# Medical and Invasive Management of Congenital and Acquired Pulmonary Vein Stenosis

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This article is part of the Topical Collection on *Cardiology/CT Surgery*

## Abstract

*Purpose of review* Pulmonary vein stenosis (PVS) is an increasingly recognized disease in infants and young children. Controversy exists regarding the best management of this disease. The hallmarks of PVS include recurrence, upstream progression, and spread to previously unaffected pulmonary veins. This review highlights invasive and medical therapies for pediatric patients with primary and secondary PVS.
*Recent findings* Catheter-based therapies for PVS are the mainstay of anatomic, large-vessel therapy. Angioplasty and stenting both have a role in the anatomic management of PVS. Repeated transcatheter interventions have been shown to improve survival. Surgical PVS intervention is an important element to PVS therapy. Primary (medical) therapy is increasingly recognized as an important element to PVS treatment. New anti-proliferative therapies have proven to be a useful adjunct to invasive therapies.
*Summary* Congenital and acquired PVS are progressive diseases that pose a growing challenge for cardiologists. Surgical and transcatheter interventions in most cases have early success but are only temporizing solutions in the face of myofibroblastic

proliferation. More recent studies focusing on benefits of immunomodulatory therapy have paved the way for the use of primary treatment alongside the anatomic therapy.

## Introduction

Pulmonary vein stenosis (PVS) in the pediatric population is a relatively rare condition making up 0.4% of congenital heart diseases [1]. The reported incidence of PVS, however, likely lags behind the current frequency seen at large pediatric centers. Some of this increase in frequency may reflect a growing awareness of PVS, while a true higher rate of PVS may be explained as well by growing rates of prematurity, chronic lung disease (CLD), and other unidentified environmental factors. PVS is often categorized as congenital (primary) or acquired (secondary), e.g., following surgical repair of partial or total anomalous pulmonary venous return. Secondary PVS is seen as a postoperative complication in ∼ 10% of cases [2, 3]. Primary PVS is often associated with chronic lung disease of prematurity, and it is widely held that pulmonary parenchymal inflammation and maldevelopment lead to arterial as well as pulmonary venous vascular changes [4•].

The pathophysiology of PVS is becoming better described. Animal models of PVS have demonstrated that discrete narrowing at the junction of the PV and left atrium is enough of a disturbance to set off a cascade of cellular and molecular pathways. These signals can induce upstream changes in intimal cells, with myofibroblast and myocyte conversion [5]. The myofibroblasts are proliferative in nature and eventually lead to worsening PVS which, when aggressive or untreated, develops into pulmonary vein atresia (PVA).

PVS has proven to be a difficult disease to manage because of its progressive and proliferative nature. Patients with bilateral disease, prematurity, and early age at onset are known to have a high mortality rate [6]. Death typically occurs during infancy and the likelihood of survival significantly increases after 1 year of age [7••]. Surgical repair alone has not been an effective solution for many patients. In the last decade, many centers have introduced new anatomic and anti-proliferative therapies to fight this relentless disease. The focus of the current review will be to describe the surveillance, treatment options, and our algorithm for patients with PVS.

# Clinical presentation

PVS is most commonly diagnosed within the first year of life—typically in premature infants with chronic lung disease. PVS can occur in isolation, but as many as half of patients will also have some other form of congenital heart disease [8].

The clinical presentation of patients with PVS is that of congestive heart failure and respiratory difficulty. Respiratory symptoms can range from mild tachypnea to severe respiratory distress. Recurrent viral or bacterial respiratory infections are common in PVS patients given their propensity for alveolar fluid retention and airway congestion. Hemoptysis is one of the later symptoms that can occur after the lungs have experienced chronic damage. If left untreated, symptoms will progress to involve severe pulmonary hypertension, right heart failure, and death.

Chest radiography in patients with pulmonary vein stenosis can provide clinical clues although the findings are non-specific. Pulmonary venous congestion can manifest on chest x-rays as Kerley B lines, pulmonary edema, or reticular opacities. Asymmetry in pulmonary vascularity or in lung volumes

may be noted if PVS is isolated to one lung; however, this asymmetry is often a late finding.

