Arrhythmogenic Difference Between the Left and Right Atria During Rapid Atrial Activation in a Canine Model of Atrial Fibrillation

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Background  Continuous rapid atrial stimulation causes atrial remodeling, but little is known about the difference in the arrhythmogenicity of the left (LA) and right atria (RA).

Methods and Results  In 14 beagle dogs, continuous rapid pacing (400 beats/min) was delivered from the right (n=7) or left (n=7) atrial appendage (RAA or LAA) for 2 weeks. The atrial effective refractory period (ERP), ERP dispersion, and inducibility of atrial fibrillation (AF) were evaluated along the time course from 4 atrial sites: (1) RAA, (2) area close to the inferior vena cava (IVC), (3) Bachmann’s bundle (BB) and (4) LA. The ERP exhibited progressive shortening at all sites, but the degree of shortening differed among them. In the RA stimulation group, ERP shortening was more prominent in the RAA and LA than in the IVC or BB. In contrast, in the LA stimulation group, ERP shortening was more prominent in the LA than in the other sites. As a result, ERP dispersion was larger in the LA stimulation group than in the RA stimulation group and the AF inducibility was higher in the LA stimulation group than in the RA stimulation group, especially at the LA site (p<0.05).

Conclusion  LAA stimulation was more arrhythmogenic than RAA stimulation in this model. This result may partly explain the importance of premature contractions occurring from the pulmonary veins in clinical cases of AF. (Circ J 2007; 71: 1629–1635)

Key Words: Atrial fibrillation; Atrial remodeling; Ion channels

It has been documented that atrial electrical remodeling characterized by shortening of the atrial effective refractory period (ERP) and a decrease in the conduction velocity plays a role in promoting atrial fibrillation (AF) by shortening the electrophysiological wavelength of the atrial muscle. However, the progression of atrial remodeling does not seem to be homogeneous and we have previously reported that both dispersion of the ERP and AF inducibility were increased during several weeks of rapid atrial pacing in a canine model of AF. Interestingly, the ERP shortening was always more prominent in the left atrium (LA) than in the sites in the right atrium (RA), and the AF inducibility was always higher in the LA than in the RA. Because it has been revealed that premature atrial activation that originates from the pulmonary veins cause AF in many clinical cases, the LA is considered to play a key role, even in clinical cases, which might be explained not only by higher arrhythmogenicity of the LA, but also by the origin of the premature atrial contractions (APC). In the present study, the arrhythmogenicity of both atria was evaluated by comparing a left and right atrial pacing model to reveal the importance of the location of rapid atrial firing in promoting AF in a canine rapid atrial pacing model of AF.

Methods

Subjects and Surgical Procedure

In 14 adult beagle dogs weighing 12.7±1.3 kg, the cardiac surface was exposed via a right thoracotomy under pentobarbital anesthesia (30 mg/kg, iv) and mechanical ventilation (Model SN-480–5, Shinano Manufacturing, Japan).
Evaluation of the Electrophysiological Properties

To obtain a stable condition, each dog was allowed to recover for 1 week after the initial surgical procedure without any pacing. Rapid atrial pacing (400 beats/min) was initiated after this recovery period and continued for 2 weeks. Pacing was performed at an output of 4-fold the diastolic threshold (4.3±0.8 V) and with a pulse width of 2 ms to obtain 1:1 capture of the atrium during rapid pacing. On days 0, 3, 7, 10, and 14 during the rapid pacing, pacing was stopped temporarily to evaluate the atrial electrophysiological properties at the 4 atrial sites. All electrograms were recorded through a polygraph system (Bioelectric AMPL, NEC, Tokyo, Japan). The analog signals were converted to digital signals and stored on a computer hard-disk (Power Lab, ADInstruments, USA) and subsequently used for analysis. During those studies, rapid pacing was ceased temporarily. All measurements were performed after pharmacological blocking of the autonomic nervous system by infusing atropine 0.04 mg/kg and propranolol 0.2 mg/kg.

Atrial Diastolic Threshold At the time of each evaluation of the electrophysiological parameters, the atrial diastolic threshold was measured at the 4 atrial sites by delivering a 300-ms cycle length pacing with a pulse width of 2 ms.

The pacing energy was 2-fold the diastolic threshold at each pacing site at the time of each evaluation. The coupling interval of the premature stimulus was shortened by 2 ms steps. The longest coupling interval of the premature beat that failed to capture the atrium was determined as the local ERP.

ERP Dispersion The ERP dispersion was evaluated as an index of the heterogeneity of the atrial refractoriness during progression of atrial electrical remodeling. The ERP dispersion was calculated as the sum of differences in ERPs between all pairs of the 4 atrial sites. The ERP dispersion was evaluated with each BCL at the time of each evaluation throughout the entire study protocol.

