The State of the Art in Pulmonary Vein Stenosis - Diagnosis & Treatment

Lourdes R. Prieto, MD.

Cleveland Clinic Foundation

Abstract

Pulmonary vein stenosis is a rare but serious complication of pulmonary vein isolation to treat atrial fibrillation. Pulmonary vein angioplasty/stenting has emerged as the treatment of choice for significantly stenotic veins. Guidelines for post ablation evaluation of the pulmonary veins, including the timing and method of surveillance for possible stenosis, the criteria for intervention, the technical aspects of intervention, and finally the surveillance post intervention, are still being developed. The relatively high rate of restenosis after intervention in a subset of patients remains a great challenge. A better understanding of the pathophysiology underlying this syndrome is needed to appropriately answer many of the remaining questions. The goal of this manuscript is to describe what has been learned about this complication and its treatment from a relatively large experience in a single institution over the past decade, and provide a comprehensive review of the existing literature in order to shed as much light on the subject as is possible, while at the same time exposing the areas that need further study.

Introduction

Over the past several years pulmonary vein stenosis has emerged as an increasingly uncommon but important complication of pulmonary vein isolation (PVI) to treat atrial fibrillation.[1] Patients manifest dyspnea on exertion, cough, hemoptysis and pleuritic chest pain as the typical symptoms, and it is frequently a life altering condition. Balloon and stent angioplasty have been performed with mixed results, but good long-term patency rates and symptom relief have been achieved when relatively large stents can be used.[2-6] Despite an extensive body of literature on this condition, routine surveillance is not always performed, leading to delayed intervention and suboptimal outcome.[7] This manuscript will describe the evaluation, treatment and mid to long-term outcome of patients with post ablation pulmonary vein stenosis based on a large ex-

perience accumulated in a single institution over the past decade.

Screening for pulmonary vein stenosis after pulmonary vein isolation

The incidence of clinically significant pulmonary vein stenosis has been dramatically reduced since the first patients presented with this complication in the late 1990's, from about 20% in the early years to 0.4-2% today.[8-11] Delivery of radiofrequency energy in the antrum rather than the ostium of the pulmonary vein, titration of energy application or use of alternative energy sources, use of intracardiac echocardiography to guide ablations, and image integration of multislice computer tomography performed prior to PVI with electroanatomical mapping during PVI are some of the most important technical advances contributing to the

Corresponding Address : Lourdes R. Prieto, M.D, Center for Pediatric and Congenital Heart Disease, Children's Hospital Cleveland Clinic, 9500 Euclid Avenue M41, Cleveland, OH 44195.

decline.[9-15] Recognizing that there is no consensus at this time on routine screening for pulmonary vein stenosis after PVI,[16] we followa protocol at our institution to assure that the small number of patients who still develop significant pulmonary vein stenosis is not missed. Imaging is performed 3 months following PVI, and repeated 3 months later only if significant stenosis is detected at the time of the first scan.

Detailed anatomy of the pulmonary veins is best defined by electrocardiographically (ECG)-gated contrast-enhanced multidetector computed tomogram (MDCT) [Figure 1]. Frequently, images are acquired with retrospectively gated helical scanning. However, despite the use of dosemodulation, these protocols are associated with higher radiation exposure. Therefore, with recent advances in scanner technology, there is a trend to scanning with prospectively triggered protocols in patients with controlled heart rate. In those patients with fast and irregular heart rate, scanning with spiral non-gated imaging is a good alternative. Images are reconstructed with overlapping 1.00- to 1.25-mm slice thickness for analysis with multiplanar reconstructions, maxi mal intensity projections, and volume rendered imaging. Semi-automated analysis and display software supports the evaluation of the images.

Figure 1: Multidetector computer tomogram shows relatively long-segment stenosis of the left inferior pulmonary vein. See normal size right superior vein for comparison. (LA = left atrium, LIPV = left inferior pulmonary vein, RSPV = right superior pulmonary vein)
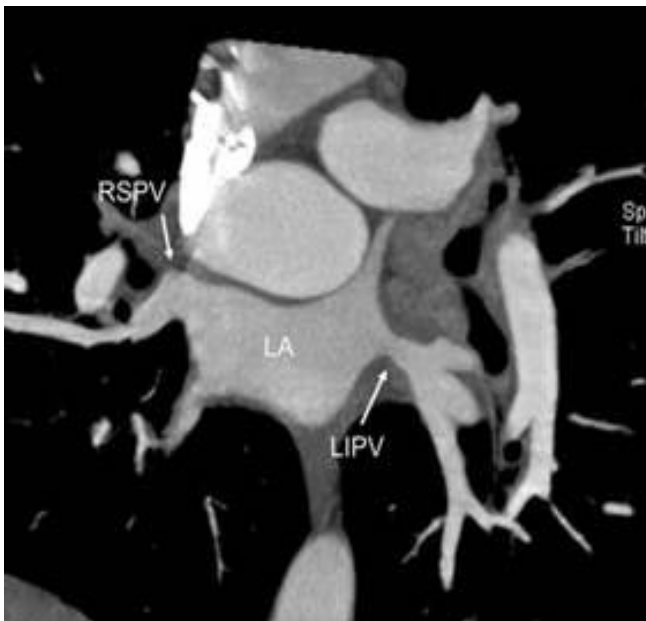
Cardiac MRI is an excellent alternative modality, and avoids exposure to ionizing radiation. It has been used in clinical care and clinical research, but is more expensive (at least in the United States) and time-consuming.[17] Transesophageal echocardiography has been considered as a screening tool also to avoid radiation exposure, but it is not always possible to evaluate each pulmonary vein with 100% sensitivity when compared to MDCT, and it is not possible to evaluate the anatomy in detail if an interventional procedure is necessary.[18, 19]