# Diagnosis and evaluation

## Echocardiography

If there is suspicion for PVS, echocardiography has historically been the first step in making the diagnosis. Echocardiographic evaluation of pulmonary veins is notoriously fraught, however. Although echocardiography provides valuable information, there are still important limitations to note with its use. Obtaining adequate images to truly interrogate the pulmonary veins may be difficult in patients for a multitude of reasons including difficult windows, prominent lung artifact, and the posterior location of the veins within the chest. In addition, redistribution of pulmonary blood flow in the setting of regional PVS can result in lower Doppler gradients in affected veins and, unexpectedly, higher Doppler gradients in unaffected pulmonary veins [9]. Finally, many premature infants with CLD also have atrial septal defects (ASDs) or patent ductus arteriosus (PDA)—increased pulmonary blood flow due to these shunts can make interpretation of Doppler gradients even more challenging.

## Cross-sectional imaging

Given the notorious limitations of echocardiography in defining pulmonary vein anatomy, cross-sectional imaging is usually necessary to diagnose PVS and guide interventions. Cardiac magnetic resonance imaging (cMR) can be considered as it often provides excellent anatomic detail with additional benefits of quantifying flows to affected and normal pulmonary veins. However, long acquisition times, need for anesthesia, and lower resolution make cMR less attractive than computed tomographic angiography (CTA).

Many infants and young children can undergo CTA without the need for anesthesia with feed and bundle protocols employed at many academic centers. CTAs also allow for evaluation of other cardiac structures, distal pulmonary vasculature as well as the underlying lung parenchyma. While CTAs are associated with exposure to ionizing radiation, the radiation doses from newer CT scanners with optimized imaging techniques has made the radiation dose during scans minimal [10]. At our center, CTA is a key component of the initial diagnosis. Importantly, serial CTA scans allow for grading of all pulmonary veins, allowing our team to track progression of PVS in each patient. Our institution uses a novel scheme to standardize grading severity and monitoring progression of disease [Fig. 1].

## Diagnostic cardiac catheterization

Cardiac catheterization remains the gold standard for definitive diagnosis of PVS, as catheterization provides angiographic as well as hemodynamic data. While much attention is appropriately paid to gradients across individual pulmonary veins in this disease, our center focuses more on right ventricular (RV) and pulmonary artery (PA) pressures. The rationale for this focus on RV and PA pressures is based upon the physiology expressed through the Gorlin equation: gradient across a stenosis is directly proportional to degree of stenosis, but also proportional to amount of flow [11]. As noted above, redistribution of
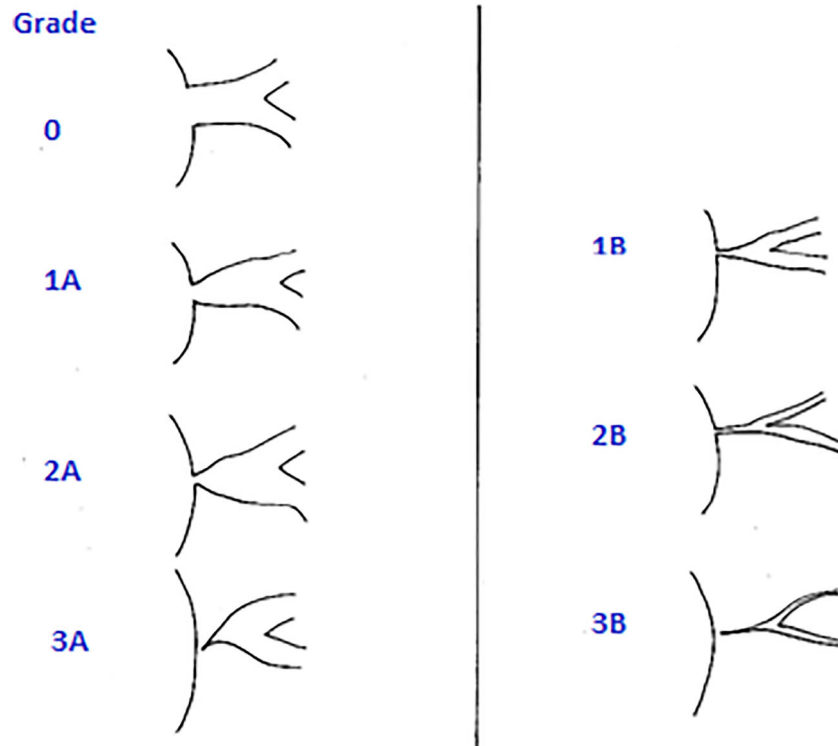
**Fig. 1.** Novel pulmonary vein stenosis grading scheme based on cross-sectional imaging or angiography. Grade 1 veins are mildly stenotic with < 50% narrowing at the insertion of the pulmonary vein to the left atrium relative to the maximal caliber of the distal vessel. Grade 2 veins are moderate to severely stenotic with > 50% narrowing. Grade 3 veins are atretic. The PVS severity is further characterized as either grade A or grade B. Grade A denotes a normal caliber to the distal vessel, whereas grade B denotes diffuse hypoplasia (vein diameter < 2 mm).

