Left atrial dilatation resulting from chronic mitral regurgitation decreases spatiotemporal organization of atrial fibrillation in left atrium

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METHODS

All animal protocols were reviewed and approved by the 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 Institutes of Health, and were conducted with the assistance/oversight of the Animal Resource Department veterinary staff. Thirty-one mongrel dogs weighing 25–30 kg were divided into three groups: control (n = 9), MR (n = 11), and RAP (n = 11).

Mitrail Regurgitation

This model was described in detail previously (25). MR was induced in 11 dogs through catheter avulsion of the mitral chordae. A 7-Fr steerable catheter with a stiff 2-mm wire hook at its terminus was placed in the left ventricle either via a transseptal sheath or through the femoral artery. This catheter was manipulated until mitral chordae were ensnared and avulsed. The extent of MR was assessed with transesophageal echocardiography (TEE). The procedure was repeated until moderate to severe MR was achieved and acute LA dilatation was observed on TEE. At the end of the procedure, the catheters were removed and the animals recovered. These animals underwent mapping studies after 4 wk of MR.

Rapid Atrial Pacing

Eleven dogs were conditioned with at least 6 wk of rapid atrial pacing until self-sustained AF was confirmed. First, atrioventricular (AV) conduction was eliminated with an AV junction radiofrequency...
(RF) ablation to prevent a tachycardia cardiomyopathy of the ventricle and congestive heart failure. The right neck was steriley prepped and draped. An active fixation atrial "J" permanent pacemaker lead and a ventricular pacing lead (Medtronic, Minneapolis, MN) were introduced into the right jugular vein through a cut-down incision and were advanced into either the right atrial (RA) appendage or the ventricle under fluoroscopic guidance. PACing parameters were tested, and the leads' position was fixed at the venous entry point. The leads were then tunneled to a subcutaneous pacemaker pocket that was created in the neck. The lead was connected to a pulse generator (Itrel, Medtronic), and appropriate atrial pacing was confirmed. The wounds were repaired, and the animals were returned to the vivarium. The atrial pacemakers were programmed to a rate of 600 beats per minute (bpm), a pulse width of 0.5 ms, and an output of 5 V. The ventricular pacemakers were programmed to a rate of 100 bpm.

**Optical Mapping Studies**

Atrial preparations for optical mapping were described previously (2). After sedation with pentothal sodium (0.25 mg/kg), a lateral thoracotomy was performed and the heart was rapidly excised. It was then perfused with cardioplegic solution (in mM: 123 NaCl, 15 KCl, 22 NaHCO3, 0.65 NaH2PO4, 0.50 MgCl2, 5.5 glucose, and 2 CaCl2, bubbled with 95% O2-5% CO2) retrogradely through the aorta. The ventricles were removed at ∼1 cm below the AV ring, and the aortic wall was incised around the coronary ostia. Separate perfusion and pressure monitoring lines were inserted in both the right coronary and circumflex arteries and fixed in position by applying sutures around the cuff of the coronary ostia. To ensure adequate atrial perfusion, all ventricular branches of the right coronary and circumflex arteries were ligated.

Atrial preparations were then transferred to a tissue chamber maintained at 37°C. The perfusion lines in both coronary ostia were perfused with modified Tyrode solution (in mM: 123 NaCl, 5.4 KCl, 22 NaHCO3, 0.65 NaH2PO4, 0.50 MgCl2, 5.5 glucose, and 2 CaCl2, bubbled with 95% O2-5% CO2) retrogradely through the aorta. The ventricles were removed at ∼1 cm below the AV ring, and the aortic wall was incised around the coronary ostia. Separate perfusion and pressure monitoring lines were inserted in both the right coronary and circumflex arteries and fixed in position by applying sutures around the cuff of the coronary ostia. To ensure adequate atrial perfusion, all ventricular branches of the right coronary and circumflex arteries were ligated.

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Temporal correlation analysis was performed on all recorded signals between all possible paired electrogram combinations in each animal. The cross-correlation function was calculated over a range of lag intervals for each electrogram combination, and the peak value was considered the correlation coefficient, representing the degree of correlation between the two signals. This method accounts for differences in activation times of the signal across electrograms (6). All of the correlation coefficients calculated from an AF recording with optical mapping were then averaged to produce a mean correlation value for each AF episode. The stability of AF DFs and organization from episode to episode was determined through pattern matching with correlation coefficients (23).

