Nonsurgical Management of Postoperative Pulmonary Vein Stenosis

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이 형 두

Postop pulmonary vein stenosis

- TAPVR or PAPVR repair
- Primary pulmonary vein stenosis
- Lung transplantation
- Radiofrequency PV isolation

Postop PV stenosis

- Pulmonary vein stenosis after repair of TAPVR : 10% of patients *ATS 2005;79:596–606 ATS 1998;* 66:1514–20
- 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%. *JTS 2005;129:* 167–74. *ATS 2006;81:* 992–95

Nonsurgical procedure for postop PV stenosis

- Balloon angioplasty
  - Conventional
  - Cutting balloon
  - Cryoballoon
- Stent implantation
  - Conventional
  - Covered stent
  - Oral sirolimus
  - Restenosis
    - Cutting balloon
    - Sonotherapy

Percutaneous balloon dilation

- **Case report** Br Heart J 1990;64:160-2
- 16 month old girl with TGA
- Senning procedure at age of 3 mo
- Reop at 8 mo, stenosis of the PV atrium by neointimal tissue asso with the bovine pericardial patch
- Dyspnea recurred at 16 months
- Balloon dilation at 18 months
- 9 mo after the procedure the patient remained symptom free

Percutaneous balloon dilation

- **Case report** Br Heart J 1994;72:85-88
- 5 year old boy with TGA
- Obstruction of PV pathway 4 yrs after the Mustard procedure at 3 mo
- Stenosis measuring 2-3 mm in diameter.
- Balloon dilatation of PV pathway obstruction with a 12 mm x 2 cm balloon
  - →increase in diameter from 3 mm to 7 mm with considerable clinical improvement
  - →7 mo after cath, clinical state deteriorated

Percutaneous balloon angioplasty

- **Case report** Interactive CardioVascular and Thoracic Surgery 15 (2012) 314–316
- 62-year old man
- Rt single-lung transplantation
- Stenosis at right inferior PV, 2 mm on CT
- Mean pressure gradient across the stenosis of 7
- Dilation with 4 mm non-compliant balloon
  → reduction in gradient to 1 mmHg
- After 2 months, Sx recurred, repeat CT scanning demonstrated a recurrence of the RIPV stenosis

Balloon dilation

- Immediate improvement is usually seen angiographically, but recurrent stenosis occurs in a large majority of patients.

Circulation. 2007;115:103-8

Conventional versus Cutting balloon

Comparison of Conventional and Cutting Balloon Angioplasty for Congenital and Postoperative Pulmonary Vein Stenosis in Infants and Young Children

Lynn F. Peng,[1,2] MD, James E. Lock,[1,2] MD, Alan W. Nugent,[1,2] MD, Kathy J. Jenkins,[1,2] MD, and Doff B. McElhinney,[1,2*] MD

Background: Pulmonary vein stenosis (PVS) is a rare and often lethal condition in children. The optimal treatment for congenital and postoperative PVS is unknown. Methods and Results: We compared outcomes of conventional balloon angioplasty performed for PVS from 1999 to 2003 against cutting balloon angioplasty performed from 2004 to 2007. A total of 100 previously undilated pulmonary veins in 54 patients were studied: 48 veins dilated with conventional balloons and 52 with cutting balloons. Acute results included significantly reduced gradients and increased lumen diameters with both treatments. Acutely, cutting balloon angioplasty and conventional angioplasty yielded similar relative reduction of the PVS gradient (median 78% vs. 63%, P = 0.08) and increase in lumen diameter (median 77% vs. 59%, P = 0.07). There was one procedural death of a critically ill infant, and four cardiac arrests, but no adverse events necessitating surgical intervention. Survival free from reintervention was poor in both groups, and shorter in the cutting balloon group (73% at 1 month, 11% at 6 months, and 4% at 1 year) than in the conventional angioplasty group (77% at 1 month, 35% at 6 months, and 23% at 1 year; P = 0.01). Conclusions: Both conventional and cutting balloon angioplasty were effective at decreasing gradient and increasing lumen size acutely in patients with congenital and postoperative PVS, but reintervention was common with both treatments. Both methods of angioplasty provided limited benefit, and neither was curative for this complex disease.

Catheterization and Cardiovascular Interventions 75:1084–1090 (2010)

Conventional versus Cutting balloon

- <5 yrs of age with congenital or postop PVS
- Conventional balloon 1999~2003 vs cutting balloon 2004~2007
- Total 100 previously undilated PV in 54 pts
- 48 veins dilated with conventional balloons, 52 with cutting balloons

Conventional versus Cutting balloon

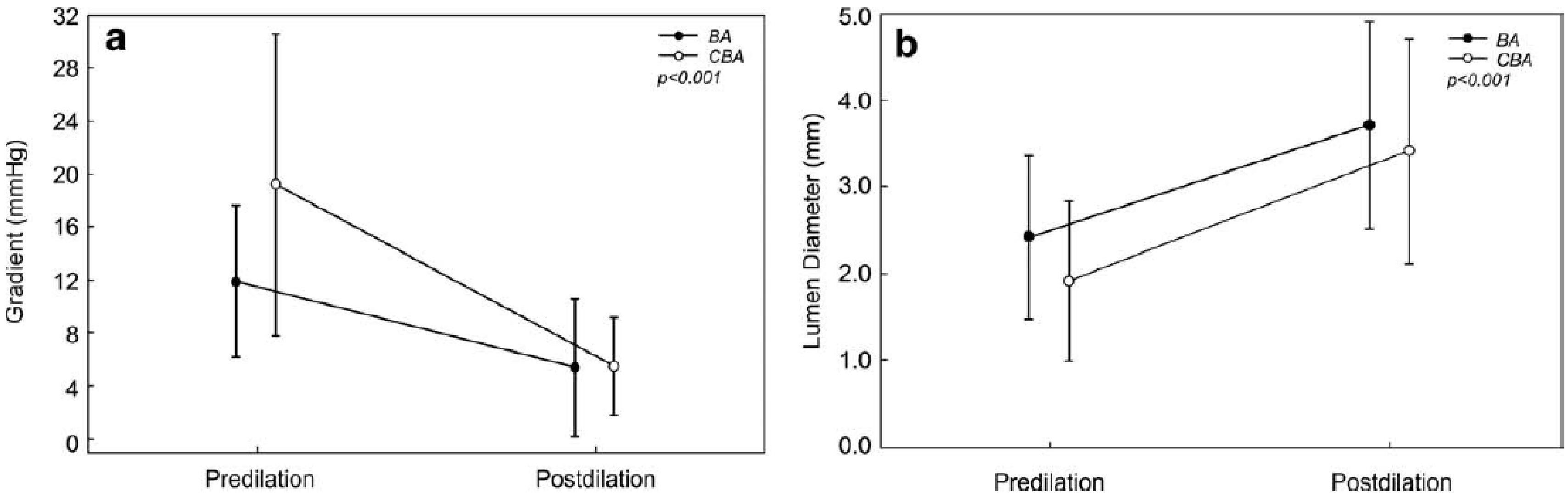


Fig. 1. **(a) PVS gradients before and after angioplasty with cutting balloons (CBA) or conventional balloons (BA). (b) MLD of stenotic pulmonary veins before and after angioplasty with cutting balloons (CBA) or conventional balloons (BA).**

Acutely, cutting balloon angioplasty and conventional angioplasty yielded similar relative reduction of the PVS gradient (median 78% vs. 63%, P=0.08) and increase in lumen diameter (median 77% vs. 59%, P=0.07).

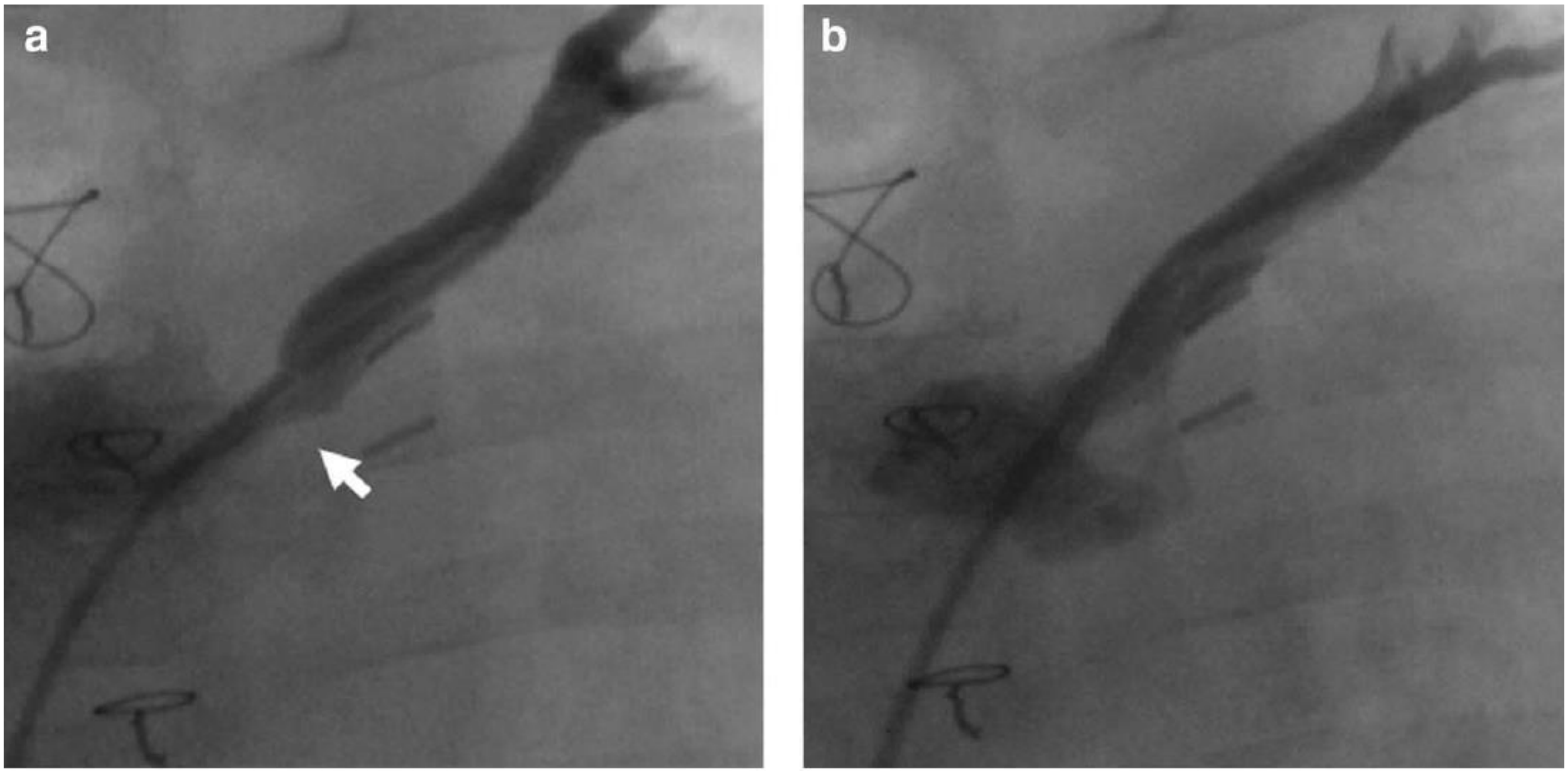


Fig. 2. Angiograms in the stenotic left upper pulmonary vein (a) before and (b) after conventional balloon angioplasty. The white arrow indicates the focal stenosis prior to dilation.

