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Transmural Characteristics of Atrial Fibrillation in Canine Models of Structural and Electrical Atrial Remodeling Assessed by Simultaneous Epicardial and Endocardial Mapping

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Abstract

Background—Epicardial mapping has demonstrated that atrial substrate may play a role in the characteristics of the resulting atrial fibrillation (AF). However, it is not known if these differences also occur in three dimensions.

Objective—To examine the 3-dimensional characteristics of AF by simultaneously analyzing AF on the epicardial (epi) and endocardial (endo) surfaces.

Methods—Dogs were divided into five groups: CHF - congestive heart failure; RAP - rapid atrial pacing; MR - mitral regurgitation; control; and Meth - methylcholine. A non-contact mapping catheter (Ensite 3000 TM, ESI) was placed in the left atrium (LA), and electrode plaques (240 unipoles) were placed over the epi surface. Several AF episodes of at least 30-seconds were recorded, and isopotential movies of activation and isochronal maps were constructed. In addition, each pair of matched electrograms were cross-correlated (XC) and analyzed with a fast Fourier-transform (FFT).

Results—The RAP model was the only one with an AF mechanism of multiple wavelets in every dog on both surfaces. In addition, when individual signals were compared, the RAP model had the least amount of similarities between the recording surfaces while the CHF model had the most as it had a higher percentage of signals with XC coefficients greater than 0.8 and a higher percentage of signals with similar dominant frequencies ($30\pm35\%$ vs $12\pm13\%$ and $66\pm30\%$ vs $26\pm10\%$, $p<0.05$).

Conclusion—Even though the RAP model had similar AF mechanisms in 3-dimensions, this did not correlate to transmural similarities. Focal mechanisms of AF may have a more uniform wavefront of activation while models with mechanisms of multiple wavelets may have more three dimensional properties.

Keywords

Mapping; Fourier analysis; Atrial fibrillation; Electrophysiology

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Introduction

Several canine models of atrial fibrillation (AF) have been developed that include models of congestive heart failure (CHF)¹, mitral regurgitation (MR)², and rapid atrial pacing (RAP)³. The CHF model has been shown to be characterized by structural remodeling. Extensive fibrosis develops along with left atrial (LA) enlargement with little or no change to the atrial effective refractory period (AERP)^{1, 4, 5}. The MR model also has LA enlargement; however the amount of fibrosis is not as extensive. Instead, there is an increase in inflammatory cells². Both of these models have an increased vulnerability to AF through conduction abnormalities. The RAP model has been shown to have persistent AF, but does not show any LA enlargement, fibrosis, or inflammation. However, there is a significant decrease in AERP³. We have previously shown differences between these different models of structural and electrical remodeling in the spatiotemporal organization of the resulting AF⁶. These results suggested that the mechanism of AF, either multiple wavelet reentry, focal driver, or mother rotor, depended on the existing atrial substrate.

Since the thickness of the atrial wall is very thin (<5mm), very few systematic studies have been performed analyzing the 3-dimensional characteristics of AF. Data directly comparing epicardial and endocardial signals are limited. In addition, there has not been a study to date examining the effects of the different types of structural and electrical remodeling on the 3-dimensional characteristics of the resulting AF. We hypothesized that the effects that atrial substrate has on AF mechanism would also translate into the 3rd dimension. The purpose of this study was to examine the 3-dimensional characteristics of AF in each model by simultaneously analyzing AF on the epicardial and endocardial surfaces to determine if there are any differences or similarities among the different models of structural and electrical remodeling.

Methods

All animal protocols were reviewed and approved by the University of California San Francisco Laboratory Animal Resource Center's Institutional Animal Care and Use Committee, conformed to the regulations for humane care and treatment of animals established by the National Institute of Health, and were conducted with the assistance/supervision of the Animal Resource Department veterinary staff.

Twenty-five mongrel dogs weighing 25–30 Kg were divided into five different animal models: control (n=7), mitral regurgitation (n=6), congestive heart failure (n=6), rapid atrial pacing (n=6), and methylcholine (n=6, given to controls).

