OBJECTIVES
We present the clinical course and management outcomes of patients with total pulmonary vein occlusion (PVO).

BACKGROUND
Pulmonary vein occlusion is a rare complication that can develop after radiofrequency catheter ablation (RFA) of atrial fibrillation (AF). The long-term follow-up data of patients diagnosed with PVO are minimal.

METHODS
Data from 18 patients with complete occlusion of at least one pulmonary vein (PV) were prospectively collected. All patients underwent RFA for AF using different strategies between September 1999 and May 2004. Pulmonary vein occlusion was diagnosed using computed tomography (CT) and later confirmed by angiography when intervention was warranted. Lung perfusion scans were performed on all patients before and after intervention. The percent stenoses of the veins draining each independent lung were added together to yield an average cumulative stenosis of the vascular cross-sectional area draining the affected lung (cumulative stenosis index [CSI]).

RESULTS
The patients’ symptoms had a positive correlation with the CSI ($r = 0.843$, $p < 0.05$) and a negative one with the lung perfusion ($r = -0.667$, $p < 0.05$). A CSI $\geq 75\%$ correlated well with low lung perfusion ($< 25\%$; $r = -0.854$, $p < 0.01$). Patients with a CSI $\geq 75\%$ appeared to improve mostly when early ($r = -0.497$) and repeated dilation/stenting ($r = 0.0765$) were performed.

CONCLUSIONS
Patients with single PVO are mostly asymptomatic and should undergo routine imaging. On the other hand, patients with concomitant ipsilateral PV stenosis/PVO and a CSI $\geq 75\%$ require early and, when necessary, repeated pulmonary interventions for restoration of pulmonary flow and prevention of associated lung disease. (J Am Coll Cardiol 2006;48:2493–9) © 2006 by the American College of Cardiology Foundation

Pulmonary vein occlusion (PVO), the most severe form of pulmonary vein stenosis (PVS), is a clinically significant complication associated with radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) (1–5). In our previous series, we reported the incidence and functional characteristics of pulmonary vein stenosis in its different degrees (6). This study focuses on the subset of patients who progressed to total occlusion. We report the long-term follow-up and clinical outcome and their relation with the radiologic and physiologic findings.

METHODS

Patients. Data from 18 patients with complete occlusion of at least 1 pulmonary vein (PV) were prospectively collected. Patients underwent RFA for AF (paroxysmal, persistent, or permanent) at our or other institutions between September 1999 and May 2004. The preprocedural evaluations followed the local protocols approved by the Institutional Review Board (Cleveland Clinic) and written consent was obtained from all patients. The demographics of the patients are listed in Table 1. The demographics of the patients are listed in Table 1.

Ablation techniques. Pulmonary vein focal ablation, circumferential electroanatomical ablation, ostial segmental ablation (distal isolation), and PV antrum isolation were used to treat AF in the 18 patients. The details of these ablation strategies were previously described elsewhere (7–9). In brief, the PV focal ablation technique was used in the earlier experience of AF ablation, where foci arising from the muscular sleeves of the PVs and triggering AF were targeted. The RF energy was delivered inside the PVs.
Circumferential ablation using the electroanatomical approach was used from 1999 to June 2000. Pulmonary vein ostial segmental ablation (distal isolation) was the predominant technique applied at our center between 2000 and 2003. By using this strategy, the PVs were isolated at their ostia at the PV-left atrial junction. The PV antrum isolation technique became the main approach by the end of 2003. RF energy was delivered with either a conventional 4-mm or 8-mm tip ablation catheter, or with a closed irrigation cool-tip ablation catheter. The initial ablation power setting was 30 W, 55°C for the 4- and 8-mm ablation catheters or 40 W, 45°C for cool-tip ablation catheter. After ablation, all patients were kept on oral anticoagulation with a controlled international normalized ratio between 2 and 3.