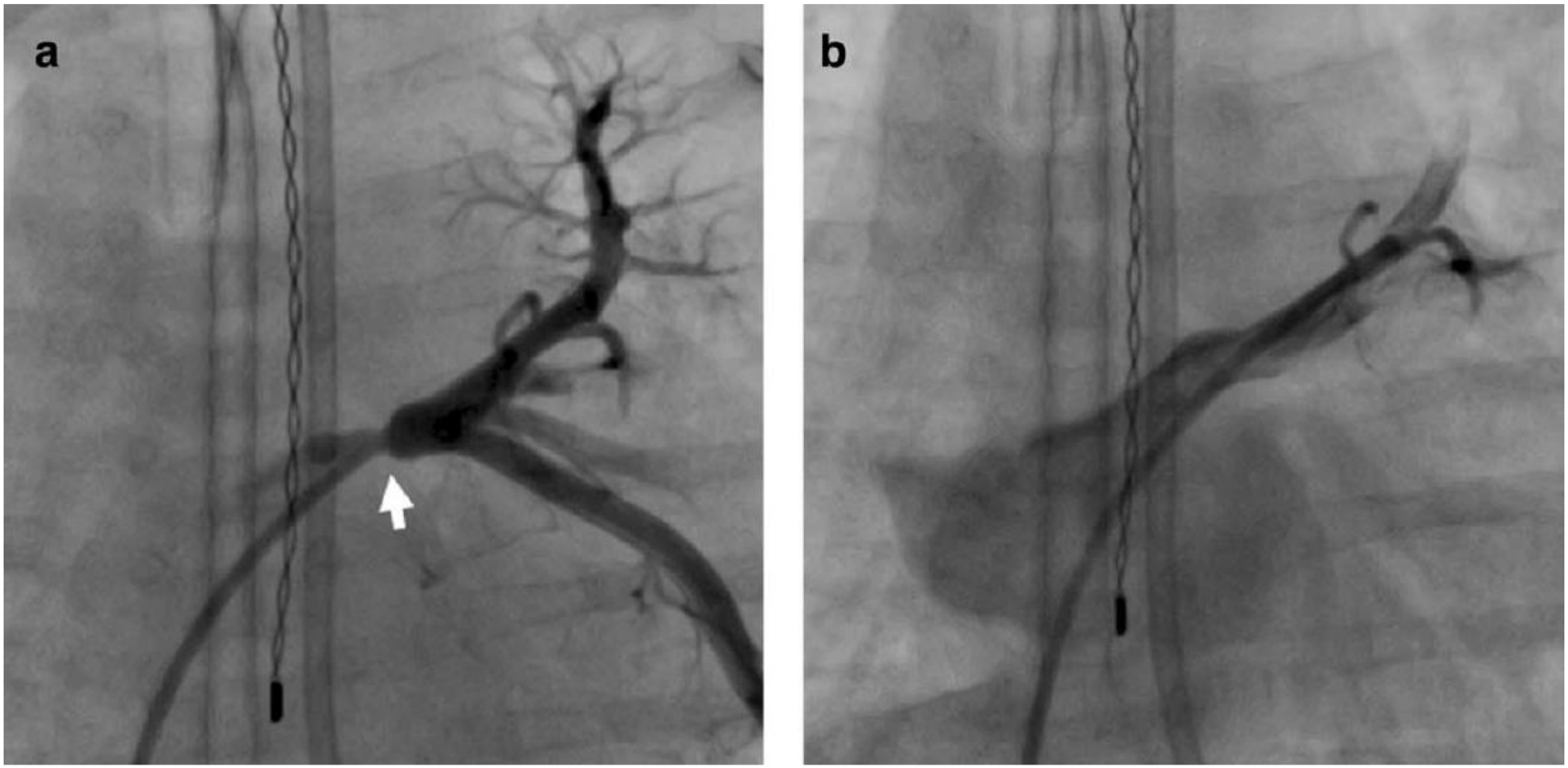


Fig. 3. Angiograms in stenotic common left pulmonary vein (a) before and (b) after cutting balloon angioplasty. The white arrow indicates the focal stenosis prior to dilation.

Conventional versus Cutting balloon

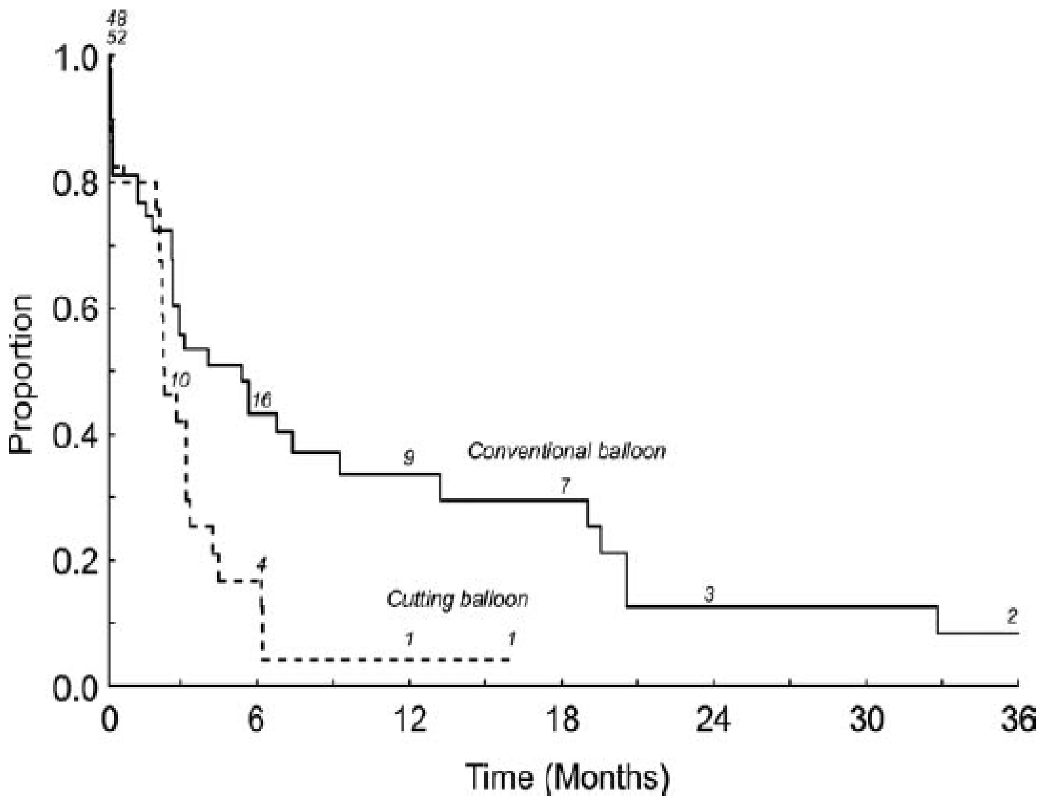


Fig. 4. Kaplan–Meier curve depicting freedom from reintervention on individual pulmonary veins after angioplasty with conventional or cutting balloons.

Survival free from reintervention was poor in both groups, and shorter in the cutting balloon group (73% at 1 month, 11% at 6 months, and 4% at 1 year) than in the conventional angioplasty group (77% at 1 month, 35% at 6 months, and 23% at 1 year; P=0.01).

Conventional versus Cutting balloon

DISCUSSION

Transcatheter Therapy for PVS

- PVS is a progressive disease and, although conventional and cutting balloon angioplasty may provide temporizing therapy in patients who develop respiratory symptoms from reobstruction, no known intervention has been shown to stop the disease.
- PVS persists and continues to progress despite interventions in the operating room or the catheterization laboratory.

Cryo-balloon angioplasty

Cryo-Balloon Angioplasty for Pulmonary Vein Stenosis in Pediatric Patients

Michael A. Bingler · Jeffrey R. Darst · Thomas E. Fagan

Pediatr Cardiol (2012) 33:109–114

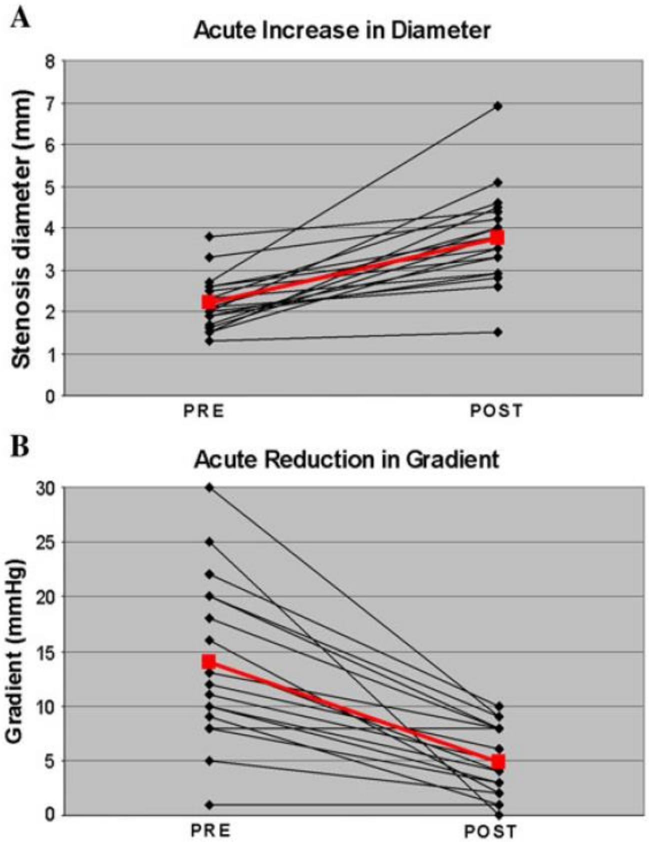


Fig. 1 Acute relief of stenosis. **a** Pre- and post-CbA PV stenosis diameter (mean shown in *red*). **b** Pre- and post-CbA mean gradient across stenotic PV (group mean shown in *red*)

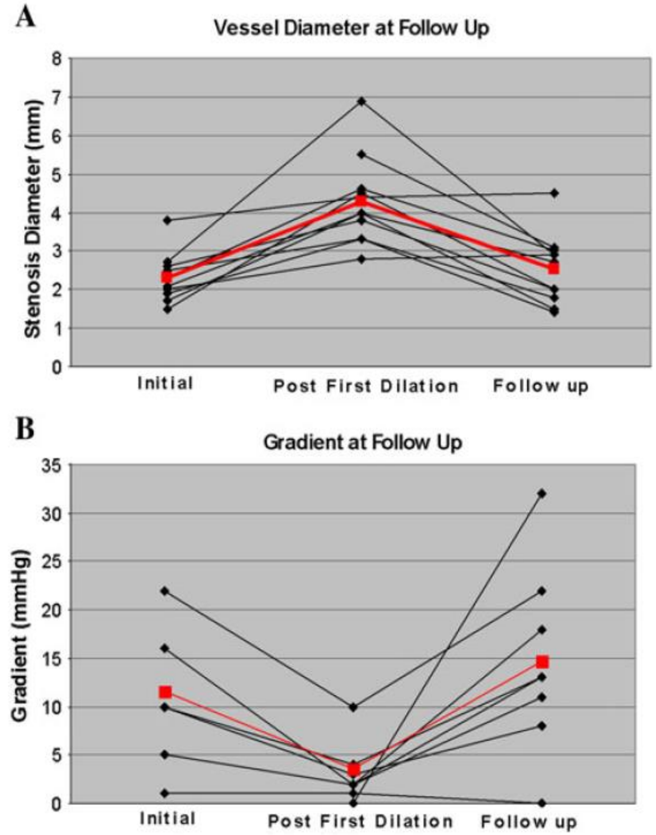


Fig. 2 Follow-up data. **a** Initial, post-CbA, and follow-up vessel diameters (mean shown in *red*). **b** Initial, post-CbA, and follow-up mean gradients (mean shown in *red*)

8/13 pt re-cath at mean 5.6 mo later

Stent implantation

CASE REPORT

Endovascular stent placement for pulmonary venous obstruction after Mustard operation for transposition of the great arteries

