Transcatheter Angioplasty for Acquired Pulmonary Vein Stenosis After Radiofrequency Ablation

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Background—Pulmonary vein stenosis has recently been recognized as a complication of radiofrequency ablation for atrial fibrillation. This study evaluates the presentation of affected patients and the role of transcatheter therapy for this patient population.

Methods and Results—This study used a retrospective review of data from 19 patients (age, 51±13 years) with pulmonary vein stenosis who underwent catheterization and angiography between December 2000 and December 2002. Quantitative perfusion and spiral CT scans were performed for initial diagnosis and follow-up. The median duration between radiofrequency ablation and the reported onset of respiratory symptoms for 18 of 19 patients was 7.5 weeks (0.1 to 48). After the onset of symptoms, all but two patients were initially misdiagnosed with a symptoms-to-diagnosis duration of 16 weeks (2–59). At initial catheterization, 17 of 19 patients had angioplasty in 30 veins with stent placement in 5 vessels when a flap occurred. Overall vessel diameter increased from 2.6±1.6 to 6.6±2.4 mm (P<0.0001). There were 4 procedure-related adverse events but no long-term sequelae. Immediate follow-up showed improved flow to involved lung segments. At a median follow-up of 43 weeks (2–92), although repeat angioplasty for restenosis was necessary in 8 of 17 patients, 15 of 17 patients currently have no or minimal persistent symptoms.

Conclusions—Pulmonary vein stenosis after radiofrequency ablation for atrial fibrillation is often misdiagnosed. Although further follow-up is necessary to determine long-term success, our data indicate better pulmonary vein flow and symptomatic improvement in the majority of patients undergoing dilation of postablation pulmonary vein stenosis. (Circulation. 2003;108:1336-1342.)

Key Words: stenosis ■ ablation ■ fibrillation ■ angioplasty

Since the pioneering work of Haissaguerre and colleagues,1 ablation in the pulmonary veins has become an acceptable alternative therapy for atrial fibrillation unresponsive to medical therapy.1,2,3,4 Since these initial reports, pulmonary vein stenosis (PVS) is a well-known but underreported complication after radiofrequency ablation (RFA). The incidence of PVS could depend on the study definition as well as the ablative technique used and has been reported as high as 42%.4 However, few data exist regarding the presentation and treatment options for patients who have this life-altering and potentially serious condition. Lack of awareness of this procedural complication among the medical community and a diversity of clinical presentations has resulted in patients being misdiagnosed.9

The objective of this study was to review our experience with transcatheter intervention for acquired PVS as a complication of RFA.

Methods

Patients

Data from patients with PVS after RFA referred to us from December 2000 to December 2002 were reviewed in accordance with our institutional review board guidelines and policy. Patients were stratified by New York Heart Association functional classification (class 1–4). The diagnosis of PVS was confirmed by contrast-enhanced spiral CT scan (retrospectively gated helical scanning with overlapping 1.00- to 1.25-mm-thick images for multiplanar reconstructions or maximal intensity projections, using a 4-detector volume zoom or 16-detector sensation 16, Siemens Medical Systems).10 Once evidence of PVS was demonstrated, a baseline quantitative nuclear perfusion scan was performed to assess the percentage of blood flow to different segments of the lung before the cardiac catheterization. Informed consent for the procedure was obtained from each patient. All patients then proceeded to the cardiac catheterization laboratory, and pulmonary vein angioplasty was performed only in those patients who had a patent pulmonary vein ostium.
Catheterization Procedure
All procedures were performed with patients under general endotracheal anesthesia. Access was obtained in both femoral veins. Patients were given 5000 U of intravenous heparin. Activated clotting times (ACT) were monitored throughout the procedure with the goal to maintain an ACT >250 U. Right heart hemodynamic data were obtained with a 7F balloon wedge catheter through the left femoral sheath. This catheter was used to obtain pulmonary artery wedge pressures and perform a wedge angiogram for mapping the individual pulmonary vein flow and to determine if any segments were completely occluded. The left atrium was entered by the transseptal technique. A V-18 floppy-tipped control wire (Boston Scientific) was manipulated across the target lesion within the pulmonary vein. Subsequently, a 5F Angled Glide catheter (Medi-tech, Boston Scientific) was coaxially introduced and used to measure a mean pressure gradient across the target lesion, angiographically study individual pulmonary vein anatomy, and position the V-18 wire into the distal pulmonary vein. The diameter and length of the target lesion and the distal pulmonary vein were measured digitally. Angiographic measurements were calibrated with the diameter of the catheter across the target lesion. An appropriately sized angioplasty balloon was chosen not to exceed the diameter of the stenotic lesion by a factor of 4 or the distal vessel by a factor of 1.5. Standard angioplasty was performed in each lesion. Stent angioplasty was reserved for when standard angioplasty resulted in a flap or when restenosis occurred during follow-up. In general, lesions were gradually dilated with a goal final diameter ≥8 to 10 mm. After balloon angioplasty, a mean pressure gradient across the lesion was again measured. Angiography was performed to measure the target lesion diameter and assess the degree of vessel injury.