**Computed tomography scan.** The diagnosis of PVO was made using computed tomography (CT) scanning. At our institute, CT scans routinely are performed at 3 months after ablation follow-up evaluation or earlier if the patient presents with symptoms consistent with PVS/PVO (In 7 of the 18 patients, preprocedural CT was performed). Patients who underwent previous ablations at other institutions also had a preprocedural CT at our center to evaluate pre-existing PVO/PVS. Once PVS/PVO diagnosis was established, serial CT scans were performed at 3-month intervals or earlier if the patients developed new symptoms related to PVS/PVO. From 2002, multislice detector CT scanning with three-dimensional reconstruction of PVs and left atrium also was available for our patients. Pulmonary vein occlusion is defined as ≥95% stenosis or complete loss of patency of the PV on CT scan. The numbers of occluded and stenotic PVs were counted. By considering the total venous drainage of each independent lung, the percentage of stenosis of the affected veins on the same side were added together to yield an average cumulative stenosis of the vascular cross-sectional area draining the affected lung (cumulative stenosis index [CSI]). CSI = sum of percent stenosis of the unilateral veins divided by the total number of ipsilateral veins (usually two):

\[
\text{CSI} = \frac{\% \text{Upper} + \% \text{Lower}}{\text{Number of ipsilateral veins}}
\]

**PV venogram and intervention.** Once a PVO diagnosis was established, a standard PV venogram was performed to verify whether dilation or stenting of a severely stenotic or occluded vessel was possible. If a wire could traverse the stenotic or occluded site, low-pressure balloon dilation of the vein was attempted by applying the angioplasty technique. If the dilation was not satisfactory or a dissection occurred, PV stent was deployed in the same setting. Acute success of the procedure was defined by improvement of PV patency on angiography, whereas long-term success was evaluated by postprocedural CT and perfusion lung scans. Repeat pulmonary venogram and intervention were performed during the follow-up if necessary.

**Lung perfusion scan.** Lung perfusion scans were performed to all patients before and after PV intervention. The relative perfusion (%) of the different lung lobes was evaluated, and the relative perfusion of each independent lung was compared with the number of occluded vessels and the CSI. The relative perfusion values of affected lungs also were compared before and after PV dilation or stenting to evaluate the success of the intervention.

**Symptom grading.** Because of the diversity of respiratory symptoms in patients with PVO and because of the absence of a current classification to grade such symptoms, we opted to evaluate all the symptoms encountered and grade them according to their severity. Symptoms included chest pain, cough, dyspnea with variable New York Heart Association (NYHA) functional class, fever, and hemoptysis. We divided our patients into 4 grades according to the severity/number of the aforementioned symptoms: grade 0 = asymptomatic; grade 1 = mild dyspnea, chest pain, or cough; grade 2 = more than 1 symptom including moderate dyspnea on exertion, chest pain, or persistent cough; and grade 3 = severe symptoms such as dyspnea on mild exertion or at rest, fever, productive cough, and hemoptysis. The different relationships between the patients’ symptoms, the CSI, and the perfusion percentage were analyzed.
Patient follow-up. The dates of the AF ablation, presentation of symptoms, diagnosis of PVO, and the PV intervention were identified. The progression of PVS/PVO in each patient was closely followed by analyzing changes in symptoms, CT findings, relative perfusion values, and drawing correlations between them throughout the course pre- and post-PV intervention.

Statistical analysis. All continuous data were presented as mean values ± SD. Pearson’s correlation coefficient was used to evaluate the relation between the CSI and lung perfusion, whereas categorical variables as symptom grading and number of procedures were correlated using Spearman’s Rank correlation coefficient (SPSS software version 11.0, SPSS Inc., Chicago, Illinois). Student paired t test was used to evaluate the clinical significance where p values <0.05 were considered significant.

RESULTS

Patient presentation. Of 1,780 patients who underwent RFA for AF during the period of 1999 to 2004 at our institution, 16 were found to have PVO of at least 1 PV, whereas 2 additional patients were referred from other institutions for further evaluation and management of their occluded PVs. The clinical presentation of these patients was variable; 4 (22.2%) patients were totally asymptomatic throughout their course (grade 0), 2 (11.1%) had mild symptoms of dry cough or dyspnea on moderate/severe exertion (NYHA class I; grade 1), 4 (22.2%) had moderate symptoms of dyspnea on mild exertion (NYHA class II/III), together with persistent cough (grade 2). Three (16.7%) patients had severe symptoms as severe dyspnea (NYHA class III/IV) with hemoptysis, fever, or pleuritic chest pain (grade 4) at their initial presentation, whereas 5 other patients (27.8%) presented with mild or moderate symptoms but developed severe symptoms along their course (grade 3).