Animal Models

Mitral Regurgitation—(MR) was induced in 6 dogs through catheter avulsion of the mitral chordae as previously described.² A 7Fr steerable catheter with a stiff 2-mm wire hook at its terminus was placed in the left ventricle via a transseptal sheath. This catheter was manipulated until mitral chordae were ensnared and avulsed. After severe MR was achieved and acute left atrial dilatation was observed on TEE, the animals were recovered and they underwent the mapping protocol (see below) after 4 weeks. This time frame of severe MR has previously been shown to increase AF vulnerability, but prior to the development of depressed LV ejection fraction²

Rapid Atrial Pacing—(RAP) was performed in 6 dogs for at least 6 weeks, as previously described⁷. AV conduction was eliminated by ablation of the AV junction, and endocardial pacing leads were placed into the right atrial appendage (RAA) and the right ventricle (RV). The pacemakers were programmed at 4 times capture threshold, with an atrial rate of 600 bpm

and a ventricular rate of 100 bpm. Six weeks follow-up was chosen to allow for enough time for self-sustained atrial fibrillation, but prior to the development of significant atrial fibrosis.
8· 9

Heart Failure—(CHF) was induced in 6 dogs via four weeks of rapid ventricular pacing via a lead placed in the RV and pulse generator set to pace at 240 bpm¹ followed by ablation of the AV node to create complete heart block. Ventricular function was monitored weekly with transthoracic echocardiography, and the mapping protocol was performed after 4 weeks of rapid ventricular pacing. Four weeks was chosen based on previous data demonstrating significant atrial fibrosis and AF vulnerability in that time.^{1· 10}

Methylcholine—(METH) infusion was used as a model of parasympathetic AF. In 6 of the Control animals, methylcholine at 1 g/250 ml saline IV¹¹ was infused until a 20-mmHg decrease in the blood pressure and a 20% decrease in heart rate or spontaneous AF was observed. Once the blood pressure stabilized, the mapping protocol was performed.

Non-Contact Mapping of Atrial Fibrillation

Animals were intubated, mechanically ventilated and anesthetized with isoflurane (2%). Surface ECG leads I, II, III, aVL, aVR, and aVF were recorded throughout the procedure. Two transeptal catheterizations were performed using a Brockenbrough needle, and two sheaths were then placed in the LA. A non-contact balloon mapping catheter (Ensite 3000, ESI) was positioned in the LA along with a standard EP catheter (EP Technologies, San Jose, CA).

Non-contact mapping was performed using the Ensite 3000 (Ensite 3000 TM, ESI) mapping system, which is described in detail elsewhere^{12–14}. The EP catheter that was also inserted into the LA, was used to create a geometry of the LA in the ESI software with a methodology that has been described elsewhere.^{15· 16} Detailed geometries (> 500 points) of the LA were obtained prior to mapping and initiation of AF. Anatomic structures were marked on the reconstructed image. The non-contact mapping system samples all 64 cavitary potentials on the balloon at 1200 Hz and inversely applies them through Laplace's equation in real time. This method generates >3,000 unipolar electrograms, projected onto the geometry of the LA. The methodology has been extensively described and validated previously^{17–19}.

Plaque Mapping Protocol

While non-contact mapping was performed on the endocardial surface, contact plaque mapping was simultaneously performed as previously described⁶ on the epicardial surface. Briefly, custom-built plaques with 240 unipoles were placed on the epicardial surface of the atria. Electrograms displaying mostly ventricular activity or 60 Hz noise were excluded from the analysis (<15%). Using the location algorithm in the ESI, each electrode of the LA plaques that was in contact with the epicardial surface was located and labeled on the LA geometry that was created.

Atrial Fibrillation Mapping

Once catheters and plaque electrodes were in place, and detailed LA geometries obtained, episodes of AF were mapped. At the time of follow-up, AF was only present in the RAP group, which was induced by chronic rapid atrial burst pacing (via the implanted pacemaker). In the other models, AF was initiated with rapid atrial burst pacing from the left atrium with a cycle length of 50 ms, a pulse width of 9.9 ms, and an output of 9.9 mA. AF was defined as a rapid, atrial rhythm that produced an irregular ventricular response and no identifiable p-wave on the surface ECG. For the CHF and RAP groups, in which the ventricles were paced during the follow-up mapping study at 50 bpm, AF was present if no identifiable p-wave was on the surface ECG during episodes of rapid atrial rhythms. Multiple 30-second epochs of AF were

recorded per animal. In the control group, for which it was more difficult to induce sustained AF, recordings lasting longer than 1 minute were analyzed. At the onset of AF, two pacing spikes were delivered at 300 ms to synchronize the ESI and plaque recordings. In order to determine the activation of the AF, isopotential movies of the endocardial activation were analyzed using the ESI software, and the epicardial activation was analyzed using customized Matlab (Mathworks, Natick, MA) programs. Isochronal maps were constructed with local activation determined by the maximum dV/dt of either the virtual electrogram (ESI) or the contact electrogram (plaques). Episodes of AF were categorized as focal, reentrant, or multiple wavelet based on the characteristics of the activation in the isopotential movies and isochronal maps. Focal activation was defined as repetitive activation occurring in a radial fashion away from a source while reentrant activation was defined as repetitive activation over the entire cycle where the latest activation neighbored the area of earliest activation. Multiple wavelets were defined as multiple sources of early activation with no stability or reentry.

