors (e.g., structural reentry, fibrillatory conduction) and tissue properties (e.g., cellular APD, structural obstacles with varying degrees of protection). The computer model of propagation we selected for this study is therefore ideal, since its low computational burden allows for both direct visualization of electrical activity and exhaustive search of the parameter landscape. As with all in silico studies

however, we cannot consider the concepts we present here to be truly confirmed. Our conclusions require validation in a biological setting, ultimately humans. Nonetheless, our findings provide a set of testable predictions that can guide the design of future experimental study.

While we have presented findings regarding the interplay between MWR and structural micro-reentry, any focal driver may produce fibrillatory conduction. For example, fixed functional reentry is also believed to play a role in driving AF [30],[31]. The principles that define the impact of rotors should be the same as those that define the impact of structural reentry. The relative eases with which rotors are initiated and terminated will determine their average lifespan, and therefore their impact on the overall duration of AF. We did not study interactions between functional substrate and focal firing [32],[33]. In this case, initiation and perpetuation of the focal driver occurs independently of intermediary events (e.g., unidirectional conduction block). Focal firing may not be terminated by activity in the surrounding functional substrate. Thus, we would expect focal firing to have a larger effect on the duration of AF than either fixed functional or structural reentry.

Finally, the changing activation pattern of AF may not be the result of fibrillatory conduction at all. Rather, multiple focal drivers distributed throughout the atria may exist simultaneously [34],[35]. Each driver emits waves that ultimately collide and extinguish against waves from other drivers. Provided that the drivers send out waves at differing rates, change position, or are active at different times, the location of wave front collisions will change dynamically. Practically speaking, these changing collision locations may be indistinguishable from the diffuse reentrant pattern of MWR and FC. Regardless, modification of the functional substrate may be helpful in eliminating these changing conduction patterns and identifying the locations of focal drivers.

6.6 Conclusion

In this study, we used a computational model to examine the interplay between structural and functional reentrant substrates during fibrillation. We found that fibrillatory conduction continued after the elimination of structural micro-reentry for a duration of time that was well predicted by a metric of the functional substrate's ability to support MWR. Thus, we propose that MWR and fibrillatory conduction are not distinct phenomena but instead exist along a single continuous spectrum of fibrillogenic propensity. The presence of structural substrate did not increase the overall duration of episodes of MWR, except in tissues with APD greater than 100ms. The likelihood of spontaneous anchoring of waves to an unexcitable obstacle and subsequent structural reentry was highest when MWR and structural reentrant frequencies were comparable. This likelihood was further heightened by increases in the degree of protection and the excitable gap of the structural circuit. Finally, we found that the probability of MWR terminating in macroscopic structural reentry decreased with increasing distance and disparity of size between internal and external boundaries. We believe this study represents the first detailed examination of the interaction between structural reentry and multi-wavelet reentry.

Bibliography

[1] Silverman ME. From rebellious palpitations to the discovery of auricular fibrillation: contributions of Mackenzie, Lewis and Einthoven. *Am J Cardiol.* 1994;73(5):384-389

[2] McMichael J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laënnec. *Br Heart J.* 1982;48(3):193-197

[3] Flegel KM. From delirium cordis to atrial fibrillation: historical development of a disease concept. *Ann Intern Med.* 1995;122(11):867-873

[4] Garrey WE. Auricular Fibrillation. *Phys Reviews.*

[5] Narayan SM, Jalife J. CrossTalk proposal: Rotors have been demonstrated to drive human atrial fibrillation. *J Physiol.* 2014;592:3163–3166.

[6] Allessie M, de Groot N. CrossTalk opposing view: Rotors have not been demonstrated to be the drivers of atrial fibrillation. *J Physiol.* 2014;592:3167–3170. 1924;4(2):215-250

[7] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J.* 1964;67:200-220

[8] Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. Cardiac Electrophysiology and Arrhythmias. *Grune and Straton, Inc.* 1985:265–275

[9] Kirchhof C, Chorro F, Scheffer GJ, Brugada J, Konings K, Zetelaki Z, Allessie M. Regional entrainment of atrial fibrillation studied by high-resolution mapping in open-chest dogs. *Circulation.* 1993;88(2):736-749

[10] Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J.* 1948;36(2):241-251

[11] Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model

of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ Res*. 1977;41(1):9-18

[12] Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23(5):447-454

[13] Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial remodeling. *Circulation*. 1998;98(20):2202-2209

[14] Ogawa M, Kumagai K, Gondo N, Matsumoto N, Suyama K, Saku K. Novel electrophysiologic parameter of dispersion of atrial repolarization: comparison of different atrial pacing methods. *J Cardiovasc Electrophysiol*. 2002;13(2):110-117

[15] Oliveira MM, da Silva N, Timóteo AT, Feliciano J, de Sousa L, Santos S, Marques F, Ferreira R. Enhanced dispersion of atrial refractoriness as an electrophysiological substrate for vulnerability to atrial fibrillation in patients with paroxysmal atrial fibrillation. *Rev Port Cardiol*. 2007;26(7-8):691-702

[16] Morita H, Zipes DP, Morita ST, Wu J. Isolation of canine coronary sinus musculature from the atria by radiofrequency catheter ablation prevents induction of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7(6):1181-1188

[17] Chou CC, Nguyen BL, Tan AY, Chang PC, Lee HL, Lin FC, Yeh SJ, Fishbein MC, Lin SF, Wu D, Wen MS, Chen PS. Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. *Heart Rhythm*. 2008;5(8):1170-1177

[18] Spector PS, Habel N, Sobel BE, Bates JHT. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol*. 2011;4:586–591

[19] Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, Benson BE, Bielau P, Bates JHT. Ablation of multi-wavelet re-entry: general principles and in silico analyses. *Europace*. 2012;14 Suppl 5:v106–v111

[20] Carrick RT, Bates ORJ, Benson BE, Habel N, Bates JHT, Spector PS. Prospectively quantifying the propensity for atrial Fibrillation: a mechanistic formulation. *PLoS:One* . 2015;10:e0118746.