The patients’ symptoms correlated with the underlying lung findings. Of the 4 asymptomatic patients, 3 showed no significant lung abnormalities at any time on CT, and 1, who had baseline amiodarone-induced pneumonia, showed no signs of new lung abnormalities. The 2 patients with grade 1 symptoms had either subsegmental atelectasis or areas of mild consolidation. The 4 patients with moderate symptoms (grade 2) had more prominent abnormalities, including pulmonary congestion and significant pleural effusion. Apart from 1, all 8 patients with severe symptoms (grade 3) suffered severe lung disease, including pulmonary infarction (3 patients), severe pneumonia and pleural effusion (4 patients), and pulmonary edema and alveolar hemorrhage in another patient. Of interest, in all these patients, the disease etiology was missed or confused with other etiologies as pulmonary embolism for the pulmonary infarction and recent onset asthma for the persistent bronchospasm. Furthermore, 2 patients received unnecessary intervention, such as placement of an inferior vena cava filter for suspicion of pulmonary embolism and partial lung resection for misdiagnosis of lung cancer.

Diagnosis. The initial diagnosis of pulmonary vein stenosis by CT was within the first 3 months after the ablation procedure in 10 patients (66.7%), after 6 months in 6 patients (22.2%), but was delayed in 2 patients up to 17 and 25 months because of loss at follow-up and delayed referral. On the other hand, the mean time for development of total occlusion in one or more pulmonary veins was 9.9 months (range 1 to 30 months) after progression of the lesions with or without symptom aggravation.

Table 2. Number of Veins Affected in Each Patient With the Associated Other Veins and the Total Stenosis Index of the Veins Draining Each Lung

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Total/Subtotal Occlusion</th>
<th>Ipsilateral Vein Stenosis</th>
<th>Other Veins</th>
<th>CSI Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>&lt;75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1 (&lt;50%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1 (&gt;50%)</td>
<td>0</td>
<td>≥75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1 (&gt;50%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>±1</td>
<td></td>
</tr>
</tbody>
</table>

The first 2 groups, having single vein occlusion with or without other insignificant stenosis with cumulative stenosis index (CSI) <75%, are considered together, whereas the rest having a CSI ≥75% are considered together.
A total of 24 occluded veins were found in the 18 patients by CT scan, with a mean of 1.4 veins per patient. Of these 24 occluded veins, the left superior PV had the greatest incidence of occlusion (54.2%), followed by the left inferior PV (29.2%), right inferior PV (8.3%), and the right superior PV (8.3%).

As shown in Table 2, of the 18 patients, 4 (27%) had single vein occlusion with no other veins affected, whereas 4 additional patients had other mild (<50%) lesions in 1 or 2 other PVs. Five patients (27%) had 2 totally occluded veins on the same side, whereas 5 other had a single vein occlusion with another significant ipsilateral vein stenosis (>50%). Of these 5 patients, 3 had additional contralateral vein stenosis as well.

The CSI was calculated in all patients. A strong positive correlation existed between the CSI and patients’ symptoms before intervention (r = 0.843, p < 0.001). A CSI of 75% was found to correlate well with the severity of the disease and the presence of severe symptoms. Of the 8 patients having single-vein occlusion with or without other mild lesions (CSI <75%) 4 were completely asymptomatic, 2 had mild symptoms (grade 1), and only 2 had moderate symptoms (grade 2). On the other hand, all patients with a CSI ≥75% were symptomatic at the time of presentation, having a median of severe (grade 3) symptoms. Accordingly, our patients were divided into 2 groups, those with a CSI <75% (100 + <50%/2) and others with a CSI ≥75% (Table 2).

Physiologic evaluation. Lung perfusion scan was performed to all 18 patients before intervention. The mean relative perfusion of the affected lung was 20.44 ± 5.6%, (range 2% to 34%). The affected lung’s relative perfusion showed a significant negative correlation with the patients symptoms (r = −0.667, p < 0.005). It was found that all patients with severe symptoms had a relative perfusion below the value of 25%, whereas all asymptomatic patients and those with mild symptoms were above this value (Fig. 1). The lung perfusion before pulmonary intervention also showed a significantly negative correlation with the CSI of the corresponding veins (r = −0.854, p < 0.01) (Fig. 2).

