

# Cryo-Balloon Angioplasty for Pulmonary Vein Stenosis in Pediatric Patients

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**Abstract** This study sought to determine the safety and effectiveness of cryo-balloon angioplasty (CbA) for pulmonary vein stenosis (PVS) in pediatric patients. Current therapy options for PVS are less than satisfactory due to recurrent progressive restenosis and neointimal proliferation. Catheterization database, hospital records, imaging studies, and pathologic specimens were reviewed for procedural-related and outcomes data in all patients who underwent pulmonary vein (PV) CbA using the Boston Scientific PolarCath Peripheral Dilation System between August 2006 and June 2009. Thirteen patients (19 PVs; median age 13 months [range 3.5 months to 18.5 years] and weight 7.9 kg [range 3.8 to 47.7]) underwent CbA. Mean PVS diameter after CbA increased from 2.19 ( $\pm 0.6$ ) to 3.77 ( $\pm 1.1$ ) mm ( $p < 0.001$ ). Mean gradient decreased from 14 ( $\pm 7.4$ ) to 4.89 ( $\pm 3.2$ ) mm Hg ( $p < 0.001$ ). Mean stenosis-to-normal vein diameter ratio increased from 0.52 ( $\pm 0.15$ ) to 0.89 ( $\pm 0.33$ ) ( $p < 0.001$ ). Eight patients underwent repeat catheterization a mean of 5.6 months ( $\pm 3.66$ ) later. Improved PVS diameter was maintained in 2 PVs. Four veins had restenosis but maintained diameters greater than that before initial CbA. In 11 PVs, the diameter decreased from 4.28 ( $\pm 1.14$ ) to 2.53 ( $\pm 0.9$ ) mm ( $p = 0.001$ ). Mean gradient increased from 3.55 ( $\pm 3.0$ ) to 14.63 ( $\pm 9.6$ ) mm Hg ( $p = 0.011$ ). All vessels underwent repeat intervention with acute relief of PVS. Stroke occurred within 24 h of CbA in 1 patient. CbA of PVS is

safe and results in acute relief of stenosis. However, CbA appears minimally effective as the sole therapy in maintaining long-term relief of PVS.

**Keywords** Pulmonary vein stenosis · Cryo-balloon angioplasty · Balloon angioplasty · Pulmonary vein angioplasty

## Background

Pulmonary vein stenosis (PVS) is a relatively rare condition with an incidence of two to three cases per year per institution in most series [16] and represents  $<0.5\%$  of all congenital heart disease [6]. It can be primary or acquired after surgical repair of anomalous pulmonary venous connection or other cardiac surgery. Historically it has been difficult to manage; if untreated, it has a poor prognosis. Although the newer “sutureless” surgical repair has shown improved results, nearly half of all patients still develop restenosis requiring reintervention [2, 15, 19, 28]. Both standard and novel transcatheter interventions have been used, both alone and in combination, but with only limited success and only in a small number of patients [1, 3, 4, 8, 17, 18, 20, 24, 26].

Cryo-balloon angioplasty (CbA) is a new therapy that combines standard balloon angioplasty with the application of cryotherapy. To date, it has been used primarily in adults for the treatment of peripheral vascular disease and renal artery stenosis [7, 10, 13, 14, 27]. It is thought to prevent neointimal hyperplasia by inducing apoptosis of smooth muscle cells, thus minimizing restenosis [14]. The objective of this study was to determine the safety and effectiveness of CbA in the treatment of PVS in pediatric patients.

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## Methods

We retrospectively reviewed the catheterization database, hospital records, imaging studies, and available pathologic specimens to collect procedural-related and outcomes data in all patients who underwent pulmonary vein (PV) CbA at Children's Hospital Colorado, Denver, CO, using the PolarCath Peripheral Dilation System (Boston Scientific, Natick, MA) between August 2006 and June 2009. Approval for the study was obtained from the Colorado Multiple Institutional Review Board.

