JACC: CASE REPORTS VOL. 29, 2024

CORONARY, PERIPHERAL, AND STRUCTURAL INTERVENTIONS

CASE REPORT: CLINICAL CASE SERIES

Novel Use of Drug-Coated Balloon Angioplasty to Treat Pulmonary Vein Stenosis

Saloni Agrawal, MD,[a] Kali A. Hopkins, MD,[a,b] Ali N. Zaidi, MD,[a,b] Barry Love, MD[a,b]

ABSTRACT

Pulmonary vein stenosis is challenging to treat due to high rate of recurrence. Multiple interventions exist but are limited by high rates of restenosis. One theory for the high rate of recurrence is vascular inflammation. Drug-coated balloon angioplasty has been used to limit restenosis caused by inhibiting inflammation in pulmonary vein stenosis. (JACC Case Rep. 2024;29:102613) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Pulmonary vein stenosis (PVS) can arise from congenital, iatrogenic, or acquired causes[1] (**Figure 1**). The incidence of severe PVS is low but remains associated with major morbidity and mortality. Treatment options are limited and have focused on transcatheter balloon angioplasty (BA) and/or stenting in persistent PVS, each of which has high rates of restenosis. Stenting also confers additional risk of stent malposition or embolization. The inflammatory component of PVS has become better recognized. We discuss 3 patients who underwent angioplasty with drug-coated balloons (DCBs) to treat the stenosis resulting from 3 different etiologies other than atrial fibrillation ablation-related complications, providing further examples to support DCB angioplasty as an effective treatment for PVS.

TAKE-HOME MESSAGES

- Diagnosis of PVS is complex and multiple etiologies can cause development of PVS.
- DCB is an effective treatment for PVS and should be considered in patients with and without atrial fibrillation ablation-related complications.

CASE 1

A 35-year-old man with history of Scimitar syndrome who underwent intra-atrial baffle of the veins to the left atrium (LA) and a second corrective surgery for left upper pulmonary vein (LUPV) stenosis in childhood presented with exertional dyspnea. Cardiac computed tomography (CT) confirmed severe stenosis of the left lower pulmonary vein (LLPV) and mild stenosis of the LUPV.

Due to bilateral iliac vein occlusion, right internal jugular vein access was obtained for hemodynamics and angiography and trans-hepatic access was required for the transseptal puncture and intervention. A multipurpose catheter was placed in a rightward anterior hepatic vein from the right internal jugular vein and a 4-F microaccess kit was used to access right hepatic vein percutaneously inferior to the right costal margin. Angiogram in the left

From the [a]Mount Sinai Hospital, New York, New York, USA; and the [b]Mount Sinai Adult Congenital Heart Disease Center, Mount Sinai Fuster Heart Hospital, New York, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 26, 2024; revised manuscript received August 12, 2024, accepted August 21, 2024.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2024.102613

