Relation Between Pulmonary Vein Firing and Extent of Left Atrial–Pulmonary Vein Connection in Patients With Atrial Fibrillation

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Background—The purpose of this study was to measure the extent of left atrial–pulmonary vein (LA-PV) connections and determine the relation to PV firing in patients with atrial fibrillation (AF).

Methods and Results—Ten close-bipolar (1 mm-spacing) Lasso electrograms were recorded circumferentially around 210 PVs (excluding 2 right middle PVs and 4 left common trunks) in 62 patients with AF. PV firing was provoked by isoproterenol (4 μg/min) and cardioversion of pacing-induced AF. The width of each LA-PV connection was measured in tenths of PV circumference, based on number of continuous close-bipolar Lasso electrode sites required for ablation (10% for each close-bipolar electrode site). One, 2, or 3 to 4 discrete LA-PV connections (discrete connection defined by ablation along 10% to 30% of PV circumference) were present in 18 (9%), 31 (14%), and 32 (15%) of 210 PVs, respectively: 1 broad connection (ablation along continuous 40% to 80% circumference) in 46 (22%) PVs; 1 broad plus other broad or discrete connections in 54 (26%) PVs; and a circumferential connection (ablation along 90% to 100%) in 29 (14%) PVs. Circumferential LA-PV connections were more common in superior than in inferior PVs (20% versus 7%, P<0.01). There was no major difference in distribution of the other types of LA-PV connections between the four PVs. PV firing occurred in 27%, 47%, and 72% of PVs with discrete only, broad and circumferential connections, respectively (P<0.01). Dissociated PV potentials after isolation were more common in arrhythmogenic (firing) PVs (32% versus 8%, P<0.01).


Key Words: arrhythmia • atrium • fibrillation • catheter ablation • veins

The triggers initiating atrial fibrillation (AF) originate most often from sleeves of left atrial myocardium extending onto the pulmonary veins (PVs) or the PV antrum.1–5 Therefore, isolation of PV myocardial sleeves was an early approach for AF ablation.1–4 The mechanism of PV firing is still unknown. Two observations suggest that PV firing may be dependent on the extent of left atrial–pulmonary vein (LA-PV) connection(s): PV isolation at the ostium usually eliminates the rapid firing originating deeper in the PV, even though ablation is not performed at the site of firing;2 and rapid firing can be provoked in fewer than half of the PVs on average per patient.1

Histological studies show that the PV myocardial sleeve is highly variable, with complex muscle bundle orientation and interspersed fibrous tissue.6 These irregularities at the junction between the LA and the PV may result in single or multiple and narrow or broad LA-PV electrical connections. The hypothesis for this study was that arrhythmogenesis (presence of PV firing) is related to the number and width of LA-PV connections for each PV.

The purpose of the study was to determine the relation between PV firing and the extent of LA-PV connections in patients with AF. The location of each LA-PV connection was identified through the use of a circular multielectrode catheter, introduced by Haissaguerre and coworkers,2 positioned just inside the PV. The width of each LA-PV connection was estimated by the width of ablation sites along the PV circumference required for LA-PV block.

Methods

Study Population

The study population consisted of 62 patients undergoing catheter ablation of paroxysmal (n=45) or persistent (n=17) AF, who had focal firing from at least 1 PV, and sinus rhythm was restored after testing for PV firing for ablation. There were 51 men and 11 women,
54±9 years of age. Structural heart disease was present in 40 (65%) patients: hypertensive heart disease in 24, coronary artery disease in 1, dilated cardiomyopathy in 1, and mild-to-moderate left ventricular hypertrophy (left ventricular wall thickness, 12 to 15 mm) with diastolic dysfunction but without known hypertension in 14. AF was present for 6.0±4.3 years, and 3±1 antiarrhythmic drugs (class I and/or III) had either failed to control AF or were not tolerated.

**Electrophysiological Study**

A magnetic resonance angiogram (MRA) with gadolinium contrast was obtained before the procedure to delineate PV anatomy. At electrophysiological study, multielectrode catheters were positioned in the right atrial appendage (RAA), coronary sinus (CS), and His bundle region. Decapolar internal cardioversion catheters (Inquiry, Irvine Biomedical) were positioned in the RA and CS in 37 patients. Double transseptal puncture was performed, and heparin was administered (activated clotting time ≥300 seconds). Angiography of each PV and intracardiac ultrasound (AcuNav, Acuson) were used to position a custom-designed circular electrode (Lasso) catheter in the proximal PV, close to the orifice. The 20-electrode Lasso catheter was positioned 5 mm inside each PV and oriented as closely as possible to the orientation of the PV orifice. The 7F Lasso catheter has 20 electrodes (1 to 2.5, 1-mm edge-to-edge spacing on the 15-mm diameter catheter and 1 to 4, 1-mm spacing on the 20-mm diameter catheter, Biosense Webster, Figure 1B).