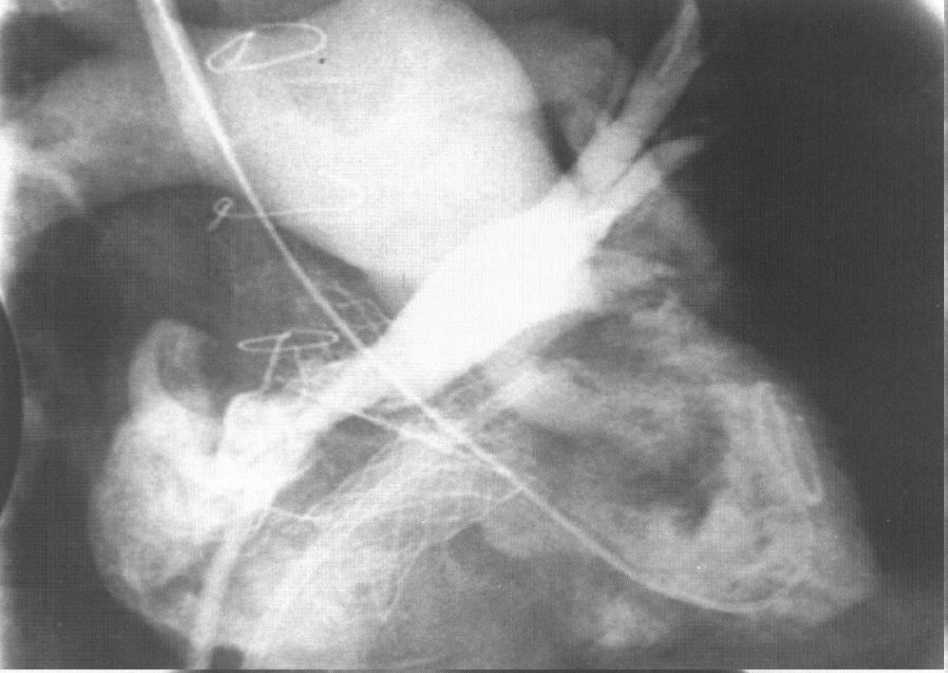
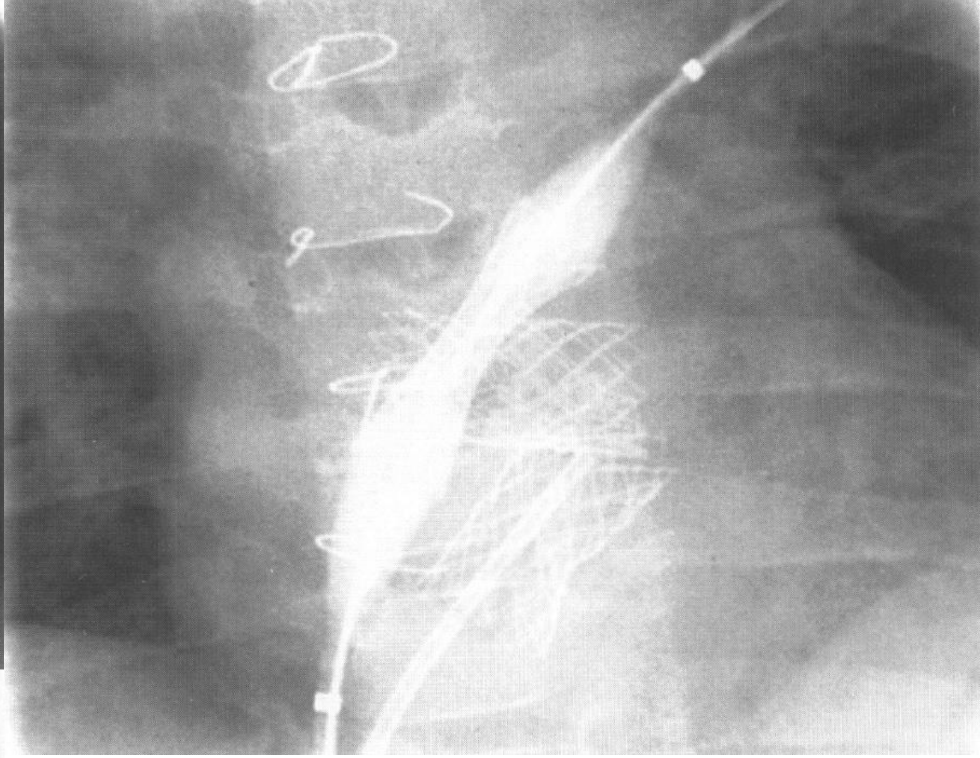
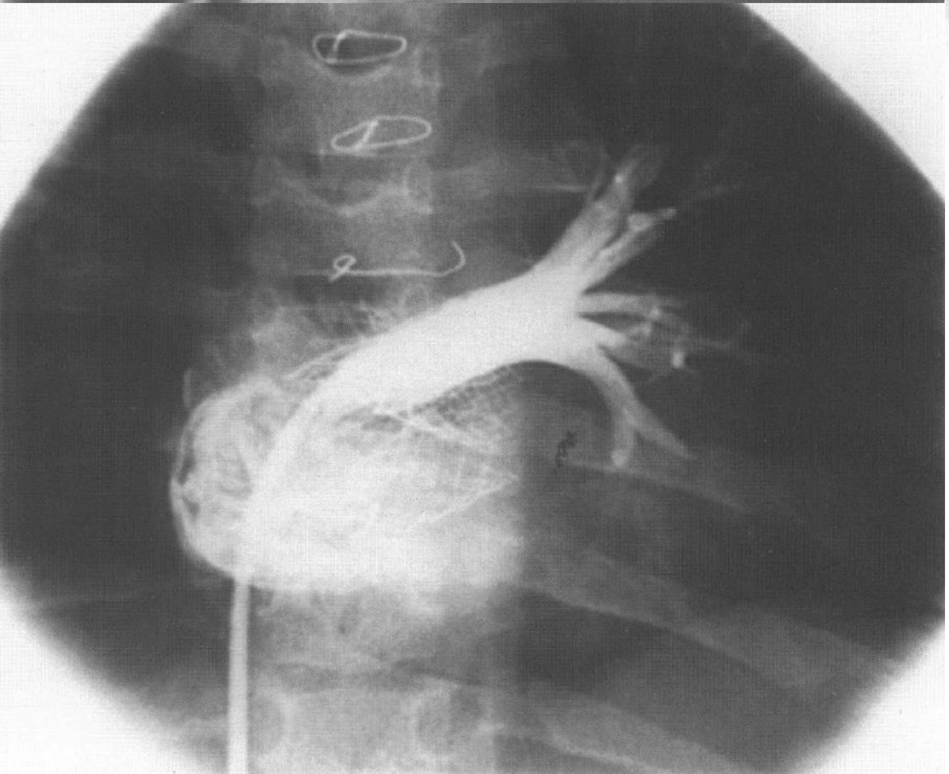
Jassim M Abdulhamed, Saad A Alyousef, Charles Mullins

Abstract
Stenting of the left pulmonary venous baffle obstruction was successfully performed in a 6 year old girl after the Mustard operation for transposition of the great arteries. She also had stent implantation in both the superior vena cava and inferior vena cava baffle junctions. These procedures were followed by sustained clinical improvement. Angiography showed that all three stents were fully patent a year after the procedure.

(*Heart* 1996;75:210–212)

A pulmonary artery angiogram was performed to visualise the pulmonary venous system. Because it suggested narrowing of the left pulmonary venous confluence we performed a detailed study of the pulmonary venous confluence.

A 7F transseptal sheath was manipulated through the right femoral vein to the systemic venous atrium. The sheath was pulled back slightly and the transseptal needle was directed anteriorly towards the pulmonary venous atrium, previously visualised during the levo phase of the pulmonary angiogram. The inferior wall of the baffle was punctured and the

Angiography
showed that all three stents were fully patent a year after the procedure.

Stent implantation

CLINICAL INVESTIGATIONS *Circ J* 2003; **67:** 187 – 190

Stent Implantation and Subsequent Dilatation for Pulmonary Vein Stenosis in Pediatric Patients

—— Maximizing Effectiveness ——

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Toshikatsu Yagihara, MD**; Shigeyuki Echigo, MD

The outcome of stent implantation and redilatation was investigated in 4 pediatric patients with 7 stenotic lesions of the pulmonary vein (PV), paying particular attention to late neointimal proliferation. The minimal diameter of the lesions increased from 0.8–3.6 (2.3±1.1) mm to 3.6–8.4 (5.1±1.6) mm immediately after stent implantation. Although the pressure gradient across the lesion was not measured in patient 4, in patients 1–3, it decreased from 4–34 (18±13) mmHg to 3–15 (7±4) mmHg. Except for case 4, who achieved a lesion diameter of 8.4 mm after initial stent dilatation, the other 6 lesions all restenosed within a few months, with an increasing pressure gradient. One patient with multiple PV stenoses associated with persistent severe pulmonary hypertension died suddenly. However, repeat dilatations were effective in all other lesions. Furthermore, in one lesion in patient 1, no serious restenosis developed for 20 months after the lesion was dilated up to 5.6 mm. Although further follow-up is mandatory, the final stent diameter within a vessel may determine long-term patency, and aggressive redilatation may be crucial for successful therapy of such a difficult disease. (*Circ J* 2003; **67:** 187 – 190)

Key Words: Dilatation; Patency; Pulmonary vein; Stenosis; Stents

Stent implantation

- 4 pts, 2 asso with TAPVR, 2 primary

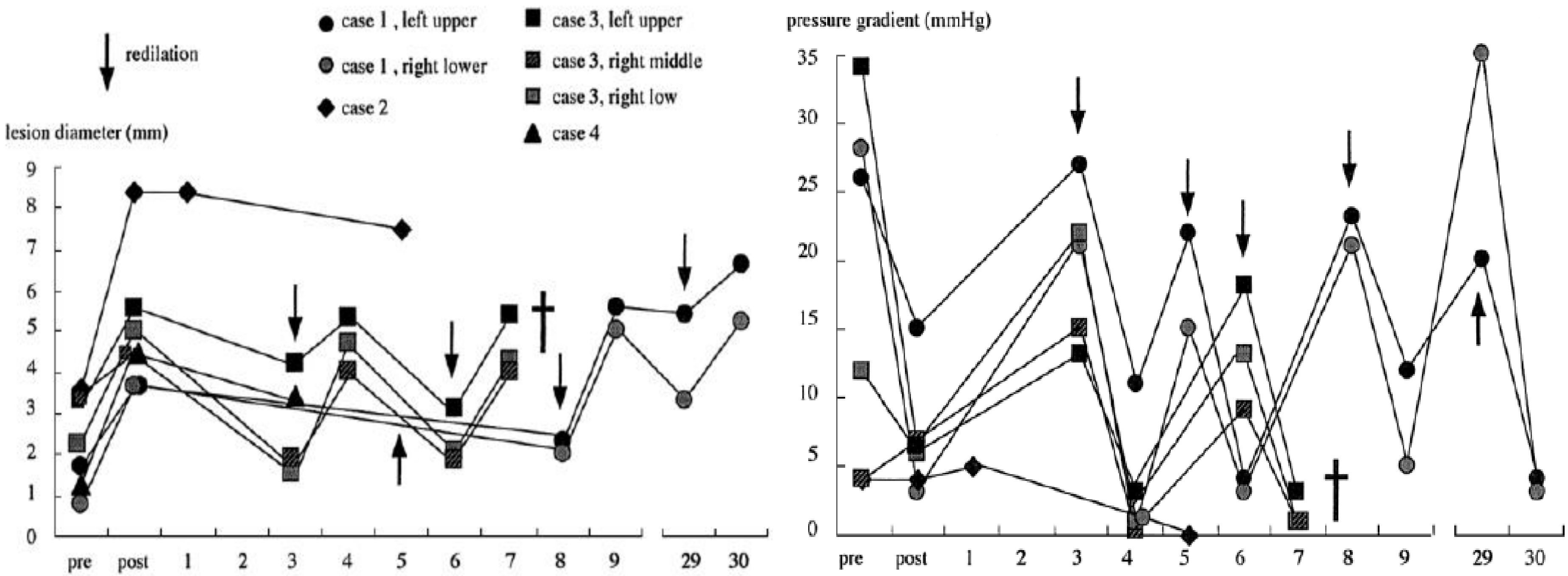

Fig 1. Changes in lesion diameter and pressure gradient.

Stent versus Balloon

Comparison of Stent Versus Balloon Angioplasty for Pulmonary Vein Stenosis Complicating Pulmonary Vein Isolation

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Dilation Versus Stenting for Pulmonary Vein Stenosis. ***Introduction:*** **Pulmonary vein stenosis (PVS) is a rare but significant complication of pulmonary vein isolation (PVI). Dilation and stent angioplasty have been described but not compared.**

Methods and Results: **All percutaneous interventions for PVS complicating PVI between December 2000 and March 2007 were reviewed. Acute success, defined as post-intervention stenosis ≤30%, and long-term outcome of dilation versus stent angioplasty were compared. Freedom from restenosis was defined as freedom from repeat intervention. Overall outcome for all interventions was examined. We studied 34 patients with 55 stenotic veins followed for a mean of 25 months. Dilation was performed in 39 veins and stenting in 40 veins (16 primarily, 24 after dilation restenosis). Acute success and restenosis rates were 42% and 72% for dilation versus 95% ($P < 0.001$) and 33% for stenting. Time to restenosis was greater for stent angioplasty ($P = 0.003$). Stents ≥10 mm in diameter had lower restenosis than smaller stents. Risk factors for restenosis included small reference vessel diameter and longer time from PVI to intervention for PVS. All but two patients experienced improvement (n = 10) or resolution of symptoms (n = 22). The mean percent stenosis decreased from 82% to 21% for the entire cohort and mean flow to the lung quadrant increased from 10% to 17%.**

Conclusion: **Stent angioplasty results in less restenosis than dilation, particularly for stents ≥10 mm. Early referral may improve long-term patency by minimizing reference vessel atrophy. Most patients with PVS post-PVI can be improved symptomatically with catheter intervention.** *(J Cardiovasc Electrophysiol, Vol. 19, pp. 673-678, July 2008)*

Stent versus Balloon

TABLE 1

Patient Characteristics (n = 44)

Age	53 ± 11
Sex	Male = 31, Female = 13
Affected pulmonary vein	LU = 32, LL = 28, RU = 13, RL = 7
Symptoms	
Dyspnea on exertion	37
Dyspnea at rest	2
Dry cough	14
Hemoptysis	10
Pleuritic chest pain	6
None	3
Mean number of catheterizations per patient	1.6
Time from last PVI to first PVS intervention (months)	11.5
Mean follow-up post-PVS intervention (months) (n = 34)	25 ± 21

LU = left upper; LL = left lower; PVI = pulmonary vein isolation; PVS = pulmonary vein stenosis; RU = right upper; RL = right lower.