It should be noted that even the most detailed noninvasive imaging modality, namely MDCT, grossly overestimates total pulmonary vein occlusion.[5, 20] As previously published, only 52% of the veins thought to be totally occluded by MDCT were in fact totally occluded by pulmonary artery wedge angiography, while 48% had a tiny opening that was crossed in every instance allowing intervention.[5]

Evaluation of the patient with pulmonary vein stenosis: When to intervene

Referral for further evaluation and possible intervention is based on the presence of symptoms and the severity of stenosis. Clinically significant stenosis that can lead to symptoms typically requires ≥ 60% narrowing of the pulmonary vein, or an absolute stenosis diameter of 4-6 mm for a 10-15 mm vessel, the normal reference diameter of a pulmonary vein. This degree of stenosis has been found to correlate with perfusion defects on quantitative measurements of lung perfusion.[21, 22] It must be kept in mind that not infrequently stenotic veins are also diffusely hypoplastic, with a reference diameter well below that of a normal pulmonary vein. Therefore a 4 mm stenosis might be reported as 50% if the reference diameter is only 8 mm, but it is a clinically significant lesion. The majority of patients with significant stenosis of two or more veins are symptomatic, but patients with severe stenosis of only one pulmonary vein do not always manifest symptoms.

Onset of symptoms has been reported to occur as early as immediately after PVI to nearly a year later, with a median between 7.5 weeks and 14.5 weeks post ablation depending on the series.[1-3] Nearly half of the patients (44%) with severe ste-

nosis of at least one pulmonary vein, defined as ≥ 70% luminal narrowing, has been reported to have no subjective symptoms at the time of diagnosis 5.2 ± 2.6 months after ablation.[1] However, studies with longer term follow-up have found that the majority of these initially asymptomatic patients do in fact develop symptoms as late as 2 years after PVI.[6] The presence of severe stenosis in more than one pulmonary vein is associated with a higher risk of symptoms.[1] Nearly 100% of symptomatic patients complain of dyspnea on exertion, and patients with more than 2 severely stenotic veins may be dyspneic at rest. About half the patients develop a chronic dry cough, and about 25% have recurrent hemoptysis. Pleuritic chest pain in the area corresponding to the affected vein is experienced by about 15% of patients.[5] A small number of patients develop significant pleural effusions, often recurring despite drainage until the pulmonary vein stenosis is relieved [Figure 2].

Figure 2: Chest roentenogram of a patient with total occlusion/ complete obliteration of the right superior pulmonary vein and severe stenosis of the right inferior pulmonary vein demonstrates a large right pleural effusion and airspace consolidation.After repeated thoracenteses the right inferior pulmonary vein was stented with resolution of the effusion within 3 weeks


In a few cases, there is a relatively abrupt presentation with fever, shortness of breath, hemoptysis, with or without a pleural effusion, mimicking the presentation of a pulmonary embolus. The pathophysiology may be similar with pul monary infarction resulting from relatively acute pulmonary venous obstruction. Several reports of the accompanying histology of post ablation pulmonary vein stenosis have described a pattern of "venoocclusive disease", interstitial edema and fibrosis, and hemosiderin-laden macrophages within the alveoli consistent with pulmonary hemorrhage.[23-25] There is likely a varying degree of injury to the pulmonary parenchyma and pulmonary vasculature, not all of which reverses after restoration of pulmonary venous patency.

Patients with no subjective symptoms are sometimes found to have decreased exercise tolerance when tested objectively with metabolic stress testing. It must be remembered that the majority of these patients had either chronic or frequent atrial fibrillation before PVI interfering with their physical performance, and therefore their "normal" subjective baseline may be far from normal. Elimination of the atrial fibrillation results in symptomatic improvement, which may hinder their perception of symptoms arising from pulmonary vein stenosis. We would therefore recommend exercise testing when it is not clear whether or not to recommend intervention. We currently perform metabolic stress testing in all patients undergoing evaluation for possible intervention. Patients who proceed to intervention have a metabolic stress test repeated at the time of their first follow-up, 3-6 months post intervention for smaller stents, and 12 months post intervention for larger stents (see section on followup below). Preliminary data in 14 patients shows a statistically significant improvement in functional capacity with a peak oxygen consumption (VO_2) of 20.8 ± 5.3 ml/kg/min before intervention increasing to 26.0 ± 5.8 ml/kg/min at follow-up (p = 0.002).

