

Twenty Years of Experience with Intra-operative Pulmonary Artery Stenting

Running Head: Intra-operative pulmonary artery stents

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ABSTRACT

Objectives: To describe our 20-year experience with intra-operative pulmonary artery stent placement and evaluate long-term patient outcomes, specifically the need and risk factors for re-intervention.

Background: Intra-operative pulmonary artery stent placement is an alternative to surgical patch arterioplasty and percutaneous angioplasty or stent placement to treat branch pulmonary artery (PA) stenosis.

Methods: We performed a retrospective review of all intra-operative pulmonary artery stents placed at our institution from 1994-2013. Patient and stent characteristics and outcome data were collected. Risk factors associated with re-intervention were identified using univariate cox regression analysis.

Results: Eighty-one PA stents were placed in 68 patients. The procedural complication rate was 4.4%. During a median follow-up period of 6 years (interquartile range (IQR) 0.9-12.7), 30 patients (44%) underwent re-intervention on the stented PA with a median time to first re-intervention of 2.6 years (IQR 0.7-4.4 years). The first re-intervention was surgical in 30% and catheter-based in 70%. Risk factors for re-intervention included age < 18 months (Hazard ratio [HR] 2.97, p=0.005) and body surface area < 0.47 m² (HR 3.20, p=0.003) at the time of stent implantation, and the presence of multiple aorto-pulmonary collaterals in patients with tetralogy of Fallot (HR 4.61, p=0.003).

Conclusions: Intra-operative PA stent implantation is a safe and effective alternative to percutaneous stent implantation and offers several advantages, including the ability to implant adult-size stents in small patients while avoiding injury to peripheral vessels, to position stents to facilitate future percutaneous stent re-dilation, and to access the PAs directly, which eliminates radiation exposure.

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INTRODUCTION

Branch pulmonary artery (PA) stenosis is a relatively common problem in congenital heart disease.

Percutaneous techniques have reduced the need for surgical pulmonary arterioplasty and are as effective as surgical arterioplasty while avoiding cardiopulmonary bypass (CPB) (1-3). However, many patients still require operative repair either due to the morphology of the stenosis, inadequate response to percutaneous techniques, small patient size prohibiting safe or effective percutaneous intervention, or the need for concomitant repair of other surgical defects (1). Re-intervention for recurrent stenosis after surgical pulmonary arterioplasty is required in 48-64% of patients and has not changed significantly over the last 40 years (2-5). Because of early restenosis, these patients can require multiple surgical or catheterization procedures early in childhood, exposing them to the risks of repeated sternotomy, CPB, and/or radiation, to name a few.

Intra-operative PA stent placement is an alternative approach. This procedure has been shown to be safe with excellent short-term efficacy (6-14). It can allow for implantation of stents that can be dilated to adult size that would be difficult to place percutaneously in small children, while avoiding ionizing radiation exposure from cardiac catheterization procedures. However, longer-term data on the outcomes of intra-operative PA stenting are limited (15).

We sought to describe our experience with intra-operative PA stent placement over the last 20 years and to examine long-term patient outcomes, specifically focusing on the incidence of and risk factors for re-intervention, due to recurrent PA stenosis.

MATERIALS AND METHODS

After receiving Institutional Review Board approval with waiver of informed consent, we performed a retrospective review of all intra-operative PA stents placed at our institution between January 1, 1994 and December 31, 2013. Patients were identified through review of the electronic medical record, cardiac

catheterization reporting systems, and surgical records. Any patient who underwent placement of an intra-operative PA stent was included. Patients were excluded if stent implantation was not attempted or if there was not sufficient documentation to know if stent implantation occurred intra-operatively. Patient data, procedural information (stent type, procedural success and complications), and follow-up data were collected. Procedural success was defined as placement of a stent without the need for removal during the operation.

Stent implantation technique:

All intra-operative PA stents were placed in the operating room on CPB. Minimal dissection of the vessels was performed for isolated stent implantation with retrograde flow within the vessel being managed with pump suckers as needed without obtaining distal vessel control. In the case of pulmonary arterioplasty followed by stent implantation, the PA was fully mobilized with distal control achieved when feasible. Stent diameter, length and position were determined based on pre-surgical angiograms obtained by cardiac catheterization. Stent diameter was determined by the size of the normal adjacent vessel (~1 mm larger than adjacent or distal PA diameter) and no more than 3 times the diameter of the narrowest stenotic PA segment. Whenever possible, stent length was chosen to avoid jailing side branches of distal vessels. Other than direct visual inspection, no other modality, including fluoroscopy, angiography or other visualization techniques (e.g., endoscopy) were utilized. Stent position was defined as ostial/proximal for stents placed prior to the first PA bifurcation and distal for stents placed after the first PA bifurcation. For stents placed in proximal or ostial locations, the proximal end of the stent was manually widened or “flared” into the main PA, helping to secure the stent in place and facilitating future access into the stent lumen during cardiac catheterization. Only balloon-expandable, bare metal stents were used, and whenever possible, medium and large diameter stents were selected (16).

Statistical Analysis:

Patient and stent characteristics and short- and long-term patient outcomes are described as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Freedom from re-intervention in overall and selected subgroups and overall survival were evaluated by Kaplan-Meier curves. Univariate and multivariable Cox regression analyses were performed to identify factors associated with re-intervention. Variables associated with re-intervention in the univariate analysis ($p < 0.1$) were incorporated into the multivariable analysis. Due to collinearity between age and body surface area at the time of initial stent implantation, only body surface area was included in the multivariable analysis. Hazard ratio (HR) and 95% confidence interval from the Cox regression were reported. A p -value < 0.05 was considered statistically significant. Analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics:

Eighty-one PA stents were placed in 68 patients (Table I). In the majority of patients (84%), stent implantation was performed as part of a procedure to repair or palliate another cardiac defect (e.g. conduit replacement). Tetralogy of Fallot (TOF) was the most common diagnosis (38%) and 11 patients (16%) had major aortopulmonary collateral arteries (MAPCA), representing 42% of the patients with TOF.

Intra-operative PA stents were most commonly placed in the left PA (59%) and to treat proximal stenoses (85%). Medium and large diameter bare metal stents were implanted in 97% of patients. PALMAZ XL Transhepatic Biliary Stent (58%, Cordis Endovascular Corporation, Santa Clara, California USA) and ev3 IntraStent® Mega™ LD Biliary Stent (29%, ev3 Endovascular, Inc. Plymouth, Minnesota USA) were utilized most frequently.