Validation of Non – Contact Electrograms

To validate the non-contact electrograms, the position of the EP catheter was labeled on the geometry of the LA that was created with the EnGuide location signal. The signals recorded from the EP catheter at that particular site were then cross-correlated with its corresponding non-contact signal that was calculated for that same site (Data Supplement fig. 1 A–C) at 3 – 5 uniformly distributed sites per dog. This same procedure was done for the AF signals in each animal and in sinus rhythm in the control, MR, and CHF dogs. The cross-correlation (XC) function was calculated at zero lag for each electrogram combination, and the peak value was considered the correlation coefficient, representing the degree of correlation between the two signals.

Signal Processing and Frequency Domain Analysis

Unipolar electrograms were obtained from the epicardial plaque electrodes filtered at 0.2 – 300 Hz and sampled at 1000 Hz (Cardiomapp, Prucka GE, Marquette, FL). All signals recorded by the ESI system were filtered at 2 – 300 Hz and sampled at 1200Hz. Two thousand forty eight virtual electrograms were exported for analysis along with the location (x, y, z coordinates) of each signal on the LA geometry. Also included in this file is the location (x, y, z coordinates) of each plaque electrode that was mapped to the LA geometry. A virtual endocardial electrogram was then matched to its corresponding labeled point from the plaque epicardial electrograms by calculating the distance between the plaque electrode and each of the 2048 virtual electrogram points. The two with the shortest distance was used as a matching pair. This was performed for each plaque labeled electrode. Data were filtered and analyzed using Matlab (The Math Works Inc, Natick, MA) as previously described.^{20, 21} Briefly, all signals were band-pass filtered using a 40–250 Hz second-order digital Butterworth filter. The absolute value of the filtered waveform was low pass filtered using a 20 Hz second-order digital Butterworth filter.

To perform the frequency domain analysis, the resulting signal was detrended and multiplied by a Hamming window. A FFT was calculated on the final digitally filtered waveform over a sliding two-second window every 1.0 seconds. The largest peak of the resulting magnitude spectrum was identified and defined to represent the dominant frequency (DF). The position of the harmonic peaks was determined based on the position of the DF. The areas under the largest peak and 3 of its harmonic peaks were each calculated over a 1 Hz window. This produced an area under 4 peaks. The total area of the spectrum was calculated from 2 Hz up to but not including the 5th harmonic peak. Higher frequencies were excluded because they were assumed to exceed the physiological range of frequencies for AF wavelets. The ratio of the power under the harmonic peaks to the total power in this range was calculated, and the resulting number was defined as the organization index (OI). The OI was theorized to represent

the organization of AF at that period in time^{20, 21}. Frequency domain analysis was performed on all of the downloaded virtual electrograms and all of the electrograms recorded by the plaque electrodes. To calculate the variance of both the OI and the DFs, spatial coefficient of variance (SCoV; SD/mean) of the DFs and OI during each episode of AF among all recording sites and temporal coefficient of variance (TCoV) of average DFs between 2-s windows were calculated. These measures were used to measure the stability of the DFs spatially and temporally.

The plaque electrograms that were recorded on the epicardial surface were then compared to its corresponding virtual electrogram from the endocardial surface. This comparison was performed with both frequency domain analysis and XC. During the FFT analysis, each 2 second window was compared between the two signals. The DFs of the signals during that window were considered similar if they fell within the frequency resolution of the FFT which was 0.48 Hz. If the signals had similar frequencies for more than 90% of the windows, it was considered a match. For the XC analysis, the plaque electrograms were upsampled to 1200Hz to match the sampling rate of the ESI signals.

Statistical Analysis

Data were expressed as the mean $\pm$ SD. Comparisons among all mapping analysis variables (DF, maximum DF, DF spatial CoV, DF temporal CoV, OI, maximum OI, OI spatial CoV, OI temporal CoV, and XC) were performed with an ANOVA between AF models. Individual comparisons were performed with a Fisher's exact test. Paired comparisons between endocardial and epicardial electrograms were performed with 2-tailed Student *t* tests. Statistical significance was defined as $p < 0.05$.

