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EDITORIAL COMMENT

Drug-Coated Balloon Angioplasty in Pulmonary Vein Stenosis

A Promising Tool*

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Pulmonary vein stenosis (PVS) is a rare condition that is either congenital or acquired and carries a high risk of morbidity and mortality. Depending on the severity of stenosis and number of veins involved, PVS can present with alarming hemoptysis, or no symptoms, but most commonly it has subtle symptoms such as dyspnea or cough and can go undetected. When severe PVS is untreated, it can lead to venous congestion, ventilation/perfusion mismatch, and pulmonary infarct. Furthermore, PVS leads to upstream vascular remodeling, extending into the pulmonary arterial tree causing pulmonary hypertension and right heart failure.[1]

Congenital PVS is caused by abnormal incorporation of the common pulmonary vein to the left atrium in cardiac development, which is a different pathology from total or partial anomalous pulmonary vein connections. PVS is often associated with other congenital heart defects, is progressive in nature with myofibroblastic proliferation, and has a poor prognosis.[2] Most of the acquired forms of PVS are secondary to pulmonary vein isolation (PVI) procedures for atrial fibrillation, with necrosis, intimal proliferation, and fibrosis at the pulmonary vein ostia. Less common etiologies of PVS include the following. 1) Fibrosing mediastinitis , a mediastinal lymph node inflammatory and fibrotic process, from histoplasmosis, tuberculosis, or immunoglobulin G_4 disease, causing external compression of the thin-walled veins leading to occlusion. 2) Pulmonary veno-occlusive disease is a rare disorder with fibrous intimal thickening of the pulmonary veins with obliteration of pulmonary venules, and it is associated with connective tissue and systemic inflammatory disease, such as scleroderma and sarcoidosis, as well as being drug-induced.[3] 3) Postsurgical PVS is a complication of surgery involving the surgical manipulation of a pulmonary vein (**Figure 1**).

In PVS post PVI, the incidence of severe symptomatic PVS post PVI has decreased substantially at <1% with new techniques over time.[4,5] However, when routine imaging is used post PVI, the rate of PVS of any severity is higher at nearly 40%, demonstrating lack of adequate detection due to subtle symptomatology.[6] Diagnosis of PVS is best detected on computed tomography angiography; however, echocardiography, lung perfusion, cardiac magnetic resonance , and invasive angiography and intravascular ultrasound are useful diagnostic modalities (**Figure 1**).

Therapy of PVS has thus far consisted of either angioplasty or stenting, including drug-eluting stents, which are usually smaller in size because they were originally intended for coronary arteries and do not exceed 5 mm, or bare-metal stents, which are available in larger sizes and were originally intended for peripheral arteries or biliary tree stenting. Historically, metal-frame stents were developed after conventional percutaneous transluminal angioplasty (PTA) to address vessel recoil, prevent abrupt vessel occlusion, and seal any vessel dissection. However, the constant metal-frame stress on the endothelial wall can produce aggressive neointimal proliferation and fibrosis leading to restenosis. Angioplasty in PVS is effective, but the rate of restenosis

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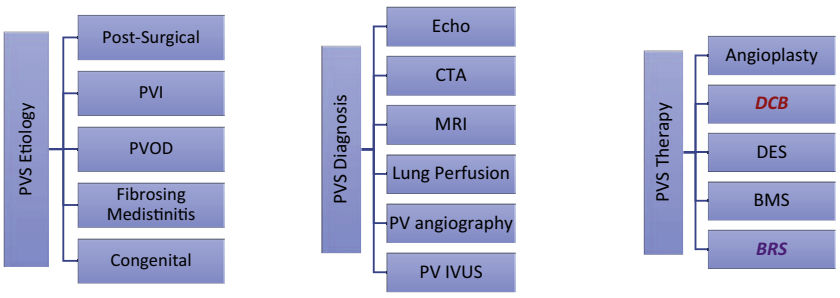
FIGURE 1 Pulmonary Vein Stenosis Etiology, Diagnosis, and Therapy



BMS = bare-metal stent; BRS = bioresorbable scaffold; CTA = computed tomography angiography; DCB = drug-coated balloon; DES = drug-eluting stent; IVUS = intravascular ultrasound; MRI = magnetic resonance imaging; PVI = pulmonary vein isolation; PVOD = pulmonary veno-occlusive disease; PVS = pulmonary vein stenosis.