All patients had previously undergone at least one prior cardiac operation and all patients had undergone at least one prior cardiac catheterization. Twenty-four patients (35%) had undergone a prior PA

intervention, either surgical or catheter-based, on the same PA that received an intra-operative PA stent. Of these, 15 patients (22%) had undergone at least one prior surgical patch arterioplasty, and 3 patients (4.4%) had undergone more than 1 arterioplasty. In addition, 12 (18%) had previous transcatheter interventions, 3 of whom (4.4%) required multiple prior catheter interventions. In these 12 patients, the median time from catheterization to intra-operative stent placement was 91.5 days (IQR 21 days to 2.5 years), whereas the median time from cardiac catheterization (including diagnostic and interventional procedures) to intra-operative stent placement was 22 days (IQR 1-65 days) for the entire cohort of patients.

Intra-operative and Hospital Outcomes:

Stent implantation was acutely successful in all patients but one (99%). This patient developed a distal pulmonary artery laceration requiring immediate stent removal. The procedural complication rate was 4.4% (n=3) and all involved a PA injury requiring repair or patch augmentation.

At hospital discharge, 92% (54/59) of patients had either no or mild residual stenosis by echocardiogram when excluding patients with an unknown degree of residual stenosis (PAs not visualized or echocardiographic images unavailable) (Table II). Of the 9 patients without a sufficient echocardiogram, 6 underwent a cardiac catheterization between 3 days and 20 months after initial stent placement. In these patients, 4 had no stent stenosis and 2 had mild stent stenosis.

Follow-Up Patient Outcomes (Figure 1):

During a median follow-up period of 6 years (IQR 0.9-12.7), 30 patients (44%) underwent re-intervention on their intra-operatively placed PA stent(s) (Table III). The median time to first re-intervention was 2.6 years (interquartile range 0.7-4.4 years). The first re-intervention was a surgical procedure in 9 (30%) patients, with all undergoing intra-operative dilation of the existing stent, along with a concomitant surgery. No patient required subsequent surgical pulmonary arterioplasty of the stented PA. Only 1

patient underwent a surgical procedure for the sole purpose of treating PA stenosis. This patient had single ventricle physiology and because of persistent unilateral lung collapse in the early post-operative period, a lung ventilation perfusion scan was performed which showed no perfusion to unilateral and ipsilateral lung supplied by the stented PA. Therefore, the patient was taken back to the operation room 7 days after the primary surgery with intra-operative stent implantation and underwent surgical thrombectomy and stent dilation with good long term result. Percutaneous intervention was not attempted. The other 8 patients underwent surgery for other indications (conduit revision [n= 4], Fontan completion [n=2], Fontan takedown [n=1] and shunt revision [n=1]. All 8 patients were able to have the existing stent re-dilated.

The first re-intervention was a percutaneous procedure in 21 (70%) patients, which included balloon angioplasty of the existing stent in 14 and placement of a new stent(s) in 7. For the 7 patients who had new stents placed, the indication was in-stent stenosis (n=2), somatic growth (n=3), stenosis distal to the intra-operative placed stent (n=2), and unknown (n=1).

In the overall cohort, the majority of patients required re-intervention for in-stent stenosis (53%) and for somatic growth (30%). Of note, no patient required re-intervention for either surgical complication or stent fracture at the time of the first re-intervention.

The overall freedom from re-intervention was 83%, 74%, 51%, and 30% at 1, 2, 5, and 10 years, respectively (Figure 2). The freedom from surgical re-intervention was 95%, 93%, 85%, and 79% at 1, 2, 5, and 10 years, respectively.

In univariate cox regression analysis, several factors were associated with an increased risk of re-intervention (Table IV). These included age less than 18 months (HR 2.97, p=0.005; Figure 3A) and body surface area less than 0.47 m² (HR 3.20, p=0.003; Figure 3B) at the time of the initial stent

implantation, a cardiac diagnosis of TOF (compared to non-TOF patients, HR 2.36, $p=0.02$; Figure 3C) and the presence MAPCA (HR 3.56, $p=0.01$). On further examination, the increased hazard seen in the TOF group was driven by the presence of MAPCA, as only TOF patients with MAPCA had a significantly higher risk of re-intervention compared to non-TOF patients (HR 4.61, $p=0.003$; Figure 3D). There were no differences in the etiology, sidedness, or location of the pulmonary stenosis in terms of risk for re-intervention. Additionally, prior intervention to treat pulmonary stenosis was not associated with re-intervention. Multivariable analysis showed that cardiac diagnosis was independently associated with re-intervention, controlling for body surface area at the time of initial stent implantation and etiology of PA stenosis (Table V).

There were no deaths or long-term complications related to intra-operative stent placement. However, 6 patients died within 30 days of surgery or prior to hospital discharge (whichever was greater) and 8 additional patients died on long-term follow up (median time between surgery and death of 6.0 years [IQR 2.1-13.6 years]). Thus, the actuarial survival was 89%, 83%, 80%, and 69% at 1, 5, 10, and 15 years (Figure 4). On univariate analysis, there were no factors associated with a higher mortality risk in our patient cohort.

DISCUSSION

Intra-operative PA stent implantation is an alternative to percutaneous PA stent implantation and surgical pulmonary arterioplasty in many patients. There are several important advantages of intra-operative compared to transcatheter stent implantation, including the ability to implant stents that can be dilated ultimately to adult-size in small patients, while avoiding injury to peripheral vessels and hemodynamic compromise. In addition, because there is direct access and visualization of the branch pulmonary arteries, the stents can be positioned with flaring of the proximal ends of the stent to facilitate future percutaneous re-dilation or subsequent stent re-implantation. The flaring increases the chance that a wire and catheter enter the stent lumen, rather than through a side-strut. Furthermore, intra-operative PA

stenting eliminates radiation exposure associated with transcatheter PA stenting. The disadvantages of intra-operative PA stent implantation include the need for a median sternotomy, a high likelihood of patients requiring future stent dilation either due to somatic growth or in-stent stenosis, exposure to cardiopulmonary bypass, and the possibility of jailing side branches of the distal PA. Importantly, these last two disadvantages may be overcome using a hybrid approach with intra-operative fluoroscopy.

Intra-operative stent placement can be performed successfully in most patients. Of patients who underwent attempted stent placement, a stent was implanted in 99% of patients. Ninety-two percent of patients had \leq mild residual pulmonary stenosis by echocardiography at hospital discharge and for those patients without an echocardiogram but subsequent PA angiography, 91% of patients had \leq mild residual stenosis. Unfortunately, not all patients underwent subsequent angiography or additional imaging, like ventilation perfusions scans or cardiac MRI, to better quantitate procedural success. Given the retrospective nature of our study, this data is lacking but will be an important indication in any future prospective studies examining intra-operative PA stenting outcomes.