**Statistical Analysis**

Data are expressed as means ± SD or medians (25–75 percentile). Comparisons among conditions were performed with single- and two-factor ANOVA where appropriate. Individual comparisons were performed with a Fisher’s exact test. Comparisons between APD50 and DF were performed with linear regression analysis and correlation between variables. Statistical significance was defined as P < 0.05.

**RESULTS**

Two hundred 2.4-s epochs of AF were analyzed in 31 atrial preparations; 43 RA and 43 LA in 9 control preparations, 31 RA and 26 LA in 11 MR preparations, and 31 LA and 26 LA in 11 RAP preparations. In five preparations, both RA and LA signals were recorded.

**Activation**

On examination of the optical mapping activation sequences, the control LA group showed two different types of activation during AF. In each animal, AF activation patterns were similar for each episode of AF. In the LA of this group, AF activation was reentrant in two and simple in four, with single wave fronts constrained around areas of slow conduc-
tion. Overall, the AF wave fronts changed directions $5 \pm 3$ times during the 2.4-s AF recording. In the raw fluorescence (isopotential) movie in the supplemental data for this article, varying wave fronts are seen, constrained around areas of slow conduction. The activation map (Fig. 2B) during a paced rhythm at 250 ms from the same direction as the dominant AF activation direction shows homogenous conduction throughout the field of view. The APD$_{80}$ map (Fig. 2C) shows APDs ranging from 76.2 to 117.8 ms. All RA control preparations had simple activation with one wave front traveling through the field of view. In three preparations an area of slow conduction was seen. The wave fronts changed directions $7 \pm 5$ times during the 2.4-s AF recording. Homogeneous conduction was also seen with pacing at 250 ms and varying APD$_{80}$ levels (Fig. 3C).

The activation patterns for the RAP group show activation sequences that were very similar to control in that the field of view would be dominated by one wave front. The difference between the control and RAP models was that the wave fronts in the RAP model showed more stability as they only changed direction $2 \pm 2$ times during the LA AF recording ($P < 0.00005$). In the LA, two preparations showed reentrant activation, whereas one showed complex activation. The three other preparations had simple activation, with one broad wave front traveling through the field of view. In the RA for five preparations, activation was simple, with an area of slow conduction in one preparation. In the sixth preparation two consistent wave fronts with collision in the center of the map were seen. Overall, the RAP wave fronts changed directions $4 \pm 3$ times. Also similar to control, the RAP model had homogeneous conduction with pacing at 250 ms.

In all of the AF episodes in the MR group, the activation movies that were seen in the LA were quite different from those seen in control or RAP groups as all of the movies showed complex activation. Wave fronts occupied less area of the field of view as there were large areas of slow conduction and block, and there were times when more than one wave front was moving through the mapped region. There was evidence of reentry, wave splitting, and wave collision, but the direction of the initial wave front remained fairly stable as there were $4 \pm 3$ direction changes during the AF recordings. Demonstrated in the movie in the supplementary data are large areas of slow conduction and a high-frequency area in the upper left corner of the field of view. The corresponding activation map during pacing at 250 ms shown in Fig. 2B has
areas of slowing. The activation movies recorded in the RA showed simple activation with one wave front traveling through the field of view, and this wave front changed directions an average of 5 ± 4 times during an AF recording.

**Dominant Frequencies**

To more quantitatively analyze these activation patterns, DF maps were constructed for each episode of AF. Examples of typical DF maps are shown in Figs. 2 and 3, whereas summary data are shown in Figs. 4–7. Figure 2A shows a representative from a control LA (corresponding to the episode shown in the movie) and demonstrates two different frequencies with most of the field of view being composed of 5.86 Hz and a small area of 6.84 Hz. The variations that were seen in APD$_{80}$ occurred even in the area that is mostly composed of a single DF. Statistical analysis showed that APD$_{80}$ did not correlate with DF (correlation = 0.41, $R^2 = 0.16$). In the control RA, the DF map (Fig. 3A) has discreet regions of both high and low frequencies of 7.3 and 5.8 Hz, respectively. Similar to the LA, a majority of the field of view of the RA was composed of a single DF, which for this particular example was 7.3 Hz. Also, the DFs did not correlate with the APD$_{80}$ (correlation = 0.56, $R^2 = 0.32$).