blood flow to healthier lung segments can result in gradients which do not reflect actual PVS severity.

Angiography should be performed, whenever possible, using a large-caliber guide catheter or sheath, with retrograde venography [Fig. 2]. The value of retrograde venography is the ability to identify the upstream arborization, which is necessarily missed with angiography from the PA side. The presence of angiographic stenosis is pathognomonic for PVS but delayed transit time to the left atrium on a PA injection is a subtle sign of intraluminal PVS. The benefit of cardiac catheterization extends past the identification and grading of PVS. At our center, catheterization also allows for vasoreactivity testing in patients with PVS and pulmonary artery hypertension (PAH). Additionally, catheterization is the platform for the majority of anatomic therapy for patients with PVS.

# Anatomic therapy

## Surgical technique

Conventional pulmonary vein stenosis repair was first described by Pacifico and colleagues in 1985 [12]. Minor modifications have been made to the original surgical technique which is still often used to this date for relief of congenital or acquired PVS. The technique involves using autologous atrial tissue to perform
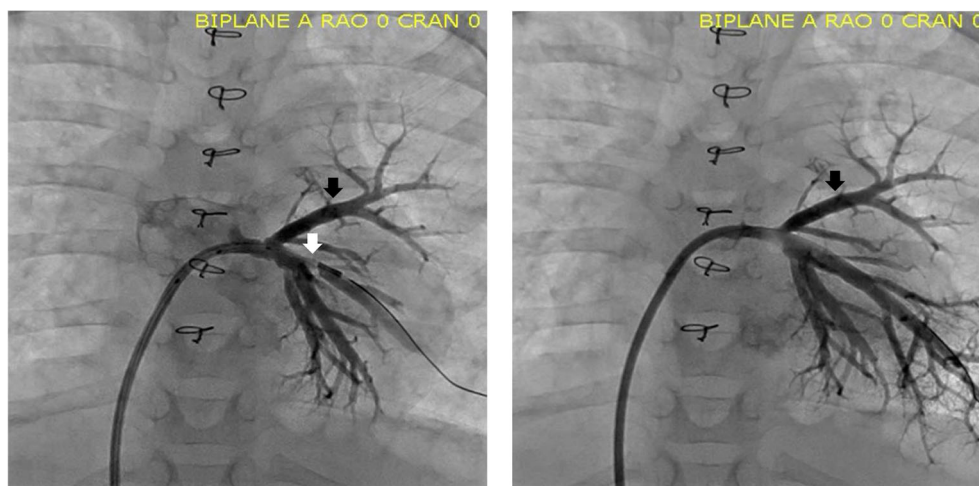
**Fig. 2.** Retrograde venography. In the frontal projection, an angiographic catheter is seen coursing from the inferior vena cava to the right atrium and then across an atrial septal defect into the left atrium and then to the left lower pulmonary vein. The panel on the left demonstrates retrograde venography highlighting important aspects of upstream arborization crucial for planning intervention. The white arrow denotes an area of stenosis in the posterior basal segmental branch of the left lower pulmonary vein that would not be identifiable by angiography from the pulmonary artery side. The right panel demonstrates improvement in stenosis after angioplasty. Of note, a prominent pulmonary vein drains the inferior segment of the left upper lobe (black arrows).