### Patients

A total of 13 patients (19 PVs; median age 13 months [range 3.5 months to 18.5 years] and weight 7.9 kg [range 3.8–47.7]) underwent CbA. Eleven had primary PVS, and 2 were status post-repair of total anomalous pulmonary venous return. Seven patients had additional structural heart lesions. Three PVs had undergone previous surgical therapy, and 3 had undergone previous transcatheter therapy. Table 1 lists the patient demographics, diagnoses, and previous treatments.

### Catheterization Details

All catheterizations were performed with the patient under general anesthesia. Access to the left atrium was by way of existing patent foramen ovale or atrial septal defect or after transseptal puncture using standard technique. Various end-hole catheters were used to access the individual PVs

and to measure pressures proximal to the area of stenosis relative to the left atrial pressures. Selective hand-injection angiograms were performed to measure the diameter of the stenosis as well as the diameter of adjacent "normal" vessel in the more proximal aspect of the respective PV. (Figures 1, 2, 3).

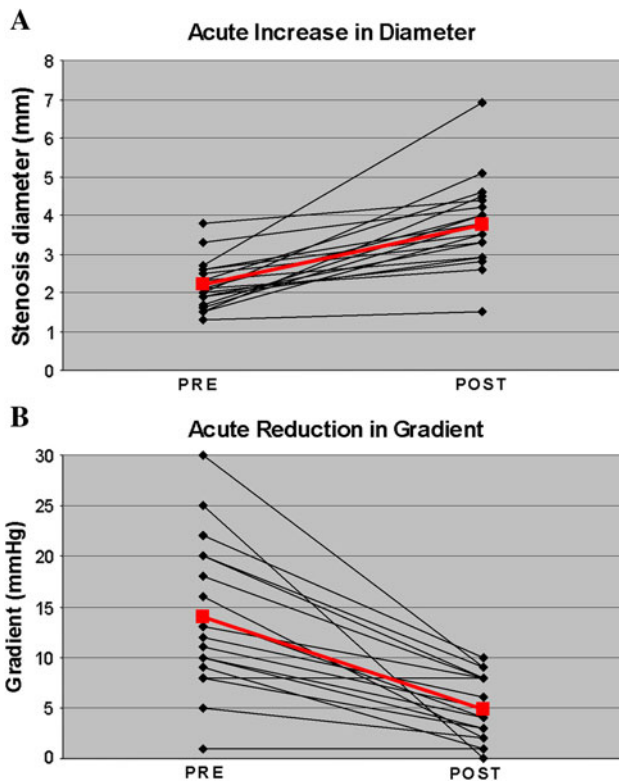
The PolarCath Peripheral Dilation System consists of a PEBAX material, nitrous oxide-expanded dual-balloon catheter. Within the balloon, the liquid nitrous oxide converts to gas, resulting in a pressure of 8 atm and a surface temperature of  $-10^{\circ}\text{C}$ . A microprocessor unit controls inflation and cooling of the balloon, which lasts for 20 s, after which the balloon is manually deflated. This inflation time is particularly important to consider in patients with stenosis or atresia of other PVs because it can result in a prolonged and significant decrease in cardiac output. Balloons are available in diameters of 4–8 mm, and are all 2 cm in length. They are delivered by way of 6F to 8F sheaths over a 0.035-inch wire.

Although not based on a specific protocol, the diameter of the CbA balloon used was selected so that it was approximately 2–3 times the minimal stenosis diameter (median 2.86 [range 1.82–3.58]) and 1–1.5 times the diameter of the adjacent normal vessel (median 1.31 [range 0.87–2.07]). In the first two patients, the vein was predilated using cutting-balloon angioplasty before treatment with a CbA of the same balloon diameter. In only one patient (no. 7) was the vein subsequently redilated using a larger-diameter standard balloon (9 mm after 8-mm CbA) during the same procedure. Final angiogram was performed to assess for both vessel injury and response

