Intracellular Calcium Dynamics and Anisotropic Reentry in Isolated Canine Pulmonary Veins and Left Atrium

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Background—Rapid activations due to either focal discharge or reentry are often present during atrial fibrillation (AF) in the pulmonary veins (PVs). The mechanisms of these rapid activations are unclear.

Methods and Results—We studied 7 isolated, Langendorff-perfused canine left atrial (LA) and PV preparations and used 2 cameras to map membrane potential alone (Vm) or Vm and intracellular calcium (Ca) simultaneously. Rapid atrial pacing induced 26 episodes of focal discharge from the proximal PVs in 5 dogs. The cycle lengths were 223±52 ms during ryanodine infusion (n=13) and 133±59 ms during ryanodine plus isoproterenol infusion (n=13). The rise of Ca preceded Vm activation at the sites of focal discharge in 6 episodes of 2 preparations, compatible with voltage-independent spontaneous Ca release. Phase singularities during pacing-induced reentry clustered specifically at the PV-LA junction. Periodic acid–Schiff (PAS) stain identified large cells with pale cytoplasm along the endocardium of PV muscle sleeves. There were abrupt changes in myocardial fiber orientation and increased interstitial fibrosis in the PV and at the PV-LA junction.

Conclusions—PV muscle sleeves may develop voltage-independent Ca release, resulting in focal discharge. Focal discharge may also be facilitated by the presence of PAS-positive cells that are compatible with node-like cells. During reentry, phase singularities clustered preferentially at sites of increased anisotropy such as the PV-LA junction. These findings suggest that focal discharge caused by spontaneous calcium release and anisotropic reentry both contribute to rapid activations in the PVs during AF. (Circulation. 2005;111:2889-2897.)

Key Words: fibrillation ■ imaging ■ calcium ■ mapping ■ anisotropy

Rapid activations are often present during atrial fibrillation (AF) in the pulmonary veins (PVs) in humans and canine models. Radiofrequency catheter ablation of the PVs eliminates these rapid activations, resulting in successful treatment of AF. Both reentry and focal discharges may contribute to the mechanisms of rapid activations in the PVs. It has been reported that node-like cells are present in the PV muscle sleeves and that these cells may be responsible for PV arrhythmogenicity. However, no histochemical stains were performed in that study to verify that these cells were indeed specialized conduction cells. The complex anatomic structure at the PV–left atrial (LA) junction is often the site of conduction block during rapid pacing. It is possible that the conduction block results in wavebreaks and leads to the formation of reentry. It is also known that the muscle sleeves of thoracic veins are capable of developing automaticity and triggered activity during sympathetic stimulation.

Methods

Animals

The research protocol was approved by the institutional Animal Care and Use Committee and conforms to the American Heart Association Guidelines. We studied 7 female mongrel dogs (22 to 28 kg).
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albumin in deionized water), equilibrated with 95% O2 and 5% CO2

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Probes) was used as a voltage-sensitive dye. Laser light of wave-

N,N-diabutyl-beta-aminonaphthalene)ethenyl)pyridium) (Molecular

neous Vm and Cai mapping in the remaining 4 preparations. We

We performed Vm mapping in the first 3 preparations and simulta-

between 80 and 85 mm Hg. Two hook electrodes were inserted into

perfused and superfused with oxygenated Tyrode’s solution

0.5°C; composition in mmol/L: NaCl 125, KCl 4.5, MgCl2

perfused and superfused with oxygenated Tyrode’s solution

A, Isolated left PV-LA preparation. Area within yellow

isolated atrioventricular groove were removed. The preparation

Hearts were rapidly removed from anesthetized dogs. After ligation

ventricular branches of the left circumflex and anterior
descending coronary arteries, the left coronary artery was immedi-

was placed in a temperature-controlled tissue bath and

Preparation (Figure 1A) was placed in a temperature-controlled tissue bath and

AV groove

LAA indicates left atrial appendage; BB, Bachmann’s

site of focal discharge (white arrow) can

with PAS reagent for cell glycogen content. Light microscopy was

slices were stained with hematoxy-

length 532 nm (Verdi, Coherent Inc) illuminated the tissues, and

epifluorescence was collected through a 600-nm long-pass filter

using epicardial registration points. We used 5 μmol/L cytochalasin

as an electromechanical uncoupler in all experiments. The ratio between the change of fluorescence intensity (Δfluores-
cence) and the total fluorescence was calculated for each pixel. The ratio was color coded with shades of red (depolarization) or blue (repolarization) and animated to show the patterns of propagation in the mapped region.

