Intra-Atrial Pressure Increases Rate and Organization of Waves Emanating From the Superior Pulmonary Veins During Atrial Fibrillation

Jérôme Kalifa, MD; José Jalife, MD; Alexey V. Zaitsev, PhD; Suveer Bagwe, MD; Mark Warren, PhD; Javier Moreno, MD; Omer Berenfeld, PhD; Stanley Nattel, MD

Background—Atrial fibrillation (AF) commonly associates with atrial dilation by poorly understood mechanisms. We hypothesized that elevation of intra-atrial pressure elicits high-frequency and spatio-temporally organized left atrial (LA) sources emanating from the superior pulmonary veins.

Methods and Results—We used a stretch-related AF model in the sheep heart to induce stable episodes of AF (>40 minutes) in 9 animals. Video movies of the LA free wall (LAFW) and LA superior pulmonary vein junction (JPV) were obtained using di-4-ANEPPS. Electrograms from the right atrium were recorded. At intra-atrial pressures >10 cm H2O, the maximum dominant frequency (DFMax) was significantly higher in the JPV than in the LAFW (12.0±0.2 and 10.5±0.2 Hz, respectively [mean±SEM]; P<0.001). Below 10 cm H2O, DFMax was similar in the JPV and LAFW (10.8±0.3 versus 10.2±0.3 Hz; P=0.6); DFMax in both JPV and LAFW was significantly higher than in the right atrium (7.8±0.3 Hz; P<0.001). Analysis of excitation direction in JPV showed positive correlation between intra-atrial pressure and the number of waves emanating from the left superior pulmonary vein (r=0.79, P<0.02) but not from the LAFW (r=0.54, P=0.09). The number of spatio-temporally periodic waves in the JPV correlated with pressure (r=0.92, P=0.002). In 3 cases, JPV rotors were identified with a cycle length equal to 1/DFMax.

Conclusion—We demonstrate for the first time that an increase in intra-atrial pressure increases the rate and organization of waves emanating from the superior pulmonary veins underlying stretch-related AF. (Circulation. 2003;108:668-671.)

Key Words: arrhythmia • fibrillation, atrial • waves • pressure, intra-atrial • veins, pulmonary

Atrial fibrillation (AF) often associates with atrial dilatation,1–3 but the underlying electrophysiological mechanisms remain unclear. The pulmonary veins (PVs) are known to play a critical role in AF.4,5 Recently, selective PV angiography in patients with paroxysmal AF suggested that AF triggers are most frequently located in dilated superior PVs.6,7 We used a model of increased intra-atrial pressure (IAP)–related AF in isolated sheep hearts to test the hypothesis that dilation induces arrhythmogenic left atrial (LA) sources emanating from the superior PVs.

Methods
Animals were used according to National Institutes of Health guidelines. Nine young sheep (18 to 25 kg) were anesthetized with pentobarbital (35 mg/kg IV). Hearts were removed, placed in cold cardioplegic solution, and connected to a Langendorff apparatus. The coronary arteries were continuously perfused at 200 mL/min via a cannula in the aortic root with warm (36 to 38°C) Tyrode’s solution (pH 7.4) equilibrated with 95% O2/5% CO2.

Stretch-Induced AF Model
We adapted a well-characterized model of stretch-related AF8,9 to the sheep heart. After perforation of the interatrial septum, all venous orifices were closed except for the left superior PV (LSPV) (merged with the right superior PV in 8 of the 9 animals) and inferior vena cava. Tubes connected to a digital IAP sensor were coupled to the inferior vena cava and LSPV at one edge and to an open-ended cannula, the height of which controlled the level of IAP. Ventricular fibrillation was induced to reduce mechanical artifacts and distortion of IAP by ventricular contraction. IAP was raised from 0 cm H2O in steps of 5 cm H2O. Burst pacing (10 seconds, 12 Hz) was applied at each step to induce AF after 3 minutes of stabilization. Once stable AF was induced, IAP was increased to 30 cm H2O and then reduced to 5 cm H2O. AF stopped in all 9 cases 10 to 20 minutes after IAP was reduced below 10 cm H2O.

Optical Mapping
We used a dual-camera, high-resolution video-imaging system and a potentiometric dye, as detailed elsewhere.10 Simultaneous recordings from the LA free wall (LAFW) and the LA superior PV junction (JPV) (Figure 1) yielded 5-second optical movies (2×128×128 pixels).

Dominant Frequency Maps
Dominant frequencies (DFs)11 in the right atrial free wall were obtained simultaneously using fast-Fourier transformation of electrical recordings.10
**Directionality, Spatio-Temporal Periodicity, and Phase Analysis**

The direction of activation was analyzed in the JPV area with the highest DF (Figure 2A). Activation times for each pixel were determined at 50% of action potential amplitude. All movies were rotated to align the edge separating the JPV and the LAFW. A selected area, the maximal size of which did not exceed the region between the LSPV and the LAFW, was considered (H11015 H11003 H1100310 mm2).