[21] Carrick RT, Benson BE, Bates JH, Spector PS. Prospective, tissue-specific optimization of ablation for multi-wavelet reentry: predicting the required amount, location and configuration of lesions. *Circ Arrhythm Electrophysiol*. 2016;9(3):e003555

[22] Carrick RT, Benson B, Habel N, Bates ORJ, Bates JHT, Spector PS. Ablation of multiwavelet re-entry guided by circuit-density and distribution: maximizing the probability of circuit annihilation. *Circ Arrhythm Electrophysiol.* 2013;6:1229–1235

[23] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol.* 2004;43(11):2044-2053

[24] Providência R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ, Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol.* 2015;8(5):1017-1029

[25] Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. *Heart Rhythm.* 2015;[Epub ahead of print]

[26] Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, Goldblatt J, Brown R, Atkinson V, Moten S, Morton JB, Sanders P, Kistler PM, Kalman JM. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J.* 2014;35(2):86-97

[27] Yang G, Yang B, Wei Y, Zhang F, Ju W, Chen H, Li M, Gu K, Lin Y, Wang B, Cao K, Kojodjojo P, Chen M. Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation. *Circ Arrhythm Electrophysiol.* 2016;9(2):e003382

[28] Teunissen C, Kassenberg W, van der Heijden JF, Hassink RJ, van Driel VJ, Zuithoff NP, Doevendans PA, Loh P. Five-year efficacy of pulmonary vein antrum isolation as a primary ablation strategy for atrial fibrillation: a single-centre cohort study. *Europace.* 2016. [Epub ahead of print]

[29] Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR. No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol.* 2015;8(6):1316-1324

[30] Davidenko JM1, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. *Nature*. 1992;355(6358):349-351

[31] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60(7):628-636

[32] Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J*. 1948;36(2):241-251

[33] Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the Moe hypothesis. *J Cardiovasc Electrophysiol*. 2013;24(3):328-335

[34] Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. *J Cardiovasc Electrophysiol*. 2005;16(12):1348-1358

[35] Haissaguerre M, Shah AJ, Cochet H, Hocini M, Dubois R, Efimov I, Vigmond E, Bernus O, Trayanova N. Intermittent drivers anchoring to structural heterogeneities as a major pathophysiologic mechanism of human persistent atrial fibrillation. *J Physiol*. 2016. [Epub ahead of print]

[36] Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, Kalyanasundaram A, Lim P, Bratasz A, Powell KA, Simonetti OP, Higgins RS, Kilic A, Mohler PJ, Janssen PM, Weiss R, Hummel JD, Fedorov VV. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J*. 2015;36(35):2390-401

6.7 Supplemental Materials

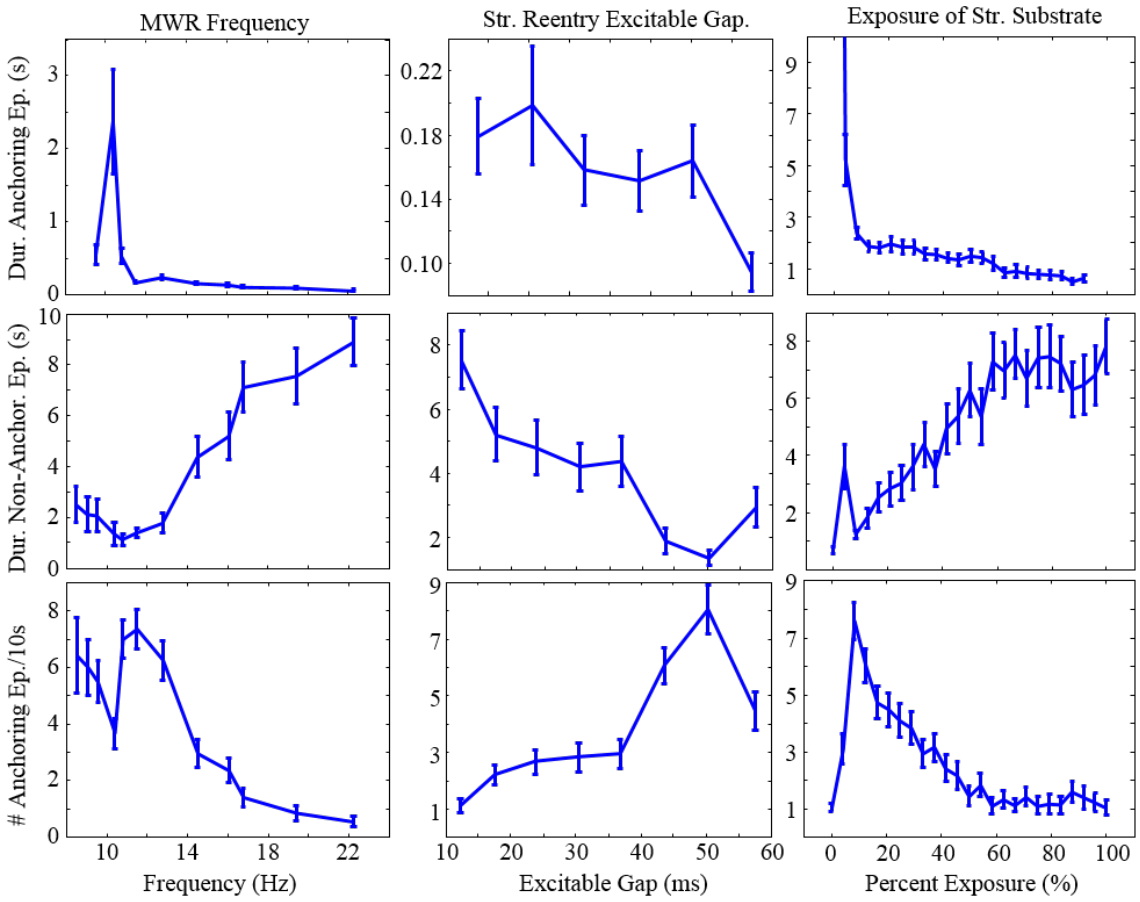

Figure 6.5: The dynamics of structural reentry. The duration of anchoring episodes (top row), time between anchoring episodes (middle row), and the number of anchoring episodes (bottom row) as functions of the frequency of MWR (left column), the excitable gap of the structural circuit (middle column), and the exposure of the structural obstacle to the surrounding tissue (right column). Error bars show 95% confidence intervals.

Chapter 7

Conclusion

Despite the enormous quantities of money, time, and energy that have been devoted to the treatment of atrial fibrillation (AF), cure remains elusive in those patients with the heaviest burdens of disease. This failure stems, at least in part, from a lack of insight into the mechanisms responsible for driving AF. In particular, the chaotic nature of multi-wavelet reentry (MWR) has proven difficult to predict and has thus far offered no obvious targets for intervention.

The first step towards identifying a practical approach for eliminating MWR is to recognize that, as with all reentrant drivers, continuous propagation in MWR requires the formation of electrical circuits. Here, waves of excitation that encounter a constantly replenishing supply of excitable tissue may propagate indefinitely. When this supply is interrupted, as by the collision of a wave with either an unexcitable anatomic boundary or ablative lesion, the reentrant propagation of the circuit terminates. Interruption of all concurrent circuits extinguishes the overall arrhythmia. However, unlike with stationary drivers such as rotors or structural micro-reentry, the circuits of MWR are both multiple and mobile. Because the position of functional reentry changes dynamically, there is no single location at which ablation will precisely eliminate specific reentrant circuits. Rather, ablation strategies must be designed around maximizing the probability of circuit interruption. We have demon-

strated that ablation of tissue regions with higher densities of circuit formation more efficiently reduces the duration of MWR than ablation of regions with lower densities.