A different protocol was used to engage the right lower pulmonary vein. To cannulate this vessel, we used a 7F modified (length) Hockeystick coronary guide catheter (Medtronic/AVE) within the left atrium and deflected off the lateral wall to allow a direct position toward the right lower pulmonary vein. This catheter was then used to guide the V-18 wire and 5F angled glide catheter as described above.

Follow-Up
Patients were evaluated 1 month after the procedure and at 3-month intervals thereafter. Clinical evaluation and quantitative perfusion scan were performed at each interval. Depending on the clinical course, other noninvasive evaluations include a chest radiograph, echocardiogram, or spiral CT scan. Repeat cardiac catheterization was performed in all patients with recurrence of symptoms and evidence of restenosis by noninvasive imaging. Although a quantitative perfusion scan was performed in all patients to document the percentage of flow across the involved lung segment, group analysis of these data are difficult to interpret secondary to bilateral involvement and collateral blood flow.

Statistical Analysis
Data were tabulated retrospectively on specific data collection forms and summarized as mean±SD. A paired Student’s t test was used to compare patient data. A probability value of <0.05 was considered statistically significant. Where a data set was missing, the results are reported based on number (n) of subsets available. The degree of PVS was graded as mild, moderate, or severe, based on a luminal narrowing of <50%, 50% to 70%, or >70%, respectively.9 Reference values for normal pulmonary vein size in adults was based on estimates from healthy control subjects.3,5,11 Briefly, each pulmonary vein narrowing was compared with nonstenotic segment dimensions in the same vessel or other pulmonary veins in the patient undergoing the procedure.

Results

Patients
Nineteen patients (male:female ratio=13:6) with a mean age of 51±13 years were considered for transcatheter dilation secondary to PVS (Figure 1). Four patients had proximal ablation in the region of the pulmonary venous ostia and 15 patients had distal ablation within the pulmonary veins.2,3

Clinical Presentation
The median onset of symptoms after RFA was 7.5 weeks (range, 0.1 to 48), with 1 patient in NYHA class 1, 3 patients in class 2, 8 patients in class 3, and 7 patients in class 4 (mean, 3.1±0.9) by the initial evaluation in our center. The median duration from the onset of symptoms to definitive diagnosis of PVS was 16 weeks (range, 2 to 59). With the exception of one patient, all were symptomatic with cough, hemoptysis, or dyspnea and had an abnormal chest radiograph with either pleural effusion or nonspecific haziness (Table 1). All but two patients were initially misdiagnosed with either pneumonia (n=11), new-onset asthma (n=3), pulmonary embolism (n=6), and/or lung cancer (n=4). Because of the incorrect diagnosis, one patient underwent placement of an IVC filter and 1 patient underwent partial resection of the left lung, which had no evidence of tumor pathologically. The correct diagnosis of PVS was rarely made before evaluation by the electrophysiologist who performed the RFA.

