Role of the Posterior Left Atrium and Pulmonary Veins in Human Lone Atrial Fibrillation

Electrophysiological and Pathological Data From Patients Undergoing Atrial Fibrillation Surgery

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Background—Surgery can eliminate atrial fibrillation (AF), but data confirming the rationale for specific lesion sets are lacking. We used postoperative electrophysiological studies to test the rationale and effects of operative pulmonary venous isolation.

Methods and Results—Fourteen patients undergoing surgical pulmonary venous isolation for drug-refractory lone AF were studied. Successful isolation was confirmed postoperatively in 13 of 14 patients. Spontaneous sustained AF was recorded from the isolated pulmonary venous region (PVR) in 4 and was induced by extrastimulus testing in another. The remaining atrial region (RAR) was in sinus rhythm in 13 patients and nonsustained AF in 1. Atrial extrastimulus testing and burst pacing in the RAR failed to induce sustained AF. In follow-up, 1 patient developed paroxysmal AF, and electrical continuity between the PVR and RAR was confirmed. Isolation was achieved with radiofrequency ablation with no further AF. Another patient developed typical atrial flutter that required ablation. AF has not recurred in any patient at 25.1±11.9 months (range, 6 to 56 months) after surgery. Atrial histopathology was consistent with tachycardia-induced changes.

Conclusions—Total electrical isolation of the PVR controlled AF with excellent clinical outcome and appeared necessary for success. The isolated PVR can sustain spontaneous or induced AF, whereas the considerably larger RAR does not. These data provide a sound rationale for PVR in eliminating AF.

Key Words: fibrillation • arrhythmia • surgery • pathology

There is increasing evidence that atrial fibrillation (AF) is a predominantly left atrial (LA) disease.1 Evidence of the LA “driving” fibrillation in the right atrium has been noted in optical mapping studies of isolated hearts2 and during intraoperative mapping in patients.3 The shortest AF cycle lengths are found in the posterior LA in dogs4,5 and patients with chronic AF.6 Cryoablation in the posterior LA has been shown to terminate experimentally induced AF.4 Finally, the role of pulmonary veins in the onset7 and maintenance of AF8 is well documented.

The mechanism by which the LA “drives” AF in humans is not fully understood. A primary electrophysiological (EP) action with focal initiators/drivers of AF from the pulmonary veins7–9 and/or spiral waves10 in the posterior LA has been suggested. LA pathology favoring reentry may be important for maintenance of AF. A number of surgical procedures have been proposed. Linear lesions are placed in the LA to eliminate “anchors” of reentry11–13 or electrically isolate the pulmonary veins together or as pairs.14–17 The rationale for each lesion set is not clear.

During the evolution of catheter ablation of AF, 14 patients with drug-refractory and highly symptomatic lone AF elected to undergo operative therapy. The surgical procedure involved isolation of the pulmonary veins and associated posterior LA (posterior LA–pulmonary venous region [PVR], Figure 1). LA tissue was biopsied, and EP studies were performed before discharge.

Methods

We studied 14 patients undergoing surgery for long-standing, drug-refractory lone AF between 1998 and 2002. In this cohort, either pulmonary vein ablation during its evolution failed (n=6) or the patients refused ablation therapy because of concerns about complications (n=8). All were medically refractory and sufficiently symptomatic to accept surgery. We evaluated the postoperative electrophysiology and histopathology in this unique cohort.

Surgical Rationale

The surgical technique had 4 components: first, the en bloc isolation of pulmonary veins and LA posterior wall that harbors initiating or perpetuating “foci”7,15; second, a line of conduction block from the
isolated segment to the mitral annulus to prevent surgically induced LA flutter around the mitral valve; third, cryoablation of the right atrial isthmus to prevent atrial flutter; and fourth, an LA appendectomy to reduce the risk of stroke (Figure 1).