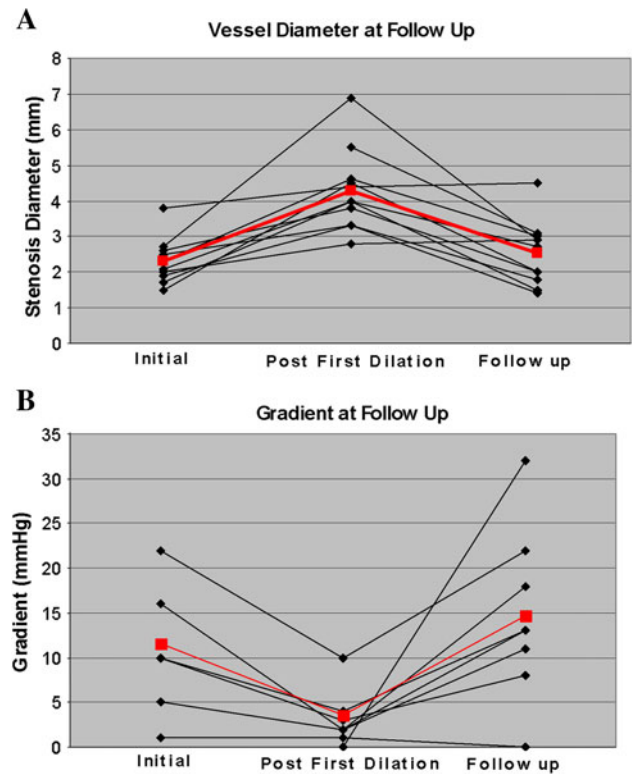
**Table 1** Patient demographics

Patient no.	Sex	Age (mo)	Wt (kg)	Vessel	Associated defects	Previous interventions
1	F	222	47.7	LU	PVS s/p stent	Sutureless surgical repair, balloon dilation, stenting and subsequent repeat dilations
2	M	60	15.6	LL	HLHS s/p Fontan	Balloon dilation
3	M	14	7	LL	HLHS/mixed TAPVR	Surgical repair of TAPVR/left veins, balloon dilation
4	F	22	9.9	LU and RU	ILD, MAS	
5	F	5	3.8	RU and RL	LPV atresia	
6	F	4	4.8	LL and RL	PVS	
7	M	44	11.6	LU	PVS	
8	F	9	7.4	RU	PVS	
9	M	51	16.2	LL	Mixed TAPVR	Surgical repair of TAPVR
10	M	13	7.9	LL	Ebstein's, PVS	
11	M	12	7.9	LPV, RU, and RM	VSD, LSVC	
12	F	4	5.4	LU and LL	ASD, VSD	
13	F	3.5	4.8	LPV	HLHS	

*s/p* status post, *ASD* atrial septal defect, *HLHS* hypoplastic left heart syndrome, *ILD* interstitial lung disease, *LL* left lower, *LPV* left pulmonary vein, *LSVC* left superior vena cava, *LU* left upper, *MAS* macrophage activation syndrome, *RL* right lower, *RM* right middle, *RU* right upper, *TAPVR* total anomalous pulmonary venous return



**Fig. 1** Acute relief of stenosis. **a** Pre- and post-CbA PV stenosis diameter (mean shown in red). **b** Pre- and post-CbA mean gradient across stenotic PV (group mean shown in red)



**Fig. 2** Follow-up data. **a** Initial, post-CbA, and follow-up vessel diameters (mean shown in red). **b** Initial, post-CbA, and follow-up mean gradients (mean shown in red)

to treatment. Postdilatation pressure measurements were obtained in the proximal vein and left atrium.

**Statistical Analysis**

Data are expressed as medians with ranges or as means with SDs when appropriate. Paired Student *t* test was used to compare differences in vessel diameter and gradient before and after CbA, and *p* < 0.05 was considered statistically significant.

