Pulmonary vein stenosis is a fascinating yet frustrating and difficult to manage condition with an exceptionally high mortality rate. Until recently, the disease was seen almost exclusively in young children with or without various forms of congenital heart disease. Pulmonary vein stenosis is a relatively rare condition. In most published series from large centers, there has been an average of 2 or 3 cases per year that require treatment. Pulmonary vein stenosis in the adult population is even more rare, and the small number of reported cases has often been associated with mediastinal processes such as neoplasms or fibrosing mediastinitis. However, with the advent of aggressive treatment strategies for atrial fibrillation, we have seen a new group of pulmonary vein stenosis patients. The stenosis appears as a complication of radiofrequency ablation procedures around the pulmonary veins. Small series of new surgical and interventional catheterization procedures for treatment of both the pediatric and adult forms of pulmonary vein stenosis suggest an improving prognosis in centers with specialized expertise. However, the prognosis of patients affected with pulmonary vein stenosis remains guarded and requires diligent follow-up and often repeated procedures. The purpose of this article is to review concepts of causation and possible treatments for this rare but serious condition as they evolve.

**Embryology and Anatomy of the Pulmonary Veins**

The left atrium and pulmonary veins initially develop separately in the 3- to 5-mm embryo (25 to 27 days gestation).1 The primordial pulmonary venous system is part of the splanchnic plexus, which initially connects to the cardinal and umbilicovitelline veins. At 27 to 29 days gestation, a small endothelial outgrowth from the posterior superior wall of the primordial left atrium develops just to the left of the developing septum primum. At 28 to 30 days gestation, this common pulmonary venous out-pouching engages the pulmonary venous portion of the splanchnic plexus and begins to drain blood from the pulmonary system. In normal development, the connections to the cardinal and umbilicovitelline systems atrophy, which results in complete separation between the pulmonary and systemic venous systems.

The sequence of connection of the out-pouching of the left atrium to the pulmonary venous plexus, followed by incorporation of the confluence of the common pulmonary venous system into the left atrium, results in the typical anatomic appearance of the normal heart. In most hearts, approximately half of the left atrium is comprised of the common pulmonary vein and the other half, which includes the left atrial appendage, forms from the primitive left atrium.2 In most hearts, the embryological confluence of structures leads to the formation of 2 right-sided and 2 left-sided pulmonary veins that enter the smooth portion of the posterior left atrium.

Failure of the out-pouching of the left atrium to connect with the pulmonary venous plexus may result in persistence of the connections of the pulmonary veins to portions of the systemic venous system,3 which leads to the various forms of partial or total anomalous pulmonary venous return. If the connection between the left atrium and the pulmonary veins fails to occur at a time in development after connections of the pulmonary venous system to the systemic venous system have become obliterated, the result is the very rare condition of complete pulmonary vein agenesis.

The syndrome of “primary” endoluminal pulmonary vein stenosis with no preceding surgery or catheter intervention has been postulated to result from abnormal incorporation of the common pulmonary vein into the left atrium in the later stages of cardiac development.3 Affected patients most often become symptomatic in the first few months to years of life, frequently have 1 or more additional cardiac anomalies, and have no active inflammation in or around the involved segments of vein. Estimates of the incidence of associated cardiac defects have ranged from 30% to 80%.4–6 The most commonly associated congenital heart defects are septal defects, but pulmonary vein stenosis has been seen in conjunction with all major types of congenital cardiac malformations. Stenosis of the pulmonary veins may appear as a relatively discrete shelf, as a longer segment of narrowing at the junction of the pulmonary vein to the left atrium that extends slightly into the pulmonary vein, or as diffuse hypoplasia of the pulmonary veins.4–7 Pulmonary vein stenosis in children and even adults with no apparent preceding or concomitant cause of stenosis has been termed “congenital”. However, except in the small group of patients with diffusely hypoplastic pulmonary veins, we prefer the term “primary” pulmonary vein stenosis as the designation. The reason for this difference in terminology is that it is becoming more apparent that the disease is often progressive and may not even be evident at birth. Some feel that the rapidity of
Clinical Picture of Pulmonary Vein Stenosis in Childhood

