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Changes in the Atrial Substrate Alters the Spatiotemporal Organization and Characteristics of Atrial Fibrillation

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia (Nattel and Opie 2006) and can occur in a variety of clinical settings. Several animal models have been developed to mimic the clinical settings in which AF occurs (Everett et al. 2000; Li et al. 1999; Morillo et al. 1995; Neuberger et al. 2006; Schuessler et al. 1992; Verheule et al. 2003; Wijffels et al. 1995). These models have individually addressed different types of atrial structural remodeling which leads to conduction abnormalities and acute and chronic atrial electrical remodeling. AF vulnerability in structurally normal hearts is very low and rarely propagates in this setting (Guerra et al. 2006; Lee et al. 2006). However, any changes in the atrial substrate either through structural or electrical remodeling can increase AF vulnerability and can create an environment in which not only can AF be initiated, but can propagate.

Advancements in the technologies available for atrial activation mapping have increased our understanding of cardiac arrhythmias and action potential propagation. In addition, several signal processing tools have been utilized to study the spatiotemporal organization of AF, and to gain insight into its characteristics and mechanisms. These tools include cross correlation (Botteron and Smith 1995), wavelet analysis (Lee et al. 2004), entropy (Akar et al. 2002; Richman and Moorman 2000), chaos theory (Garfinkel et al. 1997; Gray and Jalife 1998), signal linearity (Sih et al. 1999), and frequency domain analysis using the FFT (Everett, Kok, et al. 2001; Skanes et al. 1998; Ryu et al. 2006). All of these analyses are being used to help find organization within a seemingly chaotic rhythm, identifying and study mechanisms which could possibly be used to identify ablation sites (Pachon et al. 2004; Sanders et al. 2005), and to time defibrillation and pacing for AF termination (Everett et al. 2002; Everett, Moorman, et al. 2001). In addition, activation mapping and signal processing tools have demonstrated that the AF that occurs in within different atrial substrates has different spatiotemporal and mechanistic properties (Everett et al. 2010; Everett et al. 2006).

2. Basics of signal processing and analysis

Several parameters have been used to measure the spatiotemporal organization of AF in different animal models to aid in understanding of the different characteristics and mechanisms of the AF. One simple method is either endocardial or epicardial activation

mapping of the atrial fibrillation. For each atrial activation, the time at which the maximum first derivative (dV/dT) occurs is determined and isochronal maps are constructed. From these maps, several behavior characteristics of the AF can be determined. These characteristics include wavefront direction and propagation, the number of wavefronts, and the number of sites that exhibit early activation. However, this type of analysis if highly dependent on where the beginning and end points of the analysis window are placed, the size of the analysis window, and the accuracy of marking local activation (often determined by the maximum dV/dT). (Ideker et al. 1989) Because of these limitations, other analyses have been developed that are more objective measurements of the spatiotemporal organization of the AF. These analyses include cross correlation (Botteron and Smith 1995), frequency domain analysis using the FFT (Everett, Kok, et al. 2001; Ryu et al. 2006; Skanes et al. 1998), measuring the linking of wavefronts (Gerstenfeld, Sahakian, and Swiryn 1992), sample entropy (Richman and Moorman 2000), and wavelet analysis (Lee et al. 2004).
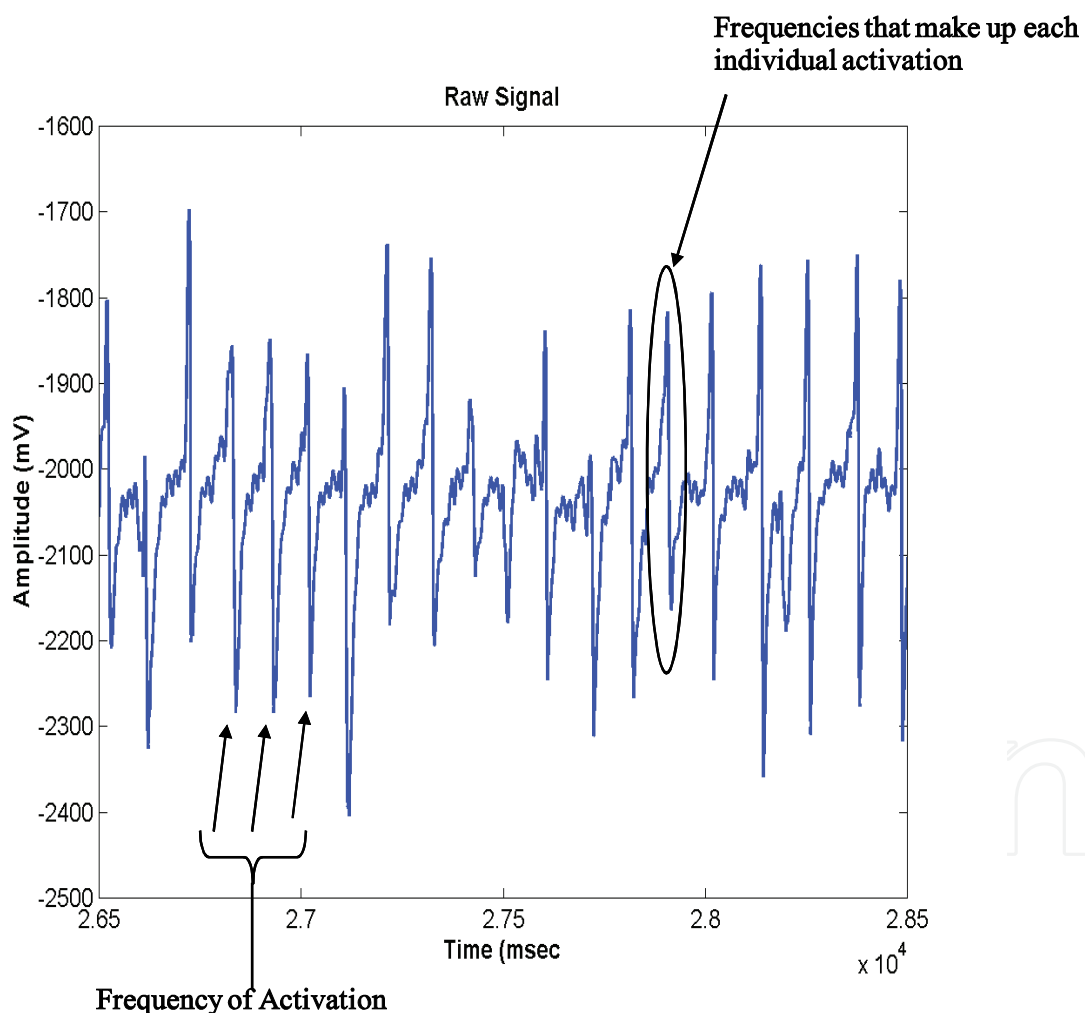

Fig. 1. An example of a raw unipolar atrial fibrillation signal. The frequencies that compose the cycle length of the fibrillation are different from the frequencies that compose the unipolar deflection that indicates an atrial activation. (Reproduced with permission from Everett TH, Olgin JE. Signal processing of fibrillatory electrograms. Aliot EE, Haissaguerre M, Jackman WM editors. Catheter Ablation of Atrial Fibrillation. Blackwell Publishing, Malden, Massachusetts.2008; 85–101.)

When performing signal analysis, some degree of signal processing is performed via filtering. In general, filtering of signals is employed to eliminate or reduce any signal components that would interfere with the analysis such as 50 or 60 Hz noise, any unwanted cardiac activation such as QRS complexes, and any far-field artifacts. Filtering is also used to enhance the signal generated by a cardiac activation. Specific signal processing aimed at signal analyses can be employed to uncover fundamental characteristics of the recorded signal and to aid in understanding the characteristics of the fibrillatory signals.

When filtering and analyzing fibrillatory electrograms, there are two types of frequency components within the signal that we need to be concerned with, and these are shown in figure 1. One is the frequency of the fibrillation which can vary from 3 – 15 Hz. The other type of frequency component of the signal is the frequencies that compose each individual activation spike. These frequencies can be greater than 20 Hz. This becomes important when performing signal analysis. One common type of signal analysis is frequency domain analysis using a fast Fourier transform (FFT) the results of which indicate the frequencies that compose the signal. The high frequency content that composes each atrial activation can dominate the FFT masking the frequency of the fibrillation. Filtering the electrograms can bring the frequency of the actual atrial activation frequency to the foreground (Botteron and Smith 1995; Everett, Kok, et al. 2001). Filtering can also increase the probability that an atrial activation occurred at that point in time, and reduce the influence of low frequency far field artifacts such as far-field QRS complexes or low frequency respiration that can create unwanted noise in the recording (Botteron and Smith 1995).