Experimental Protocol

We used low-dose ryanodine, isoproterenol, and rapid pacing to facilitate the induction of focal discharge from the PVs. We first performed burst atrial pacing at a cycle length (CL) of 50 ms repeated 5 times to evaluate the inducibility of atrial arrhythmia at baseline. We then infused ryanodine (0.5μmol/L) over a 15-minute period. Spontaneous electrical activities were mapped to determine the source of the focal discharge, if any. The same burst-pacing protocol was then repeated to test the inducibility of arrhythmias with ryanodine alone. Finally, we infused isoproterenol (0.1 to 0.2 μg/mL) for 5 minutes and repeated burst pacing. Both spontaneous and pacing-induced arrhythmias were mapped.

Histological Examination

The site of earliest activation was marked by red indelible ink on the epicardial surface. Tissues from 5 dogs were fixed in 4% neutral-buffered formalin for 1 hour and then stored in 70% alcohol. Tissues from the remaining 2 dogs were fixed in a solution containing absolute alcohol and 35% parafomaldehyde (in a 6.5:1 ratio by volume) to optimize staining for glycogen with Periodic acid–Schiff (PAS) methods. The tissues were then processed routinely and embedded in paraffin blocks. The slides were stained with hematoxylin and eosin and Masson’s trichrome to determine the correlation between activation maps and underlying histological structures and with PAS reagent for cell glycogen content. Light microscopy was used to examine these slides.

Data Analysis

Focal discharge is defined by activation arising from within the mapped region and propagating away from that site in all directions. Phase maps were constructed with a time-delay embedding method. Phase singularity, which correlates well with the site of wavebreak, is an area with an ambiguous phase wherein neighboring elements exhibit a continuous progression of phase from \( -\pi \) to \( +\pi \). A cumulative phase-singularity map was constructed by plotting phase singularities of 100 consecutive frames (400 ms) on the same map to determine the spatial dispersion of the phase singularities. Continuous variables were expressed as mean±SD. Student t tests were used to compare means. A probability value of \( p<0.05 \) was considered statistically significant.