The timing and severity of symptoms in pediatric patients with pulmonary vein stenosis appears to depend largely on the number of pulmonary veins involved and the severity of obstruction to individual pulmonary veins. Most patients present in the first months to years of life with a history of significant respiratory symptoms. Patients are often tachypneic and have recurrent pneumonias. As the disease progresses, signs of pulmonary hypertension become increasingly prominent. Patients may have diffuse or more localized evidence of pulmonary edema, based on whether 1 or more pulmonary veins are involved. Hemothystis may become a prominent symptom, especially in older patients.

Approximately one half of patients with primary pulmonary vein stenosis have some type of associated cardiac defect. It is therefore imperative that echocardiographic evaluations of patients with all forms of congenital heart disease specifically include evaluation of the pulmonary veins. Recent studies have documented progression from normal pulmonary venous flow patterns in a significant number of patients who later developed progressive pulmonary vein stenosis. Evaluation for stenotic pulmonary veins is indicated in any young patient with severe pulmonary hypertension.

Pulmonary vein stenosis may also be secondary in pediatric patients and occurs most often after anomalous pulmonary vein surgery. Clinically significant stenosis occurs postoperatively in ∼10% of patients after repair of total anomalous pulmonary venous return in most series. The site of obstruction may be at the anastomotic site of the pulmonary venous confluence to the left atrium or may occur further into the central pulmonary veins. Cases of pulmonary vein stenosis after cardiovascular surgery for lesions not in proximity to the pulmonary veins have also been reported.

Pulmonary Vein Stenosis in Adults

Primary pulmonary vein stenosis, with a pathological appearance similar to the childhood cases, has been reported rarely in unoperated adult patients. Secondary pulmonary vein stenosis in adult patients is usually associated with some identifiable underlying causative process. Until recently, involvement of the pulmonary veins by an extrinsic process such as neoplasm growth, sarcoidosis, or fibrosing mediastinitis was the association most frequently seen. In recent experience, however, the most common cause of pulmonary vein stenosis in adult patients has been radiofrequency ablation procedures for treatment of atrial fibrillation. Patients with this complication typically develop symptoms weeks to months after the ablation procedure. The diagnosis is easily missed if patients and referring physicians are not aware of the possibility of iatrogenic pulmonary vein stenosis. Patients most often present with shortness of breath and sometimes have a radiographic appearance of a localized infiltrate or localized edema. Hemothystis is not uncommon. We are aware of patients who have been treated medically for presumed pneumonia and who have even had partial pneumonectomies before the correct diagnosis was identified. The continual improvement of catheter ablation techniques has resulted in reduction, but not elimination, of this complication. Any patient who has undergone a catheter ablation procedure and presents with new respiratory symptoms should have a thorough evaluation for possible pulmonary vein stenosis.

Diagnosis and Evaluation of Pulmonary Vein Stenosis

Noninvasive tests are generally sufficient to diagnose pulmonary vein stenosis. In young children with good acoustic windows, echocardiography can visualize all pulmonary veins in nearly all patients. The finding of turbulent flow on color Doppler should raise the suspicion of pulmonary vein stenosis. Monophasic flow or flow velocities >1.6 m/s indicate potentially functionally significant obstruction (Figure 1). All pulmonary veins should be thoroughly investigated in any new patients with any type of congenital heart disease. All postoperative patients should also routinely have pulmonary venous flow evaluated echocardiographically because cases in which pulmonary vein stenosis developed late after anatomically remote surgical procedures have now been documented. Nearly half of patients with primary pulmonary vein stenosis have no associated cardiac malformation, so pulmonary veins should also be thoroughly evaluated in pediatric patients with apparently unexplained severe pulmonary hypertension.