2.1 Frequency domain analysis

In order to generate a signal, Jean Babtist Fourier, a French mathematician, first claimed that any repetitive signal could be composed of sums of sinusoids. Figure 2 shows two examples, one of a square wave (Panel A) and the corresponding sinusoids that are added together to generate this signal, and one of a triangle wave (Panel B) and its corresponding sinusoids. This same theory can also be applied to cardiac signals. Fourier also developed what is known as the Fourier transform which is based on the concept that signals can be approximated by a sum of sinusoids, each at a different frequency. The Fourier transform is then a description of what frequencies are present and how much of each frequency composes the signal. The results of a FFT are either given as a magnitude spectrum or a power spectrum as a graph of peaks at the frequencies that are present within the signal. The more a certain frequency is influencing a signal, the higher the peak. The highest peak of a magnitude spectrum is considered the dominant frequency (DF), which indicates the main frequency that composes the signal. The magnitude spectrum also composes peaks at frequencies which are integer multiples of the dominant peak called the harmonic peaks. The FFT is now being applied to cardiac electrograms during fibrillation to study the spatiotemporal characteristics of the signals. Studies have shown that the resulting magnitude spectrum from FFT calculations can vary from the recording location, and over time (Everett, Moorman, et al. 2001; Everett et al. 2006). From the results of the frequency domain analysis a couple of simple methods to quantitate differences in magnitude spectrums have been devised. A measurement of the organization of the AF signal can be obtained through either the regularity index (RI) which is defined as the ratio of the area under the dominant peak to the total area of the spectrum (Kalifa et al. 2006) or the organization index (OI) which is defined as the ratio of the area under the dominant peak *and* its harmonics to the total area of the spectrum. (Everett, Kok, et al. 2001)
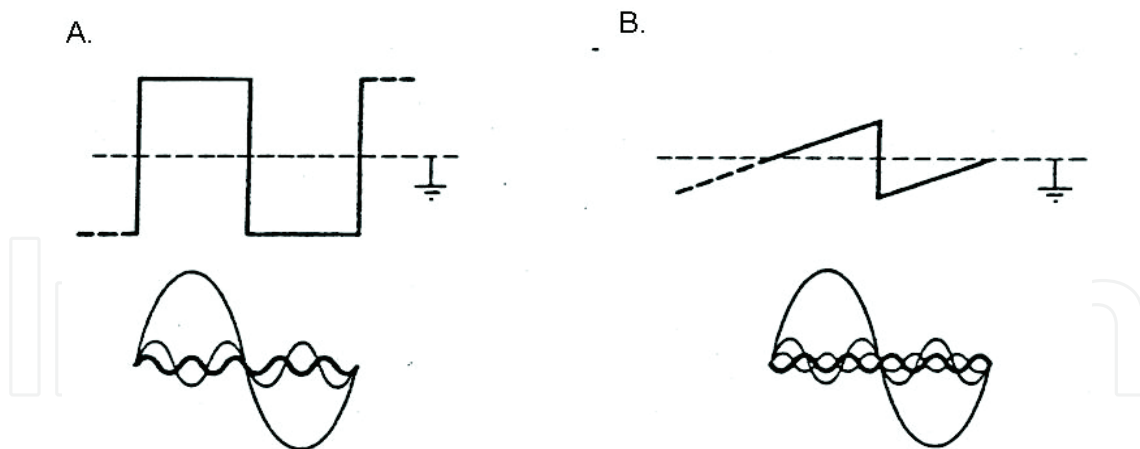
Fig. 2. Every repetitive signal can be represented by adding sine waves of different frequencies together. An example of a square wave and a triangle wave are shown with their corresponding sine waves that added together compose that particular signal. (Reproduced with permission from Everett TH, Olgin JE. Signal processing of fibrillatory electrograms. Aliot EE, Haissaguerre M, Jackman WM editors. Catheter Ablation of Atrial Fibrillation.Blackwell Publishing, Malden, Massachusetts.2008; 85–101.)

In addition to measuring the organization of a signal, FFT analysis can also be used to detect areas of conduction block. Areas of block, alter the frequency of the fibrillation at that site. The recording electrodes then record a signal that is influenced by other frequencies. These other frequencies then appear in the resulting FFT as peaks that are not associated with the dominant one as a harmonic. When compared to an isochronal map of activation during AF, the signals that result in FFTs that have secondary peaks within their magnitude spectrum were located in and around areas of conduction block (Evans et al. 1999). These extra peaks within the magnitude spectrum would also decrease the organization of the signal as measured from the resulting FFT by the OI.

3. Substrate differences among models of Atrial Fibrillation

Atrial fibrillation occurs in a variety of clinical settings, and investigators have developed several animal models to mimic those settings in which AF occurs. The most widely studied canine models include congestive heart failure (CHF), mitral regurgitation (MR), rapid atrial pacing (RAP), and a cholinergically mediated model induced with acetylcholine or methylcholine. The structural and electrical characteristics of each of these models are outlined below.

3.1 Congestive Heart Failure (CHF)
The most studied model of heart failure involves pacing the right ventricle of canine hearts at 220-240 beats per minute for 4 weeks. Although other heart failure models are being developed that show a similar atrial substrate as described below. (Lau et al. 2011; Shimano et al. 2008) As figure 3 shows, the ventricular tachycardia pacing produces a significant increase in atrial interstitial fibrosis. In addition, as figure 4 shows, there is an increase in conduction anisotropy produced by localized conduction slowing which has correlated to an increase in AF vulnerability (Li et al. 1999), and a propensity for long durations of AF
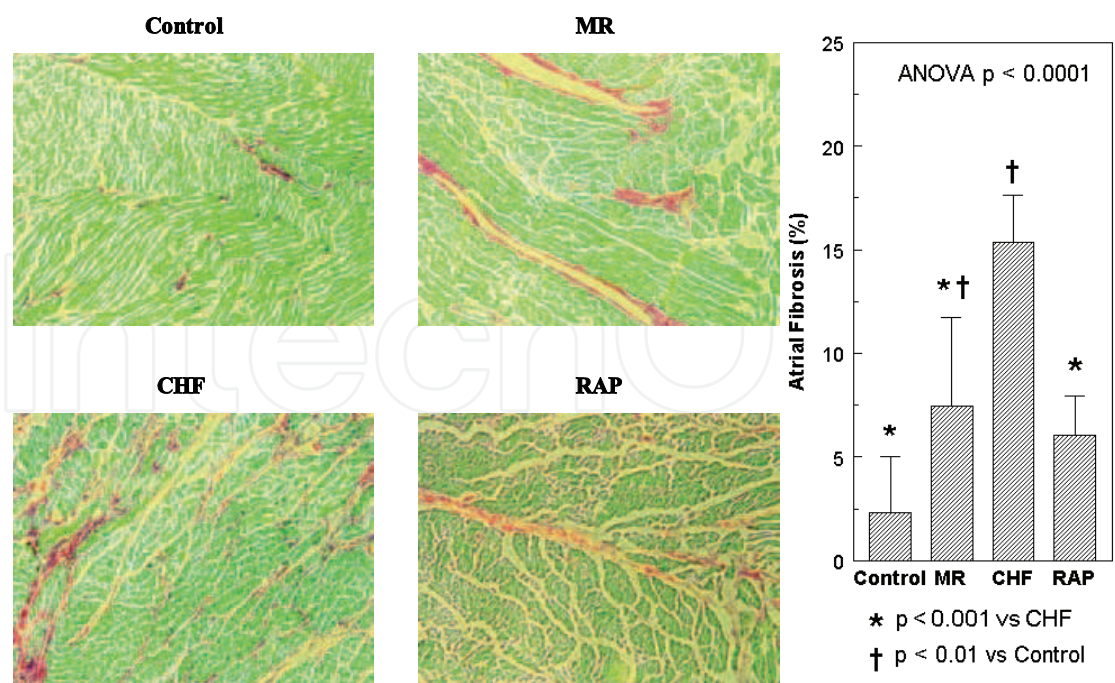
Fig. 3. Amount and distribution of fibrosis from atrial tissue samples from the canine models of Control, MR, CHF, and RAP. Each tissue sample is stained with Sirus red and magnified 100X. The CHF group had a significantly larger amount of fibrosis as compared to the other groups. (Reproduced with permission from **Everett TH**, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical remodeling. Am J Physiol Heart CircPhysiol 2006; 291: H2911 – H2923.
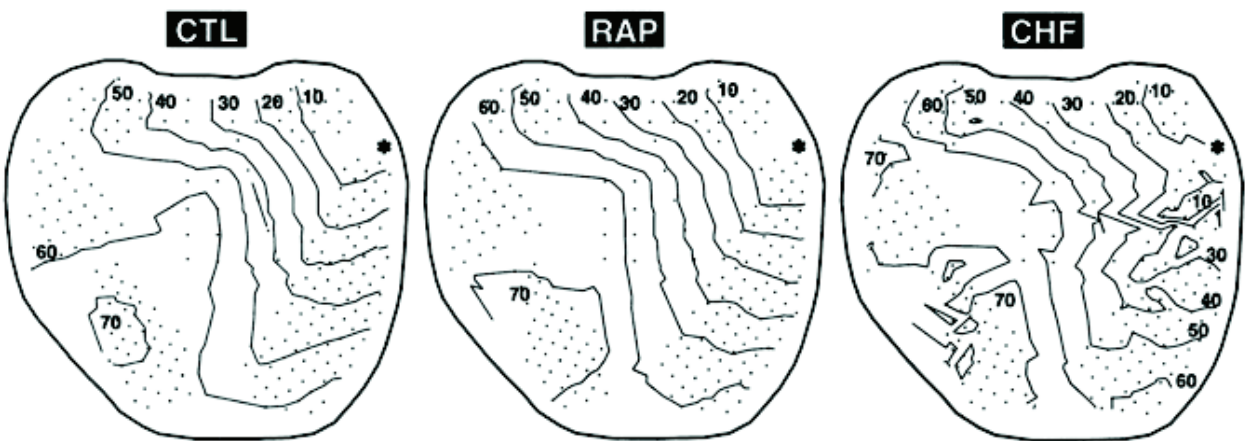

Fig. 4. Isochronal activation maps for control (CTL), rapid atrial pacing (RAP), and congestive heart failure (CHF). The CHF model, which is assocatied with structural atrial remodeling, had an increase in conduction heterogeneity as compared to the other models. The RAP model, which is associated with electrical atrial remodeling, had homogeneous conduction that was similar to control. (Reproduced with permission from Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation 1999; 100:87-95.)