Additionally, intra-operative PA stent placement can be performed safely. The rates of vascular injury and stent embolization are lower than that reported for percutaneous stent implantation (17). In our series, the total stent related complication rate was 4.4%, whereas the stent-related complication rate was 10% for percutaneous PA stent placement from a multi-center registry study (17) and 0-40% reported in a review article summarizing various reports of percutaneous PA stent implantation between 1991 and 2010 (18). Importantly, no patient died during a procedure in which intra-operative stent placement was performed, and there were no deaths as a result of a complication from intra-operative stent placement. Although the 30-day mortality rate was high at 8.8%, this was related to the high-risk nature of the patients in whom intra-operative stent placement was performed. Three patients underwent intra-operative PA stent placement while already on ECMO support. All underwent successful stent implantation but all were unable to wean from ECMO support and died. Two other patients had care

withdrawn for severe global hypoxic-ischemic brain injuries after right ventricle to pulmonary artery conduit replacement operations with concomitant intra-operative PA stent implantation. Lastly, one patient underwent a neonatal repair for TOF and absent pulmonary valve, and later underwent intra-operative stent implantation at 3 months of life. The patient died at 1 year of age, 9 months after stent implantation due to complication from ventilator dependence related to severe bronchomalacia.

Eight patients died during long-term follow-up. Seven patients had single ventricle physiology and one had TOF with pulmonary atresia and MAPCA.

In our experience, nearly 44% of patients require re-intervention of the PA stent during follow-up, and ~22% of patients require more than one re-intervention. Our 2- and 5-year freedom from re-intervention rates of 74% and 51% were nearly identical to those found in the one other study examining the long-term outcomes following intraoperative PA stent placement, in which the 2 and 5 year rates were 68% and 49%, respectively (15). This is in close approximation with reports of percutaneous PA stent placement, where re-intervention rates for stent dilation range from 26-66% during follow-up periods ranging from 0.9 to 7.2 years (18).

Re-interventions are expected whenever stents are placed in children given anticipated somatic growth. In our study, 30% of re-interventions were performed for somatic growth. To support this further, two of the main risk factors for re-intervention were age less than 18 months and body surface area less than 0.47 m² at initial implant.

A cardiac diagnosis of TOF with MAPCA is the other main risk factor for re-intervention. This is not an unexpected finding, as the PAs in patients with MAPCA are often hypoplastic and require multiple interventions, especially during the first several years of life, compared to TOF patients without MAPCA (19, 20). Furthermore, patients with MAPCA are at a higher risk of developing in-stent stenosis

secondary to neointimal proliferation (21). These patients need close monitoring, and frequent re-intervention should be expected.

Fortunately, the majority of patients who require re-intervention after placement of an intra-operative PA stent can undergo re-intervention via percutaneous techniques. We believe that this is facilitated by placing stents that can be serially balloon dilated to adult sizes and to flaring the proximal edge of the stent.

In this study, stents were placed on CPB by direct visualization alone, using pre-surgical angiography to determine stent sizes. The disadvantages to this approach include exposure to CPB and the inability to visualize, avoid, and/or treat side vessel jailing or vessel wall injury during stent implantation. In our cohort, the median CPB duration was 50 minutes (IQR 38-90 minutes) for patients undergoing isolated intra-operative PA stenting. Although difficult to determine CPB duration related to stent implantation when performed during additional cardiac procedures requiring CPB, anecdotally, most stents can be prepared and implanted in less than 15 minutes. There are alternative methods for placing intra-operative PA stents, such as hybrid-implantation, using intra-operative angiography and fluoroscopy. This is particularly useful for placing stents distally or at PA bifurcations. This helps to avoid jailing side branches and facilitates opening the side struts into side branches, if needed. Additionally, hybrid stent implantation can be done without using CPB, thereby eliminating the deleterious effects of bypass in patients not undergoing concomitant procedures. This does, however, expose patients to ionizing radiation. Thus, the risks and benefits of each modality should be considered on an individual basis.

Our current practice is to utilize intra-operative PA stent placement in patients with significant PA stenosis that is not amenable to balloon angioplasty or surgical patch arterioplasty (because of the nature of the lesion and/or poor response to prior angioplasty or arterioplasty) and who are undergoing a concomitant surgical procedure. Additionally, intra-operative PA stent placement is performed in

patients in whom a transcatheter approach is not feasible, either due to the size of the peripheral vasculature or due to hemodynamic instability during attempted stent implantation. Importantly, there have been many advances in pre-mounted stent technology in the last 5 years, allowing implantation using much smaller sheath sizes than are needed for unmounted large bare metal stents. Therefore the ultimate desired size of the stent needs to be taken into account when deciding on the appropriate therapy for a patient.

Limitations:

Due to the retrospective nature of this study, it was not possible to re-create the decision-making that went into performing surgical arterioplasty versus surgical or percutaneous stent implantation. We can make some inferences, however the exact indication for intra-operative stent implantation was sometimes unknown, and, thus, selection bias could impact our results. Likewise, stent choice and size, as well as the indications for re-intervention are difficult to delineate retrospectively.

CONCLUSION

Intra-operative PA stent implantation is technically feasible with low procedural, stent-related complications. The rates of central vascular injury and stent embolization are lower than that reported for percutaneous stent implantation (17) and radiation exposure is eliminated. Similar to what is reported with percutaneous stent implantation, re-intervention is common. When utilized in younger patients and patients with MAPCA, re-intervention for either development of in-stent stenosis and/or somatic growth should be expected. This study expands the knowledge of intra-operative PA stent placement and the impact of stents placed largely during childhood on late outcomes.

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Figure Legends:

1: Patient outcomes flow chart

2: Freedom from first re-intervention in the overall cohort stratified by the type of re-intervention (surgical versus percutaneous). The median time to re-intervention is 5.3 years for the overall cohort, as illustrated by the dotted line. The (*) indicates that no patient in any cohort was at risk after 10 years, and therefore, the figure was truncated to only include the first 10 years of follow-up.

3: Freedom from first re-intervention stratified by various clinical characteristics, including age (3A), body surface area (3B), cardiac diagnosis (3C), and cardiac diagnosis with presence of MAPCAs (3D). Median freedom from re-intervention is represented for each group by the dotted lines.

Abbreviations: BSA, body surface area; MAPCA, multiple aorto-pulmonary collateral arteries; non-TOF, diagnosis other than tetralogy of Fallot; TOF, tetralogy of Fallot.

