Clinical Presentation, Investigation, and Management of Pulmonary Vein Stenosis Complicating Ablation for Atrial Fibrillation

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Background—Although segmental or circumferential ablation is effective in eliminating pulmonary vein (PV)–mediated atrial fibrillation (AF), this procedure may be complicated by the occurrence of PV stenosis.

Methods and Results—To establish the clinical presentation, diagnostic manifestations, and interventional management of PV stenosis, 23 patients with stenosis of 34 veins complicating ablation of AF were evaluated. Each patient became symptomatic 103 ± 100 days after undergoing ablation. In 8 veins, the ablation producing the PV stenosis was a repeated procedure for continued AF. Nineteen patients presented with dyspnea on exertion, 7 with dyspnea at rest, 9 with cough, and 6 with chest pain. On multirow spiral computed tomography examination, the narrowest lumen of the affected PVs measured 3 ± 2 mm compared with 13 ± 3 mm at baseline (P ≤ 0.001). The relative perfusion of affected lung segments on isotope scans was reduced to 4 ± 3% of total perfusion compared with 22 ± 10% in unaffected segments. At percutaneous intervention, these veins showed 80 ± 13% stenosis, with a mean gradient of 12 ± 5 mm Hg. This was significantly reduced to a residual stenosis of 9 ± 8% (P ≤ 0.001) and a residual gradient of 3 ± 4 mm Hg (P ≤ 0.001). Twenty veins were treated with balloon dilatation alone, whereas 14 veins were stented with standard 10-mm-diameter bare-metal stents. Although the symptomatic response was nearly immediate and impressive, 14 patients developed in-stent or in-segment restenosis, requiring repeated interventions in 13.

Conclusions—Percutaneous intervention produces rapid and dramatic symptom relief in patients with highly symptomatic PV stenosis after radiofrequency ablation for AF. Nevertheless, alternative treatment methods will be required to decrease recurrent in-stent or in-segment restenosis. (Circulation. 2005;111:546-554.)

Key Words: fibrillation, atrial  ■  ablation, catheter  ■  pulmonary heart disease  ■  stenosis  ■  stents

The presence of focal arrhythmogenic triggers arising within pulmonary veins (PVs) in patients with atrial fibrillation (AF)7–9 is well documented. Furthermore, the elimination of AF through (1) targeted energy delivery to focal “sites” within the vein; (2) PV isolation through circumferential or segmental ablation at the venoatrial junction2,3,5,6; or (3) electrical isolation of the PVs from the left atrium (LA) by radiofrequency energy delivery outside the PV ostia7–9 confirms this mechanism.

Nevertheless, as the clinical experience with ablation has grown, the risk of PV stenosis has become more apparent. Reports suggest that 1% to 10% of patients undergoing ablation develop PV stenosis.3,4,10–15 Although several case reports have chronicled isolated experiences,16–21 the accompanying clinical manifestations and diagnostic and therapeutic interventions have been incompletely examined. This report, therefore, presents a series of 23 patients along with their presentations and long-term outcomes after intervention.

Methods

Patient Population
Sixteen patients undergoing initial evaluation and ablation at Mayo Clinic and 7 patients referred from an outside institution form the basis of this report. Data were reviewed in a manner consistent with Mayo Institutional Review Board requirements. Their clinical characteristics and ablative interventions are summarized in Table 1.

Radiofrequency Ablation Procedure
During the reference ablation, up to 30 W of radiofrequency energy (temperature ≤ 50°C) was typically directed in 20- to 30-second deliveries from an 8F steerable catheter with a 4- to 5-mm tip, either at the focal origin of the tachycardia, in a wedged-shape segment extending out toward the vein orifice, or subsequently at the orifice of the targeted vein. The end point of the ablation was the elimination of spontaneously occurring AF, AF after direct-current cardioversion, other ectopic activity, and/or all PV potentials. Each patient was followed up through telephone contact, clinic follow-up visits, and/or communication with the patient’s primary referring physician.
Preinterventional Evaluation

Before each ablation, patients underwent multirow spiral computed tomography (SCT) and transesophageal echocardiographic (TEE) examinations to assess the number and characteristics of the PVs. On return for assessment of symptomatic PV stenosis, patients underwent a repeated chest x-ray, CT scanning, TEE, and radioisotopic ventilation/perfusion (V/Q) scanning.