pulmonary venoplasty. It is important to note that with this technique the edges of the pulmonary veins themselves are directly anastomosed to patch material. Studies have demonstrated less than ideal results with 50% freedom from re-stenosis at 5 years [13, 14•]. Experts have postulated that the mixed results are related to myofibroblastic proliferation secondary to injury to anastomosed pulmonary veins.

Lacour-Gayet and colleagues described a different surgical approach in 1999 to combat the complications seen with conventional pulmonary vein repair. In this technique, the divided pulmonary veins are surrounded by an anastomosis made between the left atrium and pericardium [15]. There is no suture line directly on the pulmonary veins that could potentially propagate myofibroblastic proliferation and re-stenosis. This surgical technique has since been dubbed sutureless repair, or sutureless pericardial marsupialization. Mid-term results with the sutureless repair have been promising, demonstrating 90% freedom from re-stenosis at 5 years [16]. The external validity in translation of these results to the population with primary PVS has been limited. Conventional reviews of surgical outcomes for primary and secondary PVS continue to demonstrate recurrence [17–19].

## Transcatheter interventions

A myriad of catheter-based approaches have been applied to PVS since the early 1980s, including conventional balloon dilation/angioplasty, cryo-balloon angioplasty, high frequency sonotherapy, novel cutting balloons, local drug delivery with drug-coated balloons and stents, and even bioresorbable scaffolds [20–22]. Unfortunately, despite the approach, PVS has proven a recalcitrant, recurring disease which progresses in many cases despite any single approach listed above.

## Angioplasty

Balloon angioplasty as a therapy for PVS has been reported as early as 1982 in the literature by Driscoll and colleagues [23]. The procedure involves using a non-compliant balloon to serially dilate the stenotic region to mirror the size of the distal vessel. Prior to balloon angioplasty of an affected pulmonary vein, the operator should ensure that reliable angiography has been performed to allow for careful measurement of the minimal and maximal vein diameters. Serial balloon angioplasty should, in most circumstances, be chosen over going immediately to the goal diameter with a single large balloon catheter. Serial angioplasty allows for assessment of intimal tear, dissection, or vein rupture. Balloon angioplasty can be very effective in short-term relief of PVS. However, recurrence of PVS is expected.

Rarely, PVS is associated with resistant vascular stenotic lesions that are not amenable to simple balloon angioplasty. Resistant lesions are more commonly encountered in secondary PVS, such as following surgical repair of TAPVR. In these situations, cutting balloon angioplasty (CBA) has been used at our center and by others to relieve resistant lesions [24]. While CBA as primary therapy for PVS has been shown to be less effective than conventional balloon angioplasty, we continue to offer CBA for resistant lesions.

A novel balloon catheter which has recently emerged as a potential tool for PVS is the drug-coated balloon (DCB). DCBs were designed for peripheral artery disease angioplasty in adults with severe atherosclerosis. These balloons elute anti-proliferative agents such as paclitaxel, an mTOR-inhibitor-class anti-cancer agent. As described below, there has been enthusiasm for delivering high local concentrations of such agents to affected veins in patients with PVS [25]. However, data on DCBs in infants and children with PVS are currently lacking. Our center's preliminary experience with DCBs suggests that there may in fact be a limited role for this tool for patients with recurrent PVS, particularly those with in-stent stenosis (ISS). Unfortunately, DCBs in our experience have also been associated with early vessel loss in multiple patients. The role of DCBs in PVS remains unproven [25].