4: Overall survival of the entire cohort (n=68)

Table I: Patient and clinical characteristics (n=68)

Male sex	48 (70.6)
Caucasian race	50 (73.5)
Age ^a , years	2.6 (1.2-7.6)
< 18 months	22 (32.4)
≥ 18 months	46 (67.6)
Weight ^a , kg	12.4 (8.7-20.4)
Height ^a , cm	85.5 (74.5-123)
Body surface area ^a , m ²	0.54 (0.42-0.84)
< 0.47 m ²	25 (36.8)
≥ 0.47 m ²	43 (63.2)
Cardiac diagnosis	
TOF	26 (38.2)
With pulmonary stenosis	8 (11.8)
With pulmonary atresia	18 (26.5)
{With MAPCAs	11 (16.2)}
HLHS	13 (19.1)
Truncus Arteriosus	7 (10.3)
Other single ventricle defects	4 (5.9)
Double outlet right ventricle	3 (4.4)
l-TGA	3 (4.4)
d-TGA	2 (2.9)
AVSD	1 (1.5)
Other	9 (13.2)

Indication for surgery

Repair or palliation of another cardiac defect	57 (83.8)
Isolated branch pulmonary stenosis	11 (16.2)

Etiology of pulmonary stenosis

Acquired (including post-surgical)	57 (83.8)
Congenital	11 (16.2)

Affected pulmonary artery

Left	40 (58.8)
Right	15 (22.1)
Bilateral	13 (19.1)

Location

Ostial/Proximal	58 (85.3)
Distal	8 (11.8)
Unknown	2 (2.9)

Total number(s) of prior surgery

1	23 (33.8)
2	29 (42.6)
3	13 (19.1)
4	3 (4.4)

Prior pulmonary artery interventions 24 (35.3)

Surgical	15 (22.1)
Transcatheter	12 (17.6)

^a at time of surgery when intraoperative stent placed

Data are presented as N (%) for categorical variables and Median (25th percentile - 75% percentile) for continuous variables

Abbreviations: TOF, tetralogy of Fallot; MAPCAS, multiple aortopulmonary collateral arteries; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; AVSD, atrioventricular septal defect.

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Table II: Intra-operative and hospital outcomes

Length of intubation, days	1 (0-3)
Hospital length of stay, days	8 (6-14)
30-day hospital mortality ^a	6 (8.8)
Residual stenosis on discharge echocardiogram (if successful implant)	
None	47 (69.1)
Mild	7 (10.3)
Moderate	3 (4.5)
Severe	1 (1.5)
Unknown	9 (13.4)

^a 30-day mortality refers to death within 30 days of surgery or prior to hospital discharge, whichever is greater

Data are presented as N (%) for categorical variables and Median (25th percentile - 75% percentile) for continuous variables

Table III: Long-term patient outcomes

Duration of follow-up, years	6.0 (0.9-12.7)	(maximum 17.9 years)	
	ALL	Left	Right
Re-intervention(s)	30 (44.1)	21/53 (39.6)	14/28 (50.0)
Time to first re-intervention, years	2.6 (0.7-4.4)	2.5 (0.9-5.3)	2.6 (0.3-3.0)
Reason for (first) re-intervention			
In-stent stenosis	16 (53.3)	11 (52.4)	7 (50.0)
Somatic growth	9 (30.0)	5 (23.8)	5 (35.7)
Stent Occlusion	1 (3.3)	1 (4.8)	0 (0.0)
Distal pulmonary artery stenosis	1 (3.3)	1 (4.8)	0 (0.0)
Stent fracture	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	3 (10.0)	3 (14.3)	2 (14.3)
Type of (first) re-intervention			
Surgical	9 (30.0)	7 (33.3)	2 (14.3)
Transcatheter	21 (70.0)	14 (66.7)	12 (85.7)
Subsequent re-intervention (s)			
Surgical	12 (17.6)	10 (18.9)	2 (7.1)
Transcatheter	24 (35.3)	17 (32.1)	12 (39.3)

Data are presented as N (%) for categorical variables and Median (25th percentile - 75% percentile) for continuous variables

Table IV: Factors associated with re-intervention

Characteristics	Re-intervention		HR	95% CI	p-value ^a
	Yes (N=30)	No (N=38)			
Age at surgery, years					
< 18 months	13 (43.3)	9 (23.7)	2.97	1.40, 6.30	0.005
≥ 18 months	17 (56.7)	29 (76.3)	Ref		
Body surface area, m ²					
< 0.47 m ²	14 (46.7)	11 (28.9)	3.20	1.48, 6.89	0.003
≥ 0.47 m ²	16 (53.3)	27 (71.1)	Ref		
Cardiac diagnosis					0.01
TOF with MAPCA	6 (20.0)	4 (10.5)	4.61	1.71, 12.5	0.003
TOF without MAPCA	8 (26.7)	8 (21.1)	1.76	0.75, 4.15	0.19
Non-TOF	16 (53.3)	26 (68.4)	Ref		
TOF vs. Non-TOF	14 (46.7)	12 (31.6)	2.36	1.14, 4.89	0.02
MAPCA vs. Non-MAPCA	6 (20.0)	5 (13.2)	3.56	1.37, 9.21	0.01
Indication for surgery					0.84
Isolated branch PS	6 (20.0)	5 (13.2)	1.10	0.44, 2.74	
Repair of other defect	24 (80.0)	33 (86.8)	Ref		

Etiology of pulmonary artery stenosis					0.09
Acquired	24 (80.0)	33 (86.8)	Ref		
Congenital	6 (20.0)	5 (13.2)	2.23	0.88, 5.65	
Affected pulmonary artery					0.10
Left	15 (50.0)	25 (65.8)	Ref		
Right	9 (30.0)	6 (15.8)	2.05	0.89, 4.72	0.09
Bilateral	6 (20.0)	7 (18.4)	2.47	0.93, 6.60	0.07
Location of stenosis/stent placement					0.23
Ostial or Proximal	25 (83.3)	33 (86.8)	Ref		
Distal	5 (16.7)	3 (7.9)	1.80	0.69, 4.75	
Unknown	0 (0.0)	2 (5.3)			
Prior intervention	9 (30.0)	15 (39.5)	0.84	0.38, 1.84	0.66

^a P-value from univariate Cox regression.

Data are presented as N (%)

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref, reference category; TOF, tetralogy of Fallot; MAPCA, multiple aortopulmonary collateral arteries; PS, pulmonary stenosis.

Table V: Multivariable analysis of factors associated with re-intervention

Characteristics	AHR	95% CI	p-value ^a
Body surface area, m ²			
< 0.47 m ²	0.25	0.06, 1.08	0.06
≥ 0.47 m ²	Ref		
Cardiac diagnosis			0.01
TOF with MAPCA	6.12	1.77, 2.12	0.004
TOF without MAPCA	3.10	1.10, 8.77	0.03
Non-TOF	Ref		
Etiology of pulmonary artery stenosis			0.45
Acquired	Ref		
Congenital	0.64	0.20, 2.07	

^a P-value from multivariable Cox regression.