Catheterization
All patients proceeded to the catheterization laboratory for further investigation and possible angioplasty (Figure 1). In two patients with single pulmonary vein involvement, pulmonary artery wedge angiography demonstrated complete vessel occlusion and thus angioplasty could not be performed. In one of these patients, attempted radiofrequency recanalization of the occluded pulmonary vein was unsuccessful. The remaining 17 patients underwent angioplasty of 30 pulmonary veins (Figure 2). Precatheterization spiral CT graded the vessel lesion as mild (n=4), moderate (n=8), severe (n=10), or occluded (n=13). Pulmonary artery bala-

### Table 1. Frequency of Clinical Signs/Symptoms at Presentation

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Cough</td>
<td>17 (89)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1 (5)</td>
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</table>
loon wedge angiography demonstrated patency in 8 of 13 of the vessels, deemed occluded by CT. Angiography identified complete occlusion of a single pulmonary vein and thus the loss of respective lung segment in 5 patients. For these patients with pulmonary vein occlusion, there was a trend toward a longer symptom-to-diagnosis duration (33±22 versus 17±15 weeks, P=0.09).

Overall, an intervention was performed in 30 vessels (Table 2). Various high-pressure angioplasty balloons were inflated in each target lesion and a stent was required in 5 vessels during this initial procedure. Each stent was placed in the target lesion, and, if possible, across the pulmonary vein ostium, avoiding significant protrusion into the left atrium or crossing a low-flow distal side branch. The final lesion diameter increased from 2.6±1.6 to 6.6±2.4 mm, (P<0.0001). The peak PA pressure/systemic pressure ratio (n=11/17) decreased from 0.39±0.13 to 0.29±0.06 mm Hg (P<0.01) after intervention. The gradient across the stenotic pulmonary vein (n=27/30) decreased from 13.1±6.8 to 4.1±3.4 mm Hg (P<0.0001). Angiographic improvement was seen in all the pulmonary veins after balloon and/or stent angioplasty (Figure 3).

Adverse Events
Although there was no procedure-related death, there were 4 adverse events. Two events occurred after a balloon wedge angiogram in the setting of an occluded pulmonary vein. Immediately after a balloon wedge angiogram, one patient had hemoptysis that resulted in 48 hours of intubation and positive-pressure ventilation before complete resolution, and self-limiting pulmonary hemorrhage developed in one patient. One patient had a pulmonary vein tear that required emergent surgical repair, and one patient had an embolic event with MRI evidence of middle cerebral artery distribution stroke and transient ECG changes.

Restenosis/Catheterization
Restenosis occurred in 8 patients (47%), with all having a second catheterization and two requiring a third (Table 2). These procedures involved 19 vessels, a median of 24 (6 to 77) weeks after the primary catheterization. One patient had complete occlusion in 1 of 2 previously balloon dilated pulmonary veins 71 weeks after the initial dilation. Angiography demonstrated an overall decrease in lesion diameter from 6.4±2.3 to 2.5±0.8 mm (P<0.0001) for the remaining 18 vessels. Recanalization of pulmonary venous drainage was seen to theazygous vein in 1 patient, the intercostal veins in 1 patient, innominate vein in 1 patient, and to the ipsilateral pulmonary veins in 5 patients (Figure 4). These procedures involved standard balloon angioplasty in 2 vessels, stent angioplasty in 10 vessels, and repeat balloon angioplasty within a previously implanted stent in 6 vessels (Figure 4). The last 4 of 6 vessels with in-stent restenosis were treated with a 4×10-mm cutting balloon before standard balloon angioplasty. Overall, repeat angioplasty resulted in improved vessel diameter from 2.5±0.8 to 7.2±2.3 mm (P<0.0001), and there were no additional procedure-related adverse events.

Follow-Up
During a median follow-up of 43 weeks (2 to 92), there have been no late adverse events and no late sequelae in the patients who had a procedure-related complication. At latest follow-up, the NYHA functional class improved from 3.1±0.9 to 1.7±0.6 (P<0.0001). One patient with other preexisting comorbid conditions (ischemic heart disease, congestive heart failure) died 6 months after the second procedure as the result of hyperkalemia-induced ventricular arrhythmia. Overall, the remaining patients report a return to their usual activities of daily living with no or minimal symptoms.