The functional significance of an anatomic narrowing can be further evaluated by measuring quantitative lung perfusion in each lung quadrant (percentage of flow to the left superior, left inferior, right superior and right inferior quadrants). Although a lung quadrant does not exactly correspond to the anatomic drainage of each pulmonary vein, and there is some degree of patient to patient variability, it is fairly representative in most patients, particularly when there is unilateral pulmonary vein stenosis [Figure 3]. When there is bilateral stenosis the results can be more difficult to interpret, since percentage of flow to any one quadrant is dependant on the amount of flow to all the other areas. However, in those with

Figure 3: Quantitative lung perfusion scan of a patient with moderately severe left superior and left inferior pulmonary vein stenosis. Total flow to the left lung was measured at 24% with 13% to the upper half and 11% to the lower half. Normal flow to the left lung is about 45%
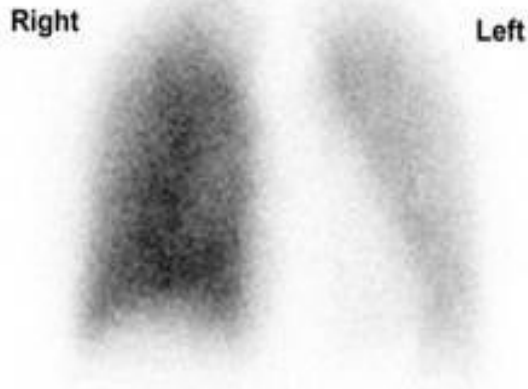
bilateral involvement it often does help determine which veins have more functionally important stenosis.

Any symptomatic patient should be considered for intervention. Whether or not patients with no obvious symptoms but severe stenosis of at least one pulmonary vein should undergo intervention remains in question in the absence of sufficient information about their natural history. There is evi dence that some of these patients will develop symptoms over the course of time, as exemplified by one patient in our experience who was symptom-free for four years after developing severe stenosis of the left superior pulmonary vein. Four years after PVI he developed intermittent fever, recurrent hemoptysis, dyspnea on exertion, and shifting infiltrates on chest roentgenogram. After extensive and unrevealing investigation for other etiologies he underwent stenting of the left superior pulmonary vein to 10 mm with complete resolution of symptoms within less than a month. Two years later he remains asymptomatic with a widely patent stent. Neumann et al[6] describe 4 initially asymptomatic patients with severe stenosis of a single vein all developing dyspnea by 2 years of follow-up. We do not, however, know what percentage of asymptomatic patients will develop problems over time. We also do not know to what extent a severely stenotic pulmonary vein could exacerbate the clinical course of relatively com-

mon cardiopulmonary problems that may arise in previously asymptomatic patients as they age, such as chronic obstructive pulmonary disease, diastolic cardiac dysfunction, or systolic cardiac dysfunction from underlying coronary artery disease.

Another concern in conservative treatment of severe pulmonary vein stenosis is the risk of progression to total occlusion. When this occurs it is not always possible to traverse the occluded segment, precluding percutaneous intervention. There is at this time no reliable way of predicting which severely stenotic veins will totally occlude. Additionally, severely stenotic pulmonary veins have the potential to develop progressive hypoplasia of the entire vein over time with its detrimental effect on outcome should intervention then become necessary, as will be explained below. Our current practice for asymptomatic patients with significant stenosis of at least one vein is to have a frank discussion about what is known and what is yet to be learned. We then make a mutual decision that the patient and the operator feel comfortable with.

Percutaneous intervention for pulmonary vein stenosis

When the syndrome of post ablation pulmonary vein stenosis began to appear for the first time in the late 1990's the only clinical model to draw from in order to guide management was primarily that of congenital pulmonary vein stenosis.[26-28] Acquired, adult onset pulmonary vein stenosis is seen very rarely in a few conditions such as fibrosing mediastinis, neoplasm, or sarcoidosis, and management has been reported sparingly, mostly in isolated case reports, with mixed results.[29, 30] The larger experience with congenital pulmonary vein stenosis was fairly dismal with universally high recurrence rates and high mortality with both transcatheter and surgical intervention.[26-28] In particular, stenting congenitally stenotic pulmonary veins had been essentially abandoned after a handful of studies documented very poor results[31, 32] With that background in mind, though realizing the pathophysiology was different, we felt we should approach this problem initially in the least invasive manner in the form of balloon angioplasty for significantly symptomatic patients. We quickly encountered high recurrence rates in the order of 70% after balloon dilation, but did observe tempo-

rary symptom relief before restenosis occurred[2, 5] [Figure 4]. We then opted to treat dilation restenosis with stent placement.

Figure 4: Time free from restenosis, defined as freedom from reintervention, for stented and balloon dilated veins. (Hazard ratio for balloon dilation 4.2, 95% confidence interval 2.4-7.3, P<0.001).
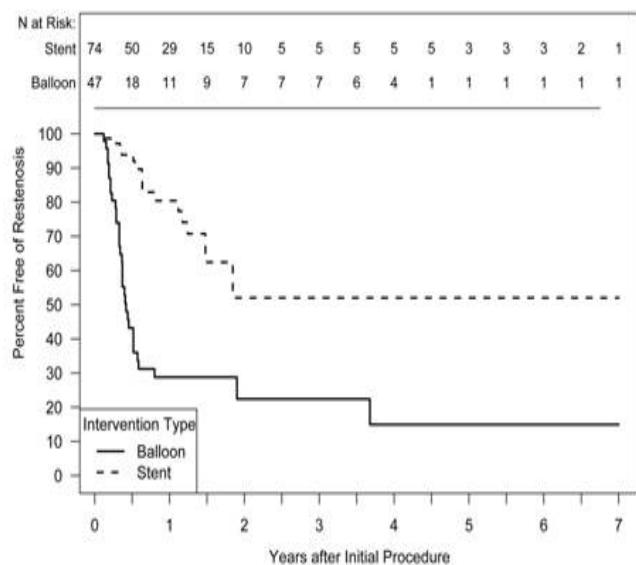
We continued to see restenosis after stenting, but began to observe that larger stents (≥ 9-10 mm diameter) did not develop restenosis.[5] Unfortunately we were not able to place such large stents in all of the veins, because a significant percentage of these injured veins do not only have discrete stenosis but also diffuse hypoplasia, sometimes with reference diameters as small as 3-5 mm [Figure 5 A-C]. (It is a known tenet of stent angioplasty work that "over-stenting" a vessel, i.e. placing a stent significantly larger than the reference vessel, leads to a proliferative reaction in the "over-stretched" vessel at the edge of the stent, resulting in edge restenosis and migration of the stenosis further into the vessel). In view of the favorable results obtained with stent placement in veins that maintained a reasonable reference diameter we began to stent primarily any vessel that admitted at least an 8 mm stent. We now have mid to long term follow-up on a large number of stented pulmonary veins, and have confirmed low restenosis rates for stents ≥10 mm, but a significant incidence of in-stent restenosis for smaller stents [Figure 6]. We therefore continue to balloon dilate very hypoplastic vessels (≤ 7 mm), knowing that the majority will develop restenosis. We have observed that after improving flow at least temporarily post dilation some of these veins increase their reference diameters, enabling placement of a larger stent at the second intervention and improving the long-term outlook.