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; Ref, reference category; TOF, tetralogy of Fallot; MAPCA, multiple aortopulmonary collateral arteries;

Figure 1: Patient Outcomes

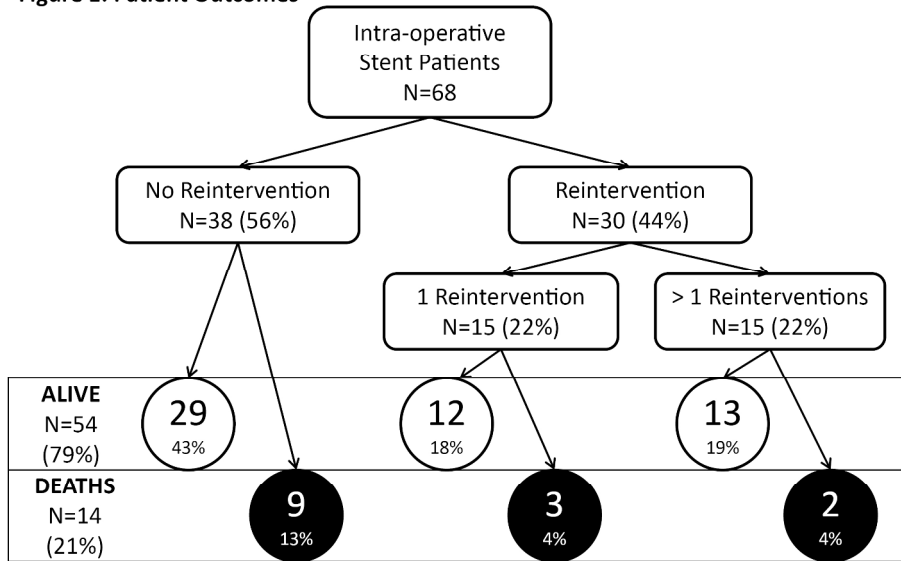


Figure 1: Patient outcomes flow chart
 Figure 1
 254x190mm (300 x 300 DPI)

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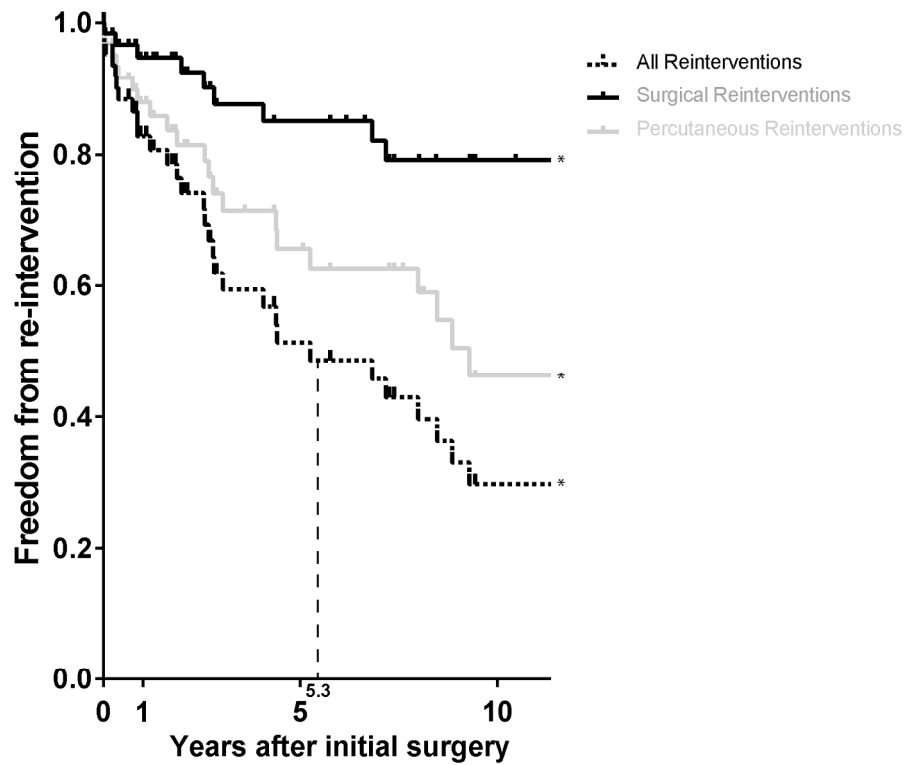
Figure 2: Freedom from (First) Re-intervention

Figure 2: Freedom from first re-intervention in the overall cohort stratified by the type of re-intervention (surgical versus percutaneous)

Figure 2

173x153mm (300 x 300 DPI)

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Figure 3: Freedom from Re-intervention Stratified by Clinical Characteristics

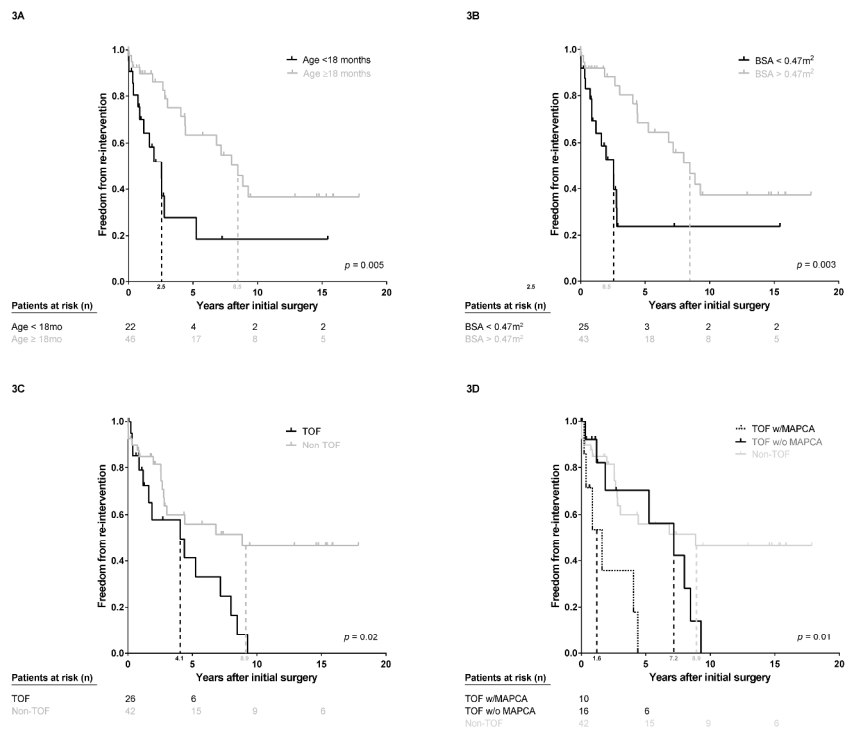


Figure 3: Freedom from first re-intervention stratified by various clinical characteristics, including age (3A), body surface area (3B), cardiac diagnosis (3C), and cardiac diagnosis with presence of MAPCAs (3D)

Figure 3

525x397mm (300 x 300 DPI)