Stent versus Balloon

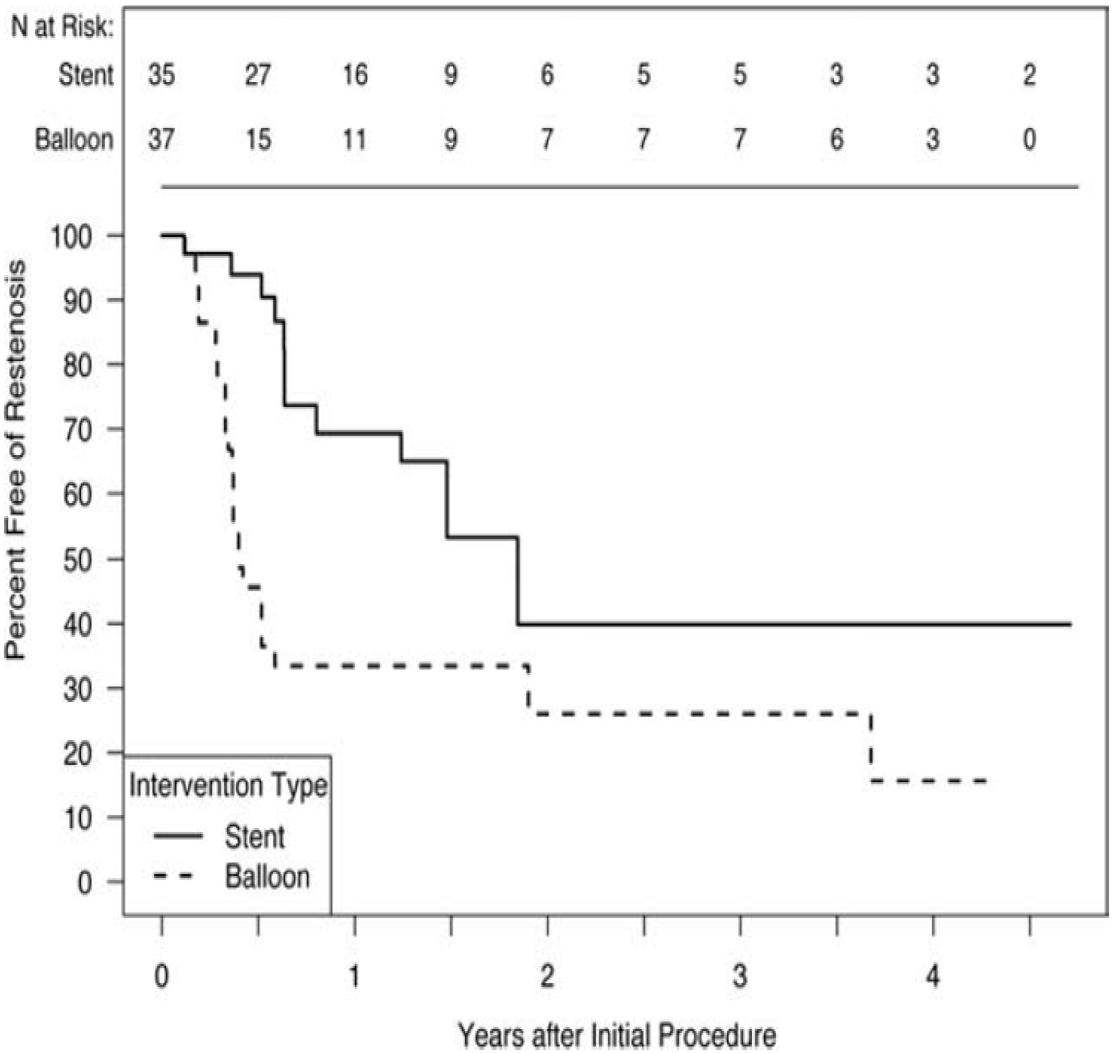

Figure 2. *Time free from restenosis for stented and balloon dilated veins. (Hazard ratio for balloon dilation 2.6, 95% confidence interval 1.4–4.8, P = 0.003).*

Stent versus Balloon

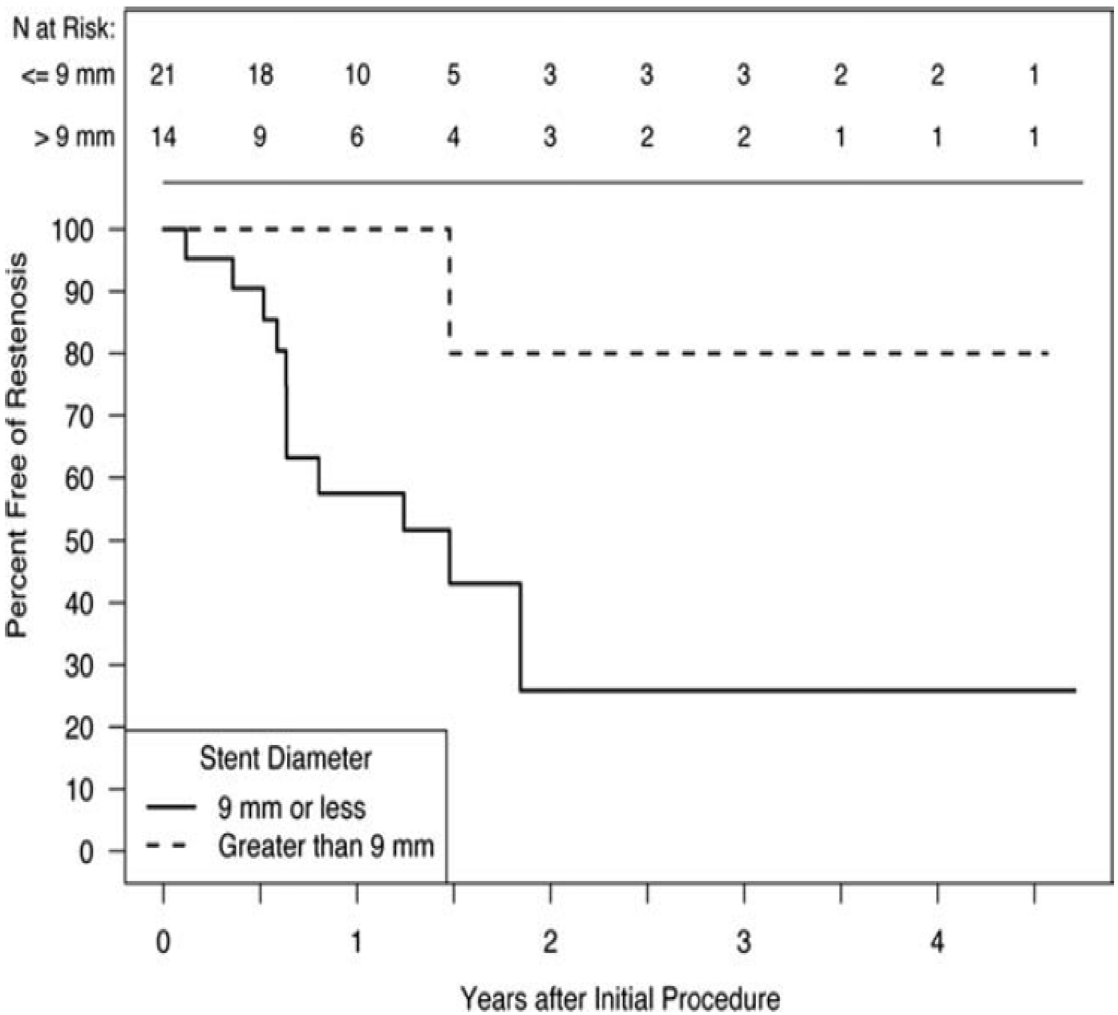

Figure 3. *Time free from restenosis for veins stented with larger stents (>9 mm) versus smaller stents (≤9 mm). (Hazard ratio for stents ≤9 mm 6.8, 95% confidence interval 1.1–44.2, P = 0.043).*

Stent versus Balloon

Comparison of Stent Versus Balloon Angioplasty for Pulmonary Vein Stenosis Complicating Pulmonary Vein Isolation

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Stent angioplasty results in less restenosis than dilation, particularly for stents ≥10 mm.

Early referral may improve long-term patency by minimizing reference vessel atrophy. Most patients with PVS post-PVI can be improved symptomatically with catheter intervention. *(J Cardiovasc Electrophysiol, Vol. 19, pp. 673-678, July 2008)*

Stent implantation

Outcomes After Stent Implantation for the Treatment of Congenital and Postoperative Pulmonary Vein Stenosis in Children

Sowmya Balasubramanian, MD; Audrey C. Marshall, MD; Kimberlee Gauvreau, ScD; Lynn F. Peng, MD; Alan W. Nugent, MBBS; James E. Lock, MD; Doff B. McElhinney, MD

Background—Pulmonary vein stenosis (PVS) is a rare condition that can lead to worsening pulmonary hypertension and cardiac failure in children, and it is frequently lethal. Surgical and transcatheter approaches are acutely successful but restenosis is common and rapid.

Methods and Results—We reviewed outcomes among patients who underwent transcatheter pulmonary vein stent implantation for congenital or postoperative PVS at <18 years of age. A total of 74 pulmonary veins were stented with bare metal, drug-eluting, or covered stents in 47 patients. Primary diagnoses included PVS associated with anomalous venous return in 51%, PVS associated with other congenital cardiovascular defects in 36%, and congenital ("de novo") PVS in 13% of patients. Median age at the time of pulmonary vein stent implantation was 1.4 years. During a median cross-sectional follow-up of 3.1 years, 21 patients died. Estimated survival was 62±8% at 1 year and 50±8% at 5 years after pulmonary vein stent implantation. Stent placement acutely relieved focal obstruction in all veins. Of the 54 stents reexamined with catheterization, 32 underwent reintervention. Freedom from reintervention was 62±7% at 6 months and 42±7% at 1 year. Stent occlusion was documented in 9 cases and significant in-stent stenosis in 17 cases. Stent implantation diameter ≥7 mm was associated with longer freedom from reintervention (hazard ratio, 0.32; *P*=0.015) and from significant in-stent stenosis (hazard ratio, 0.14; *P*=0.002). Major acute complications occurred in 5 cases.

Conclusions—Transcatheter stent implantation can acutely relieve PVS in children, but reintervention is common. Larger stent lumen size at implantation is associated with longer stent patency and a lower risk of reintervention. (*Circ Cardiovasc Interv*. **2012;5:109-117.**)

Table 1. Demographics and Diagnostic Data

Patients	47
Female	22 (47%)
Diagnosis	
Congenital PVS	6 (13%)
Totally anomalous pulmonary venous connection	9 (19%)
Partially anomalous pulmonary venous connection	2 (4%)
Hypoplastic left heart syndrome	6 (13%)
Partially anomalous pulmonary venous connection	1
Cor triatriatum	2
Pulmonary atresia/intact ventricular septum	3 (6%)
Heterotaxy	10 (21%)
Other congenital heart disease*	11 (23%)
Prior pulmonary vein surgery	29 (62%)
Prior pulmonary vein catheterization	24 (51%)
Median age at diagnosis of PVS, y	0.6 (0.01–15.8)
Median age at first intervention for PVS, y	0.9 (0.02–20.8)
Median age at first PV stent, y	1.4 (0.02–20.8)
Pulmonary vein disease	47
Common orifice of veins	
One side	14 (30%)
Both sides	6 (13%)
At least 1 atretic branch at presentation	12 (26%)
Bilateral PVS	30 (64%)
Average No. of central pulmonary veins involved at first intervention	3.3±1.4
Pulmonary vein stented	74
Right-sided veins	28 (37%)
Left-sided veins	46 (63%)
Prior surgical intervention on stented vein	39 (53%)
Prior catheter intervention on stented vein	44 (59%)

PVS indicates pulmonary vein stenosis.

*Lesions include tricuspid atresia, double inlet/outlet left ventricle, L-loop transposition of the great arteries, unbalanced complete atrioventricular canal, and atrial/ventricular septal defect.

Stent implantation

Table 2. Stent Types and Characteristics in the Cohort

	Bare Metal Stents	Drug-Eluting Stents	Covered Stents
No. of stented veins	57	7	11
No. of patients	39	5	9
Stent length, mm*	12 (8–30)	10 (8–23)	15 (8–22)
Premounted stent	23	7	3
Stented veins			
Right	23	2	3
Left	34	5	8
Preintervention			
Pre-BD MLD, mm*	2.1 (0–14.7)	2.1 (1.0–2.6)	2.4 (1.5–2.7)
Pre-stent MLD, mm*	2.7 (0.5–11.3)	2.0 (1.0–3.2)	2.4 (1.5–7)
Postintervention			
Stent lumen diameter after implant, mm*	5.9 (3.0–20)	3.5 (2.6–4.5)	6.0 (5.0–11)

MLD indicates minimum luminal diameter.

*Data are presented as frequency or median (range).