AF Inducibility To evaluate AF inducibility, the incidence of AF induction was evaluated with atrial burst pacing for 3 s at the minimal pacing cycle length that achieved a 1:1 atrial capture at each pacing site. This pacing was delivered at 4-fold the diastolic threshold with a pulse width of 2 ms. We defined AF as a spontaneous irregular atrial rhythm lasting longer than 3 s. At atrial burst pacing to induce AF was delivered 5 times at each pacing site at each evaluation point throughout the entire protocol.

Hemodynamic Parameters At day 14 (ie, end of the protocol) the following hemodynamic parameters were evaluated by cardiac catheterization: systemic blood pressure, pulmonary arterial pressure, pulmonary arterial wedge pressure, central venous pressure, and cardiac output.

Statistical Analysis Values are expressed as the mean±SE. Basic comparative statistics were analyzed with 1-way ANOVA test or paired t-test using the statistical software of JMP (SAS Institute Inc, Cary, NC, USA). A p-value <0.05 was considered significant.

Results

Atrial Diastolic Threshold The atrial diastolic threshold was measured at the 4 atrial sites at each time point of the electrophysiological evaluations. In the RA stimulation group, the diastolic threshold was 0.9±0.3 V in the RAA, 1.3±0.3 V at BB, 0.9±0.2 V in the IVC and 0.9±0.2 V in the LA at day 0. In the LA stimulation group, it was 0.9±0.1 V in the RAA, 1.1±0.2 V at BB, 1.3±0.2 V in the IVC and 1.0±0.1 V in the LA at day 0. There was no significant difference among the atrial sites or between the 2 groups. They did not show any significant changes throughout the study protocol.

Atrial Electrograms During Rapid Pacing Fig 2 is representative examples of atrial recordings during RAA or LAA pacing on day 14. In the RA stimulation group (Fig 2A), the earliest atrial signal was observed at the RAA site, which then propagated to the other sites. Although the whole 1:1 atrial capture was obtained for almost all atrial pacing, there were a few intra-atrial conduction blocks during the recording. Although intra-atrial block was observed in all dogs and at all evaluation points, the incidence of intra-atrial block was quite low (<1%). Fig 2A is an example of atrial electrograms in the LAA pacing group. In contrast, in the LA stimulation group (Fig 2B), the earliest atrial activation was observed at the LA site. Similar to the RA stimulation group, there were a
few intra-atrial conduction blocks, but their incidence was also quite low (<1%).

**Atrial ERP and Dispersion**

Fig 3 shows the ERPs at the 4 atrial sites on day 0 (ie, before the start of the rapid stimulation protocol). There was no difference between the RA and LA stimulation groups, but the ERP at the LA site exhibited shorter ERPs than the other 3 RA sites at all 3 BCLs. The frequent dependency of ERP seemed to be smaller in LA site for longer BCLs.

Fig 4 shows the changes in the ERPs at each atrial site along the time course of the pacing protocol. The vertical axis indicates ∆ERP, which was calculated as the difference between the ERPs at each evaluation point and the pre-pacing state (ie, day 0). In both the RA and LA stimulation groups, the ERPs at all atrial sites exhibited a relatively quick shortening during the initial 3 days and continued to shorten gradually until day 14. In the RA stimulation group, the degree of ERP shortening was greater in the RAA and LA sites than in the other 2 sites. In contrast, in the LA stimulation group, more prominent ERP shortening was observed only in the LA site and not in the RAA site. As a result, the degree of ERP shortening was greater in the LA site than in any of the other 3 RA sites.

Fig 5 shows the changes in ERP dispersion (ie, the sum of the difference in the atrial ERPs among the 4 atrial sites) along the time course of the pacing protocol. ERP dispersion exhibited an increase during the rapid pacing protocol.
Fig 3. Atrial effective refractory periods (ERPs) in the control state (day 0, ie, before the start of rapid pacing). There was no significant difference in the atrial ERPs between the 2 groups before rapid pacing, but the ERP at the left atrium (LA) site was shorter than that at the 3 right atrium sites. See text for details. BCL, basic cycle length; RAA, right atrial appendage; BB, Bachmann’s bundle; IVC, inferior vena cava; LAA, left atrial appendage. □ RAA stimulation (n=7); △ LAA stimulation (n=7). *p<0.05 vs RAA, BB and IVC; †p<0.01 vs RAA, BB and IVC.

Fig 4. Temporal change in the atrial effective refractory periods (ΔERP) with 3 basic cycle lengths (BCLs). The vertical axis indicates ΔERP calculated as [ERP]–[ERP at day 0] so that a negative number means a decrease in the atrial ERP. In the right atrium (RA) stimulation group, ERP shortening occurred at all 4 atrial sites, but the degree of the shortening was larger in the right atrial appendage (RAA) and left atrium (LA) sites than in the other 2 sites. In contrast, in the LA stimulation group, ERP shortening was more prominent in the LA than in the other 3 RA sites. See text for details. BB, Bachmann’s bundle; IVC, inferior vena cava. + – RAA; – – BB; — – IVC; × – LA. *p<0.05 vs BB and IVC; †p<0.01 vs RAA, BB and IVC.
in comparison with day 0 in both the RA and LA stimulation groups. In the RA stimulation group, this increase in ERP dispersion was limited with the longer BCLs and was also temporal. In contrast, the increase in ERP dispersion was much larger in the LA stimulation group, especially for the longer BCLs.