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Figure 4: Survival

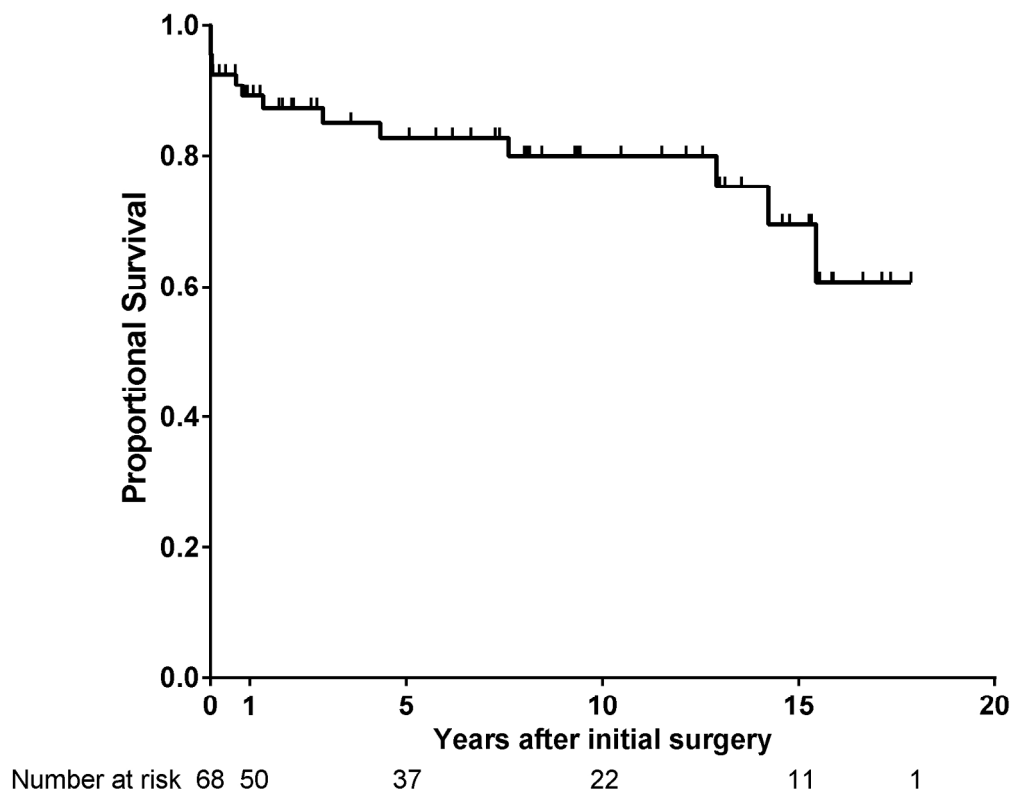


Figure 4: Overall survival of the entire cohort (n=68)
Figure 4
174x160mm (300 x 300 DPI)

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Twenty Years of Experience with Intra-operative Pulmonary Artery Stenting

Running Head: Intra-operative pulmonary artery stents

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ABSTRACT

Objectives: To describe our 20-year experience with intra-operative pulmonary artery stent placement and evaluate long-term patient outcomes, specifically the need and risk factors for re-intervention.

Background: Intra-operative pulmonary artery stent placement is an alternative to surgical patch arterioplasty and percutaneous angioplasty or stent placement to treat branch pulmonary artery (PA) stenosis.

Methods: We performed a retrospective review of all intra-operative pulmonary artery stents placed at our institution from 1994-2013. Patient and stent characteristics and outcome data were collected. Risk factors associated with re-intervention were identified using univariate cox regression analysis.

Results: Eighty-one PA stents were placed in 68 patients. The procedural complication rate was 4.4%. During a median follow-up period of 6 years (interquartile range (IQR) 0.9-12.7), 30 patients (44%) underwent re-intervention on the stented PA with a median time to first re-intervention of 2.6 years (IQR 0.7-4.4 years). The first re-intervention was surgical in 30% and catheter-based in 70%. Risk factors for re-intervention included age < 18 months (Hazard ratio [HR] 2.97, p=0.005) and body surface area < 0.47 m² (HR 3.20, p=0.003) at the time of stent implantation, and the presence of multiple aorto-pulmonary collaterals in patients with tetralogy of Fallot (HR 4.61, p=0.003).

Conclusions: Intra-operative PA stent implantation is a safe and effective alternative to percutaneous stent implantation and offers several advantages, including the ability to implant adult-size stents in small patients while avoiding injury to peripheral vessels, to position stents to facilitate future percutaneous stent re-dilation, and to access the PAs directly, which eliminates radiation exposure.

Abstract Word Count: 250

INTRODUCTION

Branch pulmonary artery (PA) stenosis is a relatively common problem in congenital heart disease.

Percutaneous techniques have reduced the need for surgical pulmonary arterioplasty and are as effective as surgical arterioplasty while avoiding cardiopulmonary bypass (CPB) (1-3). However, many patients still require operative repair either due to the morphology of the stenosis, inadequate response to percutaneous techniques, small patient size prohibiting safe or effective percutaneous intervention, or the need for concomitant repair of other surgical defects (1). Re-intervention for recurrent stenosis after surgical pulmonary arterioplasty is required in 48-64% of patients and has not changed significantly over the last 40 years (2-5). Because of early restenosis, these patients can require multiple surgical or catheterization procedures early in childhood, exposing them to the risks of repeated sternotomy, CPB, and/or radiation, to name a few.

Intra-operative PA stent placement is an alternative approach. This procedure has been shown to be safe with excellent short-term efficacy (6-14). It can allow for implantation of stents that can be dilated to adult size that would be difficult to place percutaneously in small children, while avoiding ionizing radiation exposure from cardiac catheterization procedures. However, longer-term data on the outcomes of intra-operative PA stenting are limited (15).

We sought to describe our experience with intra-operative PA stent placement over the last 20 years and to examine long-term patient outcomes, specifically focusing on the incidence of and risk factors for re-intervention, due to recurrent PA stenosis.

MATERIALS AND METHODS

After receiving Institutional Review Board approval with waiver of informed consent, we performed a retrospective review of all intra-operative PA stents placed at our institution between January 1, 1994 and December 31, 2013. Patients were identified through review of the electronic medical record, cardiac

catheterization reporting systems, and surgical records. Any patient who underwent placement of an intra-operative PA stent was included. Patients were excluded if stent implantation was not attempted or if there was not sufficient documentation to know if stent implantation occurred intra-operatively. Patient data, procedural information (stent type, procedural success and complications), and follow-up data were collected. Procedural success was defined as placement of a stent without the need for removal during the operation.