The Lasso catheter and a quadripolar mapping/ablation catheter (7F, 4-mm tip-electrode, NaviStar, Biosense Webster or Malign, Medtronic) were inserted into the LA and positioned sequentially into all PVs to identify the PVs exhibiting firing (atrial extrasystoles or initiation of AF). The methods used to provoke PV firing included the use of isoproterenol (4 µg/min) combined with cardioversion of sustained AF induced by rapid atrial pacing.

**PV Mapping and Isolation Procedure**

The 20-electrode Lasso catheter was positioned ≥5 mm inside each PV and oriented as closely as possible to the orientation of the PV orifice. Ten close-bipolar electrograms (electrodes 1 to 2, 3 to 4, 1-mm spacing on the 15-mm diameter catheter and 1 to 4, 1-mm spacing on the 20-mm diameter catheter, Biosense Webster, Figure 1B).

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**Figure 1.** A, Conventional Lasso catheter (10 electrodes, 6-mm spacing, edge-to-edge). B, Close-bipolar Lasso catheter (20 electrodes, 1 to 4, 1-mm spacing, edge-to-edge) used in this study. Close-bipolar electrograms (ie, 1 to 2, 3 to 4, 5 to 6, and so on) and conventional bipolar electrograms (1 to 3, 3 to 5, 5 to 7, and so on) were recorded simultaneously.

**Figure 2.** Single discrete LA-PV connection in the RSPV. A, Before ablation, the PVP activation sequence recorded from the close-bipolar Lasso electrodes during RAA and posterior CS pacing differed only in close-bipolar electrode 3 (arrow). Conventional-bipolar (Conven Bipolar) electrograms contain overlapping LA potentials in electrograms 1, 2, 9, and 10. Far-field LA potential (LA) in conventional-bipolar electrogram 10 during RAA pacing simulates earliest PVP. B, After 2 RF applications adjacent to close-bipolar electrodes 2 and 3, all PVP in the close-bipolar electrograms were eliminated, confirming a single discrete LA-PV connection. Conventional-bipolar electrograms 1 and 10 contain both far-field LA potentials (LA) and far-field PVPs originating from the right inferior PV, mimicking a residual LA-PV connection. Far-field PVPs were eliminated by isolation of the RIPV.
For ablation, each radiofrequency application was delivered in a stationary position, opposite the close-bipolar Lasso electrode recording the earliest PVP during RAA or CS pacing. The location of each ablation site was recorded on a 3D mapping system (CARTO, Biosense Webster or Localisa, Medtronic, Figure 3A). Radiofrequency current was delivered for 60 seconds at ≤30 W and ≤55°C electrode temperature. The PVP activation sequence was compared between RAA and CS pacing before and after each radiofrequency application. Additional radiofrequency applications were delivered at the same or subsequent sites of earliest PVP until PV isolation was achieved, defined as elimination of PVPs in all close-bipolar electrograms. The Lasso or ablation catheter was then advanced deeper into the PV to exclude residual PVPs. After ablation, isoproterenol (4 μg/min) combined with cardioversion of sustained AF (induced by rapid atrial pacing) was repeated to provoke firing within the atria and isolated PVs.

**Categorization of LA-PV Connections**

The PV circumference was divided into tenths, corresponding to the location of the 10 close-bipolar electrodes on the Lasso catheter. The LA-PV connections were categorized by width after the PV was isolated by stationary RF applications at serial sites of earliest PVP. Each continuous segment of ablation sites, separated by 1 or more unablated close-bipolar electrode sites, was considered an independent LA-PV connection. Each LA-PV connection was categorized by the width of ablation sites as "discrete," "broad," or "circumferential" if ablated along a continuous segment of ≤3, 4 to 8, or 9 to 10 close-bipolar Lasso electrodes, respectively.