(Lee et al. 2006). An investigation into the ion currents in this model has shown a decrease in I_{to}, I_{Ks}, and I_{Ca}along with an up regulation of the Na^+-Ca^{+2} exchange current. (Cha, Ehrlich, Zhang, and Nattel 2004) This remodeling in ionic currents results in an increased atrial effective refractory period (AERP). In this model, AF vulnerability has been shown to remain even after a 5 week recovery period in which the heart failure resolves (Shinagawa et al. 2002) and there is recovery of the ionic remodeling. (Cha, Ehrlich, Zhang, Shi, et al. 2004) This model has shown that structural remodeling alone can promote a substrate that enhances AF initiation and propagation.
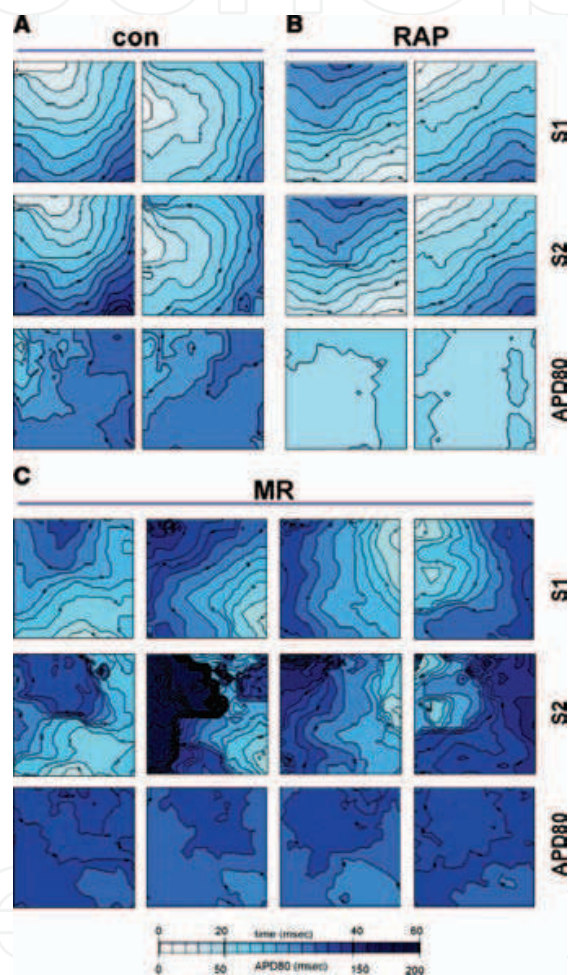
3.2 Mitral Regurgitation (MR)

Fig. 5. Conduction patterns recorded with optical mapping during pacing at 350ms (S1) and with an extrastimulus (S2) in the LA along with the APD_{80} during the S1. For the control and RAP, 2 stimulus sites are shown and similar conduction is seen at each site. For the MR group, 4 stimulus sites are shown as the conduction was more variable, and depended on the stimulation site. The MR model, which is associated with structural atrial remodeling, had an increase in conduction heterogeneity as compared to the other models. The RAP model, which is associated with electrical atrial remodeling, had homogeneous conduction that was similar to control. (Reproduced with permission from Verheule S, Wilson E, Banthia S, Everett T, Shanbhag S, Sih H, Olgin J.Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. Am J Physiol Heart CircPhysiol 2004;287: H634-H644).

Similar to the CHF model, structural changes are seen with chronic MR and these animals are more susceptible to AF. (Verheule et al. 2003) The MR model is created through catheter avulsion of the mitral chordae. After 4 weeks, structural remodeling is observed which includes LA enlargement, inflammation, fiber separation, (Verheule et al. 2003) and with only a moderate increase in interstitial fibrosis as shown in figure 3. (Everett et al. 2006) These structural changes correlated to increased conduction heterogeneity and anisotropy in the LA as shown in figure 5 (Verheule et al. 2004). Electrophysiologically, this model has demonstrated a homogeneous increase in AERP in both the RA and LA *in vivo* (Verheule et al. 2003) while figure 6 shows that with optical mapping no differences were seen in the action potential duration as compared to structurally normal hearts (Verheule et al. 2004). This model again shows that structural remodeling can increase AF vulnerability.

3.3 Rapid Atrial Pacing (RAP)

A commonly used large animal model of AF is the RAP model. This model is usually developed by placing an endocardial pacing lead into the RA and pacing the atria at 400-600 beats per minute for at least 6 weeks (Morillo et al. 1995; Verheule et al. 2004; Wijffels et al. 1995). The atrial pacing at high rates results in electrophysiological remodeling which includes a decrease in the atrial effective refractory period (AERP) (Morillo et al. 1995; Wijffels et al. 1995), action potential duration (APD) (Verheule et al. 2004; Yue et al. 1997), and an increase in the dispersion of refractoriness (Fareh, Villemaire, and Nattel 1998).
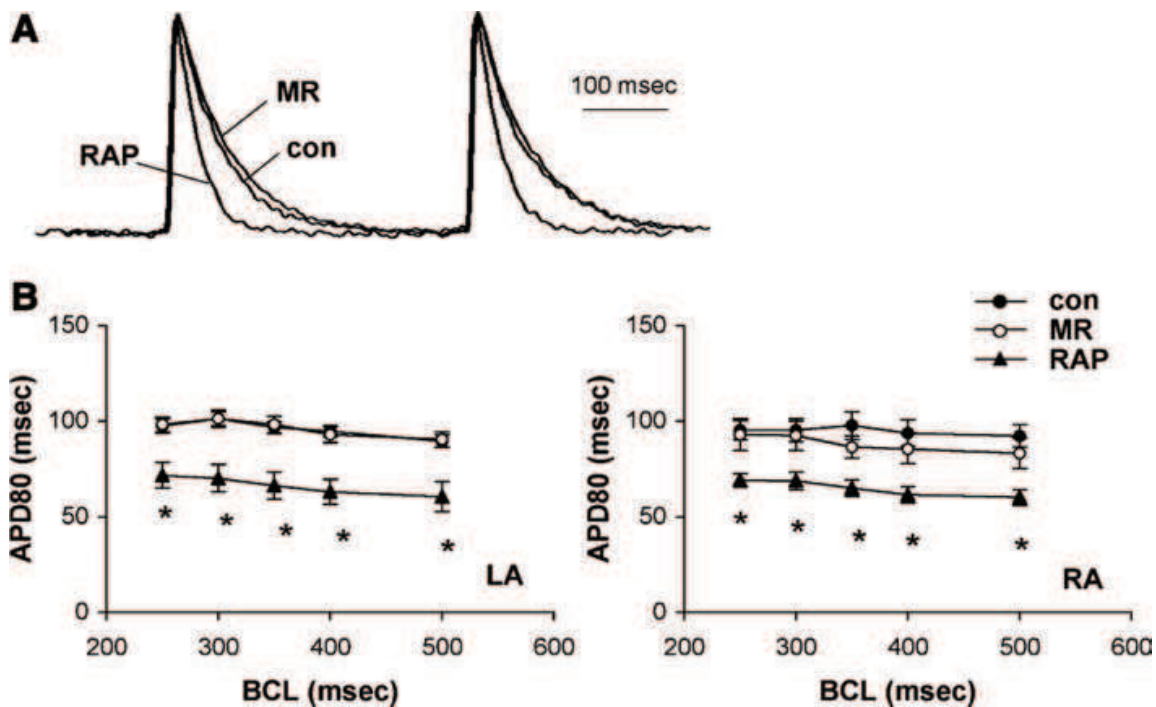

Fig. 6. Action potential duration and conduction velocity. A) Representative examples of optical action potentials at a BCL of 350 msec recorded in control, MR and RAP LA. B) APD80 as a function of the BCL in the LA (left panel) and RA (right panel). Data are mean $\pm$ s.e.m. Asterisks indicate significant difference compared to control. (Reproduced with permission from Verheule S, Wilson E, Banthia S, Everett T, Shanbhag S, Sih H, Olgin J.Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. Am J Physiol Heart CircPhysiol 2004;287: H634-H644).

Figure 6 shows an example of action potentials recorded with optical mapping and a significant decrease in APD80 is seen as compared to control atria (Verheule et al. 2004). This type of remodeling has been shown to create a substrate that increases AF vulnerability. Continued pacing promotes longer durations of AF until it eventually becomes self-sustained ("AF begets AF") (Wijffels et al. 1995).