Results

One hundred sixty four AF episodes were analyzed in 24 dogs: 23 in 7 controls, 29 in 6 MR, 45 in 6 CHF, 50 in 5 RAP, and 17 in 6 METH. AF had to be stimulated with burst pacing in all groups except the RAP group which was already in sustained AF (from persistent burst pacing). One RAP dog was excluded due to technical problems with the pacemaker, and it did not achieve persistent AF. Signals from the EP catheter were cross correlated with its corresponding non-contact signal for both sinus rhythm and AF. Figure 1 in the Data Supplement shows an example of a contact signal and a non-contact signal from a MR dog during SR and AF. As the figure shows, the signals in this example were highly correlated and had similar DFs for the AF signal. Summary data for the XC coefficients during SR are shown in Data Supplement Figure 1B, and Figure 1C shows the summary data for AF. As the figures show, the contact signal from the EP catheter correlates well with the non-contact virtual electrogram.

Global Transmural Differences in Each Group

Frequency domain analysis was used as a tool to compare the non-contact signals from the endocardial surface to the plaque signals from the epicardial surface. Figure 1 shows static DF maps created from the plaques (top panels) and the virtual signals (bottom panels) for each AF model. As the figure shows, there are differences in the measured frequencies of the recorded signals between the endocardial and epicardial surfaces. The number of dogs in each group that had stable, high DF and OI areas is shown in table 1. This table also shows which surface had the higher maximum DFs and OIs. For every group, the majority of dogs had the higher maximum AF frequencies on the endocardial surface. However, only the control and Meth groups had a majority of dogs with higher max OIs on the endocardial surface. For the control group, high DF areas were seen on both surfaces, but these were transient and none were stable. For the MR group, stable high DF areas were seen in 4/6 dogs. Each time a high DF area was observed, it was seen on both surfaces. However, each surface did not have similar DFs as the

high DF site had higher frequencies on the endocardial surface than the epicardial surface. This difference in frequencies at the high DF area is seen in Figure 1 as the location is similar, but the DFs are higher on the endocardial surface. For the CHF model, all of the dogs had a stable, high DF area on either the epicardial surface, the endocardial surface or both. In one dog, a high DF area was seen on the epicardial surface, but not on the endocardial surface, and a second dog had a high DF area on the endocardial surface, but not on the epicardial surface. Higher maximum DFs were still seen on the endocardial surface, but these were not stable. Figure 1 shows two CHF examples: one where a DF area was seen on the LA endocardial surface and not on the LA epicardial surface, and a second example where both the endo and epi surfaces had a high DF area in the same location and with similar DFs. The RAP model had no dogs with AF characterized by a high DF area. In addition, all 5 dogs had significantly higher DFs on the endocardial surface. The example shown in Figure 1 shows this difference in the DFs between surfaces as the endocardial surface has higher DFs than the epicardial surface. For the METH group, half of the dogs had stable high DF areas. However, while 5/6 dogs had the highest DFs on the endocardial surface, only 2/6 showed stable high DF areas on this surface. Figure 1 shows an example in which any high DF areas are transient, and the endocardial surface has higher DFs than the epicardial surface.

Table 2 and Table 3 show the summary data from all of the analyzed signals from the epicardial surface (contact) and the endocardial surface (virtual). As the table of DF calculations show, there are significant differences between the maximum DFs of those recorded on the epicardial surface with the contact electrograms as opposed to those recorded on the endocardial surface with the non contract electrograms for each AF model. Only the RAP model showed a significant difference in both the spatial and temporal variance of the DFs as the virtual DFs had a higher variance than the DFs calculated from contact signals. For organization, the RAP model had the lowest measured organization than the other models for both the contact and virtual signals. The MR model was the only one that showed a difference between the organization of the virtual and contact electrograms in all OI categories as the contact electrograms in this model had higher organization levels and lower spatial and temporal variances as compared to the virtual measurements.

Transmural Analysis of Individual Signals

To further investigate the differences between the endocardial and epicardial surfaces, the location of the plaque electrodes were identified on the 3D geometry of the LA created by the Enguide location software. The plaque signal was matched with its closest corresponding virtual electrogram, and XC analysis was performed between these signals. Data Supplement Figure 2 shows an example of an endocardial signal and its corresponding epicardial signal from a CHF dog. Two highly correlated signals are shown along with two signals from a different location in the LA that were not correlated. Figure 2 shows the resulting average correlation coefficients along with the location of the signals from the plaques that were used in the analysis. Table 4 lists the summary data from the DF and XC analysis of the individual signals. As the figure and table show, on average the XC values are similar with the CHF and the MR models trending toward higher XC values than the other models. These values reached significance when compared to the RAP model. The figure also shows that the different models have higher XC values in certain areas. In the CHF and MR models, the Bachmann's Bundle region had higher XC values and a greater percentage of matched DFs when compared to the same region in the other models. The RAP model had the lowest XC values with the lowest percentage of XC values above 0.8, and the lowest percentage of matched DFs. As the figure shows, for the RAP model, most of these differences occurred in the LA free wall area. As table 4 shows, when comparing the signals individually, the epicardial surface had higher DFs than the endocardial surface for all models except the METH model which trended higher, but did not reach significance. This data also shows that the structurally remodeled AF models of