**Statistical Analysis**

Values are expressed as mean±SD. The significance of the difference between type of LA-PV connection and incidence of PV firing among the right superior (RSPV), right inferior (RIPV), left superior (LSPV) and left inferior (LIPV) pulmonary veins and was assessed by χ² analysis or Fisher’s exact test. The number of ablation sites around the PV circumference (in tenths) and the number of radiofrequency applications required for PV isolation were compared among the RS, RI, LS, and LI PVs and among the types of LA-PV connections by means of ANOVA. Significant differences were measured by Scheffé’s method for pairwise comparisons. The number of radiofrequency applications required for isolation was compared between PVs with and without focal firing by means of the 2-tailed Student’s t test. A value of P<0.05 was considered statistically significant.

**Results**

Mapping and ablation was performed in 216 PVs (62 patients): 57 RSPVs, 49 RIPVs, 2 right middle pulmonary veins (RMPV), 52 LSPVs, 52 LIPVs, and 4 left common trunks. Complete isolation (elimination of all PVPs on close-bipolar electrograms) was obtained in all 216 PVs. For comparison between the 4 principal PVs, the data from the 2 RMPVs and 4 left common trunks were eliminated, leaving 210 PVs for analysis.

**Number and Type of LA-PV Connections**

The PVP activation sequence was not identical in timing and morphology between RAA and CS pacing in any of the 210 PVs before ablation. The PVP activation sequence differed in timing or morphology in only 1 or 2 adjacent close-bipolar electrodes (Figure 2) in 18 (9%) of the 210 PVs (16 patients). All 18 PVs were isolated by ablation along a single segment of 2 to 3 continuous close-bipolar Lasso electrodes, consistent with the definition of a single discrete LA-PV connection. Single discrete LA-PV connections were equally distributed (8% to 10%) in the 4 principal PVs (Table).

The PVP activation sequence differed between RAA and CS pacing in more than 2 adjacent close-bipolar electrodes in 192 (91%) of the 210 PVs. None had a single discrete LA-PV connection (isolation by ablation within 3 continuous close-bipolar electrodes). Mapping and ablation in these 192 PVs identified (1) “2 discrete” LA-PV connections (each separated by a segment of one or more close-bipolar electrodes) in 31 (14%) of the 210 PVs; (2) “3 or 4 discrete” LA-PV connections in 32 (15%) PVs (Figure 3); (3) a “single broad” LA-PV connection in 46 (22%) PVs; (4) a broad LA-PV connection with additional discrete or broad connections (“broad plus other” LA-PV connection) in 54 (26%) PVs; and (5) a “circumferential” LA-PV connection in 29 (14%) PVs (Table). Circumferential LA-PV connections were more common in the superior (LS and RS) PVs than the inferior (LI and RI) PVs (20% versus 7%, P<0.01, Table). There was no difference in the distribution of the other 5 types of LA-PV connections between the 4 principal
PVs, except that 2 discrete LA-PV connections were less common in LSPVs (p<0.05, Table).

The number of ablation sites (tenths of circumference) and number of radiofrequency applications required for isolation of PVs increased with increasing number and width of LA-PV connections, except that there was no difference between single broad and broad plus other connections (Table). There was no significant difference in the number of ablation sites in tenths of circumference (5.9±2.2) or number of radiofrequency applications (10.2±5.9) among RSPVs, RIPVs, LSPVs, and LIPVs (Table).

Location of LA-PV Connections

Single Discrete and Two Discrete LA-PV Connections

Single discrete LA-PV connections were present in 5 RSPVs, 4 RIPVs, 4 LSPVs, and 5 LIPVs (Table). The single discrete connection was located at the lower posterior region (4:00 to 6:00 o'clock positions) in 4 of 5 RSPVs and the upper posterior side (8:00 to 12:00 o'clock positions) in 3 of 4 LSPVs. There was no predominant location in the 4 RIPVs and 5 LIPVs.

In the 11 RSPVs and 2 LSPVs with two discrete LA-PV connections, one was partially or completely located on the posterior side. There was no apparent pattern in the distribution of the 2 discrete LA-PV connections in the 8 RIPVs and 10 LIPVs.

Ablation Sites for All LA-PV Connections

For all 210 PVs, the percentage of PVs requiring ablation at each of the 10 sites around the circumference is shown in Figure 4. There was a preponderance of lower and posterior sites in RSPVs, upper and posterior sites in LSPVs, and upper sites in LIPVs (p<0.01). There was no significant preponderance among the 10 sites for RIPVs.