Structurally, this model has resulted in cellular hypertrophy, altered mitochondrial morphology, loss of myofibrillar structure, glycogen accumulation, and an increase in extracellular matrix protein expression (Ausma et al. 1997; Morillo et al. 1995). However, as shown in Figure 3, these structural changes occur without a significant increase in fibrosis as compared to the CHF model. In addition, Figure 7 shows that atrial dilation does not occur in the RAP as there was no difference in atrial size between the RAP model and the structurally normal hearts of the control group. This was in contrast to the CHF and MR models which showed significant atrial dilatation. Finally, the RAP model shows homogeneous conduction as shown in Figures 4 and 5 similar to structurally normal hearts (Verheule et al. 2004).
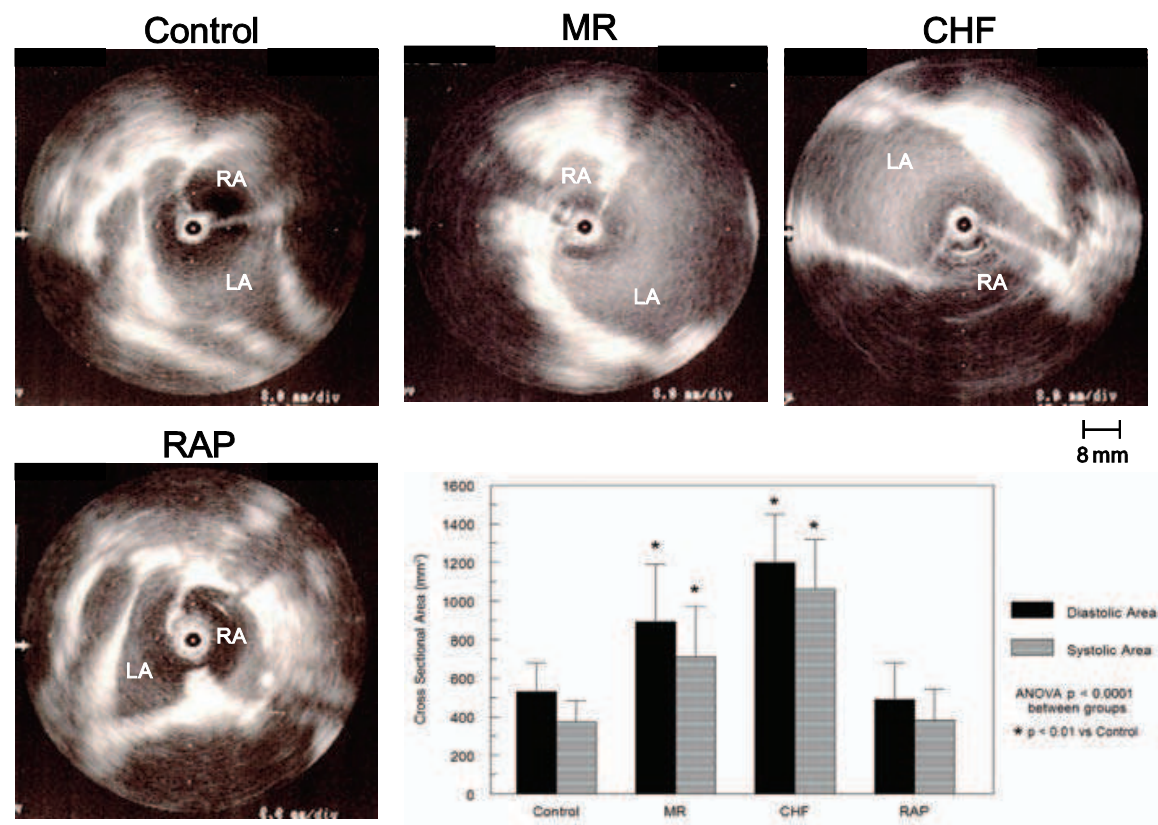

Fig. 7. Intracardiac Echo (ICE) images of the LA from each of the models studied during diastole. The ICE probe was placed at the septal wall at the level of the fossa ovalis such that the LA appendage and the mitral valve annulus were in the field of view. The cross sectional area of the LA was then measured. Also shown is summary data of the average left atrial cross sectional area for each canine AF model. A cross-sectional area was measured during both diastolic (solid bars) and systolic contractions (hatched bars.) (Reproduced with permission from Everett TH, Wilson EE, Olgin JE. The effects of atrial fibrillation substrate and spatiotemporal organization on atrial defibrillation thresholds. Heart Rhythm 2007; 4:1048-1056.)

3.4 Cholinergic agnonist

An acute model of AF that is created through infusion of drugs such as acetylcholine or methylcholine which activates K_{Ach} channels and results in a dose-dependent shortening of the action potential duration. Cholinergic agonists are given to structurally normal hearts and have shown to have little or no effect on atrial conduction properties. (Schuessler, Bromberg, and Boineau 1990; Rensma et al. 1988) In addition, no structural remodeling occurs however, an increase in AF vulnerability has been shown.

4. Characteristics of Atrial Fibrillation in the different models

In order to study the characteristics of the AF within each of the models described, several different recording devices and technologies have been utilized. For *in vivo* studies, these include plaques or ribbons of electrodes that are placed on the epicardial surface of the atria (Everett et al. 2006; Okuyama et al. 2003), and/or catheters with various arrays of electrodes that are inserted into a chamber of the atria to record endocardial signals (Everett et al. 2010; Akar et al. 2002; Lazar et al. 2004). An endocardial array that is used is non-contact mapping using the Ensite 3000 mapping system (Everett et al. 2010; Earley et al. 2006; Kadish et al. 1999; Schilling, Peters, and Davies 1999). A non-contact balloon mapping catheter is positioned in a chamber of the heart along with a standard EP catheter. Using the location algorithm in the ESI, the EP catheter can be detected as it moves around the chamber thus creating a three dimensional rendering of the atria. The catheter records 64 cavitary potentials and then inversely applies them through the Laplace equation in real time generating more than 3,000 unipolar "virtual" electrograms that are then projected on the geometry of the heart chamber. For *in vitro* studies, optical mapping is a technology which uses voltage sensitive dyes to record the activation and repolarization of cardiac tissue from several sites simultaneously which provides an increase in the spatial resolution over traditional electrode recordings (Ding and Everett 2010). Activation mapping and signal analysis techniques described above can then be performed on the signals recorded during AF to measure the spatiotemporal organization and to provide insights into the characteristics and mechanisms of the AF in each model.

4.1 Congestive Heart Failure

The CHF model is associated with structural remodeling with a significant increase in atrial fibrosis which leads to conduction abnormalities and increased AF vulnerability. Several studies have mapped the atria during AF in this model and evidence exists for both reentry and discrete, stable foci. Li et al showed that conduction abnormalities increased AF vulnerability in this model and epicardial mapping showed that the resulting AF had a mechanism of macroreentry which could be terminated with dofetilide, an I_{Kr} channel blocker (Li, Benardeau, and Nattel 2000). In a separate study, this same group when comparing endocardial versus epicardial activation again showed an AF mechanism of macrorentry which supported their previous findings (Derakhchan et al. 2001). Everett et al also performed endocardial and epicardial mapping in the CHF canine model and 5/6 dogs studied had AF characterized by stable focal mechanisms on the endocardial surface with non-contact mapping. Epicardial plaque mapping showed 4/6 dogs with focal AF (Everett et al. 2010). Figure 8C shows an example of this focal activation on the endocardial surface with non-contact mapping. From the focal source, the wave front rotates counterclockwise on both sides of the LA. A focal mechanism of AF was also reported by Stambler et al which was terminated by calcium channel blockers (Stambler et al. 2003). In a later study this group performed biatrial mapping in the CHF dogs and again showed a focal mechanism of