## Stenting

Intravascular stents have also been used to relieve venous and arterial stenoses since the early 1980s [26]. With advances in stent technologies, low-profile coronary stents can now be placed into neonatal pulmonary veins with minimal risk. The current generations of coronary stents include drug-eluting stents (DES) which elute anti-proliferative, anti-inflammatory, and anti-neoplastic agents. These agents are eluted at the local intimal level for up to 6 months post-implant [27]. Increasingly, DES are being employed to relieve PVS in infants and children [7••, 28•]. While DES have the advantages of being very low-profile and providing not only anatomic but anti-proliferative (primary) therapy, DES have limited future expansion capacity. Most DES cannot be dilated beyond 5–5.5 mm in diameter. As the adolescent child will have normally pulmonary veins of 10-12 mm diameter, these DES then can become woefully undersized in a relatively short period of time.

Other investigators have suggested that with implantation of larger diameter, bare-metal, stents (> 7 mm diameter), the late outcomes and overall

survival are better [29]. Clearly, when distal vein diameter is larger, placement of a stent which matches this distal diameter is warranted. However, over-sizing of a stent to achieve an arbitrary diameter is seldom helpful and in fact, in most cases, promotes aggressive ISS and recurrence of PVS [30, 31]. Nonetheless, as most non-coronary bare-metal stents can be dilated up to 10–12 mm in diameter, these are more ideal for PVS because they can be considered durable anatomic therapy.

## Reintervention

Because PVS is progressive both locally (recurring at the vein ostium, but also expanding upstream in an affected vein) and regionally (affecting previously normal pulmonary veins), surveillance and repeat interventions are the essential components to successful management of PVS. In the majority of cases, repeat interventions occur in the catheterization laboratory. The scope of repeat interventions includes conventional balloon angioplasty of affected veins, stent redilation to accommodate patient somatic growth, angioplasty of ISS, and placement of stents. Recent data suggest that patients who undergo repeat intervention have a significantly increased probability of survival. Cory and colleagues noted that in their cohort of PVS patients, survival was positively associated with greater frequency of catheterizations [7••]. The timing of repeat surveillance and reintervention varies. At our center, infants <1 year of age are often brought back to the catheterization laboratory every 4–6 weeks, and the frequency gradually decreases. Our patients who are 3 years of age or older typically undergo catheterization annually. Our institution's treatment algorithm is outlined below in greater detail [Fig. 3].

### Pneumonectomy and lung transplant

PVS left untreated can lead to chronic changes predisposing patients to hemoptysis. Both pulmonary and bronchial circulations empty into the left atrium through the pulmonary veins. Chronic obstruction creates distended bronchial veins, endobronchial varices, and alveolar hemorrhage leading to the substrate for hemoptysis in PVS patients [32]. Recurrent hemoptysis secondary to unilateral pulmonary venous obstruction is considered an indication for pneumonectomy as this hemoptysis can be life-threatening. Some patients with severe bilateral PVS will develop hemoptysis and severe pulmonary hypertension. In some centers, lung transplantation is offered to children with severe PVS that has led to irreversible chronic lung disease, particularly when surgical and transcatheter therapies have proven to be unsuccessful [33].