Counter-intuitively, we also found that inappropriately placed ablation could increase the duration of fibrillation. To understand why, we introduced a population dynamics framework for viewing MWR. Here, the arrhythmia is composed of a population of waves that fuse, divide, and annihilate. Multi-wavelet reentry will continue so long as the number of waves is greater than zero. Factors that promote increases in the wave population through either wave division or spontaneous wave birth lead to increases in the lifespan of fibrillatory episodes. Reciprocally, factors that decrease the population via either wave fusion or annihilation cause corresponding decreases in the duration of MWR. Which effect an ablation line will have depends upon the way it interacts with the population of waves. When it interacts with the untethered end of a wave, that wave may anchor to the ablation line, exhaust its supply of excitable tissue, and ultimately annihilate. In this case, the potential of that wave to undergo reentry is eliminated and the wave population decreases. When the ablation line interacts with the excitatory front of a wave, that wave may break in two, thereby increasing the overall population and promoting the formation of further reentrant circuits. Ablation lines placed adjacent to, but not through, regions of high circuit density predominately interact with wave fronts, and may therefore both increase the wave population and worsen the tissue's burden of disease.

We extended this probabilistic framework by identifying a key set of parameters for predicting the number of waves able to coexist simultaneously within a given tissue. We found that the ratio of tissue size, as determined by area and boundary length, and wave size, as determined by action potential duration, resistance, and capacitance, all correlated strongly with the duration of MWR episodes. This ratio, which we defined as the fibrillogenicity index, therefore represents a useful tool for

characterizing the propensity of individual tissues to support MWR. After correcting for regional differences in wave size, we expanded the effective fibrillogenicity index to account for tissues with complex, heterogeneously distributed properties. From the population dynamics perspective, it follows logically that ablation will more effectively reduce the duration of MWR when it maximizes the frequency of interactions with wave-ends. Our experiments demonstrated that the most efficient use of ablation was the application of linear lesions to partition fibrillating tissue into effectively equal regions. By combining our ability to characterize the initial propensity of a tissue to support reentry and our knowledge of the incremental effects of ablation, we developed an algorithm for designing ablation sets optimally titrated to the burden of disease in individual tissues.

This ablation algorithm is seemingly limited to tissues in which MWR is the primary mechanism responsible for driving AF. However, focal drivers with fibrillatory conduction have also been hypothesized as a potentially important mechanism. In this case, stationary sources such as rotors, sites of ectopic firing, and structural micro-reentry emit waves that break apart and conduct chaotically. So long as these focal drivers persist, the arrhythmia will continue. Focal drivers therefore represent an enticing target for ablative elimination. However in our experiments, we demonstrated that fibrillatory conduction and MWR simply represent two points along the same continuous spectrum of electrical derangement. Elimination of only focal drivers therefore still leaves the potential for MWR within the remaining functional substrate. Furthermore, elimination of the stationary driver via focal ablation creates a potential substrate for macroscopic structural reentry. Each wave has two ends where its excitatory front and refractory tail meet. If both ends are anchored to the same unexcitable boundary, the front will consume its limited supply of excitable cells and extinguish. If instead the two ends are anchored to disparate boundaries,

the wave front will encounter a replenishing supply of excitable tissue and propagate indefinitely. We demonstrated that both the distance between and relative sizes of these two boundaries determine the likelihood that waves will anchor to separate boundaries and lead to macroscopic reentry.

Thus, a comprehensive approach to treatment of AF requires elimination of focal drivers, as by focal ablation, prevention of structural tachycardia, as by connection of focal ablation to unexcitable boundaries using linear ablation, and minimization of the remaining functional substrates ability to support reentry, as with our optimized ablation algorithm.

7.1 Suggestions for Future Research

The work presented within this dissertation suggests a number of directions for future research. In particular, it will be important to validate our *in silico* findings within a biological setting.

Clinical modification of the fibrillogenicity index

In Chapter 4 of this dissertation, we demonstrated use of the Fibrillogenicity Index in predicting the propensity of simulated tissues to support MWR. The practical application of this metric will ultimately require its validation in human atrial fibrillation. This goal is complicated by the difficulty of obtaining exact measurements of several parameters composing the Fibrillogenicity Index. For example, measurements of action potential duration, membrane capacitance, and intercellular resistance all require highly specialized methods and the precise instrumentation of individual cardiomyocytes. While potentially feasible within *in vitro* cell monolayers or mechanically-paralyzed *ex vivo* cardiac tissue preparations, these techniques are effectively impos-

sible within the mechanically beating hearts of living animals. Fortunately, it may be possible to circumvent these technical challenges by using analogous, but more easily measured, parameters within a modified version of the fibrillogenicity index. Our lab recently demonstrated that the frequency of activation correlated directly with both the density of circuit formation and tissue properties. Thus, when measured with electrodes of sufficient spatiotemporal resolution, the frequency of electrogram recordings should serve as a reasonable proxy variable for APD and RC.

As with any artificial model of AF, neither cell monolayers nor animal models necessarily reflect the behavior or mechanism of true human arrhythmic disease. In testing the utility of a clinically modified version of the fibrillogenicity index ($Fb_C = (A/BL) * Freq$), it may therefore be both more appropriate and efficient to skip directly from *in silico* experiments to validation in humans. Here, values of atrial area and boundary length can be obtained easily from either the cardiac CT imaging or the electroanatomic studies that are routinely taken prior to ablative intervention. These values, combined with frequency measurements taken from several different positions within the atria, allow for calculation of Fb_C. The clinical fibrillogenicity index must then be mapped against a measure of disease burden such as episode duration or the percentage of time a patient spends in active fibrillation. These measures may be obtained from either extraneously implanted pace makers with recording capabilities or with portable telemetry devices such as Holter monitors.

This type of study will provide insight into two major questions raised by the computational work of this dissertation. First, it will answer the question of whether or not the fibrillogenicity index is in fact a useful metric of the burden of human disease. Second, it will provide an idea of how much variation there is in AF frequency, both temporally and spatially, and from patient to patient. While other studies have examined distributions of tissue frequency, they have typically done so using

measures of dominant frequency rather than centroid frequency, and with electrodes of insufficient spatiotemporal resolution (as demonstrated by the presence of electrogram fractionation). If variation is low, future studies requiring knowledge of a hearts propensity to support fibrillation may be obtained from a single global measure of atrial frequency such as a surface electrocardiogram.