AF. Radiofrequency catheter ablation of the focal site terminated the AF in 67% of the animals studied (Fenelon, Shepard, and Stambler 2003). In the CHF model, there is also evidence that suggests that focal sources of AF activation can be found in the pulmonary veins. High resolution mapping of the pulmonary veins by Okuyama et al showed that half of the AF episodes were characterized by focal sources in the pulmonary veins versus none in structurally normal hearts (Okuyama et al. 2003).
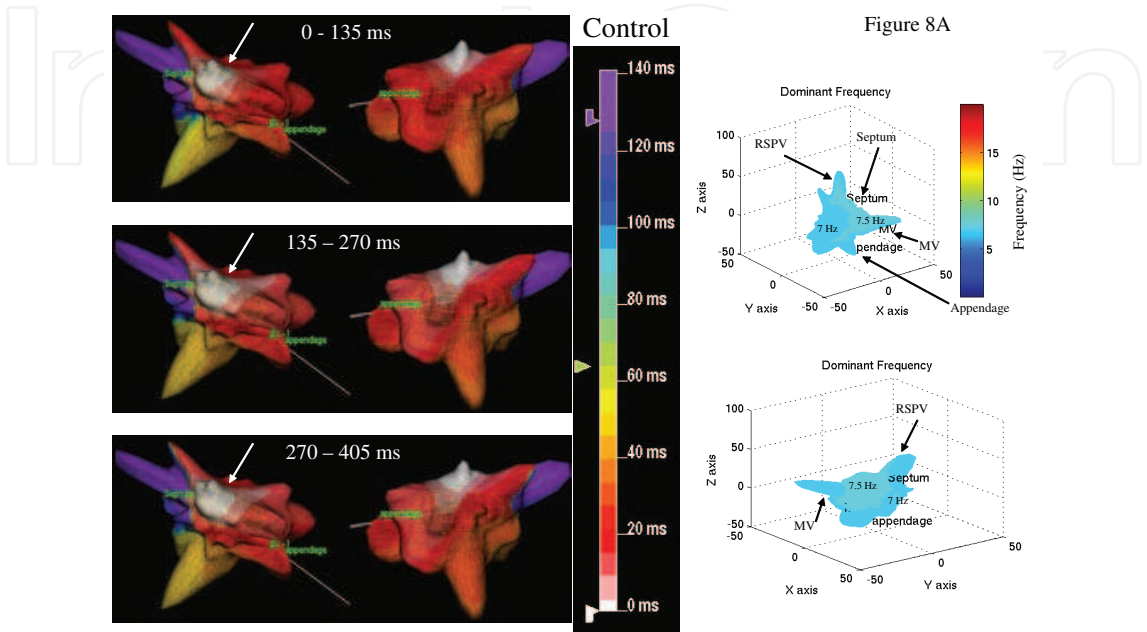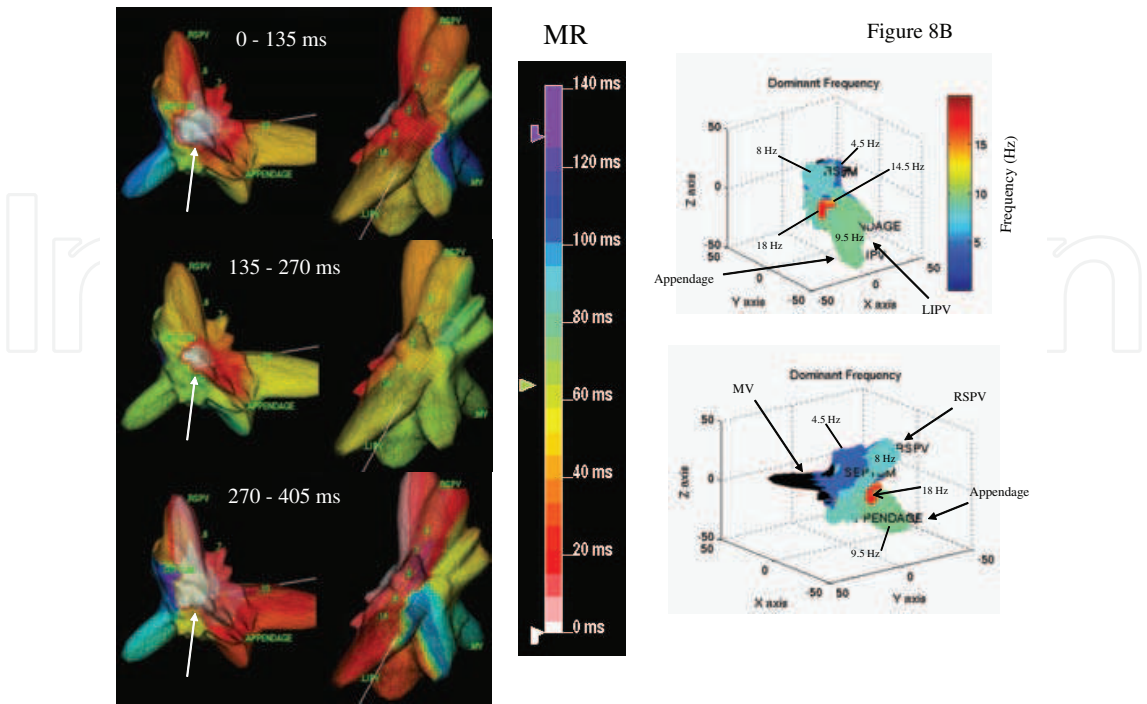

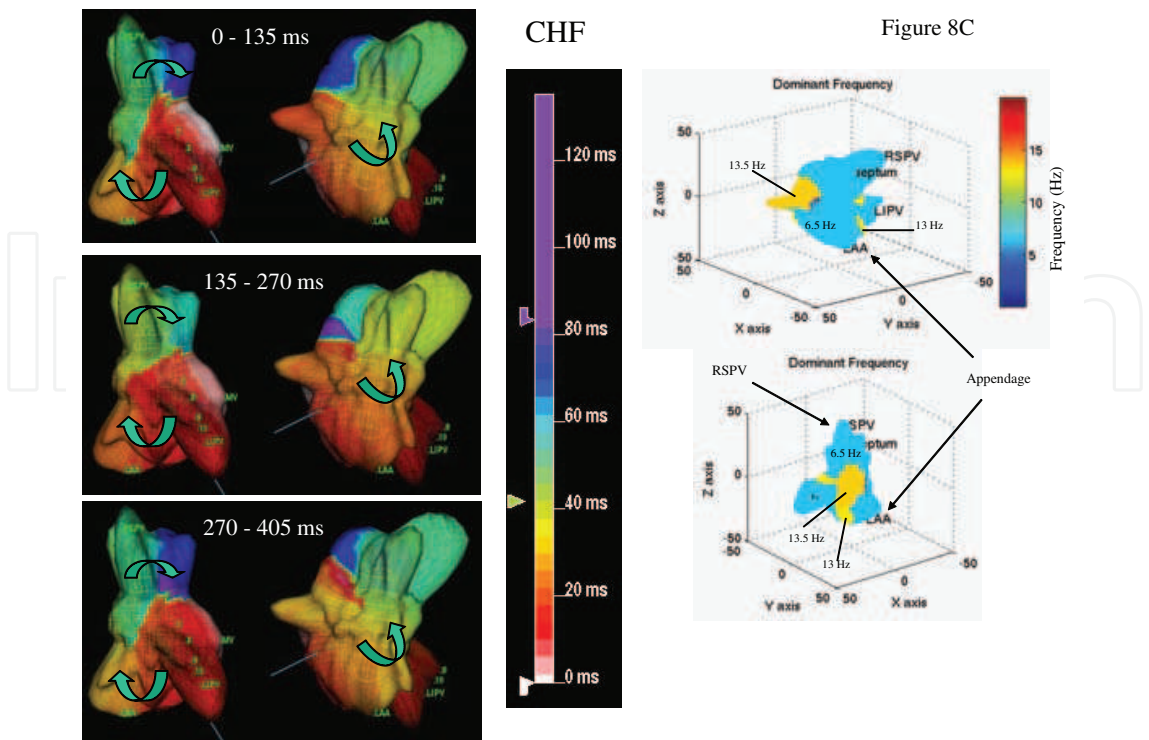Fig. 8a. (continuation)

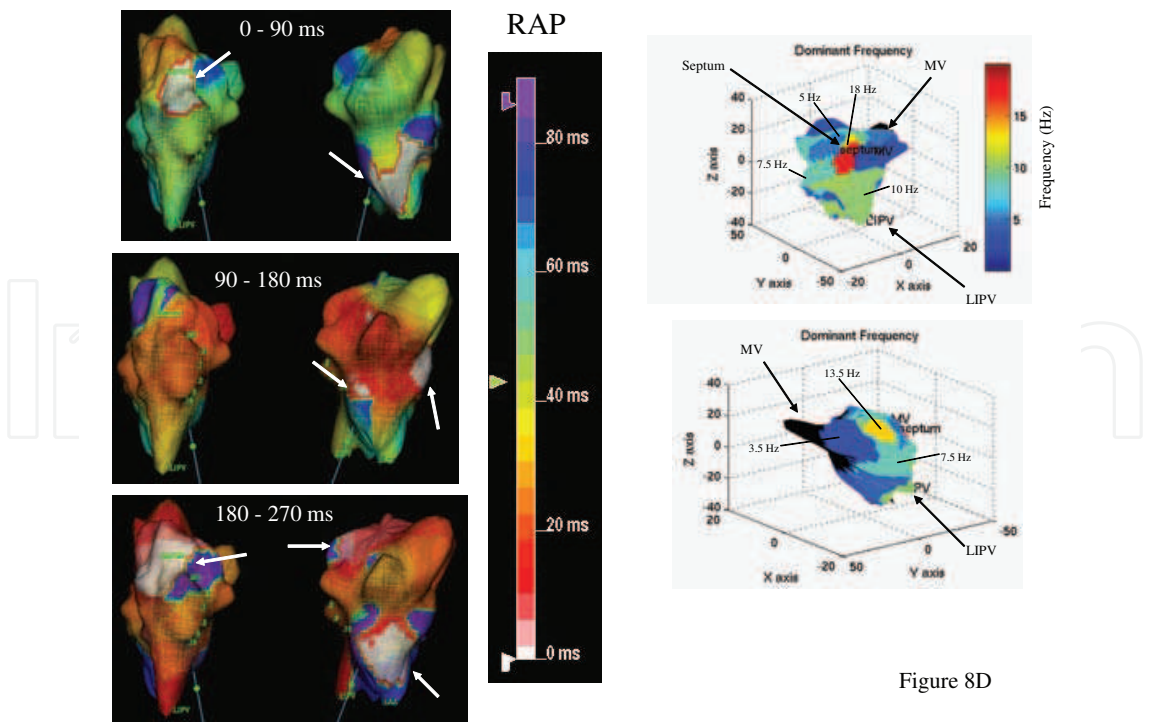Fig. 8b. (continuation)