Stent implantation technique:

All intra-operative PA stents were placed in the operating room on CPB. Minimal dissection of the vessels was performed for isolated stent implantation with retrograde flow within the vessel being managed with pump suckers as needed without obtaining distal vessel control. In the case of pulmonary arterioplasty followed by stent implantation, the PA was fully mobilized with distal control achieved when feasible. Stent diameter, length and position were determined based on pre-surgical angiograms obtained by cardiac catheterization. Stent diameter was determined by the size of the normal adjacent vessel (~1 mm larger than adjacent or distal PA diameter) and no more than 3 times the diameter of the narrowest stenotic PA segment. Whenever possible, stent length was chosen to avoid jailing side branches of distal vessels. Other than direct visual inspection, no other modality, including fluoroscopy, angiography or other visualization techniques (e.g., endoscopy) were utilized. Stent position was defined as ostial/proximal for stents placed prior to the first PA bifurcation and distal for stents placed after the first PA bifurcation. For stents placed in proximal or ostial locations, the proximal end of the stent was manually widened or “flared” into the main PA, helping to secure the stent in place and facilitating future access into the stent lumen during cardiac catheterization. Only balloon-expandable, bare metal stents were used, and whenever possible, medium and large diameter stents were selected (16).

Statistical Analysis:

Patient and stent characteristics and short- and long-term patient outcomes are described as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Freedom from re-intervention in overall and selected subgroups and overall survival were evaluated by Kaplan-Meier curves. Univariate and multivariable Cox regression analyses were performed to identify factors associated with re-intervention. Variables associated with re-intervention in the univariate analysis ($p < 0.1$) were incorporated into the multivariable analysis. Due to collinearity between age and body surface area at the time of initial stent implantation, only body surface area was included in the multivariable analysis. Hazard ratio (HR) and 95% confidence interval from the Cox regression were reported. A p -value < 0.05 was considered statistically significant. Analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics:

Eighty-one PA stents were placed in 68 patients (Table I). In the majority of patients (84%), stent implantation was performed as part of a procedure to repair or palliate another cardiac defect (e.g. conduit replacement). Tetralogy of Fallot (TOF) was the most common diagnosis (38%) and 11 patients (16%) had major aortopulmonary collateral arteries (MAPCA), representing 42% of the patients with TOF.

Intra-operative PA stents were most commonly placed in the left PA (59%) and to treat proximal stenoses (85%). Medium and large diameter bare metal stents were implanted in 97% of patients. PALMAZ XL Transhepatic Biliary Stent (58%, Cordis Endovascular Corporation, Santa Clara, California USA) and ev3 IntraStent® Mega™ LD Biliary Stent (29%, ev3 Endovascular, Inc. Plymouth, Minnesota USA) were utilized most frequently.

All patients had previously undergone at least one prior cardiac operation **and all patients had undergone at least one prior cardiac catheterization.** Twenty-four patients (35%) had undergone a

prior PA intervention, either surgical or catheter-based, on the same PA that received an intra-operative PA stent. Of these, 15 patients (22%) had undergone at least one prior surgical patch arterioplasty, and 3 patients (4.4%) had undergone more than 1 arterioplasty. In addition, 12 (18%) had previous transcatheter interventions, 3 of whom (4.4%) required multiple prior catheter interventions. **In these 12 patients, the median time from catheterization to intra-operative stent placement was 91.5 days (IQR 21 days to 2.5 years), whereas the median time from cardiac catheterization (including diagnostic and interventional procedures) to intra-operative stent placement was 22 days (IQR 1-65 days) for the entire of cohort of patients.**

Intra-operative and Hospital Outcomes:

Stent implantation was acutely successful in all patients but one (99%). This patient developed a distal pulmonary artery laceration requiring immediate stent removal. The procedural complication rate was 4.4% (n=3) and all involved a PA injury requiring repair or patch augmentation.

At hospital discharge, 92% (54/59) of patients had either no or mild residual stenosis by echocardiogram when excluding patients with an unknown degree of residual stenosis (PAs not visualized or echocardiographic images unavailable) (Table II). Of the 9 patients without a sufficient echocardiogram, 6 underwent a cardiac catheterization between 3 days and 20 months after initial stent placement. In these patients, 4 had no stent stenosis and 2 had mild stent stenosis.

Follow-Up Patient Outcomes (Figure 1):

During a median follow-up period of 6 years (IQR 0.9-12.7), 30 patients (44%) underwent re-intervention on their intra-operatively placed PA stent(s) (Table III). The median time to first re-intervention was 2.6 years (interquartile range 0.7-4.4 years). The first re-intervention was a surgical procedure in 9 (30%) patients, with all undergoing intra-operative dilation of the existing stent, along with a concomitant surgery. No patient required subsequent surgical pulmonary arterioplasty of the stented PA. Only 1

patient underwent a surgical procedure for the sole purpose of treating PA stenosis. This patient had single ventricle physiology and **because of persistent unilateral lung collapse in the early post-operative period, a lung ventilation perfusion scan was performed which showed no perfusion to unilateral and ipsilateral lung supplied by the stented PA. Therefore, the patient was taken back to the operation room 7 days after the primary surgery with intra-operative stent implantation and** underwent surgical thrombectomy and stent dilation with good long term result. Percutaneous intervention was not attempted. The other 8 patients underwent surgery for other indications (conduit revision [n= 4], Fontan completion [n=2], Fontan takedown [n=1] and shunt revision [n=1]. All 8 patients were able to have the existing stent re-dilated.

The first re-intervention was a percutaneous procedure in 21 (70%) patients, which included balloon angioplasty of the existing stent in 14 and placement of a new stent(s) in 7. For the 7 patients who had new stents placed, the indication was in-stent stenosis (n=2), somatic growth (n=3), stenosis distal to the intra-operative placed stent (n=2), and unknown (n=1).

In the overall cohort, the majority of patients required re-intervention for in-stent stenosis (53%) and for somatic growth (30%). Of note, no patient required re-intervention for either surgical complication or stent fracture at the time of the first re-intervention.

The overall freedom from re-intervention was 83%, 74%, 51%, and 30% at 1, 2, 5, and 10 years, respectively (Figure 2). The freedom from surgical re-intervention was 95%, 93%, 85%, and 79% at 1, 2, 5, and 10 years, respectively.

In univariate cox regression analysis, several factors were associated with an increased risk of re-intervention (Table IV). These included age less than 18 months (HR 2.97, p=0.005; Figure 3A) and body surface area less than 0.47 m² (HR 3.20, p=0.003; Figure 3B) at the time of the initial stent

implantation, a cardiac diagnosis of TOF (compared to non-TOF patients, HR 2.36, $p=0.02$; Figure 3C) and the presence MAPCA (HR 3.56, $p=0.01$). On further examination, the increased hazard seen in the TOF group was driven by the presence of MAPCA, as only TOF patients with MAPCA had a significantly higher risk of re-intervention compared to non-TOF patients (HR 4.61, $p=0.003$; Figure 3D). There were no differences in the etiology, sidedness, or location of the pulmonary stenosis in terms of risk for re-intervention. Additionally, prior intervention to treat pulmonary stenosis was not associated with re-intervention. Multivariable analysis showed that cardiac diagnosis was independently associated with re-intervention, controlling for body surface area at the time of initial stent implantation and etiology of PA stenosis (Table V).