Stent implantation

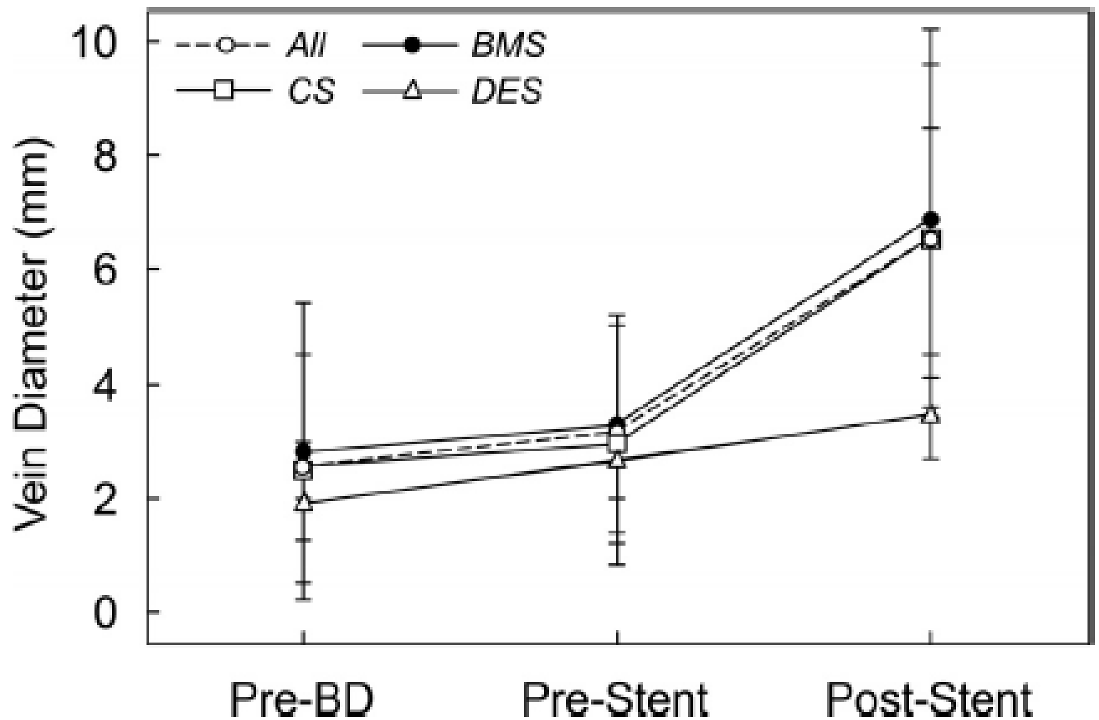


Figure 2. Mean change (±SD) in pulmonary vein diameter after balloon dilation (BD) and stent placement. Comparison of the entire cohort and selective comparison of bare metal stent (BMS) shows a significant improvement in luminal diameter after BD ($P<0.001$) and after stent implantation ($P<0.001$). In veins treated with covered stents (CS) and drug-eluting stents (DES), there was a statistically significant improvement in luminal diameter only after stent implantation ($P<0.001$, $P=0.01$, respectively).

Stent implantation

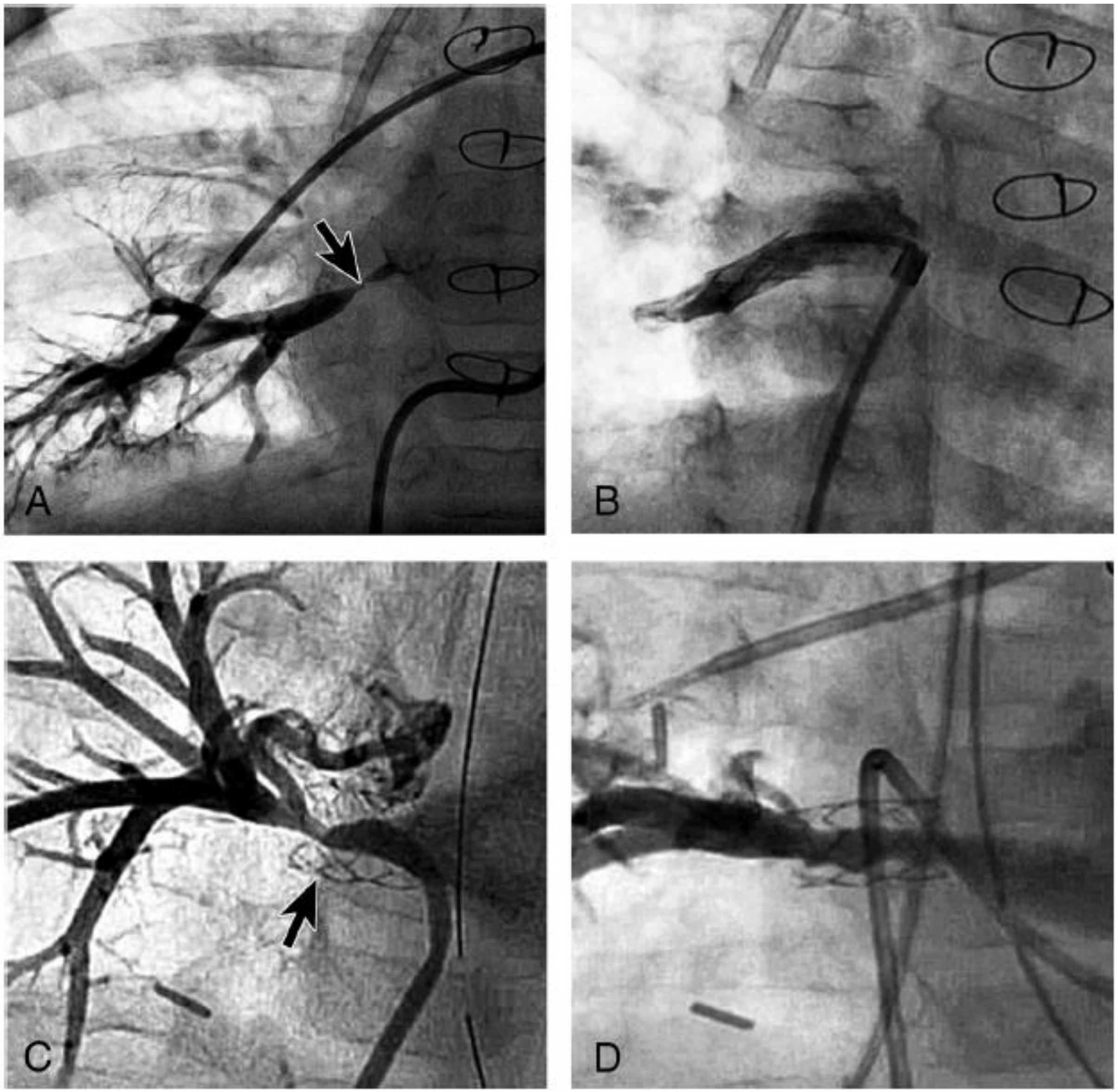


Figure 3. Representative angiogram in a patient with postoperative discrete stenosis (**arrow**) in the right lower pulmonary vein (**A**). Discrete stenosis is relieved with successful deployment of a 12-mm premounted Palmaz Genesis stent (**B**). Concentric in-stent narrowing (**arrow**) along the length of the stent (**C**) and at the pulmonary vein end of the stent (**D**) are seen at follow-up catheterization at 1 and 1.5 months, respectively.

Stent implantation

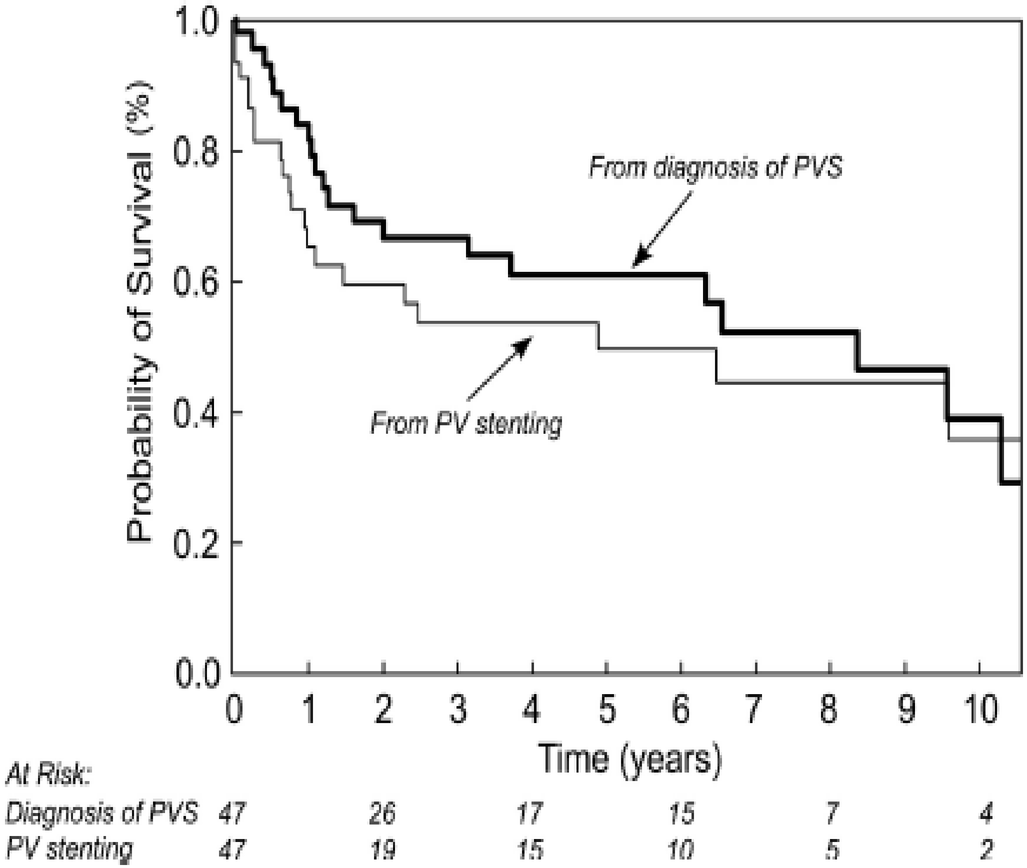


Figure 4. Kaplan-Meier curves depicting survival among the entire cohort (n=47) following diagnosis of pulmonary vein stenosis (PVS) and after stent implantation.

- Survival from the time of Dx of PVS 81±6% at 1 year, 66±8% at 2 years, and 60±8% at 5 years
- Survival from the time of first stent placement was 62±8% at 1 year, 57±8% at 2 years, and 50±8% at 5 years

Stent implantation

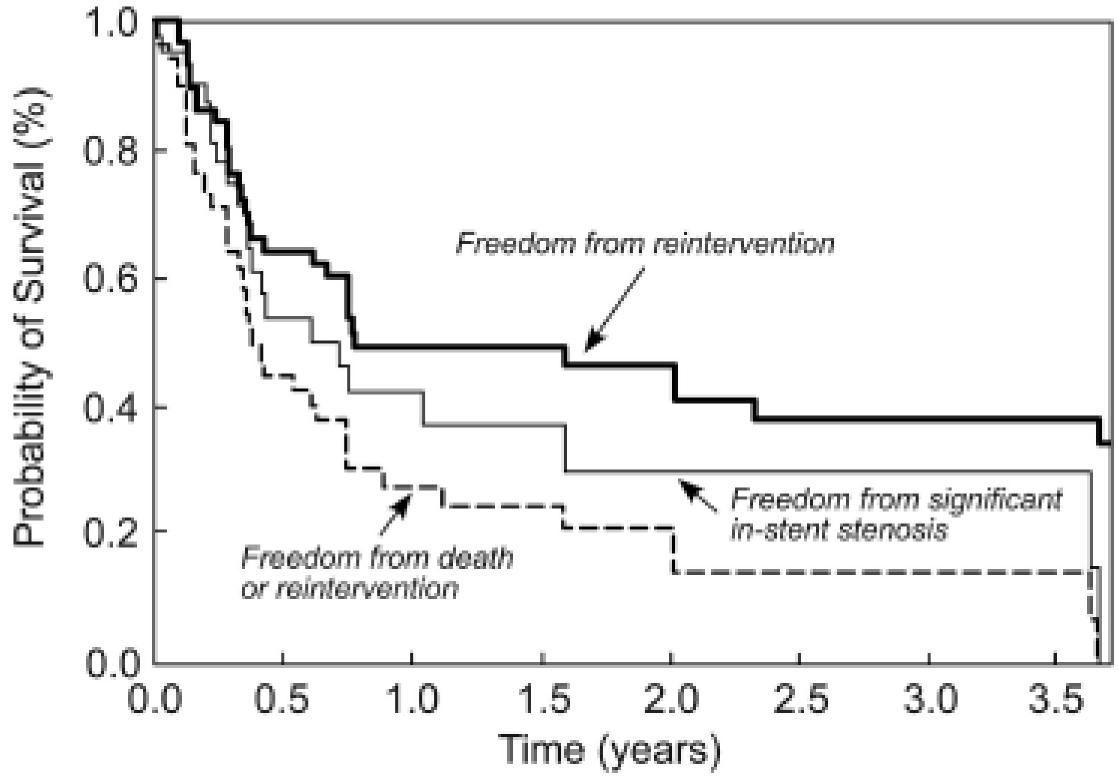
Table 3. Follow-Up Data by Stent Type

	Entire Cohort (n=54)*	Bare Metal Stents (n=43)*	Drug-Eluting Stents (n=6)*	Covered Stents (n=6)*
Follow-up duration, y	1 (0–14)	1 (0–14)	0.7 (0.2–4.1)	1.6 (0–10)
Complete occlusion	9	8	1	0
Lumen-to-stent diameter ratio	0.8 (0–1.0)	0.8 (0–10)	0.8 (0.5–1.0)	0.3 (0.3–0.5)
Severe, L:S <0.5	8 (18%)	6 (17%)	1 (17%)	3 (100%)
Moderate, L:S 0.5–0.7	9 (20%)	7 (19%)	1 (17%)	0
Mild, L:S 0.71–0.9	7 (16%)	5 (14%)	2 (33%)	0
None, L:S >0.9	20 (45%)	18 (50%)	2 (33%)	0
Pattern and location of narrowing				
Concentric	21	15	4	3
Eccentric	3	3	0	0
Location				
PV end	3	1	1	1
Middle of stent	4	2	1	1
Atrial end of stent	4	3	1	0
Along length of stent	13	12	1	1

L:S indicates lumen-to-stent diameter ratio; PV, pulmonary vein.