CHF and MR had the highest percentage of signals that had similar DFs. Listed in Figure 2 is a table showing the data correlating the distance between the matched points and the correlation coefficients. None of the animals showed any correlation between distance and degree of similarity.

Activation Patterns of AF Determined by Epicardial and Endocardial Recordings

The activation patterns of AF that were observed from recordings on the endocardial surface were compared to those seen on the epicardial surface and the results are listed in table 1. In several dogs, no discernable AF mechanism was observed on the epicardial surface, however a very stable, consistent activation pattern was seen. Each dog in each group had activation patterns that were consistent with a single AF mechanism that was seen in all AF episodes. However, as the table shows, only in the RAP group did all of the dogs have a similar AF mechanism of multiple wavefronts on both surfaces. All of the other groups had examples where there were different AF mechanisms on the endocardial and epicardial surfaces. Example endocardial isopotential maps from each model are shown in figure 3 along with DF maps from a 2 second window of AF. Example isopotential movies for each model studied are shown in the data supplement. Figure 4 shows example isochronal maps of AF from the epicardial surface of each group. For the Control group, 4/7 dogs had reentry as the mechanism of the AF on the endocardial surface while the remaining dogs showed focal activation patterns. The example in figure 3 shows a clear example of this focal activation in the Control group. Even though this example shows a stable mechanism of activation, no stable DFs were seen. Figure 4 shows uniform activation in the LA with the LA activation occurring earlier than the RA. When this dog was given methylcholine, an additional site of focal activation was seen. Figure 3E shows the isopotential maps of this dog and shows two sites of early focal activity. The DF maps show one area of high DFs in the vicinity of one of the focal sites, but no high DF areas were stable in this example. Overall, the METH group was split between AF mechanisms of multiple wavelets and focal activity. In 4/6 MR dogs, the AF was characterized by focal activation. The MR example shown in figure 3B shows an AF mechanism with a focus located near the right superior pulmonary vein (RSPV). In the DF map, the region of the RSPV has a stable, high DF area. The corresponding epicardial isochronal map that is shown in figure 4 does not show a similar activation pattern in the LA as a uniform activation pattern is seen. However, the RA has a discrete site of early activation with the LA following later. Epicardial DF maps showed a stable, high DF area in the RA. For the CHF group, 5/6 dogs showed AF characterized by focal activation on the endocardial surface. Figure 3C shows an example of this focal activation with the emanating wavefront then rotating in a counter-clockwise direction on both sides of the LA. The DF map shows two high DF areas indicating these two sites. The corresponding isochronal map from the epicardial surface shows uniform wavefronts activating each part of the mapped atria. All of the RAP dogs had AF characterized by multiple wavelets. As figure 3D shows, each isopotential map shows a new area of early activation, and the DF maps show transient DFs. The epicardial isochronal map also shows more than one area of early activation.

Discussion

This study used 5 different canine models of AF to analyze the AF electrograms that were simultaneously recorded from the endocardial and epicardial surfaces to study the characteristics of AF on both surfaces. With each of the AF models showing differences in the type of atrial remodeling and in the mechanism and characteristics of the resulting AF, this could lead to differences in the transmural characteristics of the AF. This study has demonstrated that the RAP model which is characterized by electrical remodeling has a more “disorganized” mechanism of multiple wavelets on both surfaces which correlated to the least amount of transmural similarities. The CHF model that is characterized by structural atrial

remodeling had a more “organized” mechanism of focal reentry and the most amount of quantifiable transmural similarities. Multiple wavelet reentry could be 3-dimensional, with resultant differences in epicardial and endocardial signals. Different waves could affect the different surfaces at different times and location in space. “Focal” sources may be more likely to show fewer differences between the epicardial and endocardial signals as the local wavefront may be more homogenous across the endocardium (ie. single regional wavefront). There were several examples where focal or reentrant activation was seen on the endocardial surface while single wavefronts were seen on the epicardial surface. Studies that involve AF mechanisms as a key component should factor in that the recording location (either endocardial or epicardial) may alter the results and findings.