Fig. 8c. (continuation)
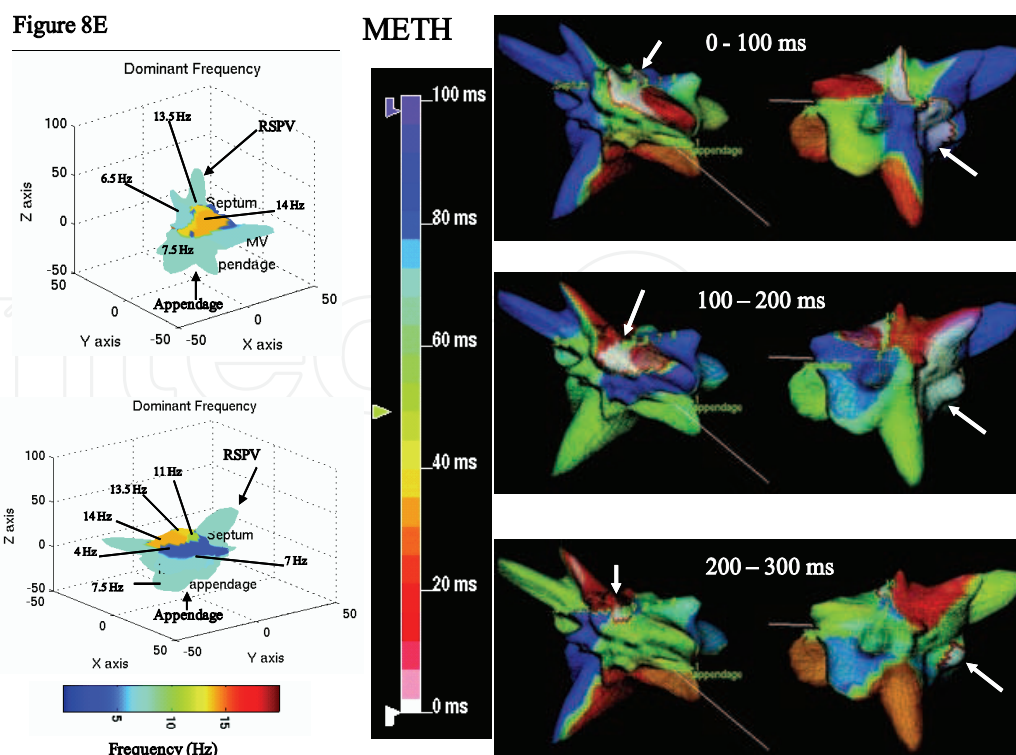

Fig. 8d. (continuation)

Fig. 8e. Isochronal maps of AF activation along with static DF maps in each of the canine models of Control (A), MR (B), CHF (C), RAP (D), and cholinergic stimulation (Meth) (E). On the isochronal maps, the colors indicate the timing of activation, with white representing the earliest activation and purple representing the latest. Curved arrows indicate the direction of reentry; straight arrows, the earliest activation of a focus. Reentry is determined by areas of earliest activation meeting areas of latest activation. In the example from the control group (A), 3 sequential maps are shown at 135-ms intervals. A stable, focal site is seen in each map. Two DF maps are shown of different views of the 3-D geometry from the same 2-second window. In the MR example, maps are shown at 135 ms intervals. A focal area of activation is seen near the RSPV. Two DF maps are shown of different views of the 3-D geometry from the same 2-second window showing a high DF area at the site of focal activation. In the CHF example, maps are also shown at 135 ms intervals and a stable, focal reentrant wavefront is seen in every map. Again, two DF maps are shown of different views of the 3-D geometry from the same 2-second window. The RAP model had AF characterized by multiple wavelets. In this example, each 90 ms window shows a different site of early activation. Two DF maps are shown from two different time periods showing the transient nature of the high DF areas. For the METH example, two stable focal sites of activation are seen in each window. Two DF maps are shown of different views of the 3-D geometry from the same 2-second window. (Reproduced with permissiom from Everett TH, Wilson EE, Hulley GS, Olgin JE. Transmural characteristics of atrial fibrillation in canine models of structural and electrical atrial remodeling assessed by simultaneous epicardial and endocardial mapping. Heart Rhythm 2010;7:506-517.)

Frequency domain analysis of electrograms recorded during AF has demonstrated that the AF is characterized by stable, high-frequency regions. Using FFT analysis, Ryu et al demonstrated that the AF had stable drivers in either the RA, LA, or both (Ryu et al. 2005). Everett et al also reported AF in the CHF model characterized by stable, high-frequency

regions. However these regions were singular and appeared in either the RA or LA with steep frequency gradients away from these sites (Everett et al. 2006). Figure 9 shows an example of a dominant frequency map during AF recorded with epicardial plaques. A singular high-frequency area is seen in the RA.
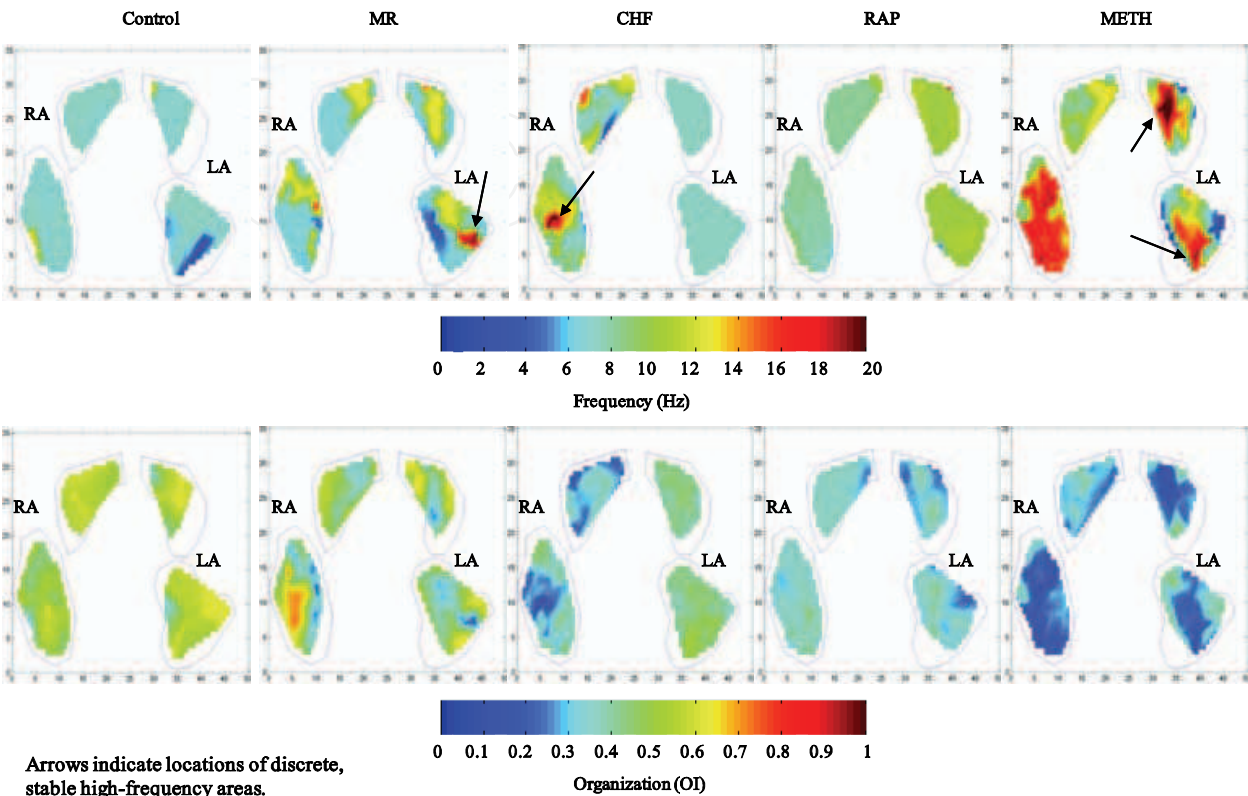

Fig. 9. Examples of static dominant frequency maps (top panels), and organization maps (bottom panels) for the canine models both structural atrial remodeling (CHF and MR) and electrical atrial remodeling (RAP and METH) along with control. DFs and OIs are shown from an FFT performed on a 2-second window of AF. Arrows indicate the location of stable, discrete high DF areas. (Reproduced with permission from Everett TH, Wilson EE, Olgin JE. The effects of atrial fibrillation substrate and spatiotemporal organization on atrial defibrillation thresholds. Heart Rhythm 2007; 4:1048-1056).

4.2 Mitral Regurgitation

The MR model is associated with structural remodeling with LA dilatation, inflammation, and fiber separation (Verheule et al. 2003), however, this model has significantly less fibrosis than the heart failure model (Everett et al. 2006), but still shows an increase in conduction heterogeneity and an increase in AF vulnerability (Verheule et al. 2004; Verheule et al. 2003). AF activation patterns on the epicardial surface have shown either stable wavefronts or focal sources. Focal sources or reentrant wavefronts were consistently seen on the endocardial surface with non-contact mapping (Everett et al. 2010). Figure 8B shows an example of the focal activation seen on the endocardial surface in MR dogs. Similar to the CHF model, the MR model had very stable activation patterns. Using linking to measure stability, it has been shown that AF in the MR model has a high degree of linked beats in both the RA and LA (Everett et al. 2006). In three separate

studies, Everett et al performed frequency domain analysis of AF signals recorded from epicardial plaques and have reported the presence of stable, high-frequency areas although they were not seen in every experiment (Everett et al. 2010; Everett, Wilson, and Olgin 2007; Everett et al. 2006). However, they were consistently seen in the LA with optical mapping (Everett et al. 2004). An example of a dominant frequency map with a discrete, high-frequency area in the LA is seen in Figure 9.