**Results**

**Initial Results**

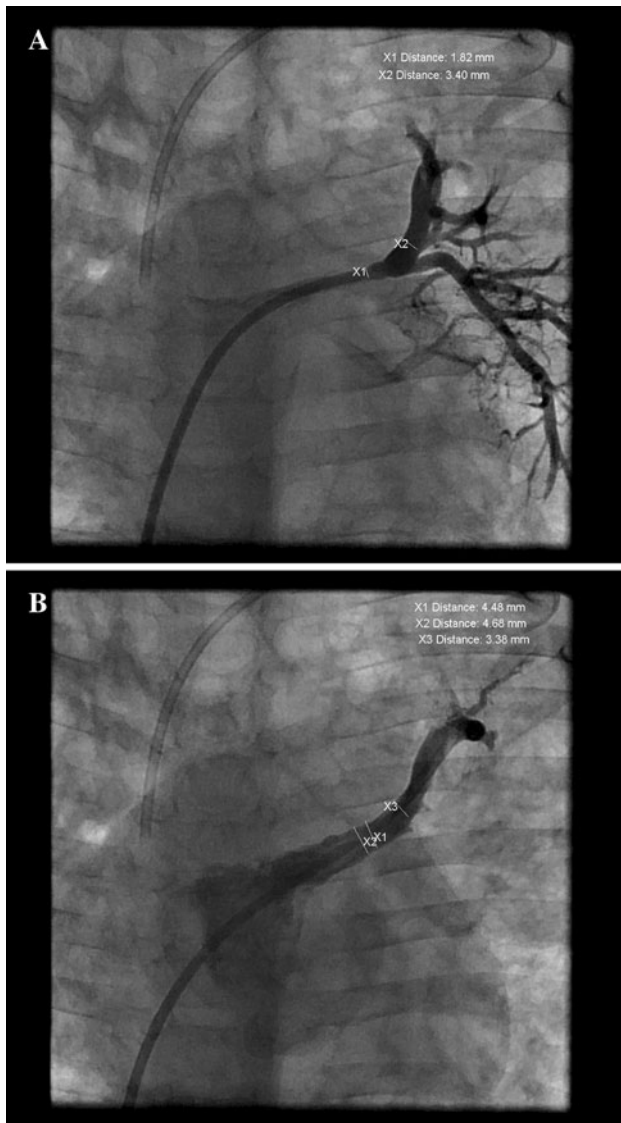
Table 2 lists both the initial result of balloon dilation using CbA as well as the findings at follow-up catheterization (where available). Acute improvement in the stenosis diameter was achieved in all cases. Angiographic PVS diameter after CbA increased from a mean of 2.19 (±0.6) to 3.77 (±1.1) mm (*p* < 0.001). Mean gradient decreased from 14 (±7.4) to 4.89 (±3.2) mm Hg (*p* < 0.001). Mean

stenosis diameter-to-normal vein diameter ratio increased from 0.52 (±0.15) to 0.89 (±0.33) (*p* < 0.001).

**Follow-Up Results**

Eight patients (11 PVs) underwent follow-up catheterization a mean of 5.6 (±3.66) months after initial CbA. Improved PVS diameter was maintained in only 2 PVs (18%). Four additional veins (36%) had restenosis but maintained a diameter greater than that before initial CbA. In 11 PVs, PVS diameter decreased from 4.28 (±1.14) to 2.53 (±0.9) mm (*p* = 0.001), and the mean gradient increased from 3.55 (±3.0) to 14.63 (±9.6) mm Hg (*p* = 0.011). Although not directly assessed or measured, there was no significant appreciable extension of the stenosis into more proximal sections of the affected PVs. All vessels both repeat intervention using CbA resulting in acute relief of the stenosis.

One patient underwent lung transplantation after repeat non-CbA. Three patients died: two from progressive PVS leading to respiratory arrest within months of initial CbA and one from unknown causes 3 months after a second CbA.



**Fig. 3** **a** Representative left upper PV injection showing focal stenosis at insertion to the left atrium. **b** Success relief of stenosis after CbA

#### Adverse Events

Stroke of unclear etiology occurred within 24 h of CbA in one patient. Although it must be assumed that this was

related to the catheterization, neither postdilation angiography nor echocardiography showed evidence of thrombus in the left atrium or PVs.