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Mean 49.0 5.4 2.7 3.1 19.0 47.1 32.6 98.3
Mean SD 7.7 4.0 1.4 0.9 13.3 5.3 7.6 100.5

Pt indicates patient; RS/LS, right/left superior; RI/LI, right/left inferior; Circ, circumferential; NA, not available; DOE, dyspnea on exertion; SOB, shortness of breath; -extol, decreased exercise tolerance; CP, chest pain; hemopt, hemoptysis; SX, symptom; and PND, paroxysmal nocturnal dyspnea. All other abbreviations are as defined in text.

*Ablated >1 time.
†Ablated elsewhere.

CT Scanning

Patients underwent evaluation according to a 2-phase protocol with a multirow SCT system (GE Medical Systems). In the first phase, a range-finding scan was undertaken at 10-mm intervals to determine the superior and inferior borders of the heart. A complete image set was then obtained after injection of 125 mL of contrast medium, yielding images at 1.25 mm. These allowed a 0.6-mm axial image
TABLE 2. Various Test Modality Findings in PV Stenosis

interest, drawn over anterior and posterior images, were divided into apical, middle, and basal regions. The geometric means of counts from the anterior and posterior images for each lung field and for each of these specific regions were derived and expressed as a percent of total right and left lung ventilation or perfusion counts. These formed the bases for comparison of perfusion in normal and stenotic segments.23

**PV Angiography, Dilatation, and Stenting**

In the catheterization laboratory, intracardiac echocardiographic (ICE) imaging was performed with a 10F multidirectional, 64-element, phased-array catheter (Acuson Corp) advanced into the right atrium.24 A Swan-Ganz catheter was advanced through the right heart to facilitate right heart hemodynamic monitoring and selective pulmonary arteriography. A second venous access site was used for transseptal catheterization, performed under fluoroscopic and ICE guidance.

PVs were imaged by ICE to corroborate the preprocedural CT and TEE findings. The pattern of blood flow and presence of any disturbance of laminar blood flow were assessed with color flow imaging. Color flow jets were also used as “contrast imaging” to locate the orifice of the PV in the case of tightly stenotic lesions. Pulsed-wave Doppler interrogation of the vein was undertaken to establish blood flow velocity and apparent gradient.

A multipurpose catheter was positioned via the transseptal sheath into the LA and advanced across the lesion of interest to measure the transstenotic gradient and to perform venography. On the basis of this imaging and ICE sizing, a balloon with an appropriate diameter and length was selected to engage each stenotic lesion. In general, a balloon-to-vein ratio of 1.0 to 1.2 was chosen, and repeated inflations of 6 to 12 atm were undertaken, as guided fluoroscopically and by ICE. In the first 3 patients, a bare-metal stent of appropriate dimensions was positioned across the residual PV stenosis, with the end of the stent positioned at the venoatrial junction, under fluoroscopic and ICE guidance. In all subsequent patients, a stent was placed only if rebound stenosis was seen after balloon dilatation.

**Follow-Up**

Eighteen to 24 hours after the interventional procedure, the CT and V/Q scans and the TEE examination were repeated. Patients were subsequently discharged on warfarin to a target international normalized ratio (INR) of 2 to 3, along with 75 mg clopidogrel per day thereafter. Low-molecular-weight heparin was given subcutaneously twice daily until the INR was malized ratio (INR) of 2 to 3, along with 75 mg clopidogrel per day thereafter. Low-molecular-weight heparin was given subcutaneously twice daily until the INR was at least 2.0. Patients were followed up by telephone contact and repeated clinic evaluation, as well as repeated studies at 3 months.

**Statistical Analysis**

All data are presented as mean±SD. Comparisons between preintervention and postintervention vessel size and lesion characteristics were made with nonparametric methods. In all patients except 7, the stenosis data could be compared with baseline information from that particular patient. Correlation between 2 variables was established by least-squares methods. A probability value ≤0.05 was taken as significant.

**Results**

**Ablative Intervention**

The details of the original ablative intervention are as described in Table 1. Twelve of 23 patients (52%) had undergone a second ablation because of recurrent AF, whereas 5 patients had previously undergone a third ablation procedure. A total of 34 vessels developed stenosis, of which 25 had been ablated once and 9 ablated twice.

**Tight Stenosis of the Left Inferior Pulmonary Vein**

Figure 1. SCT demonstration of PV stenosis affecting left inferior PV as shown in oblique view of heart.

**Symptom Development**

These patients developed symptoms over the course of 103±100 days of follow-up. Nineteen had increasing dyspnea on exertion, 7 had dyspnea at rest, and a recurrent cough was present in 9. Six had aching or burning chest pain, which was pleuritic in 5. Flulike symptoms, including fatigue, myalgia, and low-grade fever, were noted by 3 patients. Three had received a course of antibiotics for the presumptive diagnosis of bronchitis, without benefit. Three patients developed hemoptysis.