*Quantification of in-stent narrowing: entire cohort (n=44), bare metal stents (n=36), drug-eluting stents (n=6), and covered stents (n=3).

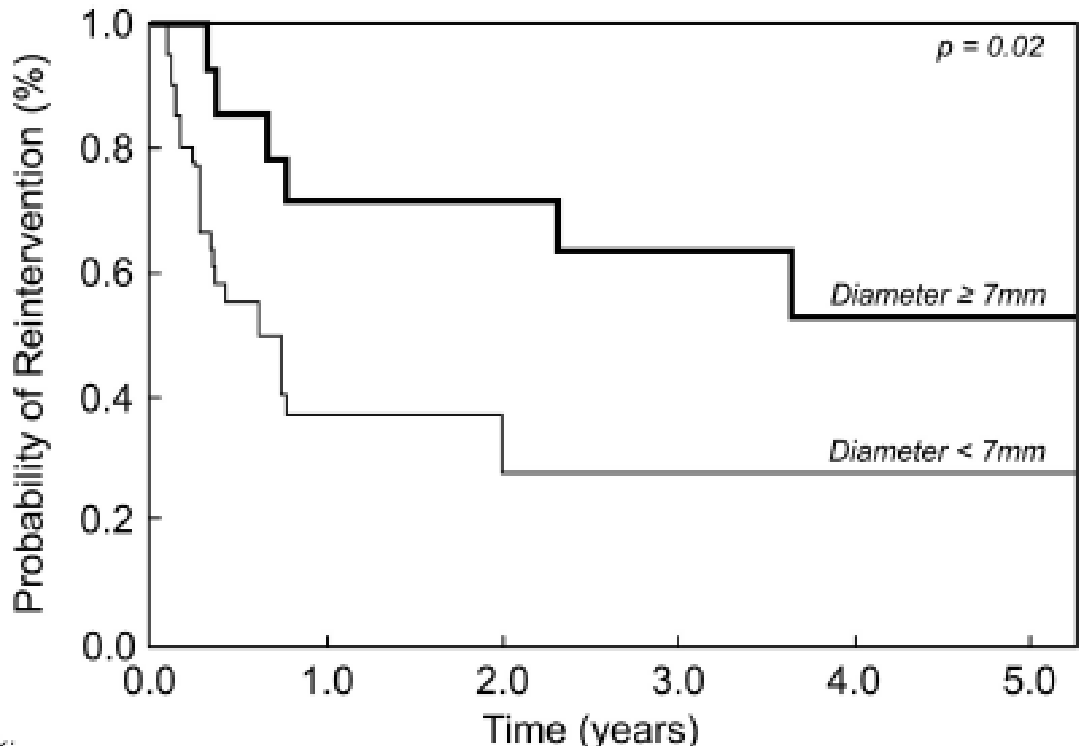
Stent implantation



At Risk:								
Reintervention	74	32	18	17	16	12	11	10
In-stent stenosis	44	14	7	4	3			
Death or reintervention	74	31	22	20	19	19	16	

Figure 5. Kaplan-Meier curves depicting freedom from re-intervention on the stented pulmonary vein freedom from diagnosis of stent occlusion or severe in-stent stenosis, and combined freedom from death or reintervention.

Stent implantation



At Risk:					
Lumen < 7mm	54	9	7	5	4
Lumen ≥ 7mm	20	9	8	6	5

Figure 6. Kaplan-Meier curves depicting freedom from reintervention on the stented pulmonary vein stratified by stent diameter at implantation. Stents implanted with a narrowest diameter ≥7 mm had a significantly (*P*=0.02) longer freedom from reintervention than those with an implantation diameter <7 mm.

Stent implantation

WHAT IS KNOWN

- Intraluminal pulmonary vein stenosis is a progressive condition that is frequently lethal in children.
- Treatment approaches for relief of luminal stenosis are acutely successful, but with limited long-term benefit.

WHAT THE STUDY ADDS

- Although intravascular stents are acutely successful in the relief of luminal stenosis, the rates of restenosis are high.
- Stents implanted at a larger diameter appear to remain patent longer with lower risk of reintervention.

Stent implantation-covered stent

Catheterization and Cardiovascular Interventions 82:E617–E620 (2013)

Angioplasty of Acquired Pulmonary Vein Stenosis Using Covered Stent

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One of the most serious complications post-catheter ablation of atrial fibrillation is the development of pulmonary vein stenosis. Controversy currently exists about the optimal treatment approach. The use of balloons and larger stents (~10 mm) results in more optimal outcome than just balloon angioplasty alone; however, even with stent implantation, recurrent restenosis may occur in 30 to 50% of patients. We report the case of a 28-year-old man who developed recurrent left inferior pulmonary vein stenosis following radiofrequency ablation for atrial fibrillation. This was initially stented with good result but soon after developed restenosis and required balloon angioplasty. Following the third episode of restenosis, stenting of the pulmonary vein was performed using a covered stent. The pulmonary vein has remained patent for the last 5 years.

Key words: AF; catheter ablation; PVS; covered stent

Stent implantation-covered stent

Fig. 4. In-stent restenosis.

Fig. 5. Covered stent implanted with good result.

28x8-12 Jomed covered stent

Stent implantation-covered stent

Treatment of Pulmonary Vein Stenosis With Expanded Polytetrafluoroethylene Covered Stents

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Atrium expanded polytetrafluoroethylene covered stents were implanted in the stenotic pulmonary veins ($n = 5$) of three patients. Use of this device was feasible in infants and the procedure was well-tolerated without major complications. The majority (4/5) of covered stents remained patent for at least 3 months after implantation. Stents remain patent in the two surviving patients 6 months after deployment.

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7 × 16 mm iCast covered stent

Stent implantation-covered stent

TABLE I. Angiographic Data for Pulmonary Vein Size Before and After Covered Stent Implantation

Patient	PV	Initial angiogram (mm)	Initial stent midpoint (mm)	4-month stent midpoint (mm)	6-month stent midpoint (mm)	Patency at last catheterization (%)
1	RU	1.9	6.9	5.6	–	81
	RM	3.0	7.0	6.5	–	93
	RL	1.2	7.0	N/A[a]	–	N/A[a]
2	LL	1.6	6.3	5.7	4.9[b]	78
3	LU	2.7	6.9	6.7	6.3	91

LL, left lower; LU, left upper; PV, pulmonary vein; RL, right lower; RM, right middle; RU, right upper.
[a]Vessel thrombosed.
[b]Preangioplasty.
– Patient expired.

The majority (4/5) of covered stents remained patent for at least 3 months after implantation. Stents remain patent in the two surviving patients 6 months after deployment.
Long-term follow up is required but short-term results are encouraging.

Oral Sirolimus with stent

Treatment of Recurrent Pulmonary Vein Stenoses With Endovascular Stenting and Adjuvant Oral Sirolimus

Guilherme Bromberg-Marin, MD, **Sotirios Tsimikas,** MD, FSCAI, FACC, **and Ehtisham Mahmud,*** MD, FSCAI, FACC

The increasing use of radiofrequency catheter ablation for the cure of atrial fibrillation has led to iatrogenic pulmonary vein stenosis as a new clinical entity. The optimal diagnostic modality and treatment for pulmonary vein stenosis and restenosis remain unclear. We report the successful treatment of pulmonary vein restenosis following percutaneous balloon angioplasty, and for the first time, following surgical bovine pericardial patch angioplasty, with endovascular stenting and adjuvant oral sirolimus. Both patients remain asymptomatic at 1 year follow-up without evidence of restenosis.

Key words: pulmonary vein stenosis; stent; sirolimus; atrial fibrillation; restenosis

Catheterization and Cardiovascular Interventions 69:362–368 (2007)

Oral Sirolimus with stent

CASE 1

- 64 yr old man, AF, 2 RF catheter-based pulmonary vein isolation
- 4 months post-PVI, progressive DOE

Oral Sirolimus with stent

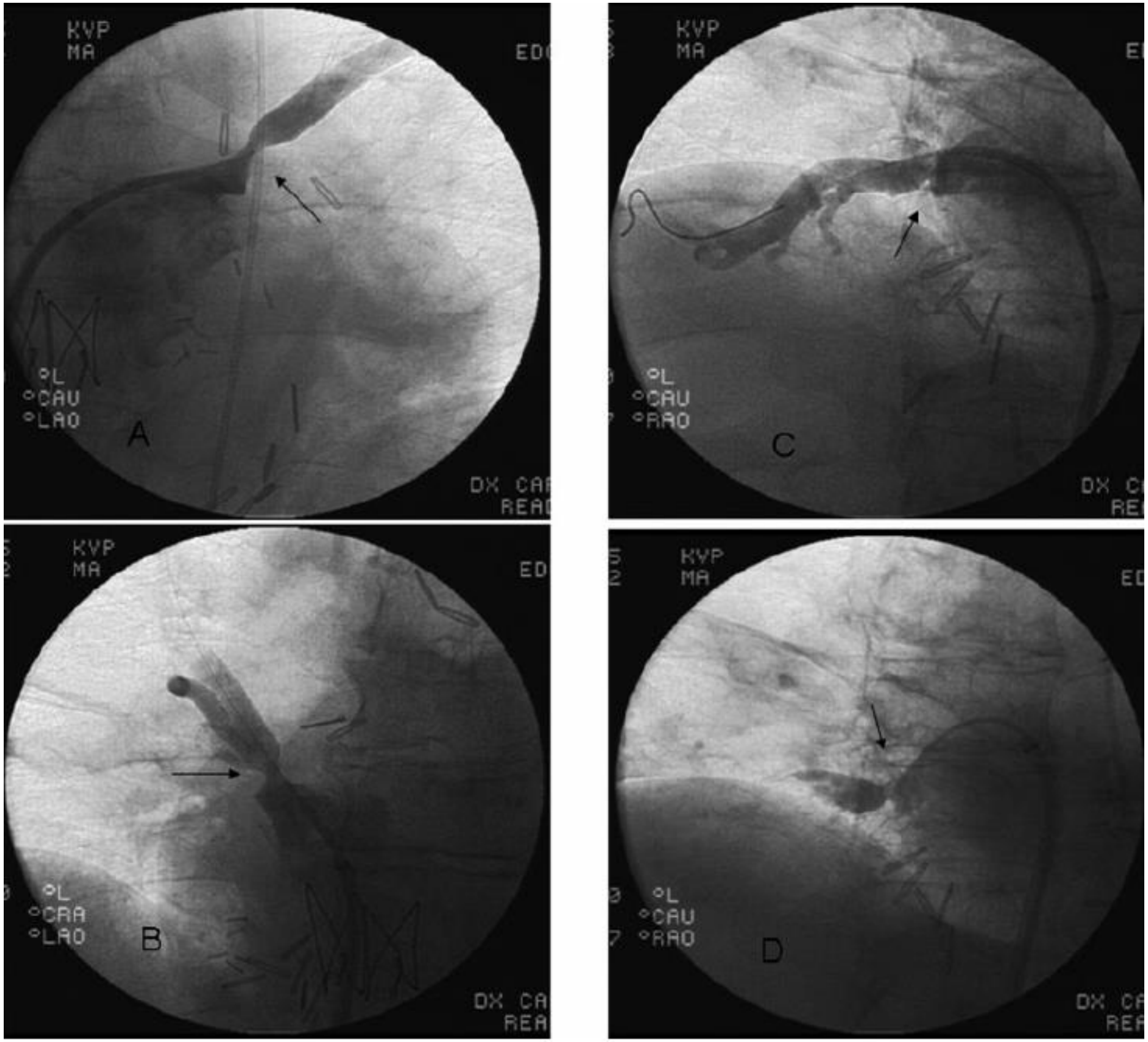

Fig. 2. Selective pulmonary vein angiography in the anteroposterior projection prior to stenting. Contrast angiography reveals severe proximal stenosis (arrows) of the (A) left upper, (B) right upper, (C) right middle, and (D) right lower pulmonary veins.