#### Discussion

To our knowledge, this is the first description of the use of CbA in the treatment of PVS. However, it is not the first novel approach that has been used to combat this frustrating lesion. Similar to other rare congenital heart diseases for which there is no established effective intervention, many varied techniques have been tried to treat stenotic PVs.

Initial transcatheter interventions with both standard and high-pressure balloon angioplasty [4] had only limited success, particularly in maintaining long-term vessel patency. Similarly, initial reports as well as a recent larger series [18, 20, 24] of cutting-balloon angioplasty demonstrated acute relief of stenosis but failed to prevent restenosis in the longer term. Our experience with CbA is similar to these in that initial dilations are quite successful but lack the longevity of successful interventions seen in other vascular beds.

Case reports and small series on stent placement [1, 17, 26] have also shown disappointing results, with most patients requiring early and often multiple reinterventions secondary to restenosis. Covered stents [8], drug-eluting stents [3], systemic chemotherapy [12], and even intrastent sonotherapy [17] have all been used with limited effect in individual patients or in small numbers of patients and primarily after previous angioplasty or stent treatment with early restenosis.

What, if anything, can be gleaned from this collection of studies when taken together? First and foremost is the fact that essentially all PV interventions, both surgical and catheter-based, are hampered by restenosis, which almost universally occurs due to neointimal hyperplasia. Although this reaction is not unique to PVs, it certainly seems to be more robust and relentless compared with the cellular response to intervention that occurs in other segments of the vasculature.

**Table 2** Acute and follow-up results

Result	Stenosis diameter (mm)	Mean gradient (mm Hg)	Stenosis: normal vessel ratio	Restenosis diameter at follow-up (mm)	Change in mean gradient at follow-up (mm Hg)
<i>n</i>	19	19	19	11	11
Pre-CbA	2.19 ( $\pm$ 0.6)	14 ( $\pm$ 7.4)	0.52 ( $\pm$ 0.15)		
Post-CbA	3.77 ( $\pm$ 1.1)	4.89 ( $\pm$ 3.2)	0.89 ( $\pm$ 0.33)	4.28 ( $\pm$ 1.1)	2.53 ( $\pm$ 0.9)
F/U				3.55 ( $\pm$ 3.0)	14.63 ( $\pm$ 9.6)
<i>p</i>	<0.001	<0.001	<0.001	0.001	0.011

F/U Follow-up

For example, neointimal hyperplasia is known to have a significant impact on both short- and long-term success in coronary artery interventions, and much of the research relating to the mechanism of neointimal proliferation comes from adult and animal-based studies. This research has suggested multiple mechanisms behind the vascular response to injury. In fact, all of the novel approaches described previously, including our own, target one or more of these mechanisms as their basis for potential efficacy.

CbA combines the dilation force of balloon angioplasty with the delivery of cold thermal energy to the vessel wall with the intent of inducing apoptosis of smooth muscle cells to prevent neointimal hyperplasia and thereby minimize restenosis [7]. Cooling time and temperature have been extrapolated mostly from in vitro and animal studies [27]. One possible reason for the poor long-term efficacy we observed is that balloon temperatures achieved and/or the time period of exposure that occur in vivo are not adequate for induction of maximum apoptosis.

Although much has been discovered about the multifactorial process that leads to PV restenosis, there is still much to learn, including how to best modulate, hamper, or even prevent it. Perhaps just as important, we must define how PVS is different than stenosis in other vascular beds. One area of research that may shed light on this process is molecular analysis of pathologic specimens of PVS [23]. Early data suggest that intimal lesional cells are myofibroblast-like based on diffuse immunoreactivity for smooth-muscle cell markers. This finding lends support for interventional techniques, such as CbA and other therapies that specifically target smooth-muscle cells.