Surgical Procedure

The surgery was performed under cardiopulmonary bypass using standard double-venous cannulation and aortic cross-clamping. The LA was entered through the interatrial sulcus, and the incision was extended superiorly and transversely toward the left superior pulmonary vein and inferiorly and transversely toward the left inferior pulmonary vein. A series of overlapping applications of a cryoprobe 15 mm in diameter, cooled at $-110^\circ$C for 2 minutes was used (Frigitronics) to join the ends of the atrial incision while encircling the left pulmonary veins along the left edge of the left pulmonary vestibule. A further 2 to 3 overlapping applications connected this line to the mitral annulus.

Cryoablation of the right atrial isthmus was carried out via a small right atriotomy over the acute margin using 2 or 3 applications of the cryoprobe. LA appendectomy was then carried out by ligation of the appendage at its base, resection of the appendage, and oversewing of the incision. Cardiac biopsies were obtained from the right atrial wall and the LA wall, from the LA appendage after resection, and from each ventricle by use of needle biopsies. Tissue samples were immediately fixed and sent for pathological examination. The tissue was divided and fixed in 100% formalin for light-microscopic examination and glutaraldehyde for electron microscopy. Before closing, 3 pairs of temporary pacing wires (Streamline temporary myocardial wires, Medtronic Inc) were attached to the heart; over the right atrium (nonexcluded segment), over the LA posterior wall (excluded segment), and over the right ventricle.

Postoperative Electrophysiology Study

An EP study was performed after surgery using the epicardial electrodes in all patients. The spontaneous rhythm in each segment was recorded with a bipolar pair (filtered at 30 to 400 Hz), and the efficacy of isolation was tested by pacing the right atrium and the isolated LA-PVR electrodes. Isolation of the LA-PVR was verified by the presence of bidirectional block between the isolated segment and the remaining atrial region (RAR). The ability to induce sustained AF (>5 minutes) was tested in both the isolated PVR and the RAR by extrastimulus pacing at cycle lengths of 600 and 400 ms with up to 3 extrastimuli and by burst pacing to a cycle length of 200 ms. The data were recorded on a Quinton EPS or Prucka 4.0 EPS systems and analyzed offline by 2 independent observers. All patients were discharged in sinus rhythm without antiarrhythmic agents or DC cardioversion. Patients were followed up clinically and by serial ECGs to document the persistence of sinus rhythm. Patients were asked to report any symptoms suggestive of recurrent AF and to obtain an ECG if symptoms occurred. All patients were contacted by telephone at the time of this report.

Results

Surgery was performed successfully in all patients. Patient characteristics are shown in Table 1. The mean cardiopulmonary bypass duration was $93\pm20$ minutes (range, 74 to 144 minutes), with a mean aortic cross-clamp time of $62\pm18$ minutes (range, 50 to 110 minutes). Preoperative coronary angiography was performed in all patients. Two patients (patients 3 and 6) had clinically unsuspected significant coronary artery disease detected that required coronary artery bypass grafting at the time of AF surgery. There were no deaths.
and only 1 minor complication (pleural effusion). The median hospital stay was 8 days (range, 6 to 25 days). The postoperative EP study was performed at a mean of 6±2 days after surgery. The clinical and EP details are shown in Table 2.

Findings at Postoperative EP Study

**Isolated Posterior LA-PVR**

A slow spontaneous isolated rhythm (Figure 2A) was noted in 7 patients (mean cycle length, 1800 ms; range, 1500 to 2500 ms), and no rhythm could be recorded in 3 patients at EP study. Sustained AF was present in the isolated LA-PVR in 4 patients (Figure 2B). AF was induced in the isolated LA-PVR by extrastimulus pacing in another single patient. In the remaining 9 patients, 1 to 10 seconds of nonsustained AF could be induced. Nonsustained episodes of pacing-induced AF repeatedly induced spontaneous bursts of rapid irregular activity, most likely caused by triggered activity, within the isolated LA-PVR in 1 patient (Figure 3).

**Remaining Atrial Region**

In 1 patient (patient 12), AF was induced during attempts to pace-terminate spontaneous atrial flutter within the RAR. As such, AF was transiently present in both atrial segments but terminated spontaneously in the RAR during the EP study (not shown). The RAR was in sinus rhythm in all remaining patients. Aggressive pacing could not induce sustained AF in the RAR in 13 patients. Atrial flutter was induced by right atrial pacing in patient 1 and was pace-terminated.