is markedly high at >50%.[7-9] Stenting has become the preferred method of PVS treatment with reduced risk of restenosis and reintervention.[10] Despite excellent procedural success rate, there remains a high rate of restenosis, often within the first 6-12 months, with a wide reintervention rate ranging from 5% to 40%, depending on the chronicity and severity of the pulmonary vein lesion, extent of upstream vascular remodeling, and type and size of the stent.[11-13] Given the pathophysiological role of intimal proliferation in PVS, drug-eluting stents theoretically should improve patency rates relative to bare-metal stents, but the smaller size and residual metal frame portend to in-stent restenosis (ISR).[14] Larger stent diameter, particularly ≥7.0 mm, has been shown to correlate with longer term patency.[15,16] Pulmonary veins with total occlusion, especially if >6 months, with upstream negative remodeling, lung tissue injury with suboptimal collateralization, and poor flow, often end up with just angioplasty or small stent implanted, with the highest rate of restenosis.[17] Optimal interventional approach with longest term patency remains undefined.

Drug-coated balloons (DCBs) have emerged in the peripheral and coronary arterial realm as a novel strategy to address the shortcoming of stents, whether they were drug-eluting or bare-metal stents. DCBs were shown to be effective in multiple studies, especially in scenarios where there is a high risk of restenosis and target lesion revascularization from small vessel caliber, calcification precluding adequate stent expansion, previously failed layer of stent, and bifurcation lesions.[18,19] Using a DCB is a better strategy in patients that do not tolerate dual antiplatelet regimen. In femoropopliteal revascularizations, DCBs have been shown to be superior to bare-metal stents in terms of target lesion revascularization, irrespective of lesions characteristics.[18] Data are lacking to demonstrate the superiority of DCBs to drug-eluting stents in peripheral arterial disease. In coronary revascularization, the early studies, both retrospective and prospective, have proven quite promising, demonstrating that using a DCB is a feasible, safe, and effective strategy, not only in treating ISR, bifurcation, or calcified lesions, but also in acute coronary syndrome, with similar rates of major adverse cardiovascular events and clinical outcomes up to 2 years. There remains a higher risk of dissection, which may necessitate stenting, and in all peripheral and coronary studies, the important role of appropriate lesion preparation was emphasized with the use of imaging tools for correct lesion sizing and lithotripsy or atherectomy for appropriate lesion preparation to allow adequate drug contact with vessel lumen.[19] Most DCBs use paclitaxel given its lipophilic characteristics, allowing drug absorption with long-lasting effects. A meta-analysis had suggested increased mortality with the use of paclitaxel DCBs in peripheral arterial disease,[20] which was later disproven on further review by multiple other studies.[21]

This case series by Salih et al[22] in this issue of *JACC: Case Reports* describes their single-center experience with 4 patients with PVS status post PVI, all involving left-sided PV. DCB sizes used were from 4 to 7 mm, and imaging follow-up demonstrating vein patency was performed at 1, 6, and 24 months, and 5 years. The longest follow-up was in a 7-mm DCB used for ISR. Shortest follow-up was in the smallest DCB used (4 mm) at 1 month. This case series proves that DCB use in PVS is quite promising, and longer term

follow-up of the smaller veins would be encouraged especially because smaller veins are where DCB may play a large role.

Given that ISR and target lesion revascularization remain quite high in PVS interventions, especially in small and chronically occluded veins, DCBs may fill a crucial gap in therapy. It is unlikely that DCBs will replace stenting altogether; pulmonary vein walls have a thinner tunica media layer relative to arterial walls, increasing the risk of dissection and reocclusion with angioplasty. Also, in cases of fibrosing mediastinitis, where the pathology is external compression, the metal frame is crucial in maintaining vessel patency. The use of a DCB as an adjunct to stenting delivering antiproliferative therapy with larger bare-metal stents or as single therapy, with stenting only if there is marked recoil or dissection, can allow for the development of a novel treatment decision tree. This would depend on etiology, symptomatology, sequelae, chronicity, collateralization, size, and length of PVS. Vessel evaluation with preprocedural imaging, intraprocedural intravascular ultrasound assessment, and lesion preparation to optimize drug delivery is essential.

DCB use is a promising therapeutic modality that may reduce reintervention rate in PVS. The field may further be altered with the advent of drug-eluting bioresorbable scaffolds in the future. Early detection with a higher index of suspicion is an integral component in the optimal therapy to prevent long-term morbidity. There is an critical need for larger studies with long-term outcomes of DCB use in PVS.

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Dr Ghobrial has served as a consultant and proctor for Medtronic congenital therapies.