Percutaneous pulmonary intervention. Pulmonary vein intervention was attempted in 17 out of the 18 patients. Cannulation of the occluded vein failed in 2 cases. The success of the procedure was evaluated by the decrease of the cumulative stenotic burden on the affected lung (detected by CT scan), as well as the improvement of the lung perfusion post intervention, where a strong positive correlation existed between improvements in the 2 variables (r = 0.929, p < 0.01).

The mean time from the diagnosis of total occlusion to the percutaneous pulmonary intervention (PPI) was 4.53 ± 5.6 (range 1 to 25) months and from the time of the last RFA before the occlusion was 8.9 ± 6.32 (range 3 to 28) months. In addition, the mean time from total occlusion to PPI was significantly different between the successful and failed groups (2.58 ± 1.88 months vs. 12.6 ± 10.74 months).

Importantly, the improvements in both the CSI and perfusion had a significantly negative correlation with the delay in intervention (time period from diagnosis of total occlusion to intervention: r = −0.497 and −0.473, respectively, p < 0.05) (Fig. 3).

Of the 15 attempted patients, 8 (54.3%) required PV dilation and stent deployment for their occluded/stenosed PVs, whereas in the other 7 patients (46.7%), only dilation was attempted. A mean of 1.87 ± 1.41 (range 1 to 6) interventions were performed for each patient. Of interest, the number of intervention had a significant positive correlation with the improvement of lung perfusion (r = 0.765, p < 0.001).
The relief of cumulative stenosis was considerable in the successful group, where the mean CSI decreased by 27.50% after intervention (95% confidence interval 11.73 to 43.27, p < 0.005). On the other hand, the incidence of restenosis in our patients was high (46%; 13 of 28 procedures done). There was only one severe complication. In this patient, cardiac perforation occurred when attempting to traverse a totally occluded vein. The follow-up for all our patients extended beyond 14 months after the PPI. All patients were asymptomatic or had very mild symptoms, especially those who underwent successful intervention.

**DISCUSSION**

**Main findings.** Our study shows that although patients with single-vessel occlusion are mostly asymptomatic, patients with concurrent ipsilateral significant stenoses or occlusion may present with diverse symptoms and corresponding lung pathology that varies with the degree of the CSI and associated lung perfusion. A CSI ≥75% and a relative perfusion <25% were found to be associated with failure of compensatory mechanisms, beyond which severe lung pathology usually develops. As an extension to our previous series, we emphasize that percutaneous intervention is warranted for partial relief of the pulmonary flow. Finally, early intervention of the affected veins appears to be of paramount importance to restore venous as well as arterial flow to the corresponding lung.

**Anatomic and physiologic considerations.** Both the pulmonary venous and arterial systems are well known to be interrelated (10–13). It has been shown that sudden occlusion of a pulmonary vein is soon followed by gradual decline and then cessation of the arterial flow to the affected segment (12,14). This is caused by a decline in the arteriovenous gradient as well as compression by the developing tissue edema (10). As a consequence, the involved alveoli are affected by the resulting ischemia and surrounding edema, leading to atelectasis, infarction, or susceptibility to infections (15). With the resulting alterations in pulmonary hemodynamics, redistribution of blood flow occurs with opening of vascular channels or neovascularization in which tissue hypoxia is known to play a role (12,14). Hence, the venous drainage of the affected segment becomes mainly dependent on the ipsilateral veins draining the healthy lobes. If the ipsilateral vein(s) is also stenosed, the impedance to the pulmonary flow increases, adding to the hemodynamic burden and the resulting lung pathology (16,17). Therefore, in case of progression to total occlusion, we found that evaluating the ipsilateral vein involved in this compensatory mechanism is of utmost importance for timely intervention.

**Pulmonary vein occlusion.** Our overall incidence for PVO of 0.8% is lower than the previous 2.1% as reported by our group (6,18), which is similar to other studies in which occlusion was reported to be 0.3% and 1.3% (4,19). The incidence in our series has decreased from 1.4% in 2000 to 0.1% in 2004. This decline is attributed to change of the ablation strategy to antral isolation, the use of continuous visualization by intracardiac echo, as well as the gain of experience.