Three Dimensional Activation During Atrial Fibrillation

When studying the transmural characteristics of electrical activation, most of the work that has been done has focused on the ventricles. Currently, there are few studies that involve simultaneous endocardial and epicardial analysis of atrial fibrillation. Schuessler et al performed simultaneous epicardial and endocardial mapping in the right atrium.²² This study showed that differences existed in the activation of the two surfaces during tachyarrhythmias which are more pronounced in areas of heterogeneous tissue structure. The authors also demonstrated that a reentrant circuit could exist transmurally in the atrial wall. Athill et al also performed simultaneous epicardial and endocardial mapping in the RA.²³ However, the authors showed similar activation patterns on both surfaces during reentry. Doshi et al performed simultaneous epicardial and endocardial mapping in the left atrium.²⁴ Focal activation was seen at the ligament of Marshall with similar propagating activation on both surfaces from this site. Finally, Derakhchan et al performed simultaneous epicardial and endocardial mapping in both the RA and LA.²⁵ The authors provide evidence for faster conduction on the RA endocardial surface than the epicardial surface. In addition, no differences in the endocardial/epicardial activation patterns in the LA were shown. The present study performed simultaneous epicardial/endocardial mapping in the LA of several different canine models. Similar to the study by Schuessler et al, differences were seen in the activation of the two surfaces during AF. In contrast, in the present study, models with structural remodeling in which the atrial tissue is altered with either fibrosis or inflammation had the most similarities. However, the exact tissue structure of the CHF and MR models used in this study is not known.

Mechanisms of Atrial Fibrillation

Several AF mechanisms have been proposed and debated.^{26, 27, 28, 29, 30} We have previously shown that differences in atrial remodeling creates a unique substrate in which the resulting AF has different characteristics for each model.⁶ The canine models that are associated with structural remodeling (MR and CHF) have been shown to have AF characterized by stable, high DF areas with steep frequency gradients away from these sites.⁶ Other studies have also provided evidence of a focal source in these models.^{7, 31, 32} The canine models that are associated with electrical remodeling (RAP) have been shown to have AF characterized by multiple wavelets. While these animals also have shown a LA – RA frequency gradient that others have shown in animal experiments³³ and clinically³⁴, no stable, discrete high DF areas were seen as with the other models.⁶ Another study has also provided evidence that the RAP model has AF characterized by multiple wavelets.³⁵ In the present study with the use of non-contact mapping, it is shown that these different models have different AF mechanisms that ranged from multiple wavelets, to focal activation and reentry and helped to support previous data for each model tested. The type of atrial remodeling (either structural or electrical) did play a role in the resulting AF mechanism. The CHF and RAP dogs which are the two extreme models as the CHF model has the most extensive structural remodeling showed a focal mechanism of AF, and the RAP model has the most electrical remodeling showed an AF mechanism of multiple wavelets.

Limitations

Endocardial mapping was performed with non-contact mapping. This technology has been extensively validated, and we did our own validation/confirmation by correlating contact electrograms with the virtual unipolar electrogram from the same site. A key element in the analysis was the ability to determine when and where atrial activations occurred on both surfaces, and non-contact mapping has proven to accurately depict atrial activations when they occur. However, it does not have the resolution to determine if focal activation is due to micro-reentry. The plaque electrodes used to map the epicardial surface did not cover the entire atria including the pulmonary veins. A mechanism was reported based on the activation that was observed in the plaque recordings. Finally, frequency domain analysis was used as an analysis tool not only for the endocardial versus epicardial comparisons, but also for identifying AF characterized by stable, high DF areas. The window of signal duration used for this type of analysis could affect the results. While shorter recording times provide greater temporal resolution, frequency resolution is sacrificed. For longer recording times, while frequency resolution is increased, the temporal resolution decreases.

Conclusion

The mechanism of AF varies depending on the substrate in which it occurs, and transmural differences in the DF characteristics occurred in a majority of dogs, for all models. Those differences included the endocardial surface had higher maximum DFs than the epicardial surface. A significant portion of the dogs that had stable, high DF areas were associated with models that are characterized by structural remodeling. These models also had a focal source as the mechanism of AF as well as a higher degree of similarities between endocardial and epicardial surfaces. This type of remodeling may promote the stability of AF drivers that have been shown to be characterized by stable, high DF areas. In addition, focal mechanisms of AF may have a more uniform wavefront of activation while models with mechanisms of multiple wavelets may have more three dimensional properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Dominant frequency maps for each of the models for both non-contact mapping of the endocardial surface (bottom panels), and the plaque electrodes that were recording on the epicardial surface (top panels). The DF maps for each AF model were calculated at the same point in time, and the differences in DFs between the surfaces are shown. An extra CHF map is shown as an example of both surfaces having similar DFs.