**Initial Physical/Laboratory Examination**

In 22 patients, the physical examination was normal, whereas one had inspiratory crackles over the affected lung region. None had evidence of pulmonary hypertension. One patient had interstitial changes on the chest x-ray film in the absence of cardiomegaly, but no radiographic abnormalities were seen in the remaining 22 patients. The average PaO₂ in the 8 patients tested was 86±16 mm Hg (saturation, 94±3%), with no change during exercise.

**CT Imaging**

Under baseline conditions (Table 2), the prestenotic PV orifice dimension of the subsequently stenosed vessels was 17±3 mm (range, 12 to 24), which decreased only modestly to 14±3 mm (range, 7 to 19; P=0.002) immediately before the therapeutic intervention. The baseline vessel diameter at the subsequent site of stenosis measured 13±3 mm (range, 8 to 18 at baseline) and decreased to 3±2 mm (range, 0.0 to 6.0) before dilatation (P≤0.001), as shown in Figure 1. The stenosis began 1.4±2.5 mm from the orifice (range, 0 to 10), and the tightest region of stenosis was 12±6 mm (range, 0.5 to 23) from the orifice into the vessel. The stenosis length ranged between 7 and 35 mm (mean, 19±6). Typically, the lesions were eccentric in morphology.

**Transeosophageal Echocardiography**

The affected PVs were well visualized in 16 of 34 Mayo cases. Lesion narrowing (mean, 5±3 mm; range, 2 to 12) was seen in 11. A pulmonary artery systolic pressure >40 mm Hg was seen in only 1 case. Flow velocities (mean, 1.7±0.6 m/s),
measured from the PVs, were ≥2.5 m/s in 3, 2.0 to 2.5 m/s in 1, 1.5 to 2.0 m/s in 6, and between 1.0 and 1.5 m/s in 6. In each case, there was turbulent blood flow with increased aliasing on color flow examination.

V/Q Imaging
Ventilation scanning was completely normal in 17 of 22 patients, with a defect in only 10 of 38 regions corresponding to affected veins (Figure 2). A perfusion defect that could be correlated with the stenotic lesion was seen in the distribution of all 34 affected veins (Figure 2; 40 of 132 segments).

The relative perfusion from an affected segment contributed between 0% and 9% (4 ± 3%) of total perfusion. This compared with a value of 22 ± 10% seen in other segments without any corresponding PV abnormality (P = 0.001). In 14 patients, quantitative analysis of perfusion indicated highly asymmetric tracer uptake within the lungs, suggesting a major impediment to PV drainage. There was a matching reduction in ventilation in only 3 patients.

Interventional Procedure
Right heart pressures in these patients were normal in all cases except 1, where the mean pulmonary artery pressure was 48 mm Hg. ICE examination showed a reduced PV orifice diameter of 10 to 17 mm (mean, 13 ± 5 mm) as well as an increased flow velocity averaging 1.6 ± 0.5 m/s (range, 0.5 to 2.6). The mean visual angiographic stenosis before intervention was 80 ± 13% (range, 60% to 100%) accompanied by a mean transstenotic gradient of 12 ± 5 mm Hg (range, 4 to 26). An angiographic example of severe stenosis of a left superior PV is shown in Figure 3. Eight- to 10-mm-diameter balloons with a length of 10 to 26 mm were deployed across the stenotic segment, and dilatation at 6 to 12 atm was undertaken. Typically, these stenotic lesions created a clear “waist” around the venoplasty balloon during early dilatation. In 3 patients, apparent thrombus was present, as judged by the appearance of the lesion and further opening of the vein with guidewire insertion alone. In 7 patients, a PV stent of 17 ± 3-mm length and 9 ± 1-mm diameter was placed in the affected vessel.

Intervention reduced the stenosis to 9 ± 8% (range, 0% to 30%; P = 0.001) and the mean transstenotic gradient to 3 ± 4 mm Hg (P = 0.001), as shown in Figure 4. The PV flow velocities decreased to 1.1 ± 0.2 m/s (range, 0.7 to 1.4; P = 0.03) with a decrease in the turbulence of flow. The procedure was complicated by transient ST-segment elevation in the inferior ECG leads and hypotension lasting <5 minutes in 1 patient. No evidence of infarction was subsequently seen on repeated ECG or enzyme testing. Another patient sustained a peripheral PV guidewire perforation with bleeding that required intubation and ventilation, and the left superior PV in a third patient dissected, causing a left-sided hemothorax that mandated chest tube placement. One stent embolized from a right PV to an iliac artery without sequelae. Each patient was otherwise treated conservatively without surgical intervention.