Another common factor related to successful therapy in PVS is that size matters. One early study found that larger PV size at the time of diagnosis is a strong independent predictor of survival in patients with total anomalous pulmonary venous return [11]. Both younger age and greater initial pulmonary artery pressure at diagnosis, both of which correlate with PV size, have been shown to be predictors of death and/or lung transplantation [9]. Unfortunately, two recent studies both found that PVS occurs more frequently in preterm infants [5, 25], suggesting that this subgroup may have an even worse prognosis.

The importance of vessel size has also been recognized in adults with acquired PVS after radiofrequency ablation or isolation for treatment of atrial fibrillation. Two of the larger series have shown that vessels achieving larger postdilation diameters (>9 mm) remain stenosis-free for longer periods, suggesting that dilation to a certain “threshold” size may result in long-term patency [21, 22].

## Future Directions

Our results demonstrate that CbA is comparable with traditional, high-pressure cutting balloons in terms of safety and acute effectiveness in decreasing PV stenosis. It has been suggested that aggressive treatment and reintervention may eventually slow the progress of PV restenosis [16, 25]. Repeat CbA intervention may have an added benefit compared with standard balloons in terms of sequential or additive decrease in intimal hyperplasia. Therefore, our current approach, in the absence of more definitive treatments, involves frequent surveillance and repeated sequential intervention and dilation primarily using CbA.

## Limitations

Our study is retrospective, and patients were not randomized. In addition, our overall sample size is small. However, given the rare occurrence of this disease, we believe that this represents a relatively large number of cases given the short time frame of the study. This likely reflects the fact that our center is a referral center for pulmonary hypertension, thus leading to the increased number of patients with PVS.

## Conclusion

Despite being uncommon, PVS remains a challenging clinical problem. Surgical repair techniques, as well as currently available catheter-based interventions, have proven to be less than optimal, and recurrent and progressive restenosis is all too common. Our report demonstrates that CbA of PVS is safe and results in acute relief of stenosis. However, CbA appears minimally effective as the sole therapy in maintaining long-term relief of PVS. Further research, including evaluation of repeat CbA therapy, is needed.

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## References

1. Cullen S, Ho SY, Shore D, Lincoln C, Reddington A (1994) Congenital stenosis of pulmonary vein: failure to modify natural history by intraoperative placement of stents. *Cardiol Young* 4:395–398
2. Devaney EJ, Chang AC, Ohye RG, Bove EL (2006) Management of congenital and acquired pulmonary vein stenosis. *Ann Thorac Surg* 81(3):992–995
3. Dragulescu A, Ghez O, Quilici J, Fraisse A (2009) Paclitaxel drug-eluting stent placement for pulmonary vein stenosis as a