Validation of the optimized ablation algorithm

In Chapter 5 of this dissertation, we presented a strategy of tissue-specific optimized ablation for the treatment of AF. This strategy also requires validation within human beings. Implementation of our proposed algorithm requires two pieces of information. First, we will need a metric of both the magnitude and spatial distribution of fibrillatory disease burden. This question will be answered by the correlation study described above. Second, we require an idea of the incremental impact of ablation. This question is more difficult to answer, particularly in humans. However, by expanding the above correlation study to include measures of disease burden both before and after standard ablative intervention, we can gather information regarding the relationship between added ablation length and the resulting decrement in AF burden.

With these two pieces of information in hand, it will then be possible to assess the impact of our proposed ablation strategy. Because testing of our algorithm requires active intervention rather than passive data collection, a randomized control trial contrasting this algorithm against standard ablative therapy (either pulmonary vein isolation or pulmonary vein isolation with additional anatomic ablation) will be necessary to demonstrate improved rates of cure.

Chapter 8

Comprehensive Bibliography

1. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol.* 2003;42(1):20-29

2. Albåge A, Johansson B, Kennebäck G, Källner G, Scherstén H, Jidéus L; Swedish Arrhythmia Surgery Group. Long-Term Follow-Up of Cardiac Rhythm in 320 Patients After the Cox-Maze III Procedure for Atrial Fibrillation. *Ann Thorac Surg.* 2015;[Epub ahead of print]

3. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of trachycardia. *Circ Res.* 1973;33(1):54-62

4. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ Res.* 1977;41(1):9-18

5. Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. Cardiac Electrophysiology and Arrhythmias. *Grune and Straton, Inc.* 1985:265–275

6. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3(6):606-615

7. Allessie M, de Groot N. CrossTalk opposing view: Rotors have not been demonstrated to be the drivers of atrial fibrillation. *J Physiol.* 2014;592(15):3167–3170

8. Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, Santanna RT, Pires LM, Kruse ML, Lima GG, Leiria TL. Clinical Differences between Subtypes of Atrial Fibrillation and Flutter: Cross-Sectional Registry of 407 Patients. *Arq Bras Cardiol.* 2015;105(1):3-10

9. Arbelo E, Guiu E, Ramos P, Bisbal F, Borras R, Andreu D, Tolosana JM, Berruezo A, Brugada J, Mont L. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc.* 2014;3(5):e000877

10. Aronson JK. One hundred years of atrial fibrillation. *Br J Clin Pharmacol.* 2005;60(4):345-346

11. Ashihara T, Haraguchi R, Nakazawa K, Namba T, Ikeda T, Nakazawa Y, Ozawa T, Ito M, Horie M, Trayanova NA. The role of fibroblasts in complex fractionated electrograms during persistent/permanent atrial fibrillation: Implications for electrogram-based catheter ablation. *Circ Res.* 2012;110(2):275-284

12. Atienza F, Almendral J, Ormaetxe JM, Moya A, Martínez-Alday JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MÁ, Tercedor L, Peinado R, Arcocha MF, Ortiz M, Martínez-Alzamora N, Arenal A, Fernández-Avilés F, Jalife J; RADAR-AF Investigators. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol.* 2014;64(23):2455-2467

13. Barbaro V, Bartolini P, Calcagnini G, Censi F, Morelli S, Michelucci A. Mapping the organization of atrial fibrillation with basket catheters. Part I: Validation of a real-time algorithm. *Pacing Clin Electrophysiol.* 2001;24(7):1082-1088

14. Beeler GW, Reuter H. Reconstruction of the action potential of ventricular myocardial fibres. *J Physiol.* 1977;268(1):177-210

15. Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2015;8(3):554-561

16. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98(10):946-952

17. Benson BE, Carrick RT, Habel N, Bates ORJ, Bates JHT, Bielau P, Spector PS. Mapping multi-wavelet reentry without isochrones: an electrogram-guided approach to define substrate distribution. *Europace.* 2014;16 Suppl 4:iv102-iv109

18. Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M, Jalife J. Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the Langendorff-perfused sheep heart. *J Cardiovasc Electrophysiol.* 2000;11(8):869-879

19. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm.* 2009;6(10):1403-1412

20. Box EG, Draper NR. Empirical Model-Building and Response Surfaces. *Wiley.* 1987:424

21. Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. *Heart Rhythm.* 2015;[Epub ahead of print]

22. Byrd GD, Prasad SM, Ripplinger CM, Cassilly TR, Schuessler RB, Boineau JP, Damiano RJ Jr. Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *Circulation.* 2005;112(9 Suppl):I7–I13

23. Calaprice A. The Ultimate Quotable Einstein. *Princeton University Press.* 2010:475,384-385

24. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association,

the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*. 2007;9(6):335-379

25. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009;2(4):349-361

26. Carrick RT, Benson B, Habel N, Bates ORJ, Bates JHT, Spector PS. Ablation of multiwavelet re-entry guided by circuit-density and distribution: maximizing the probability of circuit annihilation. *Circ Arrhythm Electrophysiol*. 2013;6(6):1229–1235

27. Carrick RT, Bates ORJ, Benson BE, Habel N, Bates JHT, Spector PS. Prospectively quantifying the propensity for atrial fibrillation: a mechanistic formulation. *PLoS:One*. 2015;10(3):e0118746

28. Carrick RT, Benson BE, Bates JH, Spector PS. Prospective, tissue-specific optimization of ablation for multi-wavelet reentry: predicting the required amount, location and configuration of lesions. *Circ Arrhythm Electrophysiol*. 2016;9(3):e003555

29. Charitos EI, Pürerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol*. 2014;63(25 Pt A):2840-2848

30. Cheema A, Dong J, Dalal D, Marine JE, Henrikson CA, Spragg D, Cheng A, Nazarian S, Bilchick KC, Almasry I, Sinha S, Scherr D, Halperin H, Berger R, Calkins H. Circumferential ablation with pulmonary vein isolation in permanent atrial fibrillation. *Am J Cardiol*. 2007;99(10):1425-1428

31. Chen J, Mandapati R, Berenfeld O, Skanes AC, Gray RA, Jalife J. Dynamics of wavelets and their role in atrial fibrillation in the isolated sheep heart. *Cardiovasc Res*. 2000;48(2):220-232

32. Chou CC, Nguyen BL, Tan AY, Chang PC, Lee HL, Lin FC, Yeh SJ, Fishbein MC, Lin SF, Wu D, Wen MS, Chen PS. Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. *Heart Rhythm*. 2008;5(8):1170-1177

33. Chugh SS, Havmoeller R, Narayanan J, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129(8):837-847

34. Chugh A. Complex Fractionated Atrial Electrograms in Catheter Ablation of Atrial Fibrillation: Dead and Buried? *Circ Arrhythm Electrophysiol.* 2015;8(5): 999-1001

35. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112(8):1142-1147

36. Correa de Sa DD, Thompson N, Stinnett-Donnelly J, Znojkiewicz P, Habel N, Müller JG, Bates JH, Buzas JS, Spector PS. Electrogram fractionation: the relationship between spatiotemporal variation of tissue excitation and electrode spatial resolution. *Circ Arrhythm Electrophysiol.* 2011;4(6):909-916

37. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med.* 2012;367(17):1587-1595

38. Courtemanche M. Re-entrant rotating waves in a beeler-reuter model of two-dimensional cardiac electrical activity. *International Journal of Bifurcation and Chaos.* 1991;1(2):431-444

39. Courtemanche M. Complex spiral wave dynamics in a spatially distributed ionic model of cardiac electrical activity. *Chaos.* 1996;6(4):579-600

40. Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *Am J Physiol.* 1998;275(1 Pt 2):H301-H321

41. Cox JL, Schuessler RB, D'Agostino HJ Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg.* 1991;101(4): 569-583

42. Cox JL. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J Thorac Cardiovasc Surg.* 1991;101(4):584-592

43. Cox JL, Jaquiss RD, Schuessler RB, Boineau JP. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. *J Thorac Cardiovasc Surg.* 1995;110(2):485-495

44. Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 1/2-year clinical experience with surgery for atrial fibrillation. *Ann Surg.* 1996;224(3):267-273

45. Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. *J Thorac Cardiovasc Surg.* 1999;118(5):833-840

46. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9(5):348-356

47. Davidenko JM, Kent PF, Chialvo DR, Michaels DC, Jalife J. Sustained vortex-like waves in normal isolated ventricular muscle. *Proc Natl Acad Sci USA*. 1990;87(22):8785-8789

48. Davidenko JM1, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. *Nature*. 1992;355(6358):349-351

49. de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allessie MA. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation*. 2010;122(17):1674-1682

50. DeSilva RA. George Ralph Mines, ventricular fibrillation and the discovery of the vulnerable period. *J Am Coll Cardiol*. 1997;29(6):1397-1402

51. Dewire J, Calkins H. State-of-the-art and emerging technologies for atrial fibrillation ablation. *Nat Rev Cardiol*. 2010;7(3):129-138

52. Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Wang P, Al-Ahmad A, Arruda M, Themistoclakis S, Bonso A, Rossillo A, Raviele A, Schweikert RA, Burkhardt DJ, Natale A. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol*. 2009;2(2):113-119

53. Di Minno MN, Ambrosino P, Dello Russo A, Casella M, Tremoli E, Tondo C. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation. A systemic review and meta-analysis of the literature. *Thromb Haemost*. 2015;115(3) [Epub ahead of print]

54. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309

55. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology* 2003;22(2):118-123

56. Eckstein J1, Zeemering S, Linz D, Maesen B, Verheule S, van Hunnik A, Crijns H, Allessie MA, Schotten U. Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: evidence from simultaneous endo-epicardial high-density activation mapping. *Circ Arrhythm Electrophysiol.* 2013;6(2):334-341

57. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm.* 2008;5(12):1658-1664

58. Estner HL, Hessling G, Ndrepepa G, Wu J, Reents T, Fichtner S, Schmitt C, Bary CV, Kolb C, Karch M, Zrenner B, Deisenhofer I. Electrogram-guided substrate ablation with or without pulmonary vein isolation in patients with persistent atrial fibrillation. *Europace.* 2008;10(11):1281-1287

59. European Heart Rhythm Association; Heart Rhythm Society, Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol.* 2006;48(4):854-906

60. Everett TH 4^{th}, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, Haines DE. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. *Circulation.* 2000;102(12):1454-1460

61. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial remodeling. *Circulation.* 1998;98(20):2202-2209

62. Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbucicchio C, Maccabelli G, Giraldi F, Bella PD. Left mitral isthmus ablation associated with PV Isolation: long-term results of a prospective randomized study. *J Cardiovasc Electrophysiol.* 2005;16(11):1150-1156

63. Fast VG, Kleber AG. Role of wavefront curvature in propagation of cardiac impulse. *Cardiovasc Res.* 1997;33(2):258-271

64. Feinberg MS, Waggoner AD, Kater KM, Cox JL, Lindsay BD, Pérez JE. Restoration of atrial function after the maze procedure for patients with atrial fibrillation. Assessment by Doppler echocardiography. *Circulation.* 1994;90(5 pt 2):II285-II292

65. Fenton F, Karma A. Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation. *Chaos.* 1998;8(1):20-47

66. Fitzhugh R. Impulses and Physiological States in Theoretical Models of Nerve Membrane. *Biophys J.* 1961;1(6):445-466

67. Flegel KM. From delirium cordis to atrial fibrillation: historical development of a disease concept. *Ann Intern Med.* 1995;122(11):867-873

68. Frankel G, Kamrul R, Kosar L, Jensen B. Rate versus rhythm control in atrial fibrillation. *Can Fam Physician.* 2013;59(2):161-168

69. Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, Coin D, Di Donna P, Giustetto C. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2008;1(4):269-275

70. Garrey WE. The nature of fibrillary contraction of the heart — its relation to tissue mass and form. *Am J Physiol.* 1914;33:397–414

71. Garrey WE. Auricular Fibrillation. *Phys Reviews.* 1924;4(2):215-250

72. Gaspo R, Bosch R, Talajic M, Nattel S. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. *Circulation.* 1997;96(11):4027–4035

73. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.*J Am Med Assoc.* 2014;285(18):2370-2375

74. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. *Nature*. 1998;392(6671):75-78

75. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339(10):659-666

76. Haïssaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clémenty J, Jaïs P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol*. 2005; 16(11):1138-1147

77. Haïssaguerre M, Shah AJ, Cochet H, Hocini M, Dubois R, Efimov I, Vigmond E, Bernus O, Trayanova N. Intermittent drivers anchoring to structural heterogeneities as a major pathophysiologic mechanism of human persistent atrial fibrillation. *J Physiol*. 2016. [Epub ahead of print]

78. Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, Kalyanasundaram A, Lim P, Bratasz A, Powell KA, Simonetti OP, Higgins RS, Kilic A, Mohler PJ, Janssen PM, Weiss R, Hummel JD, Fedorov VV. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J*. 2015;36(35):2390-401

79. Hocini M, Jaïs P, Sanders P, Takahashi Y, Rotter M, Rostock T, Hsu LF, Sacher F, Reuter S, Clémenty J, Haïssaguerre M. Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. *Circulation*. 2005;112(24):3688-3696

80. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117(4):500-544

81. Hoyt RH, Wood M, Daoud E, Feld G, Sehra R, Pelkey W, Kay GN, Calkins H; U.S. CryoCor Investigators. Transvenous catheter cryoablation for treatment of atrial fibrillation: results of a feasibility study. *Pacing Clin Electrophysiol*. 2005;28(Suppl 1):S78-S82