Figure 2. Abnormalities after ventilation/perfusion in 8 patients with PV stenosis. Left, Relative number of segments with normal vs abnormal perfusion. Right, Distribution of relative perfusion contribution of given vein segment in patients with normal perfusion vs reduced relative perfusion in segments affected by PV stenosis.

Figure 3. Right anterior oblique angiographic view of stenosed left superior PV. Segmental stenosis is narrowed to diameter of 6F multipurpose injection catheter. Also seen are collateral vessels forming above and posterior to point of stenosis.

Figure 4. Outcome of intervention for PV stenosis in 17 veins. Shown are prestenosis and poststenosis levels along with accompanying gradients. Some overlap (see text for discussion).
2. On TEE, the flow velocities decreased to 1.3 m/s at the orifice of the affected vessel. In all 20 patients who underwent repeated perfusion scanning, there was an increase in relative perfusion to 9 ± 5% (range, 0% to 25%) of total blood flow in the affected segments (P ≤ 0.001; Figure 6).

Follow-Up

All 23 patients had a substantial reduction in symptoms within minutes to 1 hour after vessel treatment. Nevertheless, 14 patients (57%) developed recurrent symptoms at 3.2 ± 2.8 months after the initial intervention, with dyspnea on exertion in 13 and cough or chest pain in 5. Two of the 14 experienced hemoptysis, whereas one reported cough and pleuritic chest pain. Thirteen patients required repeated interventions on 14 of the originally treated veins. Six of these veins had been previously dilated, whereas 8 veins were stented at the time of the original procedure. Four of these latter veins showed in-stent restenosis, whereas 4 showed in-segment PV stenosis at sites proximal or distal to the stent. Six patients also developed significant stenosis in 6 previously undilated veins. One lesion had progressed to total occlusion and could not be redilated.

Three patients again developed dyspnea on exertion, associated with cough or fatigue, requiring another intervention on 3 veins. One vessel was redilated and 2 were stented. One patient required a fourth intervention. On long-term follow-up at 18 ± 12 months (range, 3 to 34), 15 patients remain completely asymptomatic from PV stenosis, and 4 have mild and 3 have moderate symptoms.

Discussion

These data provide substantial insight into the clinical syndrome of acquired PV stenosis occurring after radiofrequency ablation for AF. Patients with this malady can be extremely symptomatic but respond almost immediately to percutaneous intervention. Although initial results are encouraging, the occurrence of restenosis, including in- and out-of-stent abnormalities, remains a concern.

PV stenosis is an established complication occurring with radiofrequency energy delivery for focal AF ablation. Robbins et al.25 reported multivessel PV stenosis after linear ablation for AF in 2 patients. The prevalence of this problem in the setting of linear ablation likely ranges between 2% and 7%.26 The exact prevalence of PV stenosis in patients undergoing focal or segmental AF ablation is becoming more clear.3,4,10–15 In one of the larger series, Chen et al.4 initially described apparent PV stenosis in 42% of their 79 patients. This represents an overestimation of this problem, however, because an increased TEE flow velocity was used to establish the diagnosis. A later study from the same group noted a 33% incidence of PV narrowing, again established by TEE methods.13 Gerstenfeld and coworkers10 have reported an 8.3% occurrence of clinically relevant PV stenosis in an early series of 40 patients undergoing focal AF ablation. Similarly, Saad and coworkers27 reported a 5% incidence of severe PV stenosis (>75%) in patients undergoing electrical isolation of their PVs. In their initial series, Haissaguerre et al.2 reported a 5% occurrence rate but have recently suggested a decrease to <1% overall with additional experience in ablation. Pappone et al.28 also reported a <1% PV stenosis rate with ablation limited to atrial tissue outside the PV orifice. Other groups have reported cases of patients with PV stenosis requiring venoplasty or stenting.16–21 In the absence of a clear-cut “denominator,” however, it is not possible to decipher the incidence of this complication in those studies.