The majority of patients undergoing pulmonary vein intervention are on warfarin at the recommendation of their electrophysiologist. Patients who are no longer having atrial fibrillation but have significant pulmonary vein stenosis are typically maintained on warfarin due to concern about sluggish flow potentially resulting in thrombosis. There is no data from which to derive recommendations, but our protocol is to continue warfarin in all patients following intervention. Patients with a newly deployed stent are started on enoxaparin the morning after the procedure at 1 mg/kg/

Figure 5 A-C: A. Pulmonary artery wedge angiogram in the left upper lung demonstrates a diffusely and severely hypoplastic left superior pulmonary vein measuring 3 mm in diameter. In addition, there is severe stenosis with a trickle of contrast entering the left atrium (black arrow). B. In contrast, selective angiogram in a left superior pulmonary vein with moderately severe discrete stenosis, but normal reference diameter. This vein was stented to 12 mm. C. After stenting the vein in panel A with a 3 mm drug eluting stent. (LSPV = left superior pulmonary vein, DES = drug eluting stent)
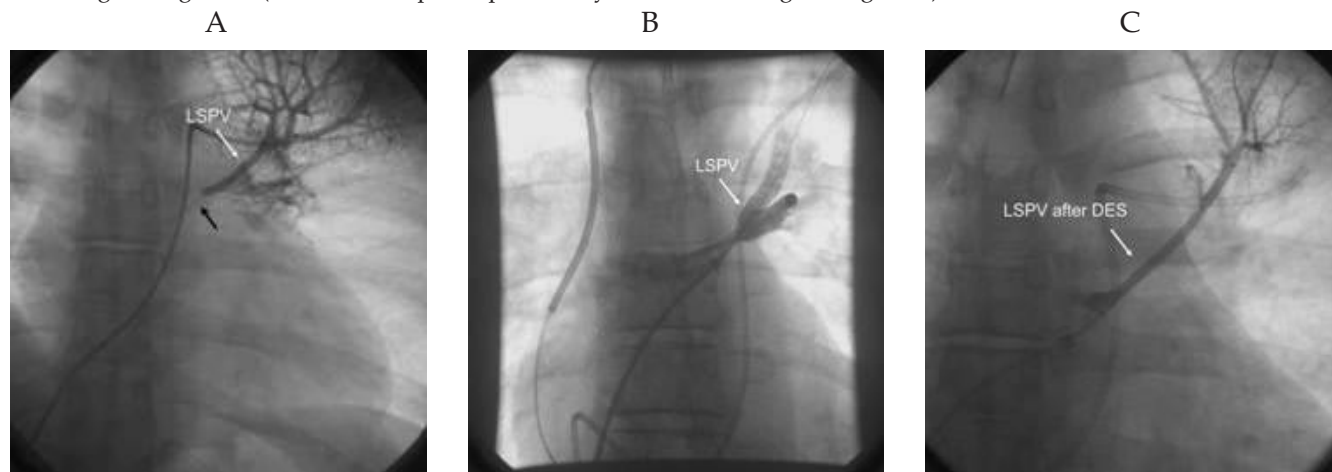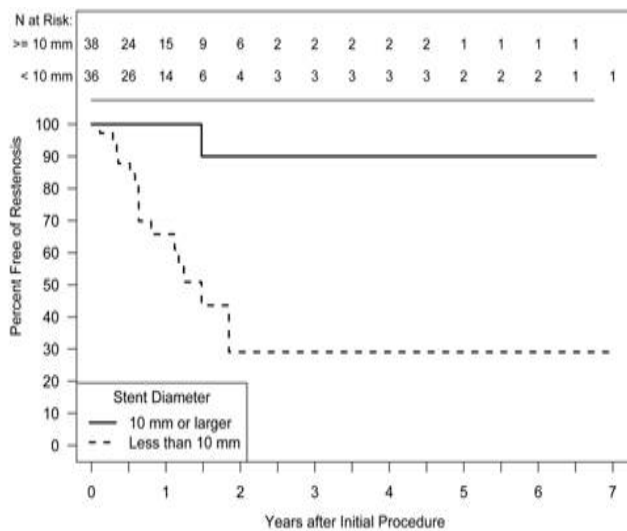
A	B	C