Figure 2. Summary data of the cross correlation between individual endocardial virtual electrograms and epicardial contact electrograms. The maps show the average correlation coefficients for all signals from all dogs in each group. A table shows the correlation between the XC coefficient and distance for each group. MLAA - medial left atrial appendage, LLAA - lateral left atrial appendage, LBB – left atrial Bachman’s bundle, LHLW – left atrial high lateral wall, LLLW – left atrial low lateral wall, LAA – left atrial appendage, LFW – left atrial free wall.

Figure 3A

Figure 3B

CHF

Figure 3C

Figure 3D

Figure 3E

METH

Figure 3E

METH

Figure 3D

Figure 3E

METH

Figure 3E

METH

CHF

Figure 3C

Figure 3D

Figure 3E

METH

Figure 3E

METH

Figure 3D

Figure 3E

METH

Figure 3E

METH

Figure 3.

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 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.

Figure 4.

Isochronal maps of AF activation from the epicardial surface in each model. For the Control, MR and CHF maps, a 150 ms window was used. For the RAP and METH groups which have higher AF activation frequencies, a 100 ms window was used. Corresponding color bars are shown with red indicating the earliest activation and blue/purple indicating late activation. Arrows indicate the direction of wavefront propagation. Each isochronal line indicates 10 ms. LAA – left atrial appendage, RAA – right atrial appendage, LFW – left atrial free wall, RFW – right atrial free wall, BB – Bachman's bundle, IVC – inferior vena cava, PV – pulmonary veins, RA – right atrium, LA – left atrium.

Table 1

AF mechanism as determined by the AF activation patterns, location of stable, high DF and OI areas, and location of higher maximum DFs and OIs.

Dog	LA AF Activation Patterns		Stable High DF		Location of Higher Max DFs		Stable OI Levels		Location of Higher Max OIs	
	Endocardial	Epicardial	Endocardial	Epicardial	Endocardial	Epicardial (or no difference)	Endocardial	Epicardial	Endocardial	Epicardial (or no difference)
Control Dog 1	focal	focal		none		X			X	
Control Dog 2	focal	focal		none	X				X	
Control Dog 3	reentry	focal		none	X					X
Control Dog 4	reentry	stable wavefronts		none	X		X (Low)		X	
Control Dog 5	focal	stable wavefronts		none	X				X	
Control Dog 6	reentry	stable wavefronts		none	X				X	
Control Dog 7	reentry	stable wavefronts		none	X				X	
MR Dog 1	focal	stable wavefronts	X	X - RA	X				X	
MR Dog 2	focal	stable wavefronts	X	X - LA	X		X (Low)		X	
MR Dog 3	reentry	stable wavefronts			X			X (Low) - RA/LA		X
MR Dog 4	focal	focal	X	X - RA/LA		X	X (High)			X
MR Dog 5	focal	multiple wave			X					X
MR Dog 6	reentry	stable wavefronts	X	X - LA	X					X
CHF Dog 1	focal	focal	X	X - LA		X	X (High/Low)	X (High/Low) - LA		X
CHF Dog 2	focal	focal	X	X - LA	X		X (High/Low)	X (High/Low) - LA	X	
CHF Dog 3	focal	stable wavefronts	X	X - LA	X					X
CHF Dog 4	focal	focal	X	X - RA	X				X	
CHF Dog 5	multiple wave	focal		X - LA	X					X
CHF Dog 6	focal	multiple wave	X		X		X (High/Low)			X
RAP Dog 1	multiple wave	multiple wave		none	X					X
RAP Dog 2	multiple wave	multiple wave		none	X					X
RAP Dog 3	multiple wave	multiple wave		none	X					X

Dog	LA AF Activation Patterns		Stable High DF		Location of Higher Max DFs		Stable OI Levels		Location of Higher Max OIs	
	Endocardial	Epicardial	Endocardial	Epicardial	Endocardial	Epicardial (or no difference)	Endocardial	Epicardial	Endocardial	Epicardial (or no difference)
RAP Dog 4	multiple wave	multiple wave	none	none	X			X (High) - RA		X
RAP Dog 5	multiple wave	multiple wave	none	none	X					X
Meth Dog 1	multiple wave	stable wavefronts		X - LA		X			X	
Meth Dog 2	focal	multiple wave	X		X		X (High/Low)	X (High) - LA		X
Meth Dog 3	multiple wave	stable wavefronts		X - RA	X				X	
Meth Dog 4	multiple foci	multiple foci			X				X	
Meth Dog 5	focal	stable wavefronts			X				X	
Meth Dog 6	reentry	stable wavefronts	X	X - RA/LA	X		X (High)		X	

It is also noted if there was a discrete low OI area. For the AF mechanism on the epicardial surface, if no discernible mechanism was observed, but the mapped area was activated by consistent, uniform wavefronts, a mechanism of stable wavefronts was listed.