ABBREVIATIONS AND ACRONYMS

BA = balloon angioplasty

CT = computed tomography

DCB = drug-coated balloon

ISR = in-stent restenosis

LA = left atrium

LUPV = left upper pulmonary vein

LLPV = left lower pulmonary vein

PVS = pulmonary vein stenosis

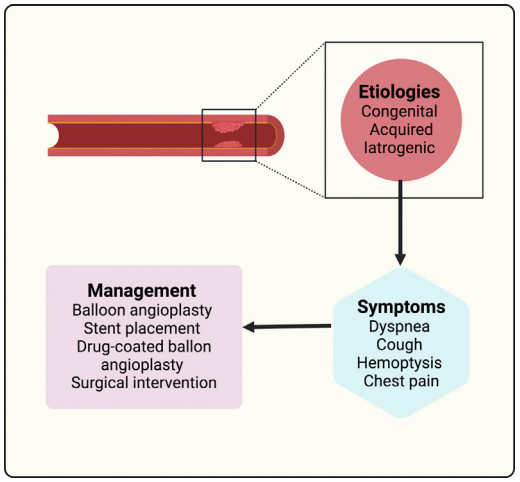
pulmonary artery showed severe obstruction of the LLPV/LA junction in levophase. A 61-cm 8-F transseptal sheath was delivered through the hepatic access to the right atrium and using a Brockenbrough needle and was advanced across the atrial septum under fluoroscopic and transesophageal echocardiogram guidance. The LLPV was entered with a 6-F Multipurpose catheter and 0.035 Platinum-tipped wire. The mean pressure in the LLPV was 20 mm Hg and the mean LA pressure was 7 mm Hg (gradient of 13 mm Hg across the LLPV stenosis) and a mean pulmonary artery pressure of 29 mm Hg. A paclitaxel-coated 10-mm balloon (InPact) was expanded across the stenosis followed by post dilation with a 12-mm high-pressure (Vida) balloon completely resolving the occlusion on angiography (**Figures 2A and 2B**). The post-angioplasty gradient from LLPV (10 mm Hg) to LA (8 mm Hg) was 2 mm Hg and the mean pulmonary artery pressure reduced to 24 mm Hg.

FOLLOW-UP. The patient was continued on rivaroxaban 20 mg daily for his history of atrial flutter. Repeat CT at 8-month follow-up was notable for sustained improvement in the LLPV and complete symptom resolution (**Figure 2B**). Echocardiogram at 13-month follow-up demonstrated stable pressure gradients.

CASE 2

A 62-year-old woman with history of pulmonary fibrosis and pulmonary hypertension requiring single left lung transplantation complicated by chronic rejection presented with worsening shortness of breath and exertional dyspnea. On further workup, angiogram showed significant stenosis of the LLPV. By cardiac catheterization, the LA was accessed from the right atrium through a patent foramen ovale. The gradient from LLPV (20 mm Hg) to LA (5 mm Hg) was 15 mm Hg and the mean pulmonary artery pressure was 27 mm Hg. A 12-mm (Powerflex) balloon was first inserted and dilated to full inflation followed by a 12-mm (InPact) paclitaxel-coated balloon, which improved the angiographic appearance of the stenosis (**Figures 3A and 3B**). The post-angioplasty gradient from LLPV (12 mm Hg) to LA (8 mm Hg) was 4 mm Hg, which remained stable at follow-up catheterization 8 months later (**Figure 3C**). However, 15 months after angioplasty, repeat catheterization revealed a 9-mm Hg gradient that was then treated with a 12-mm (InPact) paclitaxel-coated balloon followed by a high-pressure 14-mm (Vida) balloon with complete resolution of the stenosis angiographically (**Figures 3D and 3E**).

FIGURE 1 Pulmonary Vein Stenosis: Pathogenesis, Presentation, and Management



Created using BioRender.

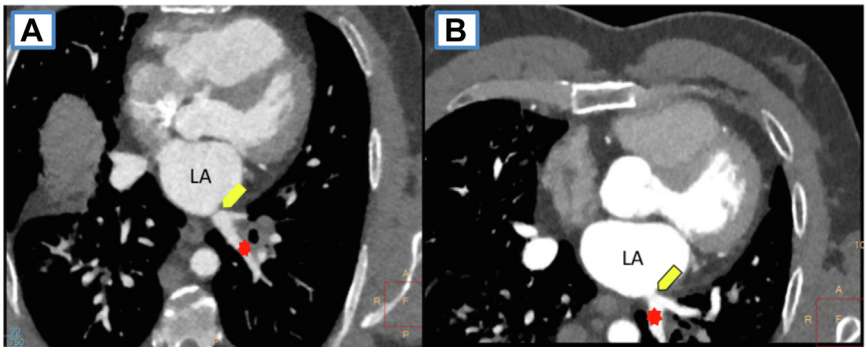
FOLLOW-UP. The patient was discharged on apixaban 5 mg twice daily for 3 months. She had dramatic improvement in her dyspnea following the first angioplasty. However, her symptoms returned leading to a second angioplasty with improvement but not resolution of symptoms. With no evidence of recurrent LLPV stenosis, the patient continues to have mild dyspnea on exertion and hypoxia requiring oxygen, which is likely multifactorial in etiology.