# Primary (medical) therapy

The angiographic and radiographic appearance of PVS belies the cellular and molecular basis of the disease. Histopathologic evaluation of PVS samples have revealed intimal hyperplasia, conversion of normal vascular layers to thickened, hypercellular vessels with proliferation of myofibroblasts—essentially, a regression of cellular differentiation to a
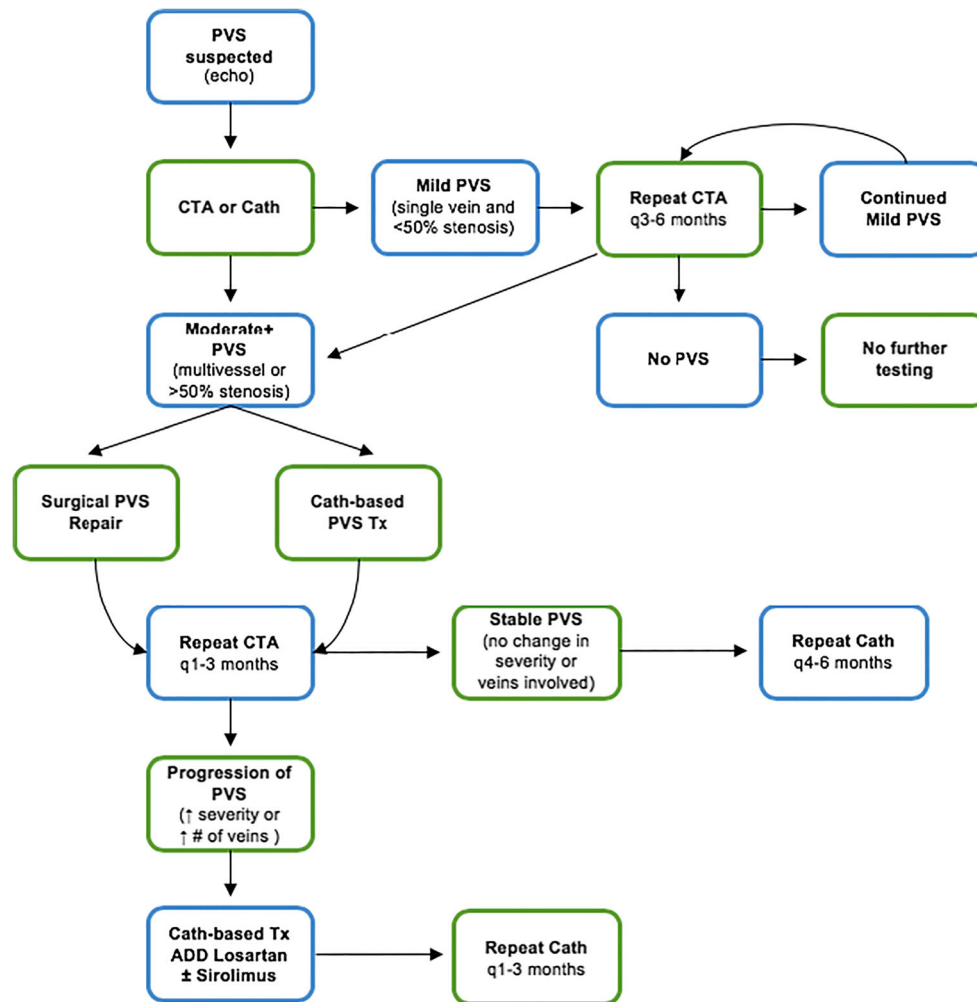
**Fig. 3.** Treatment algorithm for pulmonary vein stenosis. *PVS* pulmonary vein stenosis, *CTA* computed tomography angiography, *Tx* treatment.

more primordial, pluripotent, poorly differentiated cellular milieu. Reidlinger et al. were the first to demonstrate in 2006 an increased expression of smooth muscle antibodies and receptor tyrosine kinases in lesional cells consistent with myofibroblastic proliferation [5]. Kato et al. further elaborated on these upstream changes from pulmonary venous obstruction in a piglet model. They noted a similar endothelial to mesenchymal transition that was reversible when the obstruction was removed. Animal models of PVS have identified the involvement of specific pathways including receptor tyrosine kinases, mammalian target of rapamycin (mTOR), and TGF- in myofibroblastic proliferation of PVS. These animal models suggest an interesting interplay between pulmonary vein anatomy and molecular signaling; in one study, stenting of proximal PVS ameliorated upstream abnormal cellular signaling [34]. Conversely, altering cellular signaling through medical therapies (see below) resulted in reduced anatomic PVS burden [35].