82. Hunter RJ, Baker V, Finlay MC, Duncan ER, Lovell MJ, Tayebjee MH, Ullah W, Siddiqui MS, McLEAN A, Richmond L, Kirkby C, Ginks MR, Dhinoja M, Sporton S, Earley MJ, Schilling RJ. Point-by-Point Radiofrequency Ablation Versus the Cryoballoon or a Novel Combined Approach: A Randomized Trial Comparing 3 Methods of Pulmonary Vein Isolation for Paroxysmal

Atrial Fibrillation (The Cryo Versus RF Trial). *J Cardiovasc Electrophysiol.* 2015;26(12):1307-1314

83. Irfan G, de Asmundis C, Mugnai G, Poelaert J, Verborgh C, Umbrain V, Beckers S, Hacioglu E, Hunuk B, Velagic V, Stroker E, Brugada P, Chierchia GB. One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. *Europace.* 2015;[Epub ahead of print]

84. Jacquemet V, Virag N, Kappenberger L. Wavelength and vulnerability to atrial fibrillation: Insights from a computer model of human atria. *Europace.* 2005; 7(Suppl 2):83–92

85. Jacquemet V, Henriquez CS. Modelling cardiac fibroblasts: interactions with myocytes and their impact on impulse propagation. *Europace.* 2007;9 Suppl 6:vi29–vi37

86. Jacquemet V, Henriquez CS. Loading effect of fibroblast-myocyte coupling on resting potential, impulse propagation, and repolarization: insights from a microstructure model. *Am J Physiol Heart Circ Physiol.* 2008;294(5):H2040–H2052

87. Jaïs P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clémenty J, Haïssaguerre M. Technique and results of linear ablation at the mitral isthmus. *Circulation.* 2004;110(19):2996-3002

88. Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation.* 2008;118(24):2498-2505

89. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130(23):2071-2104

90. Jalife J, Delmar M, Anumonwo J, Berenfeld O, Kalifa J. Basic Cardiac Electrophysiology for the Clinician. *Wiley-Blackwell.* 1991;7-71

91. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. Mechanisms of wave fractionation at boundaries of

high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation.* 2006;113(5):626-633

92. Kay GN, Epstein A, Dailey S, Plumb V. Role of radiofrequency ablation in the management of supraventricular arrhythmias: experience in 760 consecutive patients. *J Cardiovasc Electrophysiol.* 1993;4(4):371–392

93. Katz AM. Physiology of the heart. *Lippincott Williams & Wilkins.* 2001:478-516

94. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes.* 2011;4(3):313-320

95. Kirchhof C, Chorro F, Scheffer GJ, Brugada J, Konings K, Zetelaki Z, Allessie M. Regional entrainment of atrial fibrillation studied by high-resolution mapping in open-chest dogs. *Circulation.* 1993;88(2):736-749

96. Kojodjojo P, Peters NS, Davies DW, Kanagaratnam P. Characterization of the Electroanatomical Substrate in Human Atrial Fibrillation: The Relationship between Changes in Atrial Volume, Refractoriness, Wavefront Propagation Velocities, and AF Burden. *J Cardiovasc Electrophysiol.* 2007;18(3):269–275

97. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation.* 1994;89(4):1665-1680

98. Kowalski M, Grimes MM, Perez FJ, Kenigsberg DN, Koneru J, Kasirajan V, Wood MA, Ellenbogen KA. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. *J Am Coll Cardiol.* 2012;59(10):930-938

99. Lalani GG, Trikha R, Krummen DE, Narayan SM. Rotors and focal sources for human atrial fibrillation: mechanistic paradigm with direct clinical relevance. *Circ J.* 2014;78(10):2357-2366

100. Lee AM, Aziz A, Didesch J, Clark KL, Schuessler RB, Damiano RJ Jr. Importance of atrial surface area and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *J Thorac Cardiovasc Surg.* 2013;146(3):593-598

101. Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, Goldblatt J, Brown R, Atkinson V, Moten S, Morton JB, Sanders P, Kistler PM, Kalman JM. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J.* 2014;35(2):86-97

102. Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the Moe hypothesis. *J Cardiovasc Electrophysiol.* 2013;24(3):328-335

103. Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation.* 1999;99(23):3028-3035

104. Lévy S, Camm AJ, Saksena S, Aliot E, Breithardt G, Crijns H, Davies W, Kay N, Prystowsky E, Sutton R, Waldo A, Wyse DG; Working Group on Arrhythmias, Working Group on Cardiac Pacing of the European Society of Cardiology, North American Society of Pacing and Electrophysiology. International consensus on nomenclature and classification of atrial fibrillation; a collaborative project of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Europace.* 2003;5(2):119-122

105. Lin T, Rillig A, Bucur T, Metzner A, Mathew S, Wissner E, Wohlmuth P, Kuck KH, Ouyang F, Tilz RR. Focal impulse and rotor modulation using the novel 64-electrode basket catheter: electrogram characteristics of human rotors. *Europace.* 2015;17(12):1791-1797

106. Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. *BMJ.* 1995;311(7016):1361-1363

107. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* 2004; 110(9):1042–1046

108. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation.* 2015;132(14): 1311-1319

109. Mansour M1, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. *Circulation.* 2001;103(21):2631-2636

110. McDowell KS, Arevalo HJ, Maleckar MM, Trayanova N. Susceptibility to arrhythmia in the infarcted heart depends on myofibroblast density. *Biophys J.* 2011;101(6):1307–1315

111. McMichael J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laënnec. *Br Heart J.* 1982;48(3):193-197

112. Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN, Kirchhof P, ATRIUM investigators. Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. *Clin Res Cardiol.* 2011;100(10):897-905

113. Miyazaki S, Kuroi A, Hachiya H, Nakamura H, Taniguchi H, Ichihara N, Takagi T, Iwasawa J, Iesaka Y. Early recurrence after pulmonary vein isolation of paroxysmal atrial fibrillation with different ablation technologies - prospective comparison of radiofrequency vs. second-generation cryoballoon ablation. *Circ J.* 2016;80(2):346-353

114. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J.* 1959;58:59-70

115. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn.* 1962;CXL:183-188

116. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J.* 1964;67:200-220

117. Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, Arribas F, Fernández-Lozano I, Bodegas A, Cobos A, Matía R, Pérez-Villacastín J, Guerra JM, Ávila P, López-Gil M, Castro V, Arana JI, Brugada J. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J.* 2014;35(8):501–507

118. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation.* 1995;91(5):1588-1595

119. Morita H, Zipes DP, Morita ST, Wu J. Isolation of canine coronary sinus musculature from the atria by radiofrequency catheter ablation prevents induction of atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2014;7(6):1181-1188

120. Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. I. Distribution of the electrotonic potential. *Biofizika.* 1977;22(2):307-312

121. Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. II. Distribution of a flat front of excitation. *Biofizika.* 1977;22(3):518-522

122. Muler AL, Markin VS. Electrical properties of anisotropic neuromuscular syncytia. III. Steady state of the front of excitation. *Biofizika.* 1977;22(4):671-675

123. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol.* 2004;43(11):2044-2053

124. Narayan SM, Wright M, Derval N, Jadidi A, Forclaz A, Nault I, Miyazaki S, Sacher F, Bordachar P, Clémenty J, Jaïs P, Haïssaguerre M, Hocini M. Classifying fractionated electrograms in human atrial fibrillation using monophasic action potentials and activation mapping: evidence for localized drivers, rate acceleration, and nonlocal signal etiologies. *Heart Rhythm.* 2011;8(2):244–253

125. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol.* 2012;23(5):447-454

126. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol.* 2012;60(7):628-636

127. Narayan SM, Jalife J. CrossTalk proposal: Rotors have been demonstrated to drive human atrial fibrillation. *J Physiol.* 2014;592(15):3163–3166

128. Nattel S, Allessie M, Haissaguerre M. Spotlight on atrial fibrillation-the 'complete arrhythmia'. *Cardiovasc Res.* 2002;54(2):197-203

129. Nattel S. Atrial electrophysiology and mechanisms of atrial fibrillation. *J Cardiovasc Pharmacol Ther.* 2003;8 Suppl 1:S5-S11

130. Nagarakanti R, Saksena S, Hettrick D, Koehler JL, Grammatico A, Padeletti L. Progression of new onset to established persistent atrial fibrillation: an implantable device-based analysis with implications for clinical classification of persistent atrial fibrillation. *J Interv Card Electrophysiol.* 2011;32(1):7-15

131. Nagumo J, Animoto S, Yoshizawa S. An active pulse transmission line simulating nerve axon. *Proc. Inst. Radio Engineers.* 1962;50:2061-2070

132. Nygren A, Fiset C, Firek L, Clark JW, Lindblad DS, Clark RB, Giles WR. Mathematical model of an adult human atrial cell: the role of K+ currents in repolarization. *Circ Res.* 1998;82(1):63-81

133. Ogawa M, Kumagai K, Gondo N, Matsumoto N, Suyama K, Saku K. Novel electrophysiologic parameter of dispersion of atrial repolarization: comparison of different atrial pacing methods. *J Cardiovasc Electrophysiol.* 2002;13(2):110-117

134. Oliveira MM, da Silva N, Timóteo AT, Feliciano J, de Sousa L, Santos S, Marques F, Ferreira R. Enhanced dispersion of atrial refractoriness as an electrophysiological substrate for vulnerability to atrial fibrillation in patients with paroxysmal atrial fibrillation. *Rev Port Cardiol.* 2007;26(7-8):691-702

135. Olshansky B, Rosenfeld LE, Warner AL, Solomon AJ, O'Neill G, Sharma A, Platia E, Feld GK, Akiyama T, Brodsky MA, Greene HL; AFFIRM Investigators. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. *J Am Coll Cardiol.* 2004;43(7):1201-1208

136. O'Neill MD, Wright M, Knecht S, Jaïs P, Hocini M, Takahashi Y, Jönsson A, Sacher F, Matsuo S, Lim KT, Arantes L, Derval N, Lellouche N, Nault I, Bordachar P, Clémenty J, Haïssaguerre M. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J.* 2009;30(9):1105-1112

137. Opolski G, Kosior DA, Kurzelewski M, Skrzyńska M, Zagórski A, Janion M, Muzolf M, Wlazłowski R, Pankiewicz B, Łoboz-Grudzień K, Breithardt G; Polish RecordAF. Baseline characteristics of patients from Poland enrolled in the global registry of patients with recently diagnosed atrial fibrillation (RecordAF). *Kardiol Pol.* 2010;68(5):546-554

138. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation.* 2002;105(9):1077-1081

139. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol.* 2009;53(9):782-789

140. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation.* 2000;102(21):2619-2628

141. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro MP, Mazzone P, Ficarra E, Di Gioia C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an

anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation.* 2001;104(21):2539-2544

142. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol.* 2006;48(11):2340-2347

143. Providência R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ, Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol.* 2015;8(5):1017-1029

144. Reant P, Lafitte S, Jaïs P, Serri K, Weerasooriya R, Hocini M, Pillois X, Clementy J, Haïssaguerre M, Roudaut R. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. *Circulation.* 2005;112(19):28986-2903

145. Rensma PL, Allessie MA., Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res.* 1988;62(2):395–410

146. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J.* 2006;152(6):1097-1103

147. Rohrbacker NJ, Kleinman NL, White SA, March JL, Reynolds MR. The burden of atrial fibrillation and other cardiac arrhythmias in an employed population: associated costs, absences, and objective productivity loss. *J Occup Environ Med.* 2010;52(4):383-391

148. Rostock T, Steven D, Hoffmann B, Servatius H, Drewitz I, Sydow K, Müllerleile K, Ventura R, Wegscheider K, Meinertz T, Willems S. Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach. *Circ Arrhythm Electrophysiol.* 2008;1(5):344-353

149. Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. *J Cardiovasc Electrophysiol.* 2005;16(12):1348-1358

150. Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. *Am Heart J.* 2007;154(5):884-892

151. Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavée C, Ploutz-Snyder R, Jalife J, Haïssaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation.* 2005;112(6):789-797

152. Sanoski CA. Clinical, economic, and quality of life impact of atrial fibrillation. *Journal of managed care pharmacy.* 2009;15(6 Suppl B):S4-S9

153. Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J.* 1948;36(2):241-251

154. Schmitt C, Zrenner B, Schneider M, Karch M, Ndrepepa G, Deisenhofer I, Weyerbrock S, Schreieck J, Schömig A. Clinical experience with a novel multielectrode basket catheter in right atrial tachycardias. *Circulation.* 1999;99(18): 2414-2422

155. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. *Cardiovasc Pathol.* 2000;9(2):95-101

156. Shivkumar K, Ellenbogen KA., Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: First multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J Cardiovasc Electrophysiol.* 2012;23(12):1277–1285

157. Silverman ME. From rebellious palpitations to the discovery of auricular fibrillation: contributions of Mackenzie, Lewis and Einthoven. *Am J Cardiol.* 1994;73(5):384-389

158. Sommer P, Kircher S, Rolf S, John S, Arya A, Dinov B, Richter S, Bollmann A, Hindricks G. Successful Repeat Catheter Ablation of Recurrent Longstanding Persistent Atrial Fibrillation with Rotor Elimination as the Procedural Endpoint: A Case Series. *J Cardiovasc Electrophysiol.* 2015;[Epub ahead of print]