Figure 6: Time free from restenosis, defined as freedom from reintervention, for veins stented with larger stents (≥ 10 mm) versus smaller stents (<10 mm). (Hazard ratio for stents < 10 mm 16.1, 95% confidence interval 2.4-109.7, P=0.005)

dose once a day for 3-4 days until a therapeutic INR (≥ 1.8) is reached. In most patients with larger stents (≥ 9-10 mm) we have discontinued warfarin after 9-12 months if there is no evidence of in-stent restenosis and no recurrence of atrial fibrillation. They are then placed on aspirin indefinitely. Patients with diffusely hypoplastic veins and/or small stents are maintained on coumadin indefinitely. We have not seen significant thrombotic complications when patients adhere to this regimen. Although it is not always possible to tell whether lumen loss is due only to in-stent restenosis or at least partially to thrombus, we have seen 3 instances of probable thrombosis of small stents combined with in-stent restenosis when warfarin has been self-discontinued. Of the 3 occluded stents 2 were successfully recanalized and redilated.

Pulmonary vein intervention: Complications

The benefit of any intervention has to be weighed against the inherent risks. There are obviously significant potential risks to pulmonary vein dilation or stenting. As with any technically challenging procedure, there is a learning curve. Due to the relative rarity and continuing decrease in the incidence of post ablation pulmonary vein stenosis, for which electrophysiologists should be commended, only a few specialized centers have gained a reasonable amount of experience.

In our center from a total of 98 patients with 173

stenotic pulmonary veins requiring 145 catheterizations, we have had 2 pulmonary vein perforations. Both required emergent pericardiocentesis in the catheterization laboratory, followed by surgical drainage due to ongoing bleeding. Both patients survived without neurologic or other sequelae. One patient suffered a cerebrovascular accident with complete neurologic recovery. One patient in whom the transseptal puncture was difficult had inadvertent perforation of the back wall of the left atrium. He underwent percutaneous pericardiocentesis without sequelae. One stent dislodged after placement and was successfully snared in the left atrium and withdrawn from the body, but the patient required a femoral vein cutdown to remove it. A few patients have had transient limited hemoptysis usually resolving within the first 24-72 hours. There has been no mortality.

The most serious complications, namely the two pulmonary vein perforations and one cerebrovascular accident, occurred in the first 30 patients. One of the perforations occurred during balloon dilation of a moderately severe stenosis with a large balloon in a vein with a large reference diameter. This lesion would now be treated with primary stenting using a smaller balloon than was used for balloon angioplasty, which would be safer. The patient who suffered the cerebrovascular accident was the second in our series, and since then we have been more aggressive with systemic anticoagulation during the procedure, maintaining the ACT around 300 seconds.

Follow-up – when and how to reintervene

The majority of patients experience symptomatic improvement after relief of pulmonary vein stenosis. Complete resolution of symptoms is usually seen when it is possible to stent the vein(s) to a normal pulmonary vein diameter. Flow to the affected lung quadrant increases significantly in most patients, but usually does not normalize.[5, 20] This is likely due to a varying degree of irreversible injury that the pulmonary vasculature has incurred prior to relief of the stenosis.[23-25]

We typically repeat a quantitative lung perfusion scan within days of the intervention, and this can then be used in follow-up. The development of in-stent restenosis is accompanied by a gradual decrease in flow to the affected lung quadrant. In

addition to providing information about the functional significance of recurrent stenosis, a lung perfusion scan is associated with less radiation exposure when compared to MDCT. Transesophageal echocardiography has been used in some centers to follow patients after pulmonary vein intervention.[33] Its usefulness may be limited in following smaller veins that continue to show abnormal flow patterns despite optimal intervention. In addition, TEE relies on increases in flow velocity as restenosis develops. Doppler flow measurements are flow dependant, and may not reliably increase in veins with low flow. The use of MRI to visualize stented veins is limited due to metal artifact, but magnetic resonance perfusion imaging may still be used to assess changes in lung perfusion.[21] Patients in whom the risk of restenosis is low (≥ 10 mm stents in all veins) are followed in one year's time with an MDCT and quantitative lung perfusion scan. As the graph in figure 6 shows, the small number of patients who develop restenosis with large stents typically do so within the first 2 years post intervention. Neumann et al found no restenosis in 10 veins stented with ≥ 10 mm stents over 4 years of follow-up.[6] Until recently we have followed patients on a yearly basis, but as further data is gathered it may become evident that after a few years of restenosis-free follow-up patients with large stents may be thought of as cured. We have begun to space follow-up to every 2 years in patients with more than 3-4 years of follow-up with no restenosis [Figure 7 A-C].

Patients with smaller stents require closer followup, being mindful of the amount of radiation exposure. We typically repeat a quantitative lung perfusion scan 3-6 months after intervention if a significant increase in flow was documented after the procedure, otherwise a MDCT is performed. Restenosis is typically accompanied by recurrence of symptoms, which also guides when to repeat imaging studies. If it appears that repeat catheterization is likely to be necessary we sometimes avoid repeating a MDCT, and rely on a decrease in perfusion and return of symptoms to decide when to re-intervene. As shown in figure 6, restenosis in small stents can be seen as early as 3 months post stenting, particularly for very small stents (≤ 6 mm), and there is a steady decline in the percent of stents free from restenosis in the first 2 years of follow-up. In the majority of cases this can be treated by stent redilation with a combination of cutting balloons and high pressure balloons [Figure 8 A, B]. We have previously reported that the use the cutting balloons in conjunction with standard high pressure balloons appears to decrease the risk of recurrent in-stent restenosis when compared to high pressure balloons alone, at least in intermediate term follow-up [34]. Cutting balloons are known to confer a more controlled vessel wall injury imparted by the longitudinal microsurgical blades, and therefore the proliferative response responsible for restenosis may be lessened.[35]