4.3 Rapid atrial pacing

The rapid atrial pacing model is associated with electrical remodeling, with a shortening of the atrial effective refractory period and action potential duration (Morillo et al. 1995; Wijffels et al. 1995). When analyzing the mechanism of AF in this model, most data points towards a mechanism of multiple wavelets. In addition, it has been shown that the longer the pacing continues, the more disorganized the AF becomes with more wavelets, shorter cycle lengths, and shorter AERPs promoting AF propagation and leading to the term "AF begets AF." (Wijffels et al. 1995)

In the persistent AF RAP models, epicardial plaque mapping by Sih et al and Everett et al has shown AF characterized by multiple wavelets with twice as many sites of early activation than other models (MR or CHF) (Everett, Wilson, and Olgin 2007) or control (Sih et al. 2000). However, one study by Wu et al showed that the pulmonary veins and ligament of Marshall were the sources of the highest frequency of activation during AF in this model (Wu et al. 2001). Endocardial non-contact mapping also showed a mechanism of multiple wavelets (Everett et al. 2010). An example of this type of activation is shown in Figure 8D. When linking is used to analyze the stability of the AF wavefronts by quantifying the number of continuous beats traveling in the same direction, the RAP model had the lowest percentage of linked beats when compared to control or the CHF and MR models.

Frequency domain analysis did not show any discrete, stable high-frequency areas with either epicardial plaque mapping (Everett et al. 2010; Everett, Wilson, and Olgin 2007; Everett et al. 2006), endocardial non-contact mapping (Everett et al. 2010), or optical mapping (Everett et al. 2004). Any high frequency areas were transient and not stable. FFT analysis of plaque AF electrograms and optical mapping signals did show that the RAP model was the only one in which the LA had consistently higher dominant frequencies than the RA (Everett et al. 2004; Everett et al. 2006).

4.4 Cholinergic induced AF

An acute model of electrical remodeling, studies using cholinergic stimulation of AF have shown a variety of AF mechanisms. It was using this model in a sheep that AF characterized by a discrete region of stable, high-frequencies was shown (Skanes et al. 1998). These areas would consist of frequencies that were higher than any other in the atrium, thus considered to be responsible for driving the AF. Further experiments showed that these discrete, stable high-frequency areas resulted from microreentrant sources (Mandapati et al. 2000), and that at a critical frequency threshold, a frequency gradient developed between the LA and RA (Mansour et al. 2001).

In a canine heart, discrete, stable-high frequency areas were seen in the LA, but they were also observed in the RA, and no LA-RA frequency gradient existed (Everett et al. 2006). Figure 9 shows an example of a dominant frequency map with 2 stable high-frequency areas

in the LA. AF recordings with epicardial plaques showed AF characterized by multiple sites with early activation and a low degree of stability as quantified by measuring the number of linked beats. Everett et al also showed that AF induced with methylcholine had varying mechanisms of multiple wavelets, multiple foci, and in some cases organized stable wavefronts were seen on the epicardial surface (Everett et al. 2010). Non-contact mapping on the endocardial surface showed different mechanisms in different experiments from multiple wavelets, multiple foci, and reentry. The example in Figure 8E shows 2 stable focal sites of activation. These differences in AF characteristics between species may be due to differences in the distribution of I_{kAch} (Sarmast et al. 2003) channels, thus varying the influence of cholinergic drugs on the atria.

5. Transmural characteristics

A couple of recent studies have shown that the atrial substrate also plays a role in the transmural characteristics of AF. In the left atrium of 5 different canine models, Everett et al simultaneously recorded AF signals from the endocardial and epicardial surfaces (Everett et al. 2010). Virtual endocardial signals (Ensite®, Endocardial Solutions, Inc. St. Paul, Minnesota) were directly compared with contact signals from plaques placed on the epicardial surface. Figure 10 shows the maximum dominant frequency on both the epicardial and endocardial surfaces for each model of Control, MR, CHF, RAP, and methylcholine. As the graph shows, the endocardial surface had significantly higher maximum dominant frequencies than the epicardial surfaces for each model. Figure 11 shows the summary data from directly comparing individual endocardial to epicardial
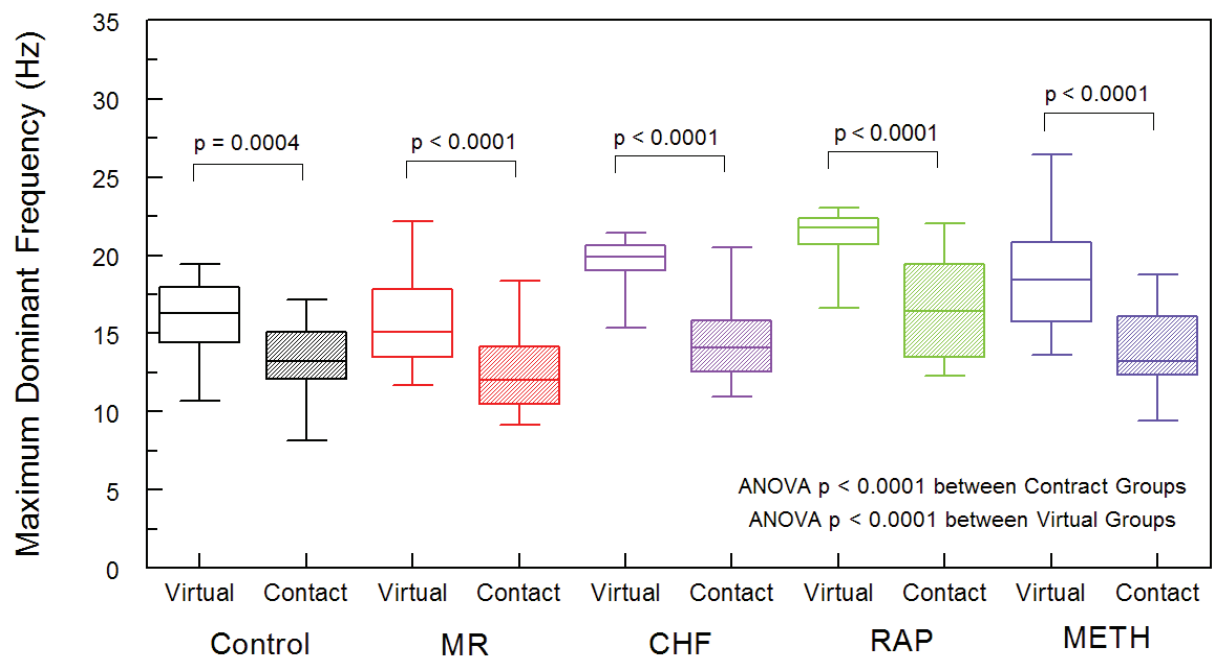

Fig. 10. Maximum dominant frequency for both the epicardial (hatched box) and endocardial (open box) surfaces for each model of Control, mitral regurgitation, heart failure, rapid atrial pacing, and cholinergic stimulation (meth). As the graph shows, the endocardial surface had significantly higher maximum dominant frequencies than the epicardial surfaces for each model.

signals. The panel on the left indicates the percentage of paired electrograms that had a cross correlation coefficient above 0.8. The panel on the right represents the percentage of paired electrograms that had matching dominant frequencies. As both of these graphs show, the structurally remodeled AF models of CHF and MR had the highest percentage of correlation coefficients above 0.8 and similar dominant frequencies. The electrically remodeled rapid atrial pacing model had the lowest percentage of both metrics. When the mechanisms on both surfaces were compared, AF characterized by multiple wavelets was seen on both the endocardial and epicardial surfaces of the RAP model which had the lowest degree of transmural similarities. The majority of the AF in the CHF model was characterized by focal sources and the highest amount of transmural similarities, however half of the CHF dogs studied had different endocardial/epicardial AF activation patterns.
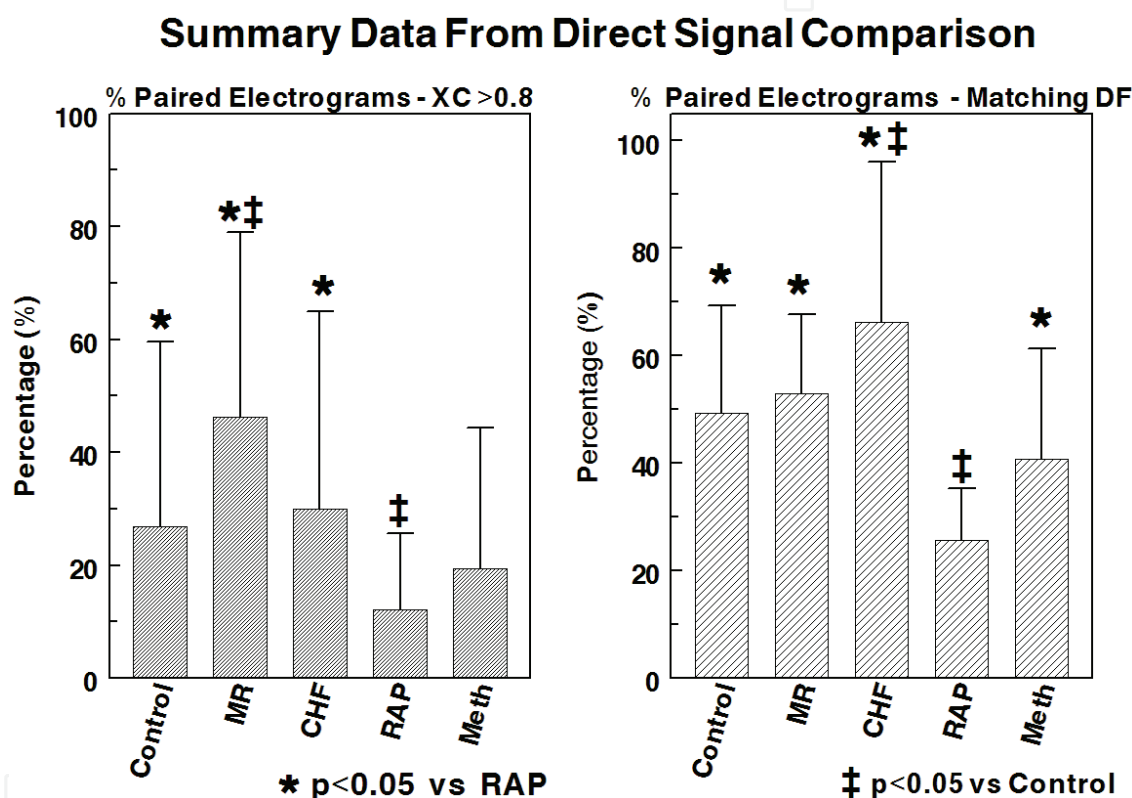