Results

Focal Discharge

No focal discharge was induced at baseline in any preparation. After application of ryanodine, 26 episodes of focal discharge were induced by burst atrial pacing in 5 of 7 preparations, including 4 preparations studied with 2 cameras and 1 preparation studied with 1 camera. Among them, 19 episodes of focal discharge originated from the left inferior PV (LIPV) in 3 preparations and 7 episodes from the left
superior PV (LSPV) in 2 preparations. Burst pacing was followed by rapid action potentials in the PVs and slightly slower but more irregular activity in the LA. The activations at the PVs included bursts of focal discharge, complete or incomplete reentrant wavefronts, and wavefronts that propagated from the LA. One preparation developed spontaneous focal discharge in the LIPV at a rate of 1 Hz. The mean duration of induced atrial arrhythmia episodes was 13±11 seconds (n=25; median, 10 seconds; range, 1 to 40) with ryanodine alone. Among them, 12 (48%) were >10 seconds. With the combined use of ryanodine and isoproterenol, sustained arrhythmias (>10 minutes) were induced in 2 preparations, whereas the duration of arrhythmias in the other 3 preparations averaged 174±231 seconds (n=15; median, 133 seconds; range, 40 to 440). Figure 1A and 1B shows a photograph and a schematic, respectively, of the anatomic structure and orientation of the optically mapped region. The mapped region included the LSPV, LIPV, left PV-LA junction, ligament of Marshall, LA free wall, and the basal portion of the LA appendage. The white arrow in Figure 1C marks the site of focal discharge. Figure 1D shows a burst pacing–induced sustained atrial arrhythmia recorded by a hook electrode in the LA. Figure 1E shows Vm recordings during AF at the sites labeled in Figure 1B. The orange, blue, and pink arrows indicate LA to PV, PV to LA, and proximal to distal PV wavefront propagations, respectively. Activity arising in the PV propagates to the LA in beats 4 and 13. Propagation blocks by conduction failure are shown in beats 5 and 9 (red bars) and by collision with an atrial depolarization in beats 2, 6, and 7. For beats 3, 8, 10, 11, 12, 14, 15, and 16, there is no clear direction of propagation between sites “a” and “g.” Therefore, arrows were not assigned to those beats. The activation CLs of the LIPV and LA in this AF episode were 157±19 ms and 180±8 ms, respectively. Isoproterenol infusion further shortened the CL of the PV focal discharge to 89±8 ms in this preparation. In 5 preparations, the mean CL of focal discharge after ryanodine administration was 223±52 ms (13 of 25 episodes in 5 dogs; median, 206 ms, range, 157 to 295). The mean CL shortened to 133±59 ms (13 of 17 episodes in 5 dogs; median, 116 ms; range, 89 to 220 ms) after isoproterenol infusion. Figure 2 shows simultaneous Ca i and Vm mapping during LIPV focal discharge. The number below each frame is the frame number since the onset of data acquisition. The corresponding field of view of each map is shown in the left upper schematics. Because there was a small angle between the 2 cameras, the shapes of the PV-LA preparation in Ca i and Vm maps look slightly different. We used registration points for spatial match. Onset of the Ca i transient was recorded at frames 693 and 732 (white arrows, Figure 2A) preceding the earliest Vm signal (white arrow, frames 696 and 735, Figure 2B) by 3 frames (12 ms). The activation then propagated toward the LA until it collided with a wavefront from the LA (frames 701, Figure 2B) or encountered a line of conduction block near the LIPV-LA junction (frame 744, Figure 2B). Yellow arrows (Figure 2A) indicate the directions of wavefront propagation, and red arrows (Figure 2A) point to a second site of calcium prefluorescence in a branch of the LSPV. However, the impulse did not propagate as far or as rapidly from this second site as from the site marked by the white arrows. Note that site “a” was at the edge of the preparation and that there was no tissue in the dark areas of the left upper schematics in Figure 2. In 6 of 12 focal-discharge episodes from 2 dogs, there was a rise in Ca i, preceding Vm activation (ie, Ca prefluorescence) at the sites of focal discharge. The largest number of consecutive cycles in which calcium prefluorescence occurred was >22 beats.

Wavebreak at the PV-LA Junction

The PV-LA junction is a frequent site of conduction block and wavebreak formation during AF. Figure 3 shows an example. Figure 3A shows uniform fluorescence in the PV-LA preparation, compatible with good perfusion and staining. In contrast, the nonperfused left ventricle did not emit fluorescence. Figure 3B shows the frames of Ca i and Vm maps when the LA was paced at a CL of 500 ms after ryanodine administration. Neither conduction block nor reentry occurred at the PV-LA junction during this pacing, but

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**Figure 2.** Dual optical mapping of focal discharge from LIPV. This is same preparation as in Figure 1. Frames of Ca i and voltage ratio (ΔF/F) maps are shown in A and B, respectively. Number below each figure is frame number, with beginning of data acquisition as time 0. Time interval between each frame was 4 ms.
burst LA pacing induced reentrant wavefronts in this preparation. Figure 3D shows the propagation of the last 2 reentrant wavefronts around a line of conduction block near the LSPV-LA junction (white line, frame 173). The phase map (left middle panel of Figure 3D) shows the formation of a phase singularity at the LSPV-LA junction (arrowhead). The reentrant wavefront was then blocked at the LSPV-LA junction (white line, frame 214). The CL of this nonsustained reentry (4 beats) episode was 184±8 ms. Figure 3C shows corresponding Ca frames for Figure 3D. Figure 3E shows bipolar hook electrode recordings. The first beat was a captured beat, followed by 4 beats of nonsustained reentry, Figure 3F shows single-pixel recordings of Ca (upper) and Vm (lower) tracings recorded at LSPV (a) and LA (b) sites during the last 4 beats of the episode in Figure 3E. No focal discharge was induced by the reentrant wavefronts in this episode.