In some cases of in-stent restenosis the pulmonary vein proximal to the stent has grown in size, and

Figure 7 A-C: A. Selective angiogram in the left superior pulmonary vein shows severe discrete stenosis. B. Following stenting to 10 mm. C. MDCT 4 years later shows a widely patent stent. (LSPV = left superior pulmonary vein)
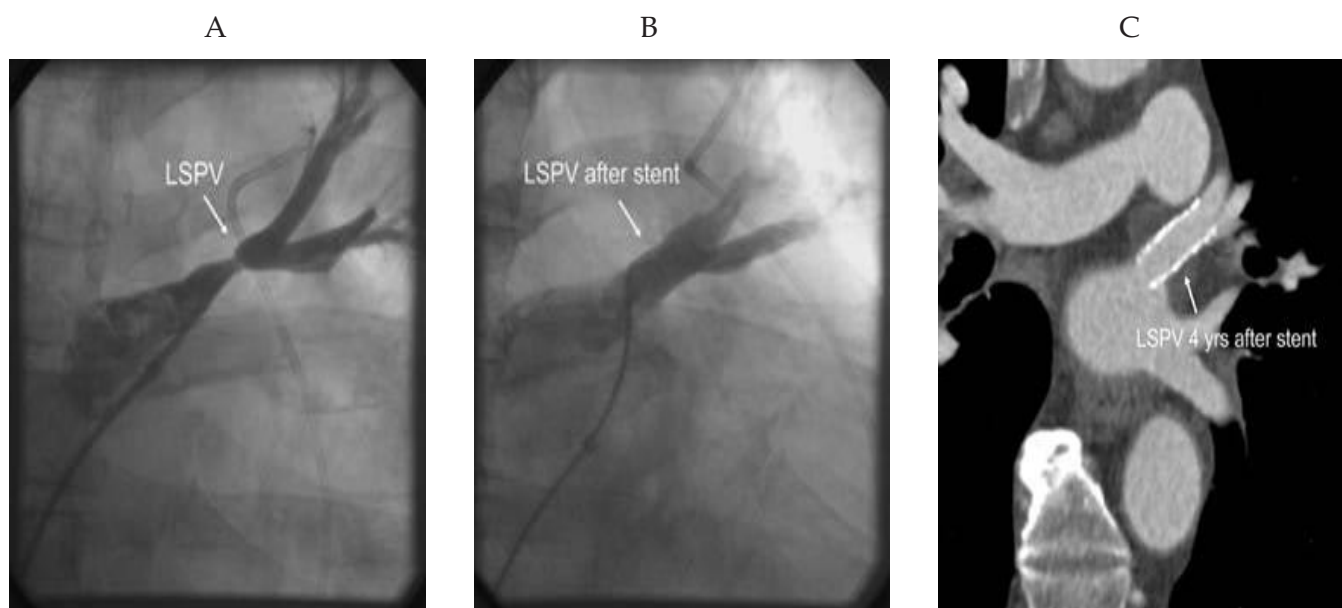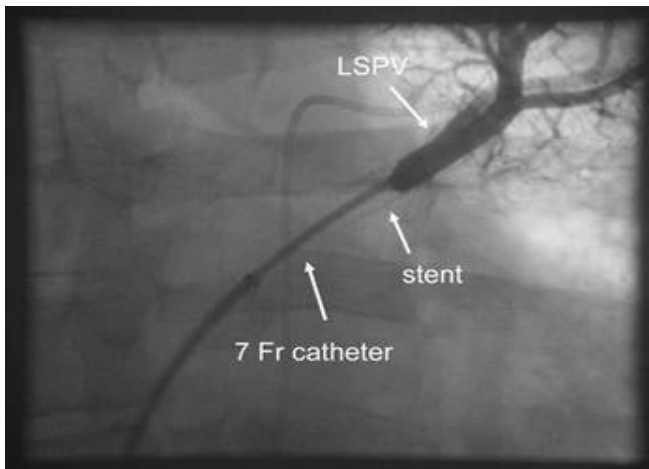
A   B   C

Figure 8 A-B: Selective angiogram in a previously stented left superior pulmonary vein shows severe in-stenosis restenosis of a 7 mm stent. The 7 Fr catheter completely occludes the remaining lumen. B. Following dilation with an 8 mm cutting balloon followed by an 8 mm high pressure balloon. (LSPV = left superior pulmonary vein)

it is possible to further enlarge the stent above its original size. For this reason, we believe it is important whenever possible to implant stents that allow dilation to larger sizes at any time post implantation, such as the unmounted Palmaz Genesis series of stents. We generally avoid using premounted stents, which are much more limited in terms of the largest diameter that can be achieved when treating restenosis, and also have less radial strength, making it more difficult to completely relieve a resistant stenosis even with high pressure balloons.