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REFERENCES

1. Masaki N, Adachi O, Katahira S, et al. Progression of vascular remodeling in pulmonary vein obstruction. *J Thorac Cardiovasc Surg*. 2020;160(3):777-790.e5.

2. Latson LA, Prieto LR. Congenital and acquired pulmonary vein stenosis. *Circulation*. 2007;115(1):103-108.

3. Montani D, Lau EM, Dorfmüller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J*. 2016;47(5):1518-1534.

4. De Greef Y, Ströker E, Schwagten B, et al. Complications of pulmonary vein isolation in atrial fibrillation: predictors and comparison between four different ablation techniques: results from the MIddelheim PVI-registry. *Europace*. 2018;20(8):1279-1286.

5. Teunissen C, Velthuis BK, Hassink RJ, et al. Incidence of pulmonary vein stenosis after radiofrequency catheter ablation of atrial fibrillation. *J Am Coll Cardiol EP*. 2017;3(6):589-598.

6. Samuel M, Khairy P, Mongeon FP, et al. Pulmonary vein stenosis after atrial fibrillation ablation: insights from the ADVICE trial. *Can J Cardiol*. 2020;36(12):1965-1974.

7. Prieto LR, Schoenhagen P, Arruda MJ, Natale A, Worley SE. Comparison of stent versus balloon angioplasty for pulmonary vein stenosis complicating pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2008;19(7):673-678.

8. Widmer RJ, Fender EA, Hodge DO, et al. Contributors toward pulmonary vein restenosis following successful intervention. *J Am Coll Cardiol EP*. 2018;4(4):547-552.

9. Buiatti A, van Olshausen G, Martens E, et al. Balloon angioplasty versus stenting for pulmonary vein stenosis after pulmonary vein isolation for atrial fibrillation: a meta-analysis. *Int J Cardiol*. 2018;254:146-150.

10. Almakadma AH, Sarma D, Hassett L, et al. Pulmonary vein stenosis—balloon angioplasty versus stenting: a systematic review and meta-analysis. *J Am Coll Cardiol EP*. 2022;8(10):1323-1333.

11. Fender EA, Widmer RJ, Mahowald MK, et al. Recurrent pulmonary vein stenosis after successful intervention: prognosis and management of restenosis. *Catheter Cardiovasc Interv*. 2020;95(5):954-958.

12. Fink T, Schluter M, Heeger CH, et al. Pulmonary vein stenosis or occlusion after catheter ablation of atrial fibrillation: long-term comparison of drug-eluting versus large bare metal stents. *Europace*. 2018;20(10):e148-e155.

13. Iversen E, Packer EJS, Sandberg SM, Bleie Ø, Hoff PI, Schuster P. Long-term follow-up in patients treated by stent implantation for post-ablation pulmonary vein stenosis. *J Interv Card Electrophysiol*. 2018;53(3):309-315.

14. Khan A, Qureshi AM, Justino H. Comparison of drug eluting versus bare metal stents for pulmonary vein stenosis in childhood. *Catheter Cardiovasc Interv*. 2019;94(2):233-242.

15. Suntharos P, Worley SE, Liu W, Siperstein M, Prieto LR. Long-term outcome of percutaneous intervention for pulmonary vein stenosis after pulmonary vein isolation procedure *Catheter Cardiovasc Interv*. 2020;95(3):389-397.

16. Li YJ, Pan X, Wang C, He B. Stent implantation for severe pulmonary vein stenosis or occlusion secondary to atrial fibrillation ablation. *Int J Cardiol*. 2020;301:85-89.

17. Hill J, Qureshi AM, Worley S, Prieto LR. Percutaneous recanalization of totally occluded pulmonary veins after pulmonary vein isolation-intermediate-term follow-up. *Catheter Cardiovasc Interv*. 2013;82(4):585-591.

18. Lee SJ, Lee HH, Ko YG, et al. Device effectiveness for femoropopliteal artery disease treatment: an analysis of K-VIS ELLA registry. *J Am Coll Cardiol Intv*. 2023;16(13):1640-1650.

19. Zhao H, Miao R, Lin F, Zhao G. Drug-coated balloon in primary percutaneous coronary intervention. *J Interv Cardiol*. 2023;2023:5210808.

20. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(24):e011245.

21. Ouriel K, Adelman MA, Rosenfield K, et al. Safety of paclitaxel-coated balloon angioplasty for femoropopliteal peripheral artery disease. *J Am Coll Cardiol Intv*. 2019;12(24):2515-2524.

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

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