Magnetic resonance imaging has been demonstrated to be an extremely useful noninvasive diagnostic technique for evaluation of the pulmonary veins. Magnetic resonance imaging can provide tomographic and 3-dimensional views of the pulmonary veins. The technique does not require ionizing radiation and may show abnormalities of the flow patterns in the pulmonary veins and pulmonary arteries. In our experience, the primary limitations of magnetic resonance imaging relate to relatively long acquisition times, sensitivity to motion artifacts and arrhythmias, and somewhat limited spatial resolution. Sensitivity to artifacts from metallic objects in the chest and contraindications in patients with a pacemaker can also be a problem in a significant portion of patients.

We have found multidetector CT angiography to be an excellent technique for detailed analysis of the pulmonary
veins in patients with known or suspected pulmonary vein stenosis (Figure 2). The primary concern with this technique, especially with small children, is the ionizing radiation should repeated studies be needed. Excellent images can be obtained rapidly and with good spatial resolution. We have found, however, that the resolution may still be inadequate to differentiate between completely occluded pulmonary veins and those with a tiny residual opening that may still be adequate for treatment by catheter techniques.26

Angiography provides the most selective and detailed views of the pulmonary veins. A pulmonary arterial catheter can be manipulated selectively to arterial segments that drain to each of the pulmonary veins. In regions with severe pulmonary vein stenosis, there may be little or no prograde flow under normal conditions. Contrast dye may actually flow “backwards” into arteries that drain into less stenotic veins. For optimal visualization, we therefore occlude a small segmental pulmonary artery with a balloon wedge catheter and inject nonionic contrast media followed by saline flush under careful fluoroscopic visualization (Figure 3). With this technique, we have been able to demonstrate even very small openings in some patients with presumed complete occlusion by noninvasive imaging. Direct visualization of nonoccluded pulmonary veins can be performed by transseptal catheterization and manipulation of the catheter through the obstructed area. Small injections of nonionic contrast are generally well tolerated and provide the most detailed pictures of the involved area of stenosis (Figure 4).

Asymmetrical pulmonary venous stenosis results in redistribution of flow between and throughout the 2 lungs. We have found that radionuclide quantitative pulmonary flow imaging provides the best evaluation of flow distribution (Figure 5). We strongly recommend this technique for any patients with pulmonary vein stenosis both before any type of intervention and as an excellent test for following patients over time.

**Treatment and Prognosis of Pediatric Pulmonary Vein Stenosis**

Patients with the pediatric form of pulmonary vein stenosis, either primary or secondary, have a very guarded prognosis. Without treatment, patients with involvement of most or all of
the pulmonary veins nearly always have relentless progression, and long-term survival is rare. The mode of demise is usually a pulmonary hypertensive crisis, intercurrent pulmonary infection, or hemoptysis. Patients with single-ventricle physiology may have progressively severe cyanosis or the clinical picture of a failing Fontan. Patients with only 1 or 2 pulmonary veins involved have a significantly more benign course. Breinholt et al found a mortality rate of 83% in patients with 3 or 4 stenosed pulmonary veins versus 0% in patients with 1 or 2 stenosed pulmonary veins.9 More cases of mild forms of pulmonary vein stenosis are undoubtedly being diagnosed in relatively asymptomatic patients as a result of increased awareness and improvements in noninvasive imaging modalities. The precise natural history of milder forms of pulmonary vein stenosis is therefore not entirely clear.