Figure 4 shows a sustained reentry episode (Figure 4D) induced by rapid LA pacing in the presence of ryanodine and isoproterenol in the same preparation as that shown in Figure 3. Figure 4A shows the orientation of the mapped area. Figure 4B is the cumulative phase-singularity map. It shows that the highest density of phase singularities (white dots) occurred around the anterior junction between the left PVs and LA. Figure 4C shows sequential frames of the phase map constructed on the basis of the activations labeled by the red bars in Figure 4E. (See Data Supplement Movies II and III.) Phase singularities (arrowheads) formed along the left PV-LA junction (frames 162 to 218). Figure 4E shows the Ca transient and Vm tracings at the LSPV (site a) and LA (site b). The CL of the reentry was 96±5 ms, shorter than that with ryanodine alone. Also note that rapid atrial pacing stopped at the beginning of the red bar. The subpanels a and b in Figure 4E show conduction block into the PV during burst LA pacing, as evidenced by 7 action potentials in the LA and only 5 in the PV.

Focal Discharge and Reentrant Wavefronts in the Same Preparation

Focal discharge and reentry mechanisms could coexist in the same preparation. The reentrant wavefronts shown in Figure
were sustained for 30 seconds. They were interrupted by a wavefront from the coronary sinus (CS) direction, followed by focal discharge in the LSPV. The triggering process is shown in Figure 5. Initially, spontaneous Ca release (yellow arrow, frame 547, Figure 5A) did not induce action potential depolarization (frame 547, Figure 5B). (See Data Supplement Movie 1.) A wavefront from the CS direction propagated toward and activated the left PVs (frames 547 to 559, Figure 5B). The next spontaneous Ca release (yellow arrow, frame 571, Figure 5A) initiated a focal discharge (white arrow, frame 575, Figure 5B). The wavefront propagated toward the LA and collided with a wavefront from the CS direction (frame 577, Figure 5B). A third cycle with calcium prefluorescence at this site is shown in frame 596 (Figure 5A), followed by a depolarization in frame 598 (Figure 5B). Figure 5C shows the actual Ca (yellow) and Vm (white) tracings at the sites of focal discharge (site a), LSPV-LA junction (site b), and LA (site c). The initial spontaneous Ca release (the first red arrow) at “a” was not followed by an action potential (frame 547). Instead, a small Ca peak (green arrow) was induced by the wavefront from the CS direction. The red and green arrows therefore indicate a spontaneous (voltage-independent) Ca release followed immediately by a voltage-dependent Ca release. The second and third spontaneous Ca releases (second and third red arrows in the upper panel, Figure 5C) preceded the Vm tracing and triggered action potentials (third and fourth beats, lower panel, Figure 5C). This is the only episode that showed 3 consecutive beats with calcium prefluorescence. Two other episodes showed 2 consecutive beats (Figure 2) with calcium prefluorescence. The remaining 3 focal-discharge episodes showed 1 beat with calcium prefluorescence. The focal discharge was sustained at a longer CL of 105 ms than that of reentry (96 ms) (Figure 5D) for 10 minutes and maintained the atrial arrhythmia (Figure 4D). In 3 experiments, we increased the ryanodine concentration to 1 μmol/L after finishing the study protocol. Afterward, burst LA pacing could no longer induce focal discharge at this concentration.

**Histological Findings**

The results of routine histological examinations confirmed the presence of complex myocardial fiber orientation in the PV and at the PV-LA junction and no evidence of ischemic injury or necrosis. Figure 6 shows an example from the preparation as shown in Figure 1. Figure 6A shows that “a” was around 4 mm from the end of the PV muscle sleeves. There is...
increased interstitial fibrosis and hence, widely separated myocytes at “a” (Figure 6B). Figure 6C is a low-power view of the area near the LIPV-LA junction. A high-power view shows abrupt changes in myocardial fiber orientation at “f” (Figure 6D). Similar abrupt changes in fiber orientation were observed in all dogs studied.