Vector-bilinear best fit was used on that area to obtain the direction of propagation of each activation.12 Velocity magnitude (H11021 H110060.06 m/s) was discarded, and 0° direction was considered toward the LSPV (perpendicular to the edge of the LAFW) and increasing counterclockwise. As illustrated in Figure 2A, wavefronts in this area directed between 120° and 240° (blue arrow) were counted as traveling from PVs to LAFW; those between 300° and 60° (red arrow) were counted as traveling from LAFW to PVs. Wavefronts were considered spatio-temporally periodic (STP) if a minimum of 4 sequential waves emerged from one edge or as breakthroughs (1) from the same location and with the same direction and (2) with a timing that varied by no more than ±1 frame (3.33 ms) from a mean.10 Phase movies were obtained as described previously.13 A rotor was defined as reentrant activity completing at least one full rotation around a phase singularity.

**Statistical Analyses**

One-way ANOVA with Bonferroni post-hoc correction was used to compare measurements in each group (OriginLab Inc). P<0.05 was considered to be significant.

**Results**

**Activation Frequencies**

In Figure 1, A and B are representative DF maps obtained from one heart at IAPs of 5 and 18 cm H2O, respectively. DF maps are superimposed on color picture of a heart for illustrative purposes. C, Bar graph showing DFMax (mean±SEM) in the JPV (blue) and LAFW (red) at IAPs <10 and >10 cm H2O (*P<0.001). D, Single-pixel recordings from JPV and LAFW at 30 cm H2O. IVC indicates inferior vena cava; CL, cycle length.

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**Statistical Analyses**

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**Results**

**Activation Frequencies**

In Figure 1, A and B are representative DF maps obtained from one heart at IAPs of 5 and 18 cm H2O, respectively. These maps clearly illustrate the strong dependence of frequency on IAP. Below 10 cm H2O, the difference between the maximum dominant frequency (DFmax) in the JPV and LAFW was not significant (10.8±0.3 versus 10.2±0.3; P=0.6; Figure 1C). However, at pressures >10 cm H2O, DFmax in the JPV was significantly higher than that in LAFW (12.0±0.2 and 10.5±0.2 Hz, respectively [mean±SEM]; n=9; P<0.001; see also representative single-pixel recordings in panel D). At all pressures, DFmax in both JPV and LAFW was significantly higher than the largest frequency recorded in the right atrial free wall (7.8±0.3 Hz; P<0.001).

**Activation Patterns**

STP wavefronts, rotors, and directionality of the electrical activation are shown in Figure 2. Clearly, the direction of propagation from LSPV to LAFW (blue symbols) was very consistent. In all movies, the directionality of local excitation in the JPV area that corresponded to the highest frequencies correlated strongly with IAP (r=0.79, P=0.02; Figure 2B). In contrast, the directionality of LAFW to LSPV had a negative and statistically nonsignificant correlation with pressure (r=0.54, P=0.09).

**JPV Rotors and AF**

As described previously,10 wavefront propagation in AF may be highly periodic, both spatially and temporally. Such spatio-temporal periodicity may take various forms, including periodic waves emerging from the edge of the recording field, breakthroughs occurring at constant frequencies, and in some cases, stable rotors.10 We found similar STP wavefronts in high IAP–associated AF. In Figure 2C, the number of STP
wavefronts (normalized to the maximum number of STP wavefronts by level of pressure) in the JPV correlated strongly with IAP \((r=0.92, P=0.002)\). Figure 2D shows an example of a rotor in the JPV, the cycle length of which (70 ms) was equal to \(1/DF_{\text{Max}}\) calculated from the same movie. Similar rotors were observed in 3 of 9 experiments.

**Discussion**

The major findings of this study are: (1) Increased IAP elicits rapidly activating sources at the junction between superior PVs and LA. (2) Within the same episodes of AF, the frequency and spatial organization increase with the level of IAP. (3) In 3 experiments, the sources were identified as JPV rotors, the cycle lengths of which were equal to \(1/DF_{\text{Max}}\) of the corresponding episode.

**JPV Sources and Stretch-Related AF**

AF is commonly associated with atrial stretch. Clinical studies suggest that rapid PV rhythms play an important role in the maintenance of AF. \(^{14,15}\) The ability of PVs to sustain reentry and focal activity has recently been demonstrated. \(^{16}\) Recently, MRI showed larger PVs in patients undergoing AF ablation than in control subjects. \(^{17}\) Moreover, there is evidence that in patients with paradoxical AF, the diameters of the superior PV ostia are markedly dilated compared with the inferior PV ostia, \(^6\) particularly when considered as arrhythmogenic PVs. \(^7\) However, the electrophysiological mechanisms linking PV and LA dilatation to maintenance of AF have not been established. In the present study, we demonstrate for the first time that the sources of rapid atrial activation during stretch-related AF are located in the PV region and that their level of spatio-temporal organization correlates with pressure. The extent to which STP wavefronts observed in the JPV are generated by microreentrant activity in the endocardial PV sleeves requires further investigation.

A pressure of 10 cm \(H_2O\) was found to be the lower limit for a clear differentiation of both \(DF_{\text{Max}}\) and directionality of waves in the JPV (to LAFW versus from the LAFW). Below 10 cm \(H_2O\), AF terminates because its reentrant sources become slow and unstable. These results strongly suggest that the JPV plays a key role in AF in the setting of LA dilation. They could provide a partial mechanistic explanation for AF maintenance in patients with cardiac heart failure and elevated atrial pressures.

Recent studies suggest that blockade of stretch-activated channels could be a new therapeutic approach to AF. \(^{9,18}\) As such, the stretch-sensitivity of the PV region could constitute a new target for antiarrhythmic therapy.

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References
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