Relation Between PV Firing and Extent of LA-PV Connections

Focal firing was provoked before ablation in 90 (43%) PVs. Focal firing was most prevalent in PVs with a circumferential
LA-PV connection (72%), followed by PVs with either a single broad connection or a broad plus other connections (47%), followed by 1 to 4 discrete connections (27%, P<0.01, Table and Figure 5). The incidence of focal firing was similar among the RSPVs (53%), LSPVs (52%), and LIPVs (50%, Table). Focal firing was less common in RIPVs (14%, P<0.01). The number of radiofrequency applications required for isolation was greater in PVs exhibiting focal firing compared with PVs without firing (11.9±6.0 versus 8.9±5.4, P<0.01).

After isolation, rapid firing did not occur in any of the PVs in the baseline state or during isoproterenol (4 μg/min), including cardioversion of pacing-induced AF. The isolated PV myocardium exhibited a slow rhythm (cycle length, 800 to 16000 ms), dissociated from the left atrial rhythm, in 39 of 210 (19%) PVs. This slow rhythm was observed in 29 of 90 (32%) PVs that exhibited firing before ablation, compared with only 10 of 120 (8%, P<0.01) PVs that did not exhibit firing before ablation. Rapid pacing (cycle length, 100 to 200 ms) with PVP capture performed inside 70 isolated PVs failed to induce rapid firing or PV tachycardia in any of the 70 PVs.

**Comparison Between Close-Bipolar and Conventional-Bipolar Electrodes**

All PVPs were recorded from both the close-bipolar and conventional-bipolar Lasso electrodes. The wider conventional-bipolar electrodes recorded larger, wider LA potentials. During RAA pacing, the larger LA potentials in the conventional-bipolar electrograms obscured some PVPs in 30 (29%) of 106 right PVs (Figure 2A) and 61 (58%) of 104 left PVs (Figure 3B). During CS pacing, the larger LA potentials obscured some PVPs in 36 (34%) of 106 right PVs (Figure 2A) but only 14 (13%) of 104 left PVs (Figure 3B). In contrast, none of the PVPs were obscured in the close-bipolar electrograms because of very small, low-frequency (far-field), or completely absent LA potentials.

The PVP activation sequence became identical during RAA and CS pacing on the close-bipolar electrograms preceding the

Figure 3. (Continued). D, After RF2. During CS pacing, PVP at close-bipolar electrode 10 was delayed and attenuated without changing the timing or morphology of the PVP at close-bipolar electrode 2, now earliest with a secondary early site at electrode 8. RAA pacing continued to show earliest PVP at close-bipolar electrode 8. RF3 was targeted at close-bipolar electrode 8 during RAA pacing. E, After RF3. PVP activation sequence in close-bipolar electrograms was similar during RAA and CS pacing (earliest PVP at close-bipolar electrode 2) but not identical. Timing and morphology of PVPs were slightly different in close-bipolar electrode 6, suggesting the presence of more than 1 remaining LA-PV connection. RF4 was targeted at close-bipolar electrode 4. F, After RF4. RF4 did not eliminate all PVPs, confirming that the slight difference in PVP activation sequence before RF4 (panel E) indicated the presence of more than 1 remaining LA-PV connection. PVP activation sequence was now identical in close-bipolar electrograms during RAA and CS pacing, suggesting only a single remaining LA-PV connection near close-bipolar electrode 5. Early far-field PVP in conventional-bipolar electrogram 10 during CS pacing simulated a different PVP activation sequence during RAA and CS pacing, suggesting more than one remaining LA-PV connection with one of the connections at electrode 10. RF5 was targeted at close-bipolar electrode 5. G, After RF5, RF5 eliminated all PVPs on the close-bipolar electrograms, indicating successful isolation and confirming only 1 residual LA-PV connection at electrode 5. Conventional-bipolar electrograms during CS pacing show far-field PVPs in electrodes 8 through 10 (originating from the LSPV), mimicking a residual LA-PV connection. Note that electrodes 8 through 10 are oriented toward the LSPV (panel A). Far-field PVPs were eliminated after isolation of the LSPV.
radiofrequency application producing complete isolation in all 210 PVs (Figure 3F), confirming that an identical PVP activation sequence during RAA and CS pacing indicates a single remaining discrete LA-PV connection. The PVP activation sequence was not identical before the final radiofrequency application on the conventional-bipolar electrograms in 44 (21%) of 210 PVs because of the recording of far-field PVPs from the adjacent PVs (Figure 3F).

After successful isolation, the recording of far-field PVPs from the adjacent PV, mimicking incomplete PV isolation, was present in 72 (34%) of 210 PVs with conventional-bipolar electrodes used compared with 5 (2%) of 210 PVs with close-bipolar electrodes used ($P<0.01$, Figures 2B and 3G). The origin of far-field PVPs was verified by mapping and ablation in the adjacent vein.