PAS staining was performed in the PVs from 2 dogs. In a dog with focal discharge (Figure 2), there were many PAS-positive cells clustered in groups along the endocardial side of the PV muscle sleeve (Figure 7A). The greatest concentration was close to the site of focal discharge, as shown in Figure 2. The PV myocytes in the midwall and in the epicardial aspect of the muscle sleeve were PAS-negative (Figure 7B). Figure 7C shows that the PAS-positive cells were larger than the PAS-negative cells and had a pale sarcoplasm. These cells are morphologically similar to the specialized conduction cells found in human patients. In addition, some PAS-positive cells were identified on the endocardial aspect of the LA at the PV-LA junction (Figure 7D). The PV of the other dog (as shown in Figure 3) contained only occasionally positive PAS cells.

**Discussion**

This study has the following major findings: First, we demonstrated that rapid pacing during ryanodine and isoproterenol infusion induced focal discharge from the PVs. The focal discharge was preceded by spontaneous (voltage-independent) calcium release. Second, the anterior PV-LA junction was commonly associated with conduction blocks, phase singularities, and reentry formation. The phase singularities during reentry did not occur randomly. Rather, they clustered around the PV-LA junction. Histopathological studies of that area showed complicated myocardial fiber orientation, suggesting that anisotropy played an important role in reentry formation. PAS-positive cells were identified in the PV near the site that showed multiple episodes of focal discharge. Third, rapid reentrant activations led to spontaneous calcium release and resulted in focal discharge in the same preparation.

**Ca\textsubscript{2+} Dynamics and Focal Discharge From the PV**

Honjo et al\textsuperscript{10} showed that rapid pacing and low-dose ryanodine shifted the leading pacemaker from the sinoatrial node to...
an ectopic focus near the right PV-LA junction. Both rapid pacing and low-concentration ryanodine can increase Ca, which may cause voltage-independent calcium release from the sarcoplasmic reticulum and activate the Na/Ca exchanger. Because PV myocytes have a less negative resting membrane potential than LA myocytes, the depolarizing currents might result in triggered activity and focal discharge in the PV but not in the LA. We demonstrated in this study that the rise in Ca preceded the upstroke ofVm at the site of focal discharge. These findings suggest that spontaneous Ca release in the PV muscle sleeves induces triggered activity, which underlies the mechanisms of focal discharge from the PVS.

Specialized Conduction Cells in the PV
Masani reported that node-like cells are present in the PV muscle sleeves of adult rats. These cells are characterized by a paucity of myofilaments and structural features similar to that of sinus node cells. Perez-Lugones et al documented the presence of pale cells with lightly stained central cytoplasm and peripheral dense myofibrils in human PVs. In contrast, the neighboring contractile myocardial cells contained more darkly stained cytoplasm. The authors concluded that specialized conduction cells are present in human PVs. However, because these tissues were obtained at autopsy, it was not possible to perform specialized stains to docu-

Figure 6. Interstitial fibrosis and myocardial fiber orientation. This is from same dog as in Figure 1. A, Low-power (×1.25 objective) view of LIPV subjected to optical mapping studies. Lower-case letters mark same a–d sites as in Figure 1. Large red dot on right upper portion of A marks site of earliest activation, as determined by optical mapping. B, Masson’s trichrome stain of area enclosed by square in A (×20 objective). There was increased interstitial fibrosis at that site. C, Lower-power (×1.25 objective) view of PV-LA junction and ligament of Marshall (LOM). D, (×10 objective) Area marked by square in panel C. There was abrupt change in myocardial fiber orientation at that site.

Figure 7. Results of PAS staining in LIPV. Tissue was from same dog as in Figure 1. A, Low-power (×4) view of PAS-stained slide. Clusters of PAS-positive cells (arrows) were seen on endocardial side of PV muscle sleeve. Midwall and epicardial cells were mostly PAS-negative. B, PAS-negative cells (arrows) in greater detail. C, PAS-positive cells with pale sarcoplasm. These cells are larger than surrounding PAS-negative cells. D, PAS-positive pale cells at PV-LA junction. These cells are located in endocardium of LA. Magnification of objective lens is ×20 for B–D.
ment the presence of specific markers for conduction cells in the PVs.

PAS staining is commonly used in cardiac pathological studies to detect glycogen within myocardial cells.13 Because Purkinje fibers contain large amounts of glycogen,17 PAS staining can be used to identify Purkinje fibers and other specialized conducting cells in the myocardium. We used this technique to stain the PVs and showed that large pale cells that had morphological characteristics compatible with these specialized conduction cells were PAS-positive, whereas other myocardial cells were not. These cells were endocardially located and were concentrated near the focal-discharge site. These findings further strengthen the hypothesis that these pale cells are in fact part of the specialized conduction system. However, because we did not record directly from these cells, it was not possible to determine whether they were the origins of focal discharge in the PVs.