CASE 3

A 21-month-old infant with history of prematurity, bronchopulmonary dysplasia, pulmonary hypertension, and chronic respiratory failure requiring tracheostomy was found to have multivessel PVS and underwent transcatheter BA of her LUPV, right upper pulmonary vein, and right middle pulmonary vein.

Eight months later, cardiac catheterization was notable for new LLPV stenosis. The pre-angioplasty gradient from LLPV (20 mm Hg) to LA (10 mm Hg) was 10 mm Hg. The atrial septum was punctured with a transeptal needle to access the LA. Then LLPV was dilated with a 4-mm (Admiral) paclitaxel-eluting balloon followed by a 6-mm drug-eluting balloon and then a high-pressure 8-mm (Optapro) balloon, which showed resolution of the stenosis on the angiogram. The post-angioplasty gradient from LLPV

FIGURE 2 Cardiac CT From Case 1: Before and After



Yellow arrows showing the site of stenosis between LLPV (marked in red) and LA (left atrium) in A and B. (B) Improved LLPV stenosis after DCB angioplasty at 8-month follow-up is shown. Created using BioRender.

(10 mm Hg) to LA (10 mm Hg) improved with no residual stenosis (Figures 4A and 4B).

FOLLOW-UP. After multidisciplinary discussion, the patient was discharged without anticoagulation or dual-antiplatelet therapy. A 6-month follow-up echocardiogram revealed a gradient of 5 mm Hg with Doppler interrogation of the LLPV (Figure 4C). Follow-up at 13 months demonstrated stable pressure gradients.

DISCUSSION

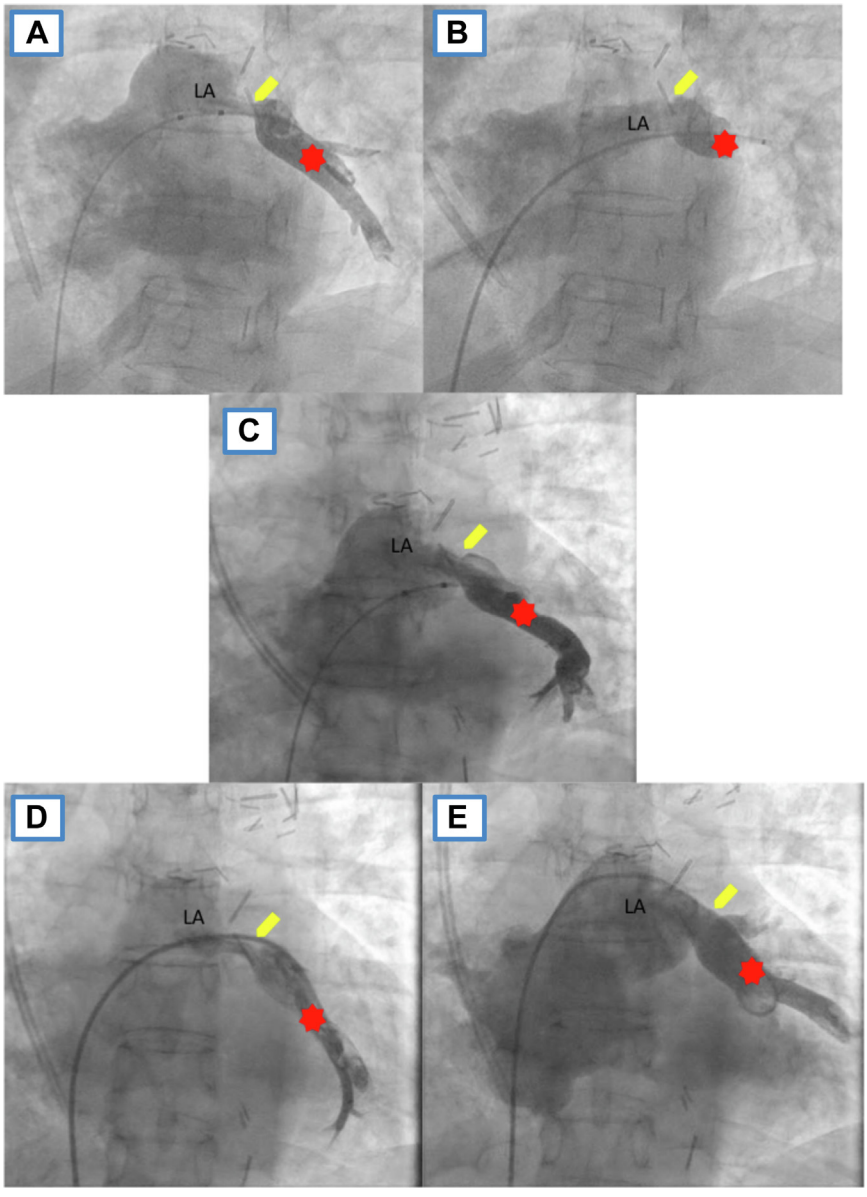
The etiology of PVS remains elusive and continues to pose a tremendous challenge within the field of congenital heart disease with a prevalence of around 1.7 cases per 100,000 children younger than 2 years.[2] PVS was first described in 1951 followed by the first direct PVS surgical repair in 1971 by Dr. Kawashima. Since then, interest in the pathophysiology and treatment of PVS has led to the understanding that PVS can largely be categorized as primary or secondary.[2]