A representative example of a DF map for the RAP LA is shown in Fig. 2C, demonstrating that most of the region consisted of 7.8 Hz and a smaller region of 5.3 Hz. The DF map for the RA (Fig. 3C) shows the entire area having the same frequency of 5.86 Hz. These findings in the RA and LA, as demonstrated by these examples, were found in all episodes in all animals in the RAP group. As with the control models,

**Fig. 2. DF (top row), activation patterns (second row), action potential duration at 80% repolarization (APD$_{80}$; third row), and organization (OI; bottom row) maps in the left atrium (LA) for control (A), mitral regurgitation (MR; B), and rapid atrial pacing (RAP; C) models. Scales are shown on right. As these images demonstrate, the AF in the LA of the MR model was significantly different from the AF in the other models. The MR DF map shows several discrete areas of different frequencies, including an area composed of the highest frequencies. This frequency pattern was not observed in the frequency maps from the other AF models. The MR organization map shows large areas of lower OI values than shown in the organization maps for the other models. Also shown is that the DFs followed conduction patterns and not the distribution of APD$_{80}$.
the DFs did not correlate with APD$_{80}$ in the LA (correlation = $-0.69$, $R^2 = 0.48$) or in the RA (correlation = $-0.61$, $R^2 = 0.37$). The average DFs are shown in Fig. 4A, and the highest DFs are shown in Fig. 4B. As Fig. 4 shows, the RAP group had frequencies similar to those of control for both the LA and RA.

In contrast to the control and RAP LA, the DF maps in the LA MR show several distinct regions of widely disparate frequencies, as shown in the example in Fig. 2B. In this example, there is a small region with the highest DF of 14.16 Hz and there is a small region with the lowest frequency of 3.9 Hz. This type of frequency map was seen in all of the MR LA preparations. Areas where slow conduction is indicated corresponded to areas of lower DFs in all episodes of AF. Similar to the control and RAP groups, the APD$_{80}$ did not correlate with DF (correlation = $-0.30$, $R^2 = 0.09$). The corresponding RA DF maps were also very similar to those of the RA in the control and RAP groups. On average, the LA of the MR group had higher mean DFs than the LA in the other groups or the RA of the MR group as shown in Fig. 4A, but this difference did not reach significance ($P = 0.22$, ANOVA). Figure 4B shows the highest DF that was measured in each AF episode. As the graph shows, the LA of the MR group had a significantly faster highest DF than the RA (10.8 ± 2.4 vs. 6.7 ± 2.9 Hz, $P < 0.04$).

Figure 5A shows the average spatial variation (coefficient of variation) in each DF map. As the figure shows, there was a significantly larger variance of DFs in the LA of the MR group compared with the RA (0.17 ± 0.06 vs. 0.067 ± 0.07, $P < 0.02$) and the LA of the other AF models, as the spatial variance was 0.06 ± 0.03 for the RAP group and 0.082 ± 0.05 for the control group ($P < 0.05$ compared with MR). This demonstrates that for each epoch of AF there is a
higher degree of variability of DFs within the mapping area of the LA of the MR dogs. The number of frequency domains per square centimeter is shown in Fig. 5B, and it shows that the LA of the MR group had a significantly higher frequency density per AF episode than the RA (2.3 ± 0.6 vs. 0.83 ± 0.6, P < 0.01) and the LA of the other AF models, as control was 1.2 ± 0.5 and RAP was 1.0 ± 0.4 (P < 0.005 vs. MR). Figure 5C shows the results from measuring the largest frequency gradient and dividing that by the distance over which it occurs. In the LA MR, this ratio was more than double that of the control or RAP groups and four times greater than the RA MR.

Spatial Organization

To quantify the “dominance” of the DF and its harmonics, organization was determined with the OI (8). An example of a control LA organization map is shown in Fig. 2A, and it is composed of discrete regions of both high and low measured organization values ranging from 0.3630 to 0.6647. Similar maps of the LA were obtained in all episodes of AF from all control animals. The organization map for the RA is shown in Fig. 3A. Similar to the LA, discrete regions of both high and low organization are seen, ranging from 0.3391 to 0.6140. Examples of organization maps for the RAP model are shown in Fig. 2C (LA) and Fig. 3C (RA). Similar to control, in these examples varying levels of organization were seen in both the LA (0.3254–0.6820) and RA (0.4672–0.5740). The measured organization for all AF episodes is shown in Fig. 6A. In the LA, the MR group had significantly lower OI levels than both control and RAP groups (0.40 ± 0.07 vs. 0.48 ± 0.06 and 0.49 ± 0.06, respectively; P < 0.05). This difference was also seen in the spatial correlation coefficients. For each AF episode all possible pairs of signals were cross-correlated, and the average correlation coefficient generated from this analysis is shown in Fig. 6B. As the figure shows, the correlation coefficients in the LA of the MR groups are significantly lower than the correlation coefficients in the LA of the other models (0.55 ± 0.1 vs. 0.73 ± 0.08 for control and 0.7 ± 0.1 for RAP; P < 0.04), indicating a lower spatial organization. There was also a difference between the LA and the RA in the MR group.
(0.55 ± 0.1 vs. 0.75 ± 0.2), but this difference did not reach significance (P = 0.068).