AF Inducibility

Fig 6 shows the change in AF inducibility at the 4 atrial sites along the time course of the rapid pacing protocol. It tended to increase in all atrial sites along the time course. In the RA stimulation group, the incidence of AF induction was higher in the RAA and LA sites than in the other 2 sites. In contrast, in the LA stimulation group, a significant increase in AF inducibility was observed only in the LA site. AF inducibility was higher in the LA stimulation group than in the RA stimulation group in the LA site, but was significantly lower in the RAA site.

Discussion

Heterogeneity in Atrial Remodeling and the Importance of the Pacing Site for Arrhythmogenicity

According to the results of this study, the shortening of the atrial ERP was not homogeneous among the 4 atrial sites evaluated. When rapid pacing was performed from the RAA site, the shortening was more prominent in the RAA and LA sites than in the other RA sites, but when rapid...
pacing was delivered from the LAA site, only the LA site exhibited a more prominent ERP shortening than the RA sites, resulting in a larger difference in the atrial ERP (i.e., ERP dispersion). Interestingly, this increased dispersion coincided with higher AF inducibility and indicated that LA rapid pacing was more arrhythmogenic than RA rapid pacing. It is now widely understood that rapid atrial firing originates from the junction of the LA and pulmonary veins, but the results in this study indicate that not only the rapid firing itself but also the localization of the rapid firing is important for promoting AF in clinical cases. This seems to coincide well with the fact that the origin of AF (i.e., the origin of frequent triggering of APCS) is commonly located in the LA or at the junction of the pulmonary veins and LA in clinical AF cases. This electrophysiological difference in the LA has been reported elsewhere, but this is the first documentation of a difference in the electrophysiological changes over time at several sites in the atria.

**Mechanism of the Difference in Response to Rapid Pacing Between the RA and LA Sites**

The mechanism of the difference in the electrophysiological response to rapid pacing between the RA and LA sites is unclear. In the RA stimulation group, the difference between the RAA and other RA sites could be understood as a result of the difference in the distance from the pacing site, because the most proximal site (i.e., RAA site) showed the most frequent firing whereas the other sites were slightly protected by conduction block between the local area and the pacing site. In the present study, we documented a few intra-atrial conduction blocks between the pacing site and the distant area, although the incidence of blocks was quite low (Fig 2). It is unclear whether this type of low-incidence intra-atrial conduction block does or does not affect the promotion of atrial electrical remodeling, but the temporal pause might protect the local atrial muscle from shortening of the ERP. On the other hand, the LA site (i.e., the area most distant from the pacing site) also exhibited more prominent ERP shortening than did the IVC or BB areas, and thus it should be considered that the LA might be more sensitive to rapid pacing, at least in regard to ERP shortening in this atrial rapid pacing model. In contrast, in the LA stimulation group, all of the RA sites exhibited less prominent ERP shortening than did the LA site, probably because of the protection afforded by the pause in atrial activation as a result of the intra-atrial conduction block between the local area and the pacing site. Considering the results of this study, there might be some mechanism involved in the greater sensitiveness of the LA to rapid pacing in comparison with the RA sites. It has been reported that there are higher expressions of Ir and SERCA2a in the LA than in the RA and that might contribute to the shorter ERP in the LA than RA. Additionally, a higher wall stress in the LA than in the RA, and a higher distribution of parasympathetic nerves, might have an influence on the difference in the responses to rapid pacing.

**Study Limitations**

First, because AV block was not produced in this model, hemodynamic worsening because of the rapid heart rate might have influenced the results. However, although the atrial pacing model with AV-block is the pure model for investigating the influence of rapid atrial firing, our model mimics real clinical AF, and thus the results themselves can be considered to reflect the clinical phenomenon.

Second, the spatial resolution of the evaluation points was low, mainly limited by a technical problem (i.e., the suturing points for the epicardial wire electrodes); however, our evaluation revealed a specific increase in ERP dispersion during rapid pacing. Finally, we did not evaluate changes in the expression of ion-channels or exchangers, which might influence atrial electrical remodeling. These points should be resolved in further studies with a different study design.

**Conclusions**

In a rapid atrial stimulation model, the stimulation site seemed to play an important role in promoting the arrhythmogenicity of AF, and LAA stimulation was more arrhythmogenic than RAA stimulation. This result may partly explain the importance of the premature contractions originating from the pulmonary veins as an origin of AF in clinical cases.

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**References**