Primary PVS results from abnormal incorporation of the pulmonary veins into the LA without any prior history of pulmonary vein injury or intervention. Mortality rates are thought to be as high as 60% at 2 years after diagnosis with primary PVS.[3] Secondary PVS results after injury or intervention to the pulmonary veins, such as after repair of anomalous pulmonary venous return with or as a complication of radiofrequency ablation in the LA to treat atrial fibrillation.[2] Less commonly it is associated with certain inflammatory diseases, as demonstrated by Case 2 in which the patient had lung transplant rejection. In some instances, the underlying etiology of PVS can be complex and a combination of primary and secondary causes are present as seen with Cases 1 and 3. Regardless of the classification, symptoms associated with PVS can include dyspnea, cough, hemoptysis, chest discomfort, or pleural effusion and often overlap with symptoms of other conditions, making the diagnosis challenging[1] (Figure 1).

When PVS is suspected, echocardiography is the most common screening modality used. CT angiography and magnetic resonance imaging are also often used in conjunction to evaluate the pulmonary vein anatomy and degree of stenosis. The gold standard remains a diagnostic cardiac catheterization, which provides concrete anatomic detail and hemodynamic data, including gradients across the stenotic pulmonary veins.

Once identified, PVS is challenging to treat due to recurrence of PVS at the site of stenosis despite anatomic intervention as well as progression of previously unaffected sites. Traditionally, transcatheter stent implantation has demonstrated reduced rates of repeat revascularizations in PVS compared with BA and is widely preferred.[4] Despite both these treatments being effective, they continue to be limited by high risk of restenosis. In fact, even though stent implantation is considered superior to BA in initial stenosis, its role has been limited by up to 30% incidence of in-stent restenosis (ISR).[4] Five-year survival in patients remains between 30% and 50% post-intervention despite improved surgical successes, suggesting that further advancements are necessary to improve long-term survival.[2] In addition to restenosis, the risk of stent migration during delivery with risk of stent embolization remains a significant risk as