Fig. 11. Summary data from directly comparing individual endocardial to epicardial signals. The panel on the left indicates the percentage of paired electrograms that had a cross correlation coefficient above 0.8. The panel on the right represents the percentage of paired electrograms that had matching dominant frequencies. As both of these graphs show, the structurally remodeled AF models of CHF and MR had the highest percentage of correlation coefficients above 0.8 and similar dominant frequencies. The electrically remodeled rapid atrial pacing model had the lowest percentage of both metrics.

In another recent study, Eckstein et al performed simultaneous endocardial/epicardial AF recordings in the left atrium in goats divided into 3 groups: acute AF, 3 weeks of rapid atrial pacing, and 6 months of rapid atrial pacing (Eckstein et al. 2011). What was shown was an increase in the electrical dissociation between the endocardial and epicardial surfaces after 3 weeks of rapid atrial pacing which increased further with 6 months of pacing. Dissychony was demonstrated by differences in epicardial/endocardial activation times and local

conduction vectors. An increase in the electrical dissociation between the endocardial and epicardial surfaces was theorized to provide a substrate for AF propagation.

6. Comparisons among models

Each animal model discussed here represents a different substrate that results in an increased AF vulnerability. While AF can be reliably initiated in any of these substrates, the mechanisms and spatiotemporal characteristics of the AF in each differs. However, some common features can be perceived from models that share common substrate properties, especially structural remodeling. The models that experienced structural remodeling known to result in alterations in conduction, (Li et al. 1999; Verheule et al. 2004; Verheule et al. 2003) had stable, discrete high frequency areas in the DF maps. Steep frequency gradients, and large areas of similar frequencies were seen away from the high frequency areas. These frequency characteristics remained stable from epoch to epoch as the stable high-frequency areas remained consistently spatially located from episode to episode. The structural changes seen in the MR and CHF models likely contribute to the frequency gradient that occurs outward from the high-frequency area as the structural remodeling promotes conduction delay and block as well as wave break. Based on the spatiotemporal data, this would suggest a stable rotor in these models with highly organized wavefronts in the other areas of the atria, which would correlate with the 'mother-rotor' theory as an AF mechanism in these models. An AF mechanism of focal reentry dominates the AF activation patterns in these models, especially in the CHF model. The CHF model also had a high degree of quantifiable transmural similarities between the endocardial and epicardial surfaces (Everett et al. 2010).

As described above, both the RAP and cholinergic models are characterized primarily by atrial electrical changes. However, how this remodeling is achieved is different for each model. The RAP model uses 6 weeks of rapid atrial pacing to achieve the desired effects. During this time, some cellular changes will occur. However, in both whole heart and optical mapping studies, no conduction abnormalities are observed (Li et al. 1999; Verheule et al. 2004). For the cholinergic model, the remodeling occurs acutely on the ionic level with no other cellular changes. While both of these models had higher dominant frequencies, lower organization levels, and lower degrees of transmural similarities when compared to the CHF and MR models (Everett et al. 2010; Everett, Wilson, and Olgin 2007; Everett et al. 2006), the similarities between the RAP and cholinergic models don't continue.

In the RAP model, no AF episodes were characterized with stable, discrete high-frequency areas or frequency gradients within the LA. However, the RAP model was also the only model in which every animal studied showed a consistent frequency gradient between the right and left atria with the LA always having significantly higher frequencies than the RA. This could be due to the smaller degree of structural changes and lack of remodeling that affects conduction in the RAP model, so that the entire LA is activated at a similar frequency masking a potential high frequency site. The AF activation patterns in the RAP model are consistently characterized by multiple wavefronts (Everett et al. 2010; Sih et al. 2000). This type of mechanism is also seen in the cholinergic model, but multiple focal sources have also been observed. Frequency domain analysis has also shown multiple stable, high-frequency areas could exist in this model (Everett et al. 2010; Everett et al. 2006).

7. Clinical data

In the clinical setting, different atrial substrates and altering the substrate through catheter ablation can alter the mechanism and spatiotemporal characteristics of the AF. As discussed with the canine heart failure model, atrial fibrosis creates a substrate that promotes AF (Guerra et al. 2006; Li et al. 1999; Lee et al. 2006). In patients with heart failure and no history of AF, atrial fibrosis was shown to alter the electrophysiological properties of the atria by increasing atrial effective refractory periods, prolonging conduction times, and decreasing bipolar voltage signal amplitudes (Sanders et al. 2003). Studies examining atrial structure in patients with AF as opposed to those in sinus rhythm have seen increased amounts of fibrosis (Boldt et al. 2004; Kostin et al. 2002; Luo, Li, and Yang 2006).

Most clinical studies comparing AF in different substrates either occurs between persistent /permanent and paroxysmal AF or before and after catheter ablation. Sanders et al performed FFT analysis on AF signals from patients with paroxysmal AF and from patients with permanent AF (Sanders et al. 2005). High frequency areas were seen in both groups, but paroxysmal AF was more likely to have the high frequency sites in the pulmonary veins compared to permanent AF which had more atrial high frequency sites. Sanders et al also looked at the effects of pulmonary vein isolation on the AF frequencies (Sanders et al. 2006). Pulmonary vein isolation resulted in a significant decrease in the dominant frequencies in patients with paroxysmal AF, but not permanent. In another study by Lazar et al, it was shown that a LA to RA frequency gradient disappears with pulmonary vein isolation (Lazar et al. 2006). Takahashi et al used signal processing techniques to show that the organization of AF increases after catheter ablation of the pulmonary veins (Takahashi et al. 2006). It was also shown that a high OI value was associated with AF termination.

Lin, et al used FFTs to study the spatial distribution of frequencies during different types of paroxysmal AF. (Lin et al. 2006) The location of the initiating foci was determined, and the area from which the AF originated had the highest dominant frequency. When the AF originated from the pulmonary veins, a LA to RA frequency gradient existed. A gradient was not seen when the AF originated from the SVC. In a study by Lazar et al, recordings were made in both the RA and LA in patients with paroxysmal and persistent AF (Lazar et al. 2004). A LA to RA frequency gradient was observed, but this gradient was only seen in patients with paroxysmal AF but not those with persistent AF.

8. Conclusions

Several different canine models have been developed to study AF. Even though each model shows an increase in AF vulnerability, the substrate that is created (either through structural or electrical remodeling) in each model that allows the AF to occur is different. These differences in substrate lead to different characteristics of the AF spatiotemporal organization and mechanisms of AF. Models that were characterized by structural remodeling had AF associated with stable, high-frequency areas and a focal source as the AF mechanism. Models that were characterized by electrical remodeling had AF associated with multiple wavefront or multiple foci. Structural remodeling may promote the stability of AF drivers that have been shown to be characterized by stable, high-frequency areas.

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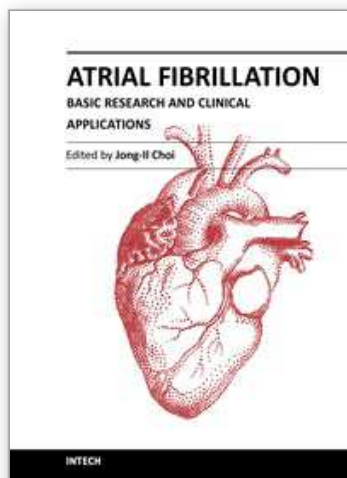
Atrial Fibrillation - Basic Research and Clinical Applications

Edited by Prof. Jong-Il Choi

Atrial Fibrillation-Basic Research and Clinical Applications is designed to provide a comprehensive review and to introduce outstanding and novel researches. This book contains 22 polished chapters and consists of five sections: 1. Basic mechanisms of initiation and maintenance of atrial fibrillation and its pathophysiology, 2. Mapping of atrial fibrillation and novel methods of signal detection. 3. Clinical prognostic predictors of atrial fibrillation and remodeling, 4. Systemic reviews of catheter-based/surgical treatment and novel targets for treatment of atrial fibrillation and 5. Atrial fibrillation in specific conditions and its complications. Each chapter updates the knowledge of atrial fibrillation, providing state-of-the art for not only scientists and clinicians who are interested in electrophysiology, but also general cardiologists.

How to reference

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