159. Spangler SG. Expansion of the constant field equation to include both divalent and monovalent ions. *Ala J Med Sci.* 1972;9(2):218-223

160. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol.* 2009;104(5):671-677

161. Spector PS, Habel N, Sobel BE, Bates JH. Emergence of complex behavior: an interactive model of cardiac excitation provides a powerful tool for understanding electric propagation. *Circ Arrhythm Electrophysiol.* 2011;4(4):586-91

162. Spector PS, Correa de Sa DD, Tischler ES, Thompson NC, Habel N, Stinnett-Donnelly J, Benson BE, Bielau P, Bates JH. Ablation of multi-wavelet re-entry: general principles and in silico analyses. *Europace.* 2012;14(Suppl 5):v106-v111

163. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J.* 2006;27(2):216-221

164. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP; ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J.* 2015;36(5):288-296

165. Stinnett-Donnelly JM, Thompson N, Habel N, Petrov-Kondratov V, Correa de Sa DD, Bates JHT, Spector PS. Effects of electrode size and spacing on the resolution of intracardiac electrograms. *Coron Artery Dis.* 2012;23(2):126–132

166. Straube F, Dorwarth U, Ammar-Busch S, Peter T, Noelker G, Massa T, Kuniss M, Ewertsen NC, Chun KR, Tebbenjohanns J, Tilz R, Kuck KH, Ouarrak T, Senges J, Hoffmann E; FREEZE Cohort Investigators. First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation. *Europac.* 2015;[Epub ahead of print]

167. Tai CT, Chen SA, Chiang CE, Lee SH, Wen ZC, Huang JL, Chen YJ, Yu WC, Feng AN, Lin YJ, Ding YA, Chang MS. Long-term outcome of radiofrequency catheter ablation for topical atrial flutter: risk prediction of recurrent arrhythmias. *J Cardiovasc Electrophysiol.* 1998;9(2):118–121

168. Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, Iguchi M, Masunaga N, Ogawa H, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GY, Akao M. Incidence of Stroke or Systemic Embolism in Paroxysmal Versus Sustained Atrial Fibrillation: The Fushimi Atrial Fibrillation Registry. *Stroke.* 2015;46(12):3354-3361

169. Tamargo J, Caballero R, Delpón E. Pharmacological approaches in the treatment of atrial fibrillation. *Curr Med Chem.* 2004;11(1):13-28

170. Tamborero D, Mont L, Berruezo A, Matiello M, Benito B, Sitges M, Vidal B, de Caralt TM, Perea RJ, Vatasescu R, Brugada J. Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ Arrhythm Electrophysiol.* 2009;2(1):35-40

171. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Sparks PB, Morton JB, Kalman JM. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *J Cardiovasc Electrophysiol.* 2012;23(3):232-238

172. Teunissen C, Kassenberg W, van der Heijden JF, Hassink RJ, van Driel VJ, Zuithoff NP, Doevendans PA, Loh P. Five-year efficacy of pulmonary vein antrum isolation as a primary ablation strategy for atrial fibrillation: a single-centre cohort study. *Europace.* 2016. [Epub ahead of print]

173. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol.* 2012;60(19):1921-1929

174. Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodriguez LM, Ghaye B, Ayers GM, Crijns HJ, Klein HU, Lau CP. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. *J Am Coll Cardiol.* 2003;42(4):752-758

175. Tung L. A bi-domain model for describing ischemic myocardial d-c potentials. *Massachusetts Institute of Technology Ph.D. Dissertation.* 1978

176. Tung R, Buch E, Shivkumar K. Catheter Ablation of Atrial Fibrillation. *Circulation.* 2012;126(2):223–229

177. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation.* 2005;112(5):627-635

178. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J.* 2010;31(11):1344-1356

179. Verma A, Lakkireddy D, Wulffhart Z, Pillarisetti J, Farina D, Beardsall M, Whaley B, Giewercer D, Tsang B, Khaykin Y. Relationship between complex fractionated electrograms (CFE) and dominant frequency (DF) sites and

prospective assessment of adding DF-guided ablation to pulmonary vein isolation in persistent atrial fibrillation (AF). *J Cardiovasc Electrophysiol.* 2011; 22(12):1309–1316

180. Verma A, Jiang C, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo C a., Haverkamp W, Weerasooriya R, Albenque J-P, Nardi S, Menardi E, Novak P, Sanders P. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812–1822

181. Vogler J, Willems S, Sultan A, Schreiber D, Lüker J, Servatius H, Schäffer B, Moser J, Hoffmann BA, Steven D. Pulmonary Vein Isolation Versus Defragmentation: The CHASE-AF Clinical Trial. *J Am Coll Cardiol.* 2015;66(24):2743-2752

182. von Eisenhart Rothe AF, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. *Europace.* 2014;16(6):812-819

183. Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E, Lewis N, Ng A, Gould P, Lee G, Joseph S, Morton JB, Zentner D, Sanders P, Kistler PM, Kalman JM. Progression of atrial remodeling in patients with high-burden atrial fibrillation: Implications for early ablative intervention. *Heart Rhythm.* 2016;13(2):331-339

184. Wang J, Bourne GW, Wang Z, Villemaire C, Talajic M, Nattel S. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. *Circulation.* 1993;88(3):1030-1044

185. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA.* 2005;293(21):2634-2640

186. Weiss JN, Qu Z, Chen PS, Lin SF, Karagueuzian HS, Hayashi H, Garfinkel A, Karma A. The dynamics of cardiac fibrillation. *Circulation.* 2005;112(8):1232-1240

187. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92(7):1954-1968

188. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary

vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J.* 2006;27(23):2871-2878

189. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-988

190. Wolf PA, Bejamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in the prevalence of atrial fibrillation: The Framingham Study. *Am Heart J.* 1996;131(4)790-795

191. Wong KC, Betts TR. A review of mitral isthmus ablation. *Indian Pacing Electrophysiol J.* 2012;12(4):152-170

192. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR. No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol.* 2015;8(6):1316-1324

193. Wright HS. Generation of resting membrane potential *Adv Physiol Educ.* 2004; 28:139-142

194. Wright M, Haïssaguerre M, Knecht S, Matsuo S, O'Neill MD, Nault I, Lellouche N, Hocini M, Sacher F, Jais P.. State of the art: catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* 2008;19(6):583–592

195. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347(23):1825-1833

196. Yang G, Yang B, Wei Y, Zhang F, Ju W, Chen H, Li M, Gu K, Lin Y, Wang B, Cao K, Kojodjojo P, Chen M. Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation. *Circ Arrhythm Electrophysiol.* 2016;9(2):e003382

197. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-e575S

198. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm.* 2006;3(12):1445-1452

199. Zimmer HG. Profiles in cardiology: Theodor Wilhelm Engelmann. *Clin Cardiol.* 2006;29:518-520