FIGURE 3 **Angiogram During Catheterization From Case 2: Before and After**

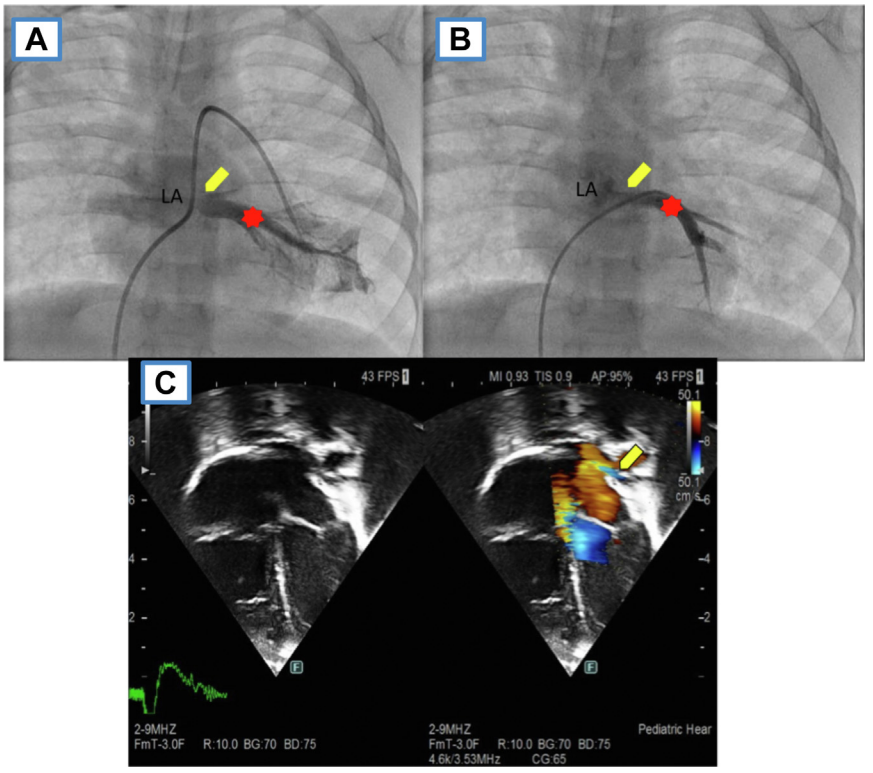


Yellow arrows showing the site of stenosis before and after DCB angioplasty in A, D, B, and E, respectively. Given the severity of stenosis, only a small jet is seen projecting into the left atrium (LA) as seen in A. After angioplasty, appropriate flow into the LA is depicted in (B). Follow-up angiogram at 8 months shows stable gradient in C requiring no further intervention. Seven months after the follow-up angiogram, recurrent stenosis is demonstrated in D followed by improvement in E. Created using BioRender.

the variably compliant stenotic region is typically difficult for stent anchoring.

Recent studies have begun to suggest that inflammatory pathways resulting in intimal hyperplasia may explain the mechanism of obstruction in PVS.[5-8] This has paved the way for development of therapies that combat these cellular level changes. Antiproliferative agents such as vinblastine and methotrexate were initially tested and have since been abandoned due to high rates of significant adverse events.[5,6] On the other hand, significant survival benefits have been noted with imatinib and bevacizumab in a retrospective nonrandomized trial.[9] Another agent, sirolimus, a mammalian target of

FIGURE 4 **Angiogram During Catheterization From Case 3 With Follow-Up TTE**



Yellow arrows showing the site of stenosis before and after drug-coated balloon angioplasty in A and B. Significant improvement in flow from the left lower pulmonary vein (LLPV) to the left atrium is seen in B after angioplasty. A repeat transthoracic echocardiography (TTE) done 6 months after the angioplasty shows stable gradient with patent LLPV (depicted by the yellow arrow), in C. Created using BioRender.

rapamycin inhibitor that targets vascular cell proliferation has been shown to have significant survival benefit in infants and children when treated with systemic therapy after stent placement.[5] Despite promising results, these studies have had small cohorts and the long-term implication of using systemic therapy is not well-established.[6]

A paclitaxel DCB is a device with targeted antiproliferative effects on vascular smooth muscle cells and fibroblasts used in percutaneous coronary and peripheral vascular interventions.[7] In clinical trials, it has been shown to treat both initial coronary artery stenosis and ISR. Similarly, angioplasty with DCB has been used in PVS and ISR resulting from post-PV isolation for atrial fibrillation ablation with promising results, but long-term results remain limited.[10]