**Symptoms and corresponding lung diseases.** All our patients with single-vein occlusion, even with concurrent ipsilateral vein stenosis and with a CSI <75%, were either asymptomatic or only mildly symptomatic, which indicates the success of their compensatory mechanism in prevention of further sequelae. On the other hand, when the CSI was ≥75%, all patients had moderate-to-severe symptoms and suffered lung-related diseases, including pneumonia, pleural effusion, and pulmonary infarction. Pulmonary findings were all associated with a corresponding decrease in the perfusion of the affected segment of the lung, which indicates depletion of the compensatory mechanisms. This finding is in line with the findings of other studies that have used lung scans and perfusion magnetic resonance for qualitative evaluation of lung perfusion to assess the condition and to guide therapy (20). Moreover, quantitatively, we found a relative perfusion of <25% in the affected lung to be indicative of the severity of symptoms and the corresponding lung pathology, and associated with a CSI ≥75%.

Of the 18 patients, only 3 had pulmonary hypertension at rest. This was only seen in the worst cases having 3 or more stenosed veins and was relieved after dilation. It was shown in a recent study that despite the absence of pulmonary hypertension at rest, there is lack of decline or even increase in pulmonary artery pressure with exercise (21). Although exercise testing was not routinely evaluated, after a relatively long follow-up period, none of our
patients had significant symptoms during moderate exertion.

The importance of timely intervention. Of the 17 patients subjected to a dilation attempt, 9 were found to have totally occluded PVs by angiogram. In these cases intervention either failed or was aborted, and attention was focused on the accompanying severe stenosis for partial relief of the hemodynamic burden. On the other hand, in all other cases, every effort was undertaken to traverse the lesion with subsequent dilation with or without stenting. Of interest, the CT findings in some cases tended to overestimate the extent of the stenotic lesions (6,22). This is an expected finding and may be due to the differences of the injected-dye course between both techniques. Such variation between the angio and CT, although minor, is very critical. Indeed, complete occlusion by CT scan should not be considered an exclusion criterion for evaluation with PV angiogram and a possible dilatation attempt. Magnetic resonance imaging may be superior to CT, although the presence of stents and its relative higher cost hinders its use.

The duration from the time of diagnosis to the intervention varied among different patients, and was a predictor of improvement of the lung perfusion post intervention. In fact, because of the delay in PV dilation in some cases, the restoration of PV patency was not accompanied by a corresponding increase in pulmonary perfusion (Fig. 3). In addition, the number of interventions had a positive correlation with the improvement of the lung perfusion. This emphasizes the high incidence of restenosis and indicates that perseverance may be worthwhile for the final outcome of procedure. In concordance with other studies we found a high incidence of restenosis despite stenting (22–25). On the contrary, Neumann et al. (23) had no incidence of restenosis after stenting when using larger stents.

Clinical implications. Our study shows that PVO can reflect slow and concealed progression of a previously insignificant narrowing. It is important to highlight the routine use of imaging techniques post RFA of AF because many patients with PVO are asymptomatic. Restoration of normal lung physiology depends on the time to intervention. Therefore, it is important not to delay dilatation especially in patients with a CSI ≥75%. Because dilation of occluded PVs is less likely to be successful, it may be preferable to dilate severely stenosed PV before they progress to complete occlusion.

Study limitations. This study reports on a limited number of cases; however, this is the largest series reported so far. In this study CSI appeared to correlate with symptoms, lung perfusion, and time to intervention. This index, although making physiological sense, has not been previously validated and further studies are required.

Conclusions. Patients with single PVO are mostly asymptomatic. On the other hand, patients with concomitant ipsilateral PVS/PVO carry a greater risk of developing severe symptoms and lung diseases when the cumulative stenosis of the cross-sectional area of the pulmonary veins draining a single lung is ≥75% and relative lung perfusion is <25%. In these patients, early and, when required, repeated PV intervention should be considered for restoration of pulmonary flow and prevention of associated lung disease.

Reprint requests and correspondence: Dr. Andrea Natale, Department of Cardiovascular Medicine, Head, Section of Cardiac Electrophysiology and Pacing, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: natalea@ccf.org.

REFERENCES