There were no deaths or long-term complications related to intra-operative stent placement. However, 6 patients died within 30 days of surgery or prior to hospital discharge (whichever was greater) and 8 additional patients died on long-term follow up (median time between surgery and death of 6.0 years [IQR 2.1-13.6 years]). Thus, the actuarial survival was 89%, 83%, 80%, and 69% at 1, 5, 10, and 15 years (Figure 4). **On univariate analysis, there were no factors associated with a higher mortality risk in our patient cohort.**

DISCUSSION

Intra-operative PA stent implantation is an alternative to percutaneous PA stent implantation and surgical pulmonary arterioplasty in many patients. There are several important advantages of intra-operative compared to transcatheter stent implantation, including the ability to implant stents that can be dilated ultimately to adult-size in small patients, while avoiding injury to peripheral vessels and hemodynamic compromise. In addition, because there is direct access and visualization of the branch pulmonary arteries, the stents can be positioned with flaring of the proximal ends of the stent to facilitate future percutaneous re-dilation or subsequent stent re-implantation. The flaring increases the chance that a wire and catheter enter the stent lumen, rather than through a side-strut. Furthermore, intra-operative PA

stenting eliminates radiation exposure associated with transcatheter PA stenting. **The disadvantages of intra-operative PA stent implantation include the need for a median sternotomy, a high likelihood of patients requiring future stent dilation either due to somatic growth or in-stent stenosis, exposure to cardiopulmonary bypass, and the possibility of jailing side branches of the distal PA. Importantly, these last two disadvantages may be overcome using a hybrid approach with intra-operative fluoroscopy.**

Intra-operative stent placement can be performed successfully in most patients. Of patients who underwent attempted stent placement, a stent was implanted in 99% of patients. Ninety-two percent of patients had \leq mild residual pulmonary stenosis by echocardiography at hospital discharge and for those patients without an echocardiogram but subsequent PA angiography, 91% of patients had \leq mild residual stenosis. **Unfortunately, not all patients underwent subsequent angiography or additional imaging, like ventilation perfusions scans or cardiac MRI, to better quantitate procedural success. Given the retrospective nature of our study, this data is lacking but will be an important indication in any future prospective studies examining intra-operative PA stenting outcomes.**

Additionally, intra-operative PA stent placement can be performed safely. The rates of vascular injury and stent embolization are lower than that reported for percutaneous stent implantation (17). In our series, the total stent related complication rate was 4.4%, whereas the stent-related complication rate was 10% for percutaneous PA stent placement from a multi-center registry study (17) and 0-40% reported in a review article summarizing various reports of percutaneous PA stent implantation between 1991 and 2010 (18). Importantly, no patient died during a procedure in which intra-operative stent placement was performed, and there were no deaths as a result of a complication from intra-operative stent placement. Although the 30-day mortality rate was high at 8.8%, this was related to the high-risk nature of the patients in whom intra-operative stent placement was performed. Three patients underwent intra-operative PA stent placement while already on ECMO support. All underwent successful stent

implantation but all were unable to wean from ECMO support and died. Two other patients had care withdrawn for severe global hypoxic-ischemic brain injuries after right ventricle to pulmonary artery conduit replacement operations with concomitant intra-operative PA stent implantation. Lastly, one patient underwent a neonatal repair for TOF and absent pulmonary valve, and later underwent intra-operative stent implantation at 3 months of life. The patient died at 1 year of age, 9 months after stent implantation due to complication from ventilator dependence related to severe bronchomalacia.

Eight patients died during long-term follow-up. Seven patients had single ventricle physiology and one had TOF with pulmonary atresia and MAPCA.

In our experience, nearly 44% of patients require re-intervention of the PA stent during follow-up, and ~22% of patients require more than one re-intervention. Our 2- and 5-year freedom from re-intervention rates of 74% and 51% were nearly identical to those found in the one other study examining the long-term outcomes following intraoperative PA stent placement, in which the 2 and 5 year rates were 68% and 49%, respectively (15). This is in close approximation with reports of percutaneous PA stent placement, where re-intervention rates for stent dilation range from 26-66% during follow-up periods ranging from 0.9 to 7.2 years (18).

Re-interventions are expected whenever stents are placed in children given anticipated somatic growth. In our study, 30% of re-interventions were performed for somatic growth. To support this further, two of the main risk factors for re-intervention were age less than 18 months and body surface area less than 0.47 m² at initial implant.

A cardiac diagnosis of TOF with MAPCA is the other main risk factor for re-intervention. This is not an unexpected finding, as the PAs in patients with MAPCA are often hypoplastic and require multiple interventions, especially during the first several years of life, compared to TOF patients without MAPCA

(19, 20). Furthermore, patients with MAPCA are at a higher risk of developing in-stent stenosis secondary to neointimal proliferation (21). These patients need close monitoring, and frequent re-intervention should be expected.

Fortunately, the majority of patients who require re-intervention after placement of an intra-operative PA stent can undergo re-intervention via percutaneous techniques. We believe that this is facilitated by placing stents that can be serially balloon dilated to adult sizes and to flaring the proximal edge of the stent.

In this study, stents were placed on CPB by direct visualization alone, using pre-surgical angiography to determine stent sizes. **The disadvantages to this approach include exposure to CPB and the inability to visualize, avoid, and/or treat side vessel jailing or vessel wall injury during stent implantation. In our cohort, the median CPB duration was 50 minutes (IQR 38-90 minutes) for patients undergoing isolated intra-operative PA stenting. Although difficult to determine CPB duration related to stent implantation when performed during additional cardiac procedures requiring CPB, anecdotally, most stents can be prepared and implanted in less than 15 minutes.** There are alternative methods for placing intra-operative PA stents, such as hybrid-implantation, using intra-operative angiography and fluoroscopy. This is particularly useful for placing stents distally or at PA bifurcations. This helps to avoid jailing side branches and facilitates opening the side struts into side branches, if needed. Additionally, hybrid stent implantation can be done without using CPB, thereby eliminating the deleterious effects of bypass in patients not undergoing concomitant procedures. This does, however, expose patients to ionizing radiation. Thus, the risks and benefits of each modality should be considered on an individual basis.

Our current practice is to utilize intra-operative PA stent placement in patients with significant PA stenosis that is not amenable to balloon angioplasty or surgical patch arterioplasty (because of the nature

of the lesion and/or poor response to prior angioplasty or arterioplasty) and who are undergoing a concomitant surgical procedure. Additionally, intra-operative PA stent placement is performed in patients in whom a transcatheter approach is not feasible, either due to the size of the peripheral vasculature or due to hemodynamic instability during attempted stent implantation. Importantly, there have been many advances in pre-mounted stent technology in the last 5 years, allowing implantation using much smaller sheath sizes than are needed for unmounted large bare metal stents. Therefore the ultimate desired size of the stent needs to be taken into account when deciding on the appropriate therapy for a patient.

Limitations:

Due to the