**TABLE 2. Postoperative EP Study Findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Isolated PVR Rhythm</th>
<th>Response to Pacing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AF</td>
<td>NA</td>
<td>Atrial flutter RF ablation for typical atrial flutter</td>
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<tr>
<td>2</td>
<td>Nil</td>
<td>Nonsustained AF</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
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<td>Nil</td>
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<tr>
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<td>Nil</td>
<td>Nil</td>
<td>RF ablation for recurrent AF</td>
</tr>
<tr>
<td>6</td>
<td>AF</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>AF</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Nil</td>
<td>Nonsustained AF</td>
<td></td>
</tr>
<tr>
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<td>AF</td>
<td>NA</td>
<td></td>
</tr>
<tr>
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<tr>
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<td>12</td>
<td>AF</td>
<td>NA</td>
<td>AF in RAR spontaneously terminated</td>
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<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Nil</td>
<td>Nil</td>
<td>PVR not isolated</td>
</tr>
</tbody>
</table>

**Figure 2.** Dissociation and spontaneous fibrillation of PVR. A, Dissociated automatic rhythm at cycle length 1600 ms in PVR during right atrial pacing recorded postoperatively. B, Sustained fibrillation within isolated PVR. Atrial electrogram (A) and far-field ventricular electrogram (V) are labeled.

**Figure 3.** Demonstration of triggered activity in isolated PVR. A, Sinus rhythm as seen in V, and right atrial electrogram (RAR). Pacing in PVR causes suppression of automatic rhythm (cycle length, 1800 ms). B, Rapid atrial pacing induces nonsustained fibrillatory activity. First automatic impulse (arrow) is followed by a burst of rapid irregular activity that is probably caused by triggered activity.
Follow-Up
Two patients had clinically documented recurrent arrhythmia (patients 1 and 5) requiring repeat EP study and radiofrequency (RF) ablation.

In patient 1, atrial flutter was induced at the postoperative EP study. One week after surgery, the patient had documented spontaneous atrial flutter. At EP study, entrainment mapping during atrial flutter confirmed this to be isthmus dependent. Termination of flutter occurred on the second RF application, suggesting the presence of a small gap in the surgically created cryoablation line. Bidirectional block was subsequently confirmed. The patient has since remained in sinus rhythm.

In patient 5, at the initial postoperative EP study, the LA-PVR was shown to be isolated, with a spontaneous rhythm at a cycle length of 1600 ms (Figure 2A). The patient developed recurrent paroxysmal AF 2 weeks after surgery. At repeat EP study, electrical continuity between the previously isolated LA-PVR and the RAR was documented (Figure 4A). Mapping of the LA in sinus rhythm located a gap in the cryoablation line at the inferolateral aspect of the isolated LA-PVR. RF ablation was performed to close the gap, resulting in effective isolation of the LA-PVR with a single lesion (Figure 4B).

During longer-term follow-up, all patients remain in sinus rhythm at a mean of 25.1±11.9 months (range, 6 to 56 months) after surgery.

LA Pathology
Histology from the LA appendage and posterior wall showed findings compatible with tachycardia-induced changes. A number of consistent findings included myocyte hypertrophy with enlarged fibers, increased number of mitochondria, and enlarged nuclei. Widening and loss of definition of Z bands (Z-band streaming) were also seen. Abundant cytoplasmic vacuoles of various sizes were empty or contained a finely granular material. Increased glycogen was noted.

Aside from mild fibrosis beyond that expected for the patient’s age in 1 patient (patient 4), significant fibrosis was not seen. Loss of myofibrils around the nucleus was seen in the majority of cases. In a few cases, this was severe, with unmasking of the tubuloreticular system. An increased number of lipofuscin granules were seen. Importantly, there was no inflammation, no vascular lesions, and no amyloid deposits.