**Discussion**

This study confirmed the hypothesis that the occurrence of PV firing is related to the extent of LA-PV connections. PV firing was most common in PVs with a circumferential LA-PV connection (72%). Focal firing was also more frequent in PVs with a single broad LA-PV connection (with or without additional connections) than in PVs with 1 to 4 discrete LA-PV connections (47% versus 27%, $P<0.01$). The PVs exhibiting firing also required a greater number of radiofrequency applications for isolation. Although the mechanism of PV firing is still unknown (ie, reentry versus triggered activity), these observations suggest that the substrate for PV arrhythmogenesis includes wider and possibly thicker LA-PV connections. Circumferential or broad LA-PV connections may help support reentrant circuits or facilitate triggered activity and may be markers for more extensive PV myocardial sleeves that could support ectopic foci.

The elimination of rapid firing within the PV by interruption of LA-PV connections in this and previous studies also supports the relation between the extent of LA-PV connections and focal firing. Rapid firing could not be provoked in any of the PVs after isolation. PV isolation may interrupt a component of the reentrant circuit or disconnect an isolated myocardial bundle responsible for triggered activity. An alternative explanation is that PV ostial ablation may result in local denervation.

A slow, dissociated PV rhythm after isolation occurred more often in arrhythmogenic PVs (32% versus 8%, $P<0.01$). The slow rhythm in the isolated PVs probably has a different mechanism (presumably automatic) from the rapid firing before ablation.

This study found that circumferential LA-PV connections are more common in the superior PVs than inferior PVs (20% versus 7%, Table). However, there was no major difference in the distribution of the other 5 types of LA-PV connections between 4 principal PVs (Table). LA-PV connections were more frequently located in the lower posterior region of the circumference in RSPVs, upper posterior region in LSPVs, and upper region in LIPVs and were equally located around the circumference in RIPVs (Figure 4).

The high resolution provided by the close-bipolar electrodes minimized overlapping LA potentials and far-field PVPs originating from the adjacent PV (Figures 2 and 3). Combined with differential atrial pacing, close-bipolar electrodes helped differentiate between a single discrete and broad or multiple LA-PV connections. A PVP activation sequence differing in timing or morphology in only 1 or 2 adjacent close-bipolar electrograms identified a single discrete LA-PV connection. A PV containing a second LA-PV connection with a very long conduction time might be expected to exhibit a nearly identical PVP activation sequence during RAA and CS pacing. However, a second LA-PV connection was not present in any of the 18 PVs in this study, exhibiting a nearly identical PVP activation sequence during differential atrial pacing. All 192 PVs with a different PVP activation sequence during RAA and CS pacing had multiple discrete, broad, or circumferential LA-PV connections. After 1 or more radiofrequency applications, even a slight difference in PVP activation sequence during RAA and CS pacing indicated multiple or wide residual LA-PV connections (Figure 3E).

**Clinical Implications**

The present study was designed to obtain insight into the relation between PV firing and type of LA-PV connection and was not designed to define a new approach for ablation.
Wide, circumferential isolation, including the antrum of the right and left PVs, has been shown to increase ablation success.3–5 The results of this study suggest that more extensive circumferential ablation may be required for the arrhythmogenic PVs. The close-bipolar Lasso electrodes and differential atrial pacing used in this study may help localize residual PVPs by differentiating near-field from far-filed PVPs.

Limitations of the Study
The principal limitation of this study is that the categorization of the type of LA-PV connections is greatly dependent on the position of the Lasso and ablation catheters. If the two catheters are positioned deeper in the PV or off axis with the PV orifice (part deeper in the PV), the number and width of ablation sites (defining the LA-PV connections) would be less than if ablation is performed closer to the PV orifice. Conversely, if the catheters are positioned well outside of the PV orifice, isolation would require circumferential lesions, incorrectly identifying a “circumferential LA-PV connection.” This problem is compounded by the lack of stability of the Lasso catheter. To minimize these sources of error, the investigators used a combination of the MRA, PV angiogram, and intracardiac ultrasound to try to position the Lasso and ablation catheters close to and parallel to the PV orifice and stored the initial location of the Lasso catheter as well as ablation sites with the use of one of the 3-D mapping systems.

Another limitation of this study is that some of the 120 PVs that did not exhibit rapid firing during the provocation maneuvers may manifest firing at other times. This could alter the relation between PV firing and type of LA-PV connections.

References
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