Temporal Organization

To quantitate how stable the pattern of AF was over time, temporal organization was determined. The results from calculating the temporal coefficient of variance of the DFs showed that for all of the AF models there was <10% temporal variability in the DFs between AF episodes. Figure 7, A and B, shows the results from correlating subsequent DF and OI maps, respectively, from each 2.4-s epoch of AF. These two graphs show the results from correlating subsequent DF and OI maps. The DF and OI maps generated from different AF episodes within the same preparation were cross-correlated, and these graphs show that the maps were highly correlated. These results indicate that both the frequencies and the organization had a high degree of stability between AF episodes for all models. These results also correlate with the results from the optical mapping activation sequences, as the activation sequences were very similar from AF episode to episode in each preparation.

DISCUSSION

This study has shown that with optical mapping a difference in the activation and the spatiotemporal organization can be demonstrated in the LA of the MR model compared with the other models. For all of the animal models, in the RA there was no difference among conduction, DF, and OI, but this was not the case for the LA. AF in the LA MR model had a region of higher DFs, an overall increased spatial variance in the DFs, and a decrease in spatial organization compared with the LA of the control or RAP models. For all examples in both the RA and LA for all animal models, the DFs followed the patterns of conduction but did not correlate with the APD. In all models, the frequencies and the OI remained stable from episode to episode, demonstrating that the AF activation was similar from episode to episode for all groups. This held true even for the MR LA, despite the increase in the spatial variability of the DFs. The increased variance of frequencies that was seen in the LA MR group created large frequency gradients that occurred over small distances, and this characteristic was not seen in the RA or in the RA and LA of the other models. Activation maps
of the LA MR showed wave splitting and/or reentry around areas of slow conduction and, at times, multiple wave fronts traveling through the field of view simultaneously. With all other activation movies, one wave front would dominate the 2 × 2-cm area.

Mechanisms of Atrial Fibrillation

A popular theory for the mechanism of AF is reentry consisting of multiple simultaneous wavelets (18). This theory was validated by Allessie et al. (1), and it was shown that four to six wavelets are needed for the continuous propagation of AF. Recently, the multiple-wavelet theory has been challenged by the work of Jalife et al. (11), which demonstrated that the mechanism of AF is due to a high-frequency “mother-rotor” with fibrillatory conduction emanating from the high-frequency source. The data from the LA in the MR model of the current study certainly support the mother-rotor theory with fibrillatory conduction. A stable, high-frequency area was seen with large frequency gradients in all of the LA MR preparations. The structural heterogeneities observed in the LA of the MR model, which lead to increased nonuniform anisotropy, may provide anchoring points for high-frequency rotors, possibly producing these high-frequency sources (10–14 Hz).

In the case of the control and RAP groups, it is unknown whether the wave fronts seen with optical mapping are the result of multiple wavelets, a macroreentrant circuit, or a high-frequency source in a part of the atrium not in the field of view. However, large gradients in DFs and organization were not seen in these models, which would rule out fibrillatory conduction and add further support to a mechanism of multiple wavelets in the control and RAP models.

In another study by our group, we (25) showed that the MR model has an increased amount of fibrosis and inflammation in the LA, which was not observed in the RAP or control models. In addition, we found a longer effective refractory period in the MR model compared with the RAP model. Optical mapping of the appendage and free wall in both the RA and LA during programmed stimulation showed conduction abnormalities in the LA in the MR group (24). The ultrastructural changes that are observed in the LA of the MR model could lead to the altered conduction of wave fronts traveling through the 2 × 2-cm area, leading to a different mechanism of AF in the MR model. This different mechanism of AF in the MR model could contribute to the decrease in the spatiotemporal organization of the AF in the LA from that measured in the control or RAP models.