Repair of primary and secondary forms of pulmonary vein stenosis has been attempted with similar techniques and with similar outcomes. Pulmonary vein stenosis after repair of anomalous pulmonary venous return occurs in ≈10% of patients.10,11 This can be a particularly devastating complication in patients with associated single-ventricle physiology. Advances in the technique of surgical repair of pulmonary vein stenosis have been based on the concept of reducing trauma to the veins in hopes of reducing any stimulus for regrowth of obstructive tissue. A technique by which the pericardium around the pulmonary veins is attached to the left atrium avoids any stitches in the cut edges of the pulmonary veins and is now considered the best approach.27–29 Limited experience suggests that this sutureless marsupialization may be superior to previous approaches that used direct anastomosis after resection of stenotic segments or patching of the stenotic veins. Overall, freedom from reoperation or death at 5 years, however, is still only ≈50%.28,29 Patients with milder degrees of stenosis and stenosis of only 1 or 2 pulmonary veins clearly have a better prognosis. Progressive pulmonary vein stenosis isolated to 1 lung may be survivable even though flow studies demonstrate little or no flow to the involved lung. Pneumonectomy may be necessary for hemoptysis. In a small number of patients with unrelenting progression and development of severe pulmonary hypertension, lung transplantation has been successful.30 Short-term results in patients who survived long enough to undergo bilateral sequential lung transplantsations have been good, but the long-term prognosis is guarded at best.

Figure 3. Pulmonary artery wedge angiogram of a patient with severe left superior pulmonary vein stenosis caused by radiofrequency ablation for atrial fibrillation. Note the balloon catheter wedged in the superior segment of the left lung, which allows excellent visualization of the vein on levophase.

Figure 4. A, Right common pulmonary vein angiogram in a patient with confluence of the right pulmonary veins proximal to the left atrial chamber. There is a moderately severe stenosis at the connection of these veins to the left atrium. The stenosis was dilated with a cutting balloon, followed by a high-pressure angioplasty balloon. B, A follow-up angiogram 5 months later shows persistent excellent result in this patient.
Restenosis, however, occurs in >50% of patients within 1 year. Stent implantation has been associated with a better medium-term prognosis. We have found that if the caliber of the vein allows deployment of a relatively large stent (at least 9 to 10 mm in diameter), long-term patency can often be achieved. However, we and others have clearly seen recurrent stenosis inside stents within months to a few years. Cutting balloon angioplasty and further dilation of stents with recurrent stenosis has been successful in some cases. Although repeat procedures are often necessary, patency of the veins can be maintained and symptoms are improved in the majority of patients. Drug-eluting stents are not applicable to this patient population because drug-eluting stents that can be enlarged to adequate diameters (generally >12 mm) are not currently available.

Summary
Pulmonary vein stenosis is a rare condition with a bimodal age distribution. In pediatric patients the primary (ie, not associated with any preceding surgery) form of the disease may be related to inadequate embryological connections between the intrapulmonary venous system, the common pulmonary vein, and the left atrium. However, the stenosis is usually not static, and postnatal worsening of stenosis may be caused by abnormal proliferation of unusual myofibroblastic cells. It is not clear whether the same cell type may be involved in secondary pulmonary vein stenosis after surgical procedures that involve the pulmonary veins, such as in patients with anomalous pulmonary venous return. Recurrence of stenosis in both primary and secondary forms of pediatric pulmonary vein stenosis occurs in the majority of patients. Our current approach to most of these patients is to attempt surgical repair with the sutureless marsupialization procedure. Patients must then be followed carefully, and noninvasive imaging is usually adequate for screening. Catheter intervention is performed in veins with evidence of increasing stenosis. We generally perform high-pressure balloon dilation or cutting balloon dilation initially. Repeat procedures are frequently needed, but we have found that these repeat procedures may eventually slow the progress of restenosis. Placement of stents in the pulmonary veins of pediatric patients is usually considered only as a final mode of therapy before lung transplantation.

Pulmonary vein stenosis in adult patients is now most commonly associated with prior radiofrequency ablation procedures for atrial fibrillation. Balloon angioplasty and stenting are reasonably successful in treating these patients. Repeat procedures are commonly needed, but aggressive intervention to prevent complete occlusion has resulted in good long-term clinical results.

Disclosures
None.

References


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