Discussion
Main Findings
Multiple operative procedures with differing lesion sets have been described for AF. Although variable success has been reported, insight into the mechanism of benefit has been sparse. This study demonstrated that the surgically isolated
posterior LA-PVR could sustain AF independently of the remainder of the atrium. Furthermore, EP testing after surgery demonstrated that the larger remaining atria, including the entire right atrium, the LA septum, and the perimitral region, did not sustain AF after aggressive pacing. There was no clinical AF during follow-up. Clearly, the posterior LA-PVR possesses unique properties that provide the ability to maintain sustained AF. These data are compelling for the role of the LA and rationale for isolation of this region. This is highlighted by patient 5, who developed recurrent AF after recovery of the conduction from the nonexcluded LA to the posterior LA-PVR and subsequent elimination of AF after isolation by catheter ablation. It is noteworthy that most of the successful operations, including the MAZE procedure and its modifications, incorporated total isolation of the pulmonary veins.

Previous studies have provided few data on LA pathological changes in patients with lone AF, and none have correlated pathological abnormalities with electrophysiological observations in the postoperative period. The population in this study had a striking absence of structural changes in the LA known to promote reentry, such as inflammation and fibrosis. The abnormalities seen are most compatible with tachycardia-induced atrial myopathy.

**Possible Mechanisms of Sustained AF in the Isolated Posterior LA-PVR**

**Multiple-Wavelet “Random” Reentry**
The single electrode pair in the segment allowed assessment of vulnerability but not detailed voltage mapping. It is estimated, on the basis of measurements by Pappone et al., that the isolated region is approximately 50% of the LA surface area. It was striking that the smaller isolated posterior LA pulmonary venous segment was unable to sustain fibrillation, spontaneously in most cases, whereas the larger remaining atrial segment was unable to do so despite aggressive pacing. If multiple-wavelet “random” reentry were the sole underlying mechanism for AF in this area, one would need to propose a very short atrial wavelength in the isolated region and a sufficiently long wavelength that prevented AF elsewhere. Although reentry is not ruled out, it is postulated that alternative mechanisms, such as focal discharge or self-sustained rotors with fibrillatory conduction, underlie the sustained AF in this small area of tissue.

**Focal Discharges**
The isolated LA-PVR in this study, when not in fibrillation, demonstrated bursts of irregular pacing-induced atrial activity suggestive of triggered activity in 1 patient and a slow dissociated “automatic” rhythm in 11 patients. The inclusion of all 4 pulmonary veins and the posterior LA in the isolated region, as well as high postoperative sympathetic activity, may have contributed to the high rate of automatic rhythm. Focal discharges from the pulmonary veins and posterior LA are important in the initiation of AF in younger patients with structurally normal hearts. Increasingly, evidence suggests that the same events may maintain AF by continuing to trigger the arrhythmia. Given the relative similarity between the patients in this series and those undergoing AF ablation, it is likely that focal firing played a role.

**Stable Reentry**
Animal studies have demonstrated that relatively stable reentry (rotors) with fibrillatory conduction in the LA can maintain AF. Cryoablation of a rapid regular source in the interposteroinferior LA in a canine pacing-induced model of AF terminated sustained AF. Unfortunately, the widely spaced (≈1 cm) bipolar atrial electrograms from the isolated LA-PVR precluded further mapping or spectral analysis to determine whether there was evidence of spatiotemporal periodicity suggesting stable rotors of reentry.

**LA Pathology**
Histopathological findings from both the LA posterior wall and the LA appendages were most compatible with tachycardia-induced atrial myopathy. A striking absence of fibrosis and inflammation is noted. There are few data on pathological changes associated with AF in humans. We previously reported 11 cases of lone AF with biopsies from both atria that showed the absence of inflammation and insignificant fibrosis. Connelly et al. reported pathological changes in atrial appendage tissue obtained at the time of the MAZE procedure similar to those found in our study. The underlying AF pathogenesis was mixed in this case series, and the authors did not comment on any relationship between pathogenesis and pathological changes. Conversely, Frustaci et al. found abnormal atrial histology in biopsies of the atrial septum from a group of patients with drug-resistant paroxysmal AF. Inflammatory changes compatible with a myocarditis were present in two thirds of patients, raising the question of the diagnosis of “lone” AF. We found no evidence of inflammation in this or other series.