Previous Studies

Frequency domain analysis. Recently, frequency domain analysis has become more commonly used as a tool for measuring the spatiotemporal organization of AF. Karaguezian et al. (12) performed FFTs on AF bipolar electrograms recorded from different areas of the RA in canines and showed that the FFTs had either a dominant peak with discrete harmonics or broad-band spectra. From the frequency domain, Sih et al. (20) and Lovett and Ropella (15) both used coherence to measure the phase consistency between signals. Even though both studies showed a decrease in the coherence with AF, there was some degree of variability (15, 20). With the use of acquiring signals with high-density optical mapping, frequency domain analysis performed on these signals has provided new insights into the mechanisms of AF. It has been shown that in acetylcholine-induced AF there exist discrete areas of stable DFs during AF, which have further supported the hypothesis that AF is not composed of random wave fronts but has some degree of organization (16, 22). However, these studies were performed in normal hearts under acetylcholine. In the current study, optical mapping was used to record signals during AF in control dogs and chronic canine models of AF conditioned with RAP and MR. In all animals, discrete areas of stable DFs were observed, supporting previous work and further supporting the hypothesis that AF is not completely random but has a degree of organization. It was also shown that APD did not correlate with DF, further supporting work by Berenfeld et al. (4). This study also showed that AF in the LA of the MR model was composed of a higher DF that occupied a small region of the mapped area. This area of higher DF was not seen in the RAP (despite having significantly shorter APD90) or control groups, suggesting that the mechanism of AF in the MR group may be different than AF in the RAP or control groups.

Left atrium versus right atrium. Differences between the RA and LA during AF have been well characterized. Morillo et al. (19) showed that after 6 wk of rapid atrial pacing, the LA has shorter atrial effective refractory periods and shorter AF cycle lengths than the RA. Sih et al. (21) also showed that there existed shorter AF cycle lengths in the LA for both acute and chronic AF. It was also reported that, with the development of persistent AF, there were marked differences in the activation maps between the RA and the LA (21). In recent studies, the differences between RA and LA AF have been analyzed with frequency domain analysis. Berenfeld et al. (3) showed that in an acetylcholine AF model in sheep hearts the LA had higher DFs and a smaller number of DFs per square centimeter than the RA. Subsequently, Mansour et al. (17) performed simultaneous RA and LA optical mapping of AF and showed that there existed a gradient of DFs from left to right. Berenfeld et al. (4) then showed that there existed a specific frequency of ~6.5 Hz when one-to-one conduction from the LA to the RA began to break down, transforming activation in the RA into fibrillatory conduction. At the cellular level, Li et al. (14) showed that there existed ionic differences between RA and LA myocytes that may play a role in the differences seen between the RA and the LA during AF. In the present study, with high-resolution optical mapping, differences in the spatiotemporal organization of AF between the RA and the LA were only seen in the MR model of AF. In both control and RAP models, the activation and measured organization parameters were very similar not only between the RA and LA but also between the models. The models we studied are distinct from the acetylcholine-induced AF model, because this model is reliant on pharmacological stimulation and the distribution of frequencies may not be secondary to distributions of acetylcholine-mediated K+ channels. In addition, we have studied a model (MR) that has structural changes (tissue discontinuities) in the LA.

Limitations

In this study, BDM was used to eliminate motion artifacts. It has been shown that this excitation-contraction uncoupler alters the characteristics of the APD (5, 27). However, we have
shown that conduction abnormalities are not related to the APD. Also, in the current study we have shown that the DFs were not related to the APD. Because of the limitation of optical mapping, the entirety of both the LA and the RA were not mapped simultaneously. Therefore, it is not known whether the high-frequency areas seen in the LA MR group are driving the AF in this particular model. However, the purpose of this study was to determine whether the characteristics of AF in both atria were different in this model of LA dilatation, because we had shown marked differences in conduction without differences in APD in this model. In addition, simultaneous RA and LA recordings were not made, so the spatiotemporal organization of the AF could not be compared between the RA and the LA in the same AF episode. However, there was marked reproducibility of measured parameters from episode to episode in the same preparation (when the mapping area was the same), suggesting the consistency of the findings in each atria.

In conclusion, AF in the RA has similar characteristics in all animal models but AF in the LA in the chronic MR model shows an increase in dispersion of frequencies and a decrease in spatiotemporal organization compared with AF in control or RAP models. This study also shows that there exist differences in spatiotemporal organization between the RA and the LA in the MR model. Tissue discontinuities in the MR LA appear to produce steep frequency gradients and lower organization of AF and may provide a substrate for high-frequency sources. The atrial dilatation in the MR model may produce an AF substrate that is different from that of control or RAP models.

GRANTS

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REFERENCES