- bridge to heart–lung transplantation. *Pediatr Cardiol* 30(8): 1169–1171
4. Driscoll DJ, Hesslein PS, Mullins CE (1982) Congenital stenosis of individual veins: clinical spectrum and unsuccessful treatment by transvenous balloon pulmonary dilation. *Am J Cardiol* 49(7):1767–1772
  5. Drossner DM, Kim DW, Maher KO, Mahle WT (2008) Pulmonary vein stenosis: prematurity and associated conditions. *Pediatrics* 122:e656–e661
  6. Edwards J (1960) Congenital stenosis of pulmonary veins. Pathologic and developmental considerations. *Lab Invest* 9:46–66
  7. Fava M, Loyola S, Polydorou A et al (2004) Cryoplasty for femoropopliteal arterial disease: late angiographic results of initial human experience. *J Vasc Interv Radiol* 15:1239–1243
  8. Gordon BM, Moore JW (2010) Treatment of pulmonary vein stenosis with expanded polytetrafluoroethylene covered stents. *Catheter Cardiovasc Interv* 75:263–267
  9. Holt DB, Moller JH, Larson S, Johnson MC (2007) Primary pulmonary vein stenosis. *Am J Cardiol* 99:568–572
  10. Jefferies JL, Dougherty K, Krajcer Z (2008) First use of cryoplasty to treat in-stent renal artery stenosis. *Tex Heart Inst J* 35(3):352–355
  11. Jenkins KJ, Sanders SP, Orav EJ, Coleman EA, Mayer JE Jr, Colan SD (1993) Individual pulmonary vein size and survival in infants with totally anomalous pulmonary venous connection. *J Am Coll Cardiol* 22(1):201–206
  12. Jenkins KJ, Tan PE, Perry SB, et al (2001) Proliferative pulmonary vein stenosis: variable patterns of progression and preliminary results using adjunct chemotherapy. *Circulation* 104(Suppl II)
  13. Karthik S, Tuite DJ, Nicholson AA et al (2007) Cryoplasty for arterial restenosis. *Eur J Vasc Endovasc Surg* 33:e40–e43
  14. Kataoka T, Honda Y, Bonneau HN, Yock PG, Fitzgerald PJ (2002) New catheter-based technology for the treatment of restenosis. *J Interv Cardiol* 15(5):e371–e379
  15. Lacour-Gayet F, Rey C, Planche C (1966) Pulmonary vein stenosis. Description of a sutureless surgical procedure using the pericardium in situ. *Arch Mal Coeur Vaiss* 89(5):633–636
  16. Latson LA, Prieto LR (2007) Congenital and acquired pulmonary vein stenosis. *Circulation* 115:103–108
  17. McMahon CJ, Mullins CC, El Said HG (2003) Intrastent sonotherapy in pulmonary vein restenosis: a new treatment for a recalcitrant problem. *Heart* 89:e6
  18. McMahon C, McDermott M, Walsh K (2006) Failure of cutting balloon angioplasty to prevent restenosis in childhood pulmonary venous stenosis. *Catheter Cardiovasc Interv* 68:763–766
  19. Najm HK, Caldarone CA, Smallhorn J, Coles JG (1998) A sutureless technique for the relief of pulmonary vein stenosis with the use of in situ pericardium. *J Thorac Cardiovasc Surg* 115(2):468–470
  20. Peng LF, Lock JE, Nugent AW, Jenkins KJ, McElhinney DB (2010) Comparison of conventional and cutting balloon angioplasty for congenital and postoperative pulmonary vein stenosis in infants and young children. *Catheter Cardiovasc Interv* 75:1084–1090
  21. Prieto LR, Schoenhagen P, Arruda MJ, Natale A, Worley SE (2008) Comparison of stent versus balloon angioplasty for pulmonary vein stenosis complicating pulmonary vein isolation. *J Cardiovasc Electrophysiol* 19(7):673–678
  22. Qureshi AM, Prieto LR, Latson LA et al (2003) Transcatheter angioplasty for acquired pulmonary vein stenosis after radiofrequency ablation. *Circulation* 108:1336–1342
  23. Reidlinger WF, Juraszek AL, Jenkins KJ et al (2006) Pulmonary vein stenosis: expression of receptor tyrosine kinases by lesional cells. *Cardiovasc Pathol* 5:91–99
  24. Seale AN, Daubeney PE, Magee AG, Rigby ML (2006) Pulmonary vein stenosis: initial experience with cutting balloon angioplasty. *Heart* 92(6):815–820
  25. Seale AN, Webber SA, Uemura H et al (2009) Pulmonary vein stenosis: the UK, Ireland and Sweden Collaborative Study. *Heart* 95(23):1944–1999
  26. Tomita H, Watanabe K, Yazak S et al (2003) Stent implantation and subsequent dilatation for pulmonary vein stenosis in pediatric patients—maximizing effectiveness. *Circ J* 67:187–190
  27. Wildgruber MG, Berger HJ (2008) Cryoplasty for the prevention of arterial restenosis. *Cardiovasc Intervent Radiol* 31:1050–1058
  28. Yun TJ, Coles JG, Konstantinov IE et al (2005) Conventional and sutureless techniques for management of the pulmonary veins: evolution of indications from postrepair pulmonary vein stenosis to primary pulmonary vein anomalies. *J Thorac Cardiovasc Surg* 129(1):167–174