Discussion
Acquired PVS is a known but often underrecognized complication of RFA for atrial fibrillation.\textsuperscript{1,–6,12–22} Our study emphasizes the importance of early recognition of signs and symptoms of PVS. In addition, our data support that this is a significant cause for death and life-altering problems. Since catheter ablation for atrial fibrillation is a relatively new procedure, not only patients but physicians outside the realm of a tertiary care center are often unaware of the specifics of the procedure and hence the potential complication. All but two patients in our series were misdiagnosed as having other respiratory ailments, and there was significant delay in the definitive diagnosis. Patients underwent unnecessary procedures including bronchoscopy, pleurocentesis, IVC filter, and lung resection. Many patients were also inappropriately treated for pneumonia or pulmonary emboli. Prompt recognition and early referral to an interventional cardiologist could theoretically preclude unnecessary procedures and ineffective treatment as well as prevent development of completely occluded vessels.

A number of imaging modalities have been used in the evaluation of PVS, including transthoracic echocardiography, transesophageal echocardiography, quantitative perfusion scan, spiral CT scan (Figure 5), and MRI.\textsuperscript{12–19,21–22} Although previous reports have demonstrated MRI to be superior to transesophageal echocardiography in defining pulmonary venous anatomy,\textsuperscript{17} there are few data comparing MRI to spiral CT.
scan as the imaging modality to delineate abnormalities of pulmonary venous anatomy as well as associated abnormalities of the mediastinum/hilum (eg, enlarged nodes) or of the lung (eg, focal edema or hemorrhage). Although spiral CT scans were accurate in defining mild to severe degrees of stenosis, many vessels deemed occluded were found to be patent by use of the balloon wedge angiogram technique. This probably is related to the dye being forced through a collapsed and severely stenotic vessel, with otherwise undetectable flow under normal conditions. Angiography with balloon wedge injection is the definitive diagnostic modality, and we recommend catheterization in all patients, even if the pulmonary veins appear occluded by other imaging modalities.

<table>
<thead>
<tr>
<th>TABLE 2. Primary Catheterization and Recatheterization</th>
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<tr>
<td>Primary catheterization†</td>
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<tr>
<td>Patient A LUPV</td>
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<tr>
<td>Patient B LUPV</td>
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<tr>
<td>Patient C LUPV</td>
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<tr>
<td>Patient D LLPV</td>
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<tr>
<td>Patient E LUPV</td>
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<tr>
<td>Patient F LLPV</td>
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<tr>
<td>Patient G LUPV</td>
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<tr>
<td>Patient H LLPV</td>
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<tr>
<td>Patient I LUPV</td>
</tr>
<tr>
<td>Patient J RUPV</td>
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<tr>
<td>Patient K LLPV</td>
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<tr>
<td>Patient L LLPV</td>
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<td>Patient M LUPV</td>
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<tr>
<td>Patient N LUPV</td>
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<tr>
<td>Patient O LUPV</td>
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<tr>
<td>Patient P RUPV</td>
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<td>Patient Q LUPV</td>
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<tr>
<th>TABLE 2. Continued</th>
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<tbody>
<tr>
<td>Recatheterization‡</td>
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<tr>
<td>Patient B-2 LUPV</td>
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<tr>
<td>Patient C-2 LLPV</td>
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<tr>
<td>Patient F-2 RUPV</td>
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<tr>
<td>Patient F-3 LLPV</td>
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<tr>
<td>Patient F-3 LLPV</td>
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<td>Patient G-2 LLPV</td>
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<td>Patient I-3 LLPV</td>
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<tr>
<td>Patient J-2 RUPV</td>
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<td>Patient L-2 LLPV</td>
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<tr>
<td>Patient O-2 LLPV</td>
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<tr>
<td>Patient O-2 LLPV</td>
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<tr>
<td>Patient O-2 RUPV</td>
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Change in vessel diameter is given for each pulmonary vein. LUPV indicates left upper pulmonary vein; LLPV, left lower pulmonary vein; RUPV, right upper pulmonary vein; and RLPV, right lower pulmonary vein.