Unfortunately patients with small stents and recurrent stenosis remain at risk for recurrence, but

Figure 10: Pulmonary artery wedge angiogram in the left upper lung demonstrates total occlusion with complete obliteration of the left superior pulmonary vein on levophase. (LSPV = left superior pulmonary vein)
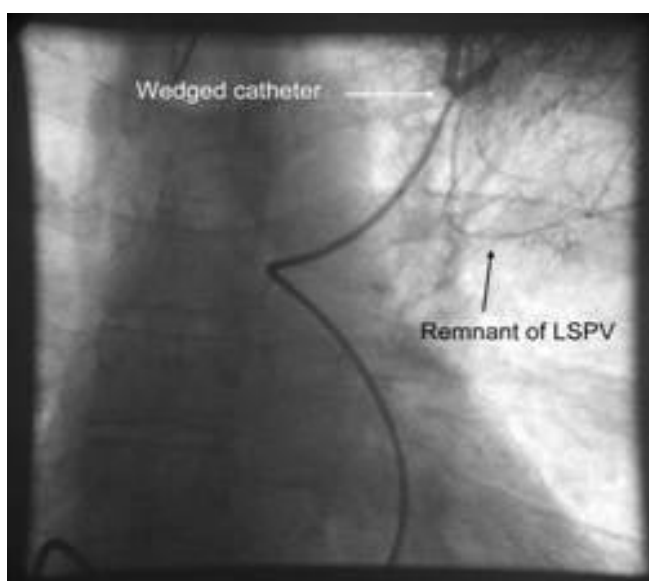
the risk is diminished when the stent can be made larger, which is sometimes the case. We have also observed that in some cases after 1-2 redilations of in-stent restenosis the reactivity of the vessel begins to diminish, and we begin to see long-term patency even in the smaller stents. In the small number of patients with repeated recurrences we have considered the use of covered stents, but the availability of these stents in the diameters and lengths needed for pulmonary veins is limited. We have one patient in our series in whom such stent was implanted inside a bare metal stent (iCAST covered stent, Atrium Medical Corporation, New Hampshire), and 5 years later it remains patent based on stable perfusion and lack of symptoms. It has not been possible to evaluate this stent by MDTC due to excessive metal artifact. We continue to be concerned about restenosis at the edge of a covered stent as has been reported by others,[36] and therefore do not use them routinely. Drug eluting stents (DES) are not currently commercially available in diameters larger than 3.5 mm in the United States, but could be considered for severely hypoplastic veins. We have used a DES (CYPHER® Stent, Cordis Corporation), in one patient [Figure 5C], and it has remained patent after 18 months of follow-up. Systemic treatment with anti-proliferative agents, such as sirolimus, has been reported in two patients with no significant restenosis detected by imaging after 3-6 months of follow-up, and persistent symptom improvement after 12-18 months.[37] More data is needed to make any recommendation, but these agents could be considered for patients with multiple recurrences and persistent symptoms, with close follow-up of potential

Figure 11 A-B: A. Pulmonary artery wedge angiogram in the left upper lung demonstrates total occlusion of the left superior pulmonary vein but with a good size vein still present. B. Following successful recanalization and stenting to 10 mm. The stent remains widely patent one year later. (LSPV = left superior pulmonary vein)
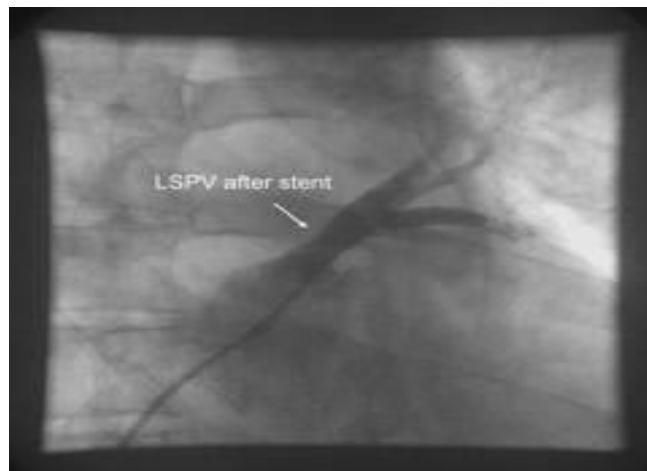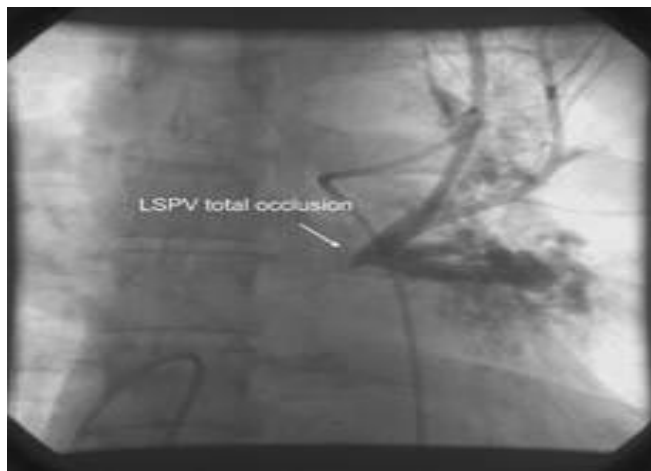
side effects.