In each of the cases discussed here, DCB angioplasty was effective in treating complex PVS secondary to diverse etiologies and improving symptoms in the short-term based on pressure gradients and angiographic data. In both Cases 1 and 3 no repeat intervention has yet been required with directed pulmonary vein DCB angioplasty and both these patients have had sustained improvement in their LLPV gradients on repeat catheterization. In Case 2, a repeat DCB angioplasty was required 15 months from the initial angioplasty with good results. We speculate that restenosis occurred as the DCB was placed at the site of a surgical anastomosis. Regardless, it appears that DCB may provide an alternate therapeutic modality that may reduce reintervention rates or increase the time between interventions in PVS. However, additional larger studies with long-term outcomes are needed to assess the DCB angioplasty effect on long-term morbidity and mortality.

CONCLUSIONS

PVS is challenging to treat due to recurrence despite anatomic intervention. Our patients underwent DCB angioplasty to limit restenosis caused by inflammatory pathways by triggering antiproliferative effects. In the present report, we demonstrate the use of DCB angioplasty in PVS resulting from multiple etiologies with good short-term results.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Saloni Agrawal, The Mount Sinai Hospital, 1468 Madison Avenue, New York, New York 10029, USA. E-mail: Saloni.Agrawal@mountsinai.org.

REFERENCES

1. Simard T, Sarma D, Miranda WR, et al. (2023). Pathogenesis, evaluation, and management of pulmonary vein stenosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2023;81(24):2361-2373.

2. McLennan DI, Solano ECR, Handler SS, Lincoln J, Mitchell ME, Kirkpatrick EC. Pulmonary vein stenosis: moving from past pessimism to future optimism. *Front Pediatr*. 2021;9:747812.

3. Amin R, Kwon S, Moayedi Y, Sweezey N. (2009). Pulmonary vein stenosis: Case report and literature review. *Can Respir J*. 2009;16(6):e77-e80.

4. Fender EA, Widmer RJ, Mahowald MK, Hodge DO, Packer DL, Holmes DR Jr. Recurrent pulmonary vein stenosis after successful intervention: prognosis and management of restenosis. *Catheter Cardiovasc Interv*. 2020;95(5):954-958.

5. Patel JD, Briones M, Mandhani M, et al. Systemic sirolimus therapy for infants and children with pulmonary vein stenosis. *J Am Coll Cardiol*. 2021;77(22):2807-2818.

6. Shorofsky MJ, Morgan GJ, Mejia E, et al. Management of complex pulmonary vein stenosis at altitude combining comprehensive percutaneous interventional treatment with sirolimus, pulmonary hypertension medications and intraluminal imaging with optical coherence tomography. *Pediatr Cardiol*. 2023;44(5):1125-1134.

7. Ito K, Kato K, Tanaka H. Experience using drug-coated balloon venoplasty for acquired pulmonary vein stenosis after radiofrequency ablation. *J Cardiol Cases*. 2020;23(1):3-5.

8. Cohen JL, Glickstein JS, Crystal MA. Drug-coated balloon angioplasty: a novel treatment for pulmonary artery in-Stent stenosis in a patient with Williams syndrome. *Pediatr Cardiol*. 2017;38(8):1716-1721.

9. Callahan R, Kieran MW, Baird CW, et al. Adjunct targeted biologic inhibition agents to treat aggressive multivessel intraluminal pediatric pulmonary vein stenosis. *J Pediatr*. 2018;198:29-35.e5.

10. Salih M, Alom M, Kazem A, DeVille B, Potluri S. Drug-coated balloon venoplasty to treat iatrogenic pulmonary vein stenosis. *JACC Case Rep*. 2023;24:102019.

KEY WORDS drug-coated balloon angioplasty, paclitaxel, pulmonary vein stenosis, restenosis