Perez-Lugones et al4 found specialized conduction cells in 4 patients with AF but not in 6 patients without AF. These findings imply an association between these cells and the occurrence of AF. The fact that we discovered large numbers of pale cells in a dog with multiple episodes of focal discharge is compatible with an association between these cells and PV arrhythmogenesis.

Wavebreak and the PV-LA Junction

A major finding of our study is the clustering of phase singularities near the PV-LA junction, where complex myocardial fiber orientation was noted on the histological sections. It is well known that myocardial fiber orientation and anisotropy are important in the induction and maintenance of reentry.18,19 We7 have described discontinuous muscle sleeves along the anterior PV-LA junction and showed that rapid pacing can result in conduction blocks along the PV-LA junction. Arora et al8 reported significant conduction slowing in the canine proximal PV. This conduction slowing and the repolarization heterogeneities within the PV were thought to be the substrates for reentry. However, no histopathological studies were performed in that study to rule out the possibility of anisotropic reentry. In the present study, we used histopathological sections to determine myocardial fiber orientation and the amount of fibrosis in the PVs. We confirmed the presence of significant anisotropy in the PV and at the PV-LA junction. The consecutive phase-singularity maps showed that there was a clustering of phase singularities around the PV-LA junction, suggesting that wavebreak occurs preferentially at sites of increased anisotropy. The findings in the present study suggest that in addition to electrophysiological heterogeneity,4 structural heterogeneities, such as fibrosis and anisotropy, play important roles in the generation of reentry in the PV and at the PV-LA junction. Therefore, anisotropic reentry due to structural complexity could be alternative mechanisms for reentry formation within the PV muscle sleeves and at the PV-LA junction.

Induction of Focal Discharge by Reentry

A third major finding is that rapid sustained reentrant activations can induce spontaneous Ca release at the proximal PV, leading to PV focal discharge in the same preparation. We20,21 previously documented that wavefronts from the LA propagated to the PV and that pharmacological interruption of this PV-LA communication played an important role in chemoversion AF in dogs. These PV-LA interactions increase the activation rates of PV, which might facilitate Ca accumulation and the development of focal discharge from the PV. Radiofrequency ablation of the PV-LA junction reduces or eliminates PV-LA interactions, thus reducing the activation rate and the possibility of focal discharge in the PVs. We propose that the latter mechanism might be important in the successful termination of AF by PV isolation procedures.

Clinical Implications

Sympathetic tone is an important factor that triggers paroxysmal AF.22 A major arrhythmogenic mechanism in heart failure is altered ryanodine receptor function.23 A combination of abnormal ryanodine receptors and increased sympathetic tone during exercise can cause triggered activity and ventricular arrhythmia.24 In the present study, we extended these observations to the PV muscle sleeves by showing that they were more susceptible to triggered activity than atrial tissue during isoproterenol and ryanodine administration. An implication of this finding is that triggered activities in the PVs may play important roles in the generation and maintenance of AF. Pharmacological therapies that prevent triggered activity in the PVs may be effective in AF control.

Limitations

There are at least 2 limitations. First, cytochalasin D may have direct effects on Ca2+ cycling and may facilitate the induction of reentry or focal discharge. However, rapid LA pacing at baseline failed to induce any sustained atrial arrhythmia in the preparation. Focal discharge was observed only after ryanodine and isoproterenol administration. Therefore, our results cannot be explained by the presence of cytochalasin D. Furthermore, we used only 5 μmol/L cytochalasin D. Others4 have documented that reentry and focal discharge can be induced even in the presence of 25 μmol/L cytochalasin D. Second, we mapped the epicardial surface only. It is not possible to completely rule out transmural microreentry as a mechanism of repetitive focal discharge. However, the conclusion of our study is supported by spontaneous calcium release preceding the first beat of the focal discharge. It is therefore unlikely that transmural reentry with focal epicardial breakthrough explains the first focal discharge within the PV.

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