More advanced structural and pathological changes in the atria have been reported in patients with chronic AF, with marked myocyte hypertrophy, loss of myofibrils with replacement by glycogen granules, and interstitial fibrosis. This appears to be duration dependent. There are experimental data from animal models of AF that the mechanism of the arrhythmia depends on the model studied and the amount of fibrosis present. Models of congestive heart failure and mitral regurgitation are associated with significant fibrosis that may facilitate micro-reentry and fibrillatory conduction. It is thus important to put the current EP observations into a histopathological context, because fibrosis does not appear to play a role in the maintenance of AF in this population. Rather, the changes closely resemble those seen in pacing-induced remodeling and “hibernating” ventricular myocytes exposed to chronic low-flow ischemia.

**Possible Role of the Posterior LA in Human Lone AF**
The data in this study argue for a primary EP role of the posterior LA, including the pulmonary veins, in human lone AF. Possible mechanisms include rapid continuous firing from the pulmonary veins (analogous to rapid atrial pacing).
resulting in atrial electrical remodeling and the onset of persistent AF. Alternatively, the anatomy or electrophysiology of the PVR may promote reentry, resulting in the maintenance of AF. Recent work using noncontact mapping has demonstrated significant conduction abnormalities in the posterior LA during sinus rhythm in patients with paroxysmal AF.\textsuperscript{32} Lines of functional conduction block were correlated to underlying fiber orientation in pathology specimens from hearts without AF. Hence, underlying tissue architecture in the posterior LA may form the substrate for functional reentry in the absence of significant atrial disease. The contribution of each mechanism (triggered activity versus reentry) within the isolated LA-PVR is impossible to ascertain without high-resolution mapping techniques.

**Role of Surgery for Lone AF**

A consistently successful and safe ablation procedure is intuitively preferable to surgery for patients with symptomatic, medically refractory lone AF. The cohort of patients in this report are a select group who were sufficiently motivated to undergo surgery during evolution of catheter ablation methods. The unique data collected from these patients support the principle of isolation of the pulmonary veins and posterior LA as a curative therapy, regardless of the method used. Ultimately, operative therapy using thoracoscopic techniques may assume a greater role for definitive therapy of AF.

**Study Limitations**

The patients in this cohort form a subset of patients with AF. Further study is needed to determine whether these observations apply to those with more advanced atrial disease.

Measurements of the surface area of the isolated LA-PVR are difficult to perform with clinically available technology. Our estimate is based on measurements from Pappone et al using customized software and a nonfluoroscopic mapping system and is provided as a rough guide only.

EP assessment of the isolated LA-PVR and RAR was limited to a single widely spaced bipolar electrode sited at the time of surgery. More detailed mapping using multiple electrodes might have provided further insights into the mechanism of sustained AF in the LA-PVR. Nonetheless, the presence or absence of localized AF (spontaneous or pacing-induced) within the segments could be documented by use of these electrodes. The noninducibility of AF in the RAR despite aggressive stimulation was striking in contrast to the presence of spontaneous sustained AF in the LA-PVR.

Clinical follow-up suggests that the RAR did not sustain spontaneous AF. Access to the LA in the postoperative state was difficult to justify in this population because they were well, with no recurrent AF. Multielectrode mapping from the posterior LA in patients with chronic AF undergoing cardiac surgery has demonstrated rapid repetitive activity originating in the areas of the pulmonary veins,\textsuperscript{7} suggesting that the pulmonary veins have a role in the maintenance of sustained AF. On the basis of the absence of significant fibrosis as a substrate for reentry and histological findings compatible with tachycardia-induced myopathy, we speculate that triggered activity played a significant role in the AF localized to the LA-PVR. In the absence of further data, a significant role for reentry cannot be discounted.

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**References**

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