*Where stent placement is not specified, only balloon dilation was performed.
†This portion of the table shows the involved pulmonary veins at the primary catheterization that was amenable to intervention with a balloon and/or stent.
‡This portion of the table shows data from additional procedures performed for restenosis.
In both the acquired and congenital forms, PVS uniformly has been a frustrating lesion to treat for cardiac surgeons and interventional cardiologists, with restenosis being a common occurrence. Surgical approach has been tried in some instances, with variable results, depending on the technique used, anatomy, and timing of surgery. In children, balloon angioplasty for PVS has been uniformly unsuccessful. In addition, endovascular stenting of the pulmonary veins in children has met with little clinical success. On the other hand, stent placement in the pulmonary veins after extrinsic compression in adults has yielded some clinical success. The application of energy in the region of the pulmonary veins results in formation of organizing thrombus, necrotic myocardium, endovascular contraction, and proliferation of elastic lamina, in addition to intimal proliferation. This provides a substrate for angioplasty or stent placement different from other acquired or congenital forms of PVS and hence transcatheter therapy could potentially be successful. Surgery for this lesion may not be optimal because of the often-found long segment of stenosis, which may extend beyond the surgical field and be a significant risk for restenosis. Currently, there are no published series on the transcatheter management of PVS secondary to RFA, and the few published case reports available have variable results. Our results show that transcatheter management performed early after diagnosis and aimed at producing a widely patent pulmonary vein ostium can significantly improve the patient’s outcome. Importantly, our patients had an overall significant improvement in NYHA functional class. However, these results must be viewed with caution as restenosis was common, and 8 patients required repeat catheterization.

Although restenosis has occurred with balloon as well as stent angioplasty, some case reports have demonstrated early success. Vance et al reported a case in which they used a balloon and self-expandable stent in stenotic pulmonary veins with effective 1-year follow-up. We performed (when a flap occurred) stent angioplasty in affected veins. Though longer follow-up is needed to evaluate the restenosis rate in our series, restenosis within the stent occurred in 6 vessels in 4 patients, with resolution after repeat balloon angioplasty within the previously deployed stent. For the latter 4 of these 6 vessels, a cutting balloon was used initially followed by standard balloon angioplasty, with complete resolution of the balloon waist and a 1- to 2-mm increase in the stent diameter. Hosking et al concluded that restenosis within stents in...
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role in restenosis within congenitally stenotic pulmonary

that the myofibroblastic neoproliferative process plays a key

in pulmonary veins is due to the inherent nature of the pulmo-

nary vein and stent diameter rather than a function of the stent

Thus, if distal vessel diameter is adequate, large stent

diameters would be crucial in maximizing patency of the pulmonary veins.

Although there is clearly a procedural risk for these patients, 3 of our 4 adverse events occurred during our early experience. The only adverse event in the last 20 procedures was 1 patient with a transient pulmonary hemorrhage. We therefore recommend vigilance when performing balloon pulmonary artery wedge contrast injections to avoid trauma to the alveoli when there is minimal or no outlet to the left atrium.

In addition to anatomic obstructions, a number of factors have been postulated as influencing restenosis of the pulmonary veins, including low-velocity venous flow, vessel cali-

ber,26 and intimal proliferation.31,32 Sadr et al36 have shown that the myofibroblastic neoproliferative process plays a key role in restenosis within congenitally stenotic pulmonary veins. Perhaps future therapies for patients with PVS after RFA could also be targeted at arresting the neoproliferative stage, such as the use of immunosuppressive agents, chemother-

apy, and radiation.

This study, despite being the largest series of patients with PVS caused by RFA, remains limited by sample size. In addition, with only mid-term follow-up the true incidence of restenosis as well as symptomatic relief remain unknown. Other limitations are inherent to the fact that this is a retrospective analysis.

In conclusion, pulmonary vein stenosis after RFA causes significant morbidity and is a potentially life-altering problem. A high index of suspicion should be maintained after a patient has undergone RFA for atrial fibrillation. Angiogra-

Figure 5. Spiral CT scan. A, What appeared to be complete occlusion of the left upper pulmonary vein (arrows) 30 days after radiofrequency ablation therapy for atrial fibrillation was found to be amenable to angioplasty during balloon wedge angiography. B, Subsequent angioplasty resulted in reestablishment of for-

ward flow despite the thickened edematous walls of the vein with adjacent inflammatory changes of the left hilum.

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