Oral Sirolimus with stent

CASE 1

- 64 yr old man, AF, 2 RF catheter-based pulmonary vein isolation
- 4 months post-PVI, progressive DOE
- Bovine pericardial patch angioplasty with reimplantation of all four PVs
- 3 months later, his symptoms recurred → recurrence of PVS in 3 of the 4 PVs

Oral Sirolimus with stent

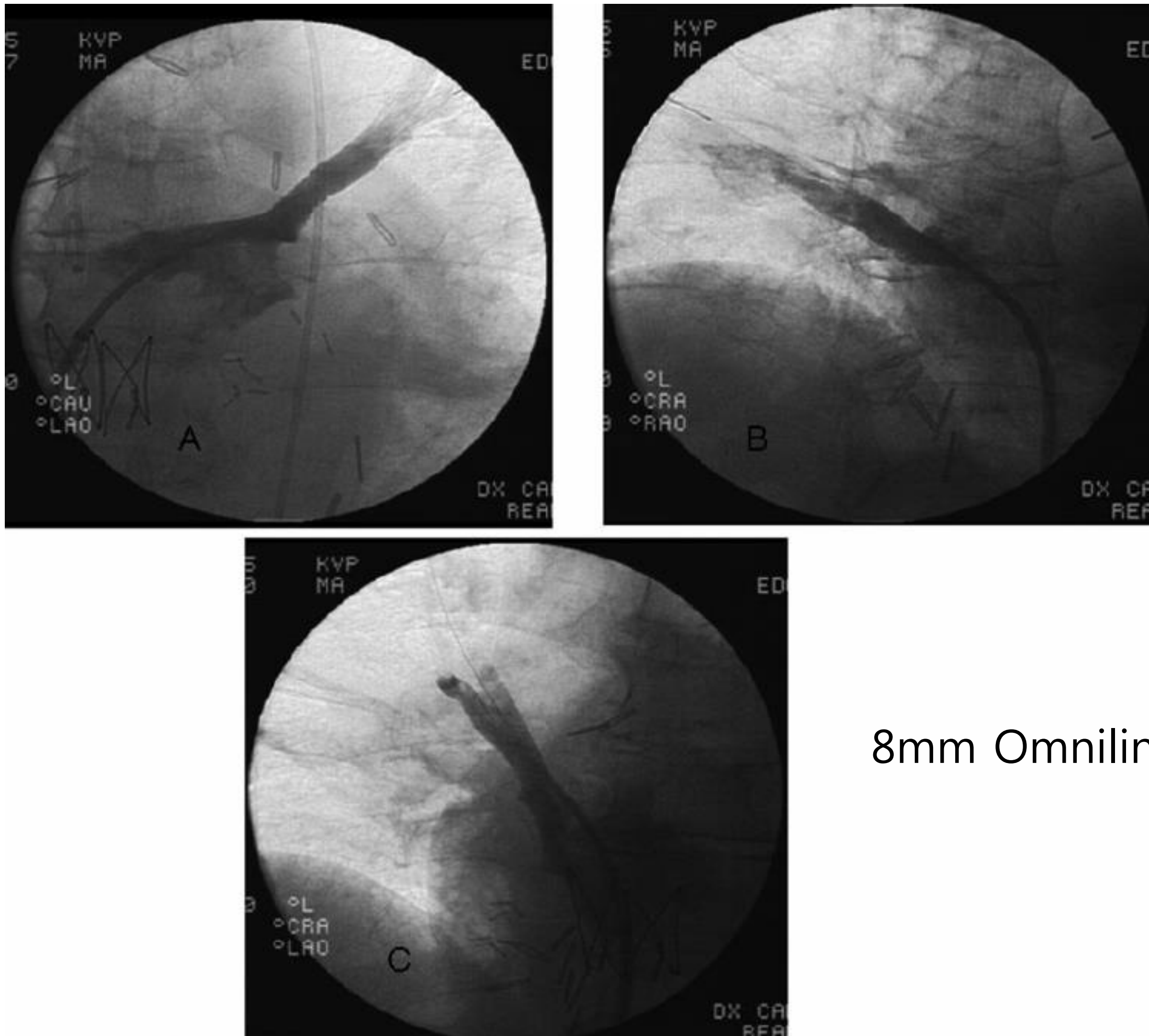

Fig. 3. Selective pulmonary vein angiography in the anteroposterior projection after stenting. Contrast angiography demonstrates widely patent stents in the (A) left upper, (B) right middle, and (C) right upper pulmonary veins without any residual stenosis.

8mm Omnilink stent

Oral Sirolimus with stent

- Empiric treatment with aspirin, clopidogrel, and warfarin for 3 months
- Oral sirolimus (2 mg daily for 30 days after a load of 5 mg) following the procedure with a weekly CBC
- He remains free of Sx, without recurrence of AF, and with excellent exercise capacity 1 year after PV stenting.

Oral Sirolimus with stent

CASE 2

- 46 yr old diabetic man, PVI and IVC/tricuspid isthmus RFA
- 6 mo later, progressive DOE and hemoptysis → balloon angioplasty
- 4 mo later, recurrent DOE and hemoptysis → 7 & 9mm stent in LUPV and LLPV
- Aspirin, clopidogrel, and warfarin for 3 months in addition to oral sirolimus (2 mg daily for 30 days after a load of 5 mg)
- Asymptomatic 18 mo after PV stenting
- Oral sirolimus has significant antirestenotic effects in pts undergoing coronary stent implantation for de novo or restenotic lesions

Oral Sirolimus with stent

Systematic Review of Effectiveness of Oral *Sirolimus* After Bare-Metal Stenting of Coronary Arteries for Prevention of In-Stent Restenosis

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Neointimal hyperplasia after percutaneous coronary intervention is a major determinant of in-stent restenosis (ISR). Drug-eluting stents (DES) mitigate neointimal hyperplasia and thereby lead to a lower rate of ISR compared with bare-metal stents (BMS). Recent studies have demonstrated that short-term use of oral sirolimus after BMS leads to a significant reduction in ISR. We therefore sought to do a systematic review of studies to determine the angiographic and clinical benefits of early short-term use of oral sirolimus after BMS of native coronary arteries. We conducted PubMed, Embase, Cochrane database review, and Web of Science search of studies comparing oral sirolimus after BMS to BMS alone or DES. Outcomes analyzed were ISR and target lesion revascularization (TLR) as well as major adverse cardiovascular events. A total of 488 patients from 4 studies were included in the review (2006 to 2010). Three studies, comparing BMS alone versus BMS plus oral sirolimus, demonstrated significant reduction in ISR in the oral sirolimus group. Two of these studies also demonstrated significant reduction in TLR at 6-12 month follow-up. The fourth study comparing BMS plus oral sirolimus versus DES showed a lower but nonsignificant reduction in TLR in addition to significant cost saving in the group treated with oral sirolimus. In conclusion, our systematic review demonstrates that early short-term systemic use of sirolimus after BMS resulted in a significant reduction in ISR and TLR. In addition, ISR rates were comparable to DES with the added benefit of cost saving. (Am J Cardiol 2013;112:1322−1327)

Oral Sirolimus with stent

- Sirolimus, a macrocyclic lactone, is a potent immunosuppressive and antimitotic agent, first approved in 1999 as an antirejection drug in renal transplant recipients.
- Total duration of sirolimus use: 30 days in 2 studies and 14 days in the other 2 studies
- Minor side effects in almost ¼: rash (2% to 3%), angioedema (0% to 2%), fever (0% to 5%), and gastrointestinal side effects (diarrhea 2.5% to 12%, enteritis 0% to 2%, gastritis 1% to 9%, constipation 0% to 4%, and mouth ulceration 2.5% to 16%)
- **Conclusion** : Early short-term systemic use of sirolimus after bare-metal stents resulted in a significant reduction in in-stent restenosis

Intrastent sonotherapy

CASE REPORT

Intrastent sonotherapy in pulmonary vein restenosis: a new treatment for a recalcitrant problem

C J McMahon, C E Mullins, H G El Said

Heart 2003;**89**:e6 (http://www.heartjnl.com/cgi/content/full/89/2/e6)

A 2 year old boy developed recurrent pulmonary vein stenosis after surgical repair of infradiaphragmatic pulmonary venous connection. He had required implantation of stents in the left and right sided pulmonary veins at 7 and 13 months of age, respectively. By 2 years of age he had undergone three catheterisation procedures and two surgical procedures to treat recurrent pulmonary vein stenosis. His right ventricular pressure was suprasystemic and catheterisation showed severe neointimal proliferation of both left and right sided stents. At this time the stents were dilated by balloon with simultaneous intrastent sonotherapy. Three months later the patient's clinical improvement was significant, his right ventricular pressure had decreased, and Doppler velocity had decreased across both left and right sided stents.

resistance of 31.5 Wood units. There was significant neointimal buildup in both left and right sided pulmonary veins. Two 10 mm intratherapeutic stents were implanted following a transseptal procedure increasing the diameter of the left pulmonary vein from 2 mm to 4.8 mm and the right upper pulmonary vein from 1.9 mm to 4.5 mm. The RV systolic and end diastolic pressures decreased from 174/4.16 mm Hg to 88/2.12 mm Hg and the RV to femoral arterial ratio from 1.4 to 0.9 after stent implantation.

At 13 months of age, he developed restenosis of both left and right sided pulmonary vein stents. Two additional 10 mm intratherapeutic stents were placed within the left pulmonary vein stents. The left pulmonary venous pressure decreased from 32 mm Hg to 13 mm Hg and RV systolic and end diastolic pressure decreased from 80/5 mm Hg to 65/8 mm Hg at the end of the intervention. The left sided venous stenosis increased from 2.6 mm to 6.2 mm. When he was 2 years old

Intrastent sonotherapy

- 2 yr old boy, PVS after IC-TAPVR repair
- Stent implantation in Lt PV at 7 mo, Rt PV at 13 mo
- By 2 yrs of age, 3 cath and 2 surgical procedures to treat recurrent PVS, the stents dilation with simultaneous intrastent sonotherapy