The prevalence of this problem has decreased because of a variety of factors, including (1) abandonment of in-vein ablation at the site of the AF focus; (2) limiting ablation at or outside the orifice of the vessel; (3) the use of ICE to guide catheter placement and monitor energy delivery; (4) a reduction in target ablation temperature and the amounts of energy deliveries; and (5) increased operator experience.12 This report represents 6.0% of the initial 203 patients who underwent PV ablation at this institution.12 In the first 100 patients undergoing ablation, 11 developed a stenotic lesion, whereas only 1 has developed a stenotic lesion requiring intervention in the last 100 patients. This “learning curve” has also been documented by Saad et al.,15 who underscored the importance of experience, ablation outside the PV, and intracardiac ultrasound use for decreasing moderate and severe PV stenosis occurrence from 7.9% to 1.4%. Recent review of the European experience with AF ablation documented PV ste-
nosis rates approaching 20% in the centers performing <50 PV isolation procedures.29

The exact pathology of PV stenosis has not been elucidated. In the present series, patients undergoing a first dilatation procedure had both soft and more fibrotic components of PV pathology. In most cases, a clear-cut waist in the venoplasty balloon was seen with balloon inflation. In some cases, 10 to 12 atm of pressure were required for elimination of that apparent scarring. In 3 cases, the stenosis was partially reopened simply by passing a guidewire through it. This, and subsequent in-stent restenosis, suggests a component of neointimal hyperplasia and/or thrombus as well. No pathological specimens were obtained for histology, however. Taylor and coworkers30 found both extensive architectural remodeling and fibrosis, as well as neointimal hyperplasia. In parallel studies, we have also found neointimal hyperplasia in a canine model of PV stenosis occurring with both radiofrequency and ultrasound energy delivery31 and a marked inflammatory process.32 Additional studies will be required to elucidate further the molecular and histological pathways of this problem.

Regardless of pathology, these patients were highly symptomatic. Most presented with dyspnea on exertion as the initial manifestation of this process, which typically evolved over the course of 1 to 3 months. Although pleuritic chest pain is a late manifestation of the process, hemoptysis was uncommon during follow-up in this series. Both processes are likely related to complete vessel or branch occlusion in these individuals. Blood gas assessment and pulmonary function testing were not useful as screening measures for early stenosis. These symptoms and chest x-ray changes may lead to an erroneous diagnosis of bronchitis or other pulmonary parenchymal process, delaying establishment of PV stenosis. In a recent series of PV stenosis, patients were often misdiagnosed by their primary care givers as having bronchitis.27 This occurrence of “garden-variety” respiratory symptoms could also contribute to an underestimation of the prevalence of this process.

CT Scanning
CT evaluation was the most helpful in identifying the location and extent of the stenoses. Establishment of the true endocardial PV orifice was a straightforward and reproducible process. Postprocessing of the very thin axial slices allowed near-isotropic voxel coronal, oblique, sagittal, and 3D renderings for review and measurement. There was a limited yet significant correlation between the extent of stenosis seen on the CT scan images and that at the time of angiography. This is likely due to the difference in imaging plane for each technique. The angiographic views were right and left anterior oblique to the patient, whereas the CT views were orthogonal to the vessel. Vessels may still be patent on venography, even if they appear occluded on CT imaging. Comparable experience with magnetic resonance imaging is limited.33

V/Q Scanning
V/Q scanning was helpful for establishing the pathophysiology of the stenosis and its progression. Ventilation abnormal-
Furthermore, the utility of brachytherapy and surgical intervention are also unclear, and the latter has been disappointing when used as treatment for congenital stenosis.36,37

Limitations
First, although this is the largest interventional series with the longest duration of follow-up published to date, the numbers remain small and may or may not apply to all patients with ablation-induced PV stenosis. Assessment of the relative merits of simple balloon dilatation versus stenting is also hampered by the limited number of patients with stenosis. Given this, a PV stenosis registry will be required to further assess the impact of this process and treatment in resolution of symptoms. Furthermore, these data reflect the learning curve present in this new venue of occlusive disease. The study also fails to indicate precisely which of the multiple energy deliveries in a single vein created the stenosis. On the basis of our prior review, this occurrence is most likely due to multiple deliveries.

Clinical Implications
It has been established that changes in ablation approaches and traversing the ablation learning curve have reduced the rate of this complication at individual, high-volume centers. Nevertheless, with the currently widespread application of ablation for AF, this problem will undoubtedly continue to affect many patients in the “real world.” Recently reported cases of late progressive PV stenosis in patients with minor abnormalities on initial postablation venography or follow-up CT scanning further predict a higher prevalence over time.11,38 Furthermore, the presence of PV stenosis is commonly misdiagnosed and underestimated in the absence of surveillance of all patients undergoing PV ablation. As such, preventive approaches and effective therapy for this process will continue to be critical. The diagnostic and interventional strategies outlined in this report represent an important and early step along that pathway.

References


Clinical Presentation, Investigation, and Management of Pulmonary Vein Stenosis Complicating Ablation for Atrial Fibrillation

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