Since the plaque electrodes also covered the RA, it was noted if a high DF or OI area was seen in this atrium.

RA - right atrium, LA - left atrium.

Table 2

Dominant Frequency Calculations

		Mean DF (Hz)	Max DF (Hz)	DF Spatial CoV	DF Temporal CoV
Control	Virtual	7.38±0.86	15.79±2.9*	0.31±0.08	0.27±0.10
	Contact	7.45±1.12	13.3±2.5	0.30±0.10	0.27±0.09
MR	Virtual	6.87±0.97	15.8±2.8*	0.35±0.08	0.35±0.13*
	Contact	7.12±1.08	12.5±2.5	0.33±0.07	0.30±0.05
CHF	Virtual	7.79±0.75	19.5±1.7*	0.34±0.06*	0.22±0.09
	Contact	7.93±0.83	14.8±3.1	0.26±0.12	0.19±0.07
RAP	Virtual	8.30±1.4*	21.1±2.0*	0.42±0.05	0.38±0.03
	Contact	8.91±1.0	16.6±3.2	0.29±0.06	0.23±0.05
METH	Virtual	7.50±1.18	18.5±3.7*	0.37±0.05	0.31±0.06
	Contact	7.31±0.97	14.0±2.7	0.34±0.13	0.31±0.12
ANOVA (between groups)	Virtual	<0.0001	<0.0001	<0.001	<0.001
	Contact	<0.0001	<0.0001	0.013	NS

* p < 0.05 between Contact of that model

Table 3

Organization Index Calculations

		Mean OI	Max OI	OI Spatial CoV	OI Temporal CoV
Control	Virtual	0.44±0.06*	0.60±0.06*	0.17±0.03	0.20±0.05
	Contact	0.41±0.06	0.55±0.07	0.16±0.03	0.18±0.03
MR	Virtual	0.40±0.05*	0.57±0.05*	0.21±0.03*	0.23±0.03*
	Contact	0.47±0.05	0.60±0.06	0.17±0.04	0.19±0.03
CHF	Virtual	0.45±0.10	0.63±0.11	0.22±0.04*	0.18±0.05
	Contact	0.44±0.04	0.62±0.08	0.20±0.06	0.17±0.03
RAP	Virtual	0.35±0.08	0.41±0.09*	0.19±0.05	0.17±0.08*
	Contact	0.33±0.02	0.47±0.01	0.20±0.02	0.19±0.01
METH	Virtual	0.38±0.05*	0.55±0.05	0.20±0.03*	0.20±0.03
	Contact	0.41±0.08	0.56±0.01	0.17±0.04	0.19±0.03
ANOVA (between groups)	Virtual	<0.0001	<0.0001	<0.001	<0.0001
	Contact	<0.0001	<0.0001	<0.0001	0.02

* p < 0.05 between Contact of that model

Table 4

Summary Data from Direct Endocardial/Epicardial Signal Comparison

Canine Model	Average Signals	Average XC	% XC > 0.8	Average DF Endo	Average DF Epi	% DF Match
Control	55±19	0.76±0.07	27±33§	6.22±0.98§	6.83±1.14*§	49±20§
MR	55±10	0.78±0.05§	46±33 [†] §	5.69±1.14 [†] §	6.05±0.66* [†] §	53±15§
CHF	54±13	0.77±0.04§	30±35§	6.86±0.72 [†]	7.89±1.72* [†] §	66±30 [†] §
RAP	58±13	0.74±0.04	12±13 [†]	7.08±0.91 [†]	8.76±1.26* [†]	26±10 [†]
Meth	48±11	0.75±0.05	19±25	6.69±1.12	7.25±1.23§	41±20§
ANOVA		P = 0.01	P<0.0001	P<0.0001	P<0.0001	P<0.0001

* p<0.01 in paired t-test between Endo and Epi DFs

[†] p<0.05 vs Control

§ p<0.05 vs RAP