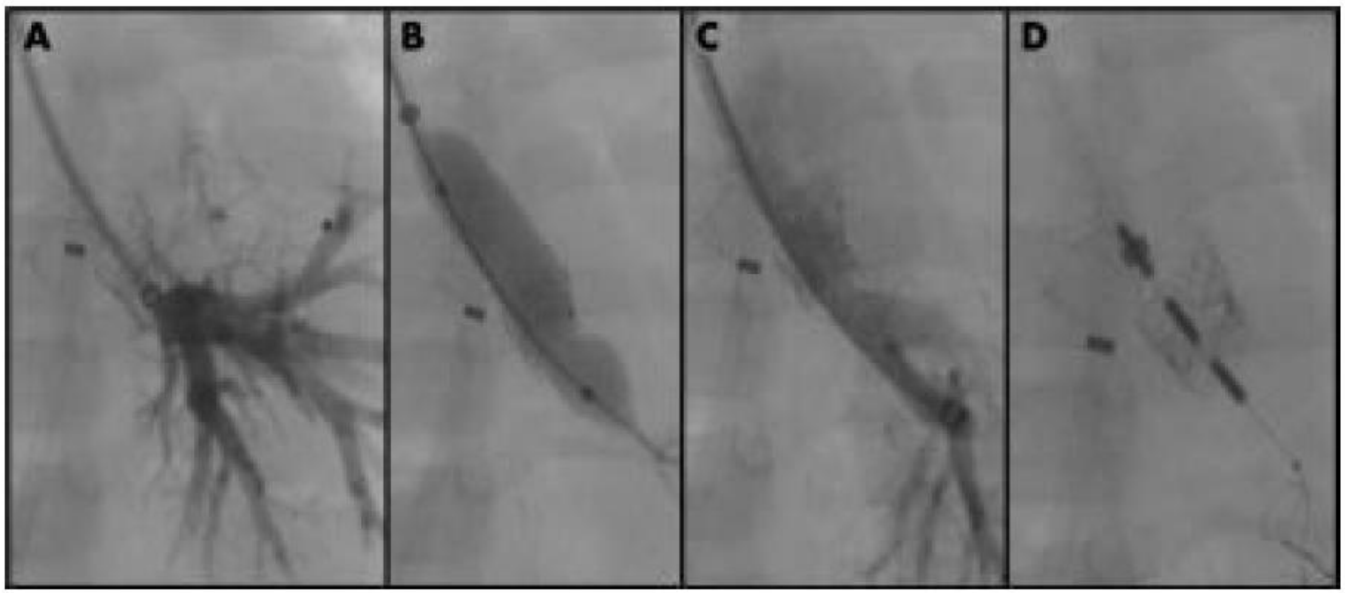
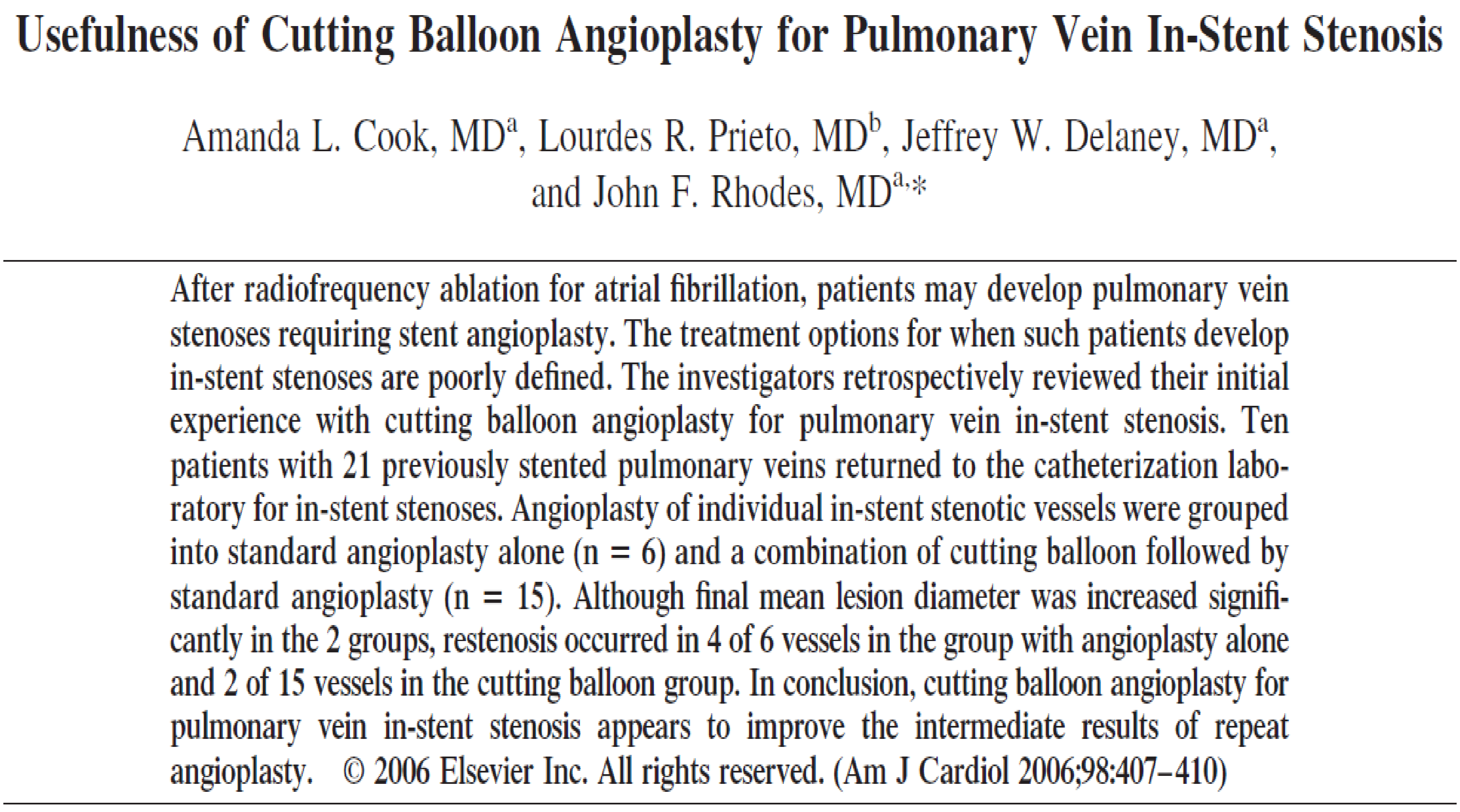


Figure 2 (A) Sheath within the stent in the left lower pulmonary vein. Contrast injection shows severe neointimal buildup with patent vessel diameter occluded by sheath. (B) Balloon dilatation of the stent. (C) Angiography following balloon dilatation. (D) Intrastent sonotherapy after balloon dilatation.

Intrastent sonotherapy

- 3 mo later significant clinical improvement
- The rationale
  - pathophysiology of neointimal growth
    - → Initial vessel damage
    - → proliferation of smooth muscle cells in the media
    - → their aggregation in the intima
    - → accumulates extracellular matrix
  - High intensity ultrasound
    - → acoustic cavitation disintegrating the smooth muscle skeleton
    - → prevents smooth muscle cell migration
- **A European multi-center trial investigating anti-restenotic effect of intravascular sonotherapy after stenting of de novo lesions (EUROSPAH: EUROpean Sonotherapy Prevention of Arterial Hyperplasia).** Int J Cardiovasc Intervent 2004;6(2):53-60
  - CONCLUSION: The use of sonotherapy following stent implantation in de novo lesions does not reduce intra-stent neointimal hyperplasia, or effect the angiographic restenosis rate compared to sham treatment.

Cutting balloon for in-stent stenosis



Usefulness of Cutting Balloon Angioplasty for Pulmonary Vein In-Stent Stenosis

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and John F. Rhodes, MD[a,*]

After radiofrequency ablation for atrial fibrillation, patients may develop pulmonary vein stenoses requiring stent angioplasty. The treatment options for when such patients develop in-stent stenoses are poorly defined. The investigators retrospectively reviewed their initial experience with cutting balloon angioplasty for pulmonary vein in-stent stenosis. Ten patients with 21 previously stented pulmonary veins returned to the catheterization laboratory for in-stent stenoses. Angioplasty of individual in-stent stenotic vessels were grouped into standard angioplasty alone (n = 6) and a combination of cutting balloon followed by standard angioplasty (n = 15). Although final mean lesion diameter was increased significantly in the 2 groups, restenosis occurred in 4 of 6 vessels in the group with angioplasty alone and 2 of 15 vessels in the cutting balloon group. In conclusion, cutting balloon angioplasty for pulmonary vein in-stent stenosis appears to improve the intermediate results of repeat angioplasty. (Am J Cardiol 2006;98:407–410)

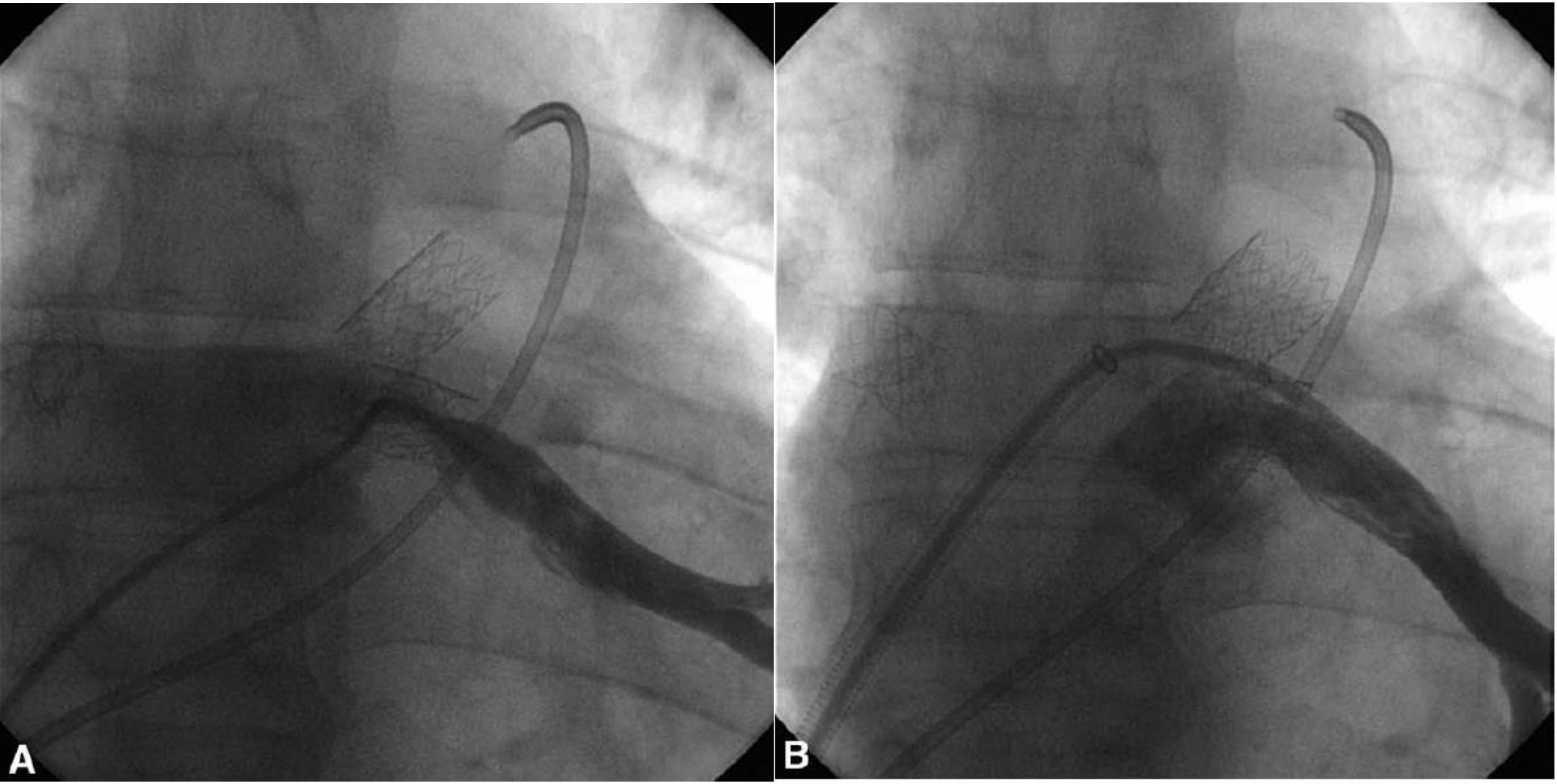

Figure 1. *(A)* In-stent stenosis is identified by angiography 6 months after primary stent angioplasty of the left lower pulmonary vein. The excessive intimal proliferation can be seen inside the pulmonary vein stent. *(B)* Final angiogram after successful cutting balloon angioplasty with a 6 × 10 mm balloon followed by standard angioplasty with a 12-mm Z-Med II balloon.

Cutting balloon for in-stent stenosis

Table 1
Catheterization data for in-stent stenosis angioplasty, group 1

Patient	PV	Angiogram (mm)	Sequential Standard Balloons	Angiogram (mm)
1	LU	1.6	6 → 10 mm	8.2
	LL	2.1	8 → 12 mm	10.8
	RU	2.2	8 → 12 mm	10.1
2	LU	0.8	5 → 8 mm	7.8
	LL	2.5	8 → 12 mm	11.2
3	LU	1.3	6 → 10 mm	9.5

LL = left lower; LU = left upper; PV = pulmonary vein; RL = right lower; RU = right upper.

Table 2
Catheterization data for in-stent stenosis angioplasty, group 2

Patient	PV	Angiogram (mm)	Cutting Balloon	Standard Balloon	Angiogram (mm)
1	LU	1.5	5 × 10 mm	8 mm	7.8
	LL	2.2	6 × 10 mm	10 mm	9.6
2	LU	0.8	4 × 10 mm	10 mm	8.4
	LL	2.5	6 × 10 mm	10 mm	9.2
3	LU	1.3	5 × 10 mm	10 mm	10.1
	LL	2.2	6 × 10 mm	10 mm	10.8
4	RU	1.8	5 × 10 mm	10 mm	9.8
	RL	0.7	4 × 10 mm	10 mm	8.1
5	LU	Occluded	Intervention not done		
	LL	1.2		10 mm	8.4
6	LU	2.5	6 × 10 mm	12 mm	11.0
	LL	2.6	6 × 10 mm	12 mm	10.1
	RU	2.0	6 × 10 mm	12 mm	10.5
7	LU	1.2	5 × 10 mm	12 mm	10.1
	LL	2.5	6 × 10 mm	12 mm	9.8
	RU	2.1	6 × 10 mm	12 mm	11.5

Restenosis occurred in 4 of 6 vessels in the group with angioplasty alone and 2 of 15 vessels in the cutting balloon group at median 30wks

Conclusion