## Vinblastine and methotrexate

The first chemotherapeutic trial for PVS in human subjects involved vinblastine and methotrexate [36]. Vinblastine is cell cycle specific and works by binding to mitotic spindle proteins preventing cell division. Methotrexate inhibits the enzyme dihydrofolate reductase preventing the formation of building blocks essential to DNA, RNA, and protein synthesis. These agents were chosen based on the treatment for desmoid tumors as their histology demonstrated similar myofibroblastic proliferation to PVS. One of the major setbacks during this study was medication toxicity leading to treatment delays and interruptions. Unfortunately, compared with controls, patients treated with vinblastine/ methotrexate fared far worse.

## Imatinib and bevacizumab

Two of the specific receptor tyrosine kinases upregulated in Reidlinger's immu-noreactivity study included Platelet Derived Growth Factor (PDGFR) and vas-cular endothelial growth factor receptor-2 (VEGF-2) [5]. Callahan and col-leagues strategically selected imatinib with or without bevacizumab to target these receptors in their prospective trial to treat multivessel intraluminal PVS as adjuncts to anatomic interventions. Imatinib was administered orally as a once daily tablet with the dose of 340 mg/m$^2$. Bevacizumb was administered intra-venously with the dose of 10 mg/kg every 2 weeks. Kaplan-Meier analysis demonstrated 77% probability of survival at 72 weeks in the imatinib with or without bevacizumab group while the control group demonstrated a < 40% probability of survival. Adverse effects from drug toxicity were minimal [37••].

## Sirolimus

Sirolimus inhibits mTOR similar to the compounds used in drug-eluting stents discussed earlier. Prior literature has established that mTOR is heavily involved in proliferation of a variety of cell types. Its use in PVS was first published in 2006 for adult iatrogenic PVS secondary to radiofrequency ablation for atrial fibrillation. Daily oral sirolimus was prescribed at a dose of 2 mg in conjunc-tion with bare-metal stenting. The two patients followed in this study were noted to be asymptomatic without re-stenosis 1 year from interventions [38]. Systemic sirolimus use in the pediatric population for PVS has not been reported on in the literature although some centers have begun clinical trials. Systemic sirolimus has been used to prevent in-stent stenosis for peripheral pulmonary artery disease. Hallbergson and colleagues demonstrated reduction in in-stent stenosis with target serum sirolimus levels between 6 and 10 ng/mL. Medication toxicities were minimal in the cohort of 10 patients studied [39]. Extrapolating these results to pediatric patients with PVS demonstrates a posi-tive outlook for the utility of systemic sirolimus but more research is needed to validate this claim.

## Losartan

Losartan acts by selectively blocking the type 1 angiotensin II receptor, which is known to inhibit pathways downstream of TGF- signaling. In 2014, Zhu and colleagues demonstrated in a piglet model of PVS that losartan treatment decreased intimal hyperplasia and pulmonary hypertension [35]. Losartan was initiated prophylactically prior to the development of significant

myofibroblastic proliferation in contrast to how it would be used in human patients with PVS. Losartan has yet to be trialed in human subjects. Further clinical trials are needed to prove the utility of losartan in treating PVS in humans.

# Conclusion

Congenital and acquired PVS represent a progressive disease with high rate of recurrence. This disease, increasingly seen in premature infants, has proven to be a challenge for cardiologists to manage. Surgical and transcatheter interventions in most cases have early success but are only temporizing solutions in the face of myofibroblastic proliferation. The physician should employ both anatomic as well as "primary" therapy (medical therapy). It is our center's approach to utilize primary therapy in all patients with evidence of moderate PVS. Importantly, anatomic treatment should be continued during primary therapy, as the studies above indicate PVS proximally elicits upstream cellular signaling alterations.

More recent immunohistological studies have paved the way for a new type of therapy for patients with PVS. Signaling pathways allowing for myofibroblastic proliferation in PVS are now known and can specifically be targeted. Early investigations are already underway to determine whether anti-proliferative medications such as losartan, imatinib/bevacizumab, or sirolimus may be disease-modifying therapies that can change the outcomes for these patients. These therapies in conjunction with anatomic therapies have already demonstrated promising preliminary results.

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## Publisher's Note