Importance of prompt diagnosis and timely intervention for pulmonary vein stenosis

In addition to the diameter of the stent and the reference diameter of the pulmonary vein (which determines the diameter of the stent), we have identified one more risk factor for restenosis: the time interval from pulmonary vein isolation to intervention for pulmonary vein stenosis.[5] These factors are clearly interrelated. Pulmonary vein stenosis post PVI is known to be progressive at least in the first 6-12 months post ablation, with potential worsening of any given stenosis during this period. Of significant concern due to its impact on long-term outcome, there can also be progressive hypoplasia of the entire pulmonary vein proximal to the stenosis over time. This may be due in part to the degree of initial injury to the pulmonary vein, but as documented histologically there can be pulmonary vascular occlusive changes with intimal hyperplasia and medial thickening of both large and small pulmonary veins and arteries within the lung that are likely progressive and probably not fully reversible.[23-25] These changes could result in irreversibly decreased pulmonary venous flow with secondary atrophy of the major vein. We have seen normal sized veins with reference diameters of 12 mm and severe discrete stenosis 3 months post PVI shrink down to 7 mm at the time of intervention 3 months later [Fig 9 A,B]. There may be some degree of reversibility to this "veno-occlusive" process accounting for the observed growth in some of these veins after

intervention, and the observed further increase in perfusion that we and others[6] have seen months after intervention when restenosis does not occur. However, complete normalization of either the size or the flow from moderately hypoplastic veins does not occur in our experience.

As mentioned before severe stenosis can also progress to total occlusion, sometimes precluding percutaneous intervention. Just as progressive stenosis can reach the point of total occlusion, total occlusion can reach the point of total obliteration or thrombosis of the entire pulmonary vein [Figure 10]. Total occlusion is sometimes treatable percutaneously [Figure 11 A,B], total obliteration or total occlusions that cannot be recanalized can only be treated by lung resection when warranted due to severe symptoms.[24]

There are no established guidelines at this time recommending routine screening for pulmonary vein stenosis following PVI, but it is suggested at least for centers beginning to perform the procedure for the first time.[16] The downside of screening all patients post PVI includes primarily cost and radiation exposure if MDTC is used, but as discussed above other imaging modalities with no or less radiation exposure are available. Waiting for symptoms to signal the presence of PVS will miss patients who despite severe stenosis are, at least subjectively, asymptomatic. Without screening, symptomatic patients may undergo extensive evaluation and unnecessary testing for their respiratory symptoms before the correct diagnosis is made. We have encountered patients who have

undergone bronchoscopy, lung biopsy, and even partial lung resection for a suspected malignancy before the diagnosis of pulmonary vein stenosis was considered. Waiting for significant symptoms, or waiting for the correct diagnosis to be made, may delay intervention and adversely affect outcome for the reasons discussed above. Further study is needed to evaluate the validity of routine screening. At our institution we believe that all patients should be screened, and referred promptly for evaluation when severe stenosis is detected. That is not to say that every patient should undergo intervention if significant stenosis is detected 3 months post PVI. In some cases ongoing remodeling of the pulmonary vein in the first few months post PVI in fact results in improvement rather than worsening of the stenosis, though significant improvement is not typically seen when the narrowing is very severe.[9] A judgment call has be to made taking into account the degree of stenosis, the size of the reference vessel and the clinical picture.

It is imperative that all clinicians caring for patients who have undergone pulmonary vein isolation for atrial fibrillation be knowledgeable about the presentation of pulmonary vein stenosis, and maintain a high index of suspicion for this entity. Pulmonologists, to whom these patients are often referred for evaluation of dyspnea and/or hemoptysis, should always consider pulmonary vein stenosis in their differential diagnosis. Despite nearly a decade in existence, and a large body of literature about post ablation pulmonary vein stenosis, we continue to see pa tients who go as far as having an open lung biopsy before the diagnosis of pulmonary vein stenosis is finally made. It is in part from these unnecessary biopsies that we have learned about the histological findings of a "veno-occlusive" pattern, alveolar hemorrhage, and interstitial fibrosis[25] as the pathophysiologic processes underlying severe pulmonary vein stenosis, processes that likely continue to smolder as long the stenosis is not relieved.

Future directions

We have learned that post ablation pulmonary vein stenosis carries a better prognosis than would have been predicted from other models of pulmonary vein stenosis. With close follow-up, we are able to maintain pulmonary vein patency and improve symptoms in a large majority of patients [Table 1].

However, we continue to be challenged by high restenosis rates for either balloon dilation or stentangioplasty of small veins requiring repeated interventions.The ultimate goal is complete elimination of this complication by further technical advances in ablative techniques. In the meantime, further advances in stent technology may come to our aid. Drug-eluting stents (DES) are currently commercially available only in very small sizes (≤ 3.5 mm) to treat coronary artery stenosis. Trials in peripheral arterial disease using larger DES have not shown definite superiority over bare metal stents in that setting,[38] but they remain untested in pulmonary veins. In light of the significant proliferative reaction associated with either balloon or stent angioplasty of the pulmonary veins, the use of DES seems to be the next logical step in improving restenosis rates for smaller vessels. Unfortunately DES larger than 3.5 mm in diameter are not currently available in the United States, either commercially or for research purposes. However, larger trials in peripheral arterial disease are planned in the near future, and may make DES available to be tried in small pulmonary veins. Research on biodegradable stents shows promise, but is still far from widespread clinical applicability.[39] Investigation of congenital pulmonary vein stenosis at the cellular level has revealed that the proliferative reaction is caused by a relatively undifferentiated myofibroblast, a cell that is also found in certain rare neoplasms.[40] At least one anti-proliferative agent effective against this cell type has been identified, but the toxicity profile may be prohibitive.[41] Research into other such agents is ongoing. The lessons we have and will continue to learn from post ablation pulmonary vein stenosis will hopefully not only benefit patients with this relatively new syndrome, but also carry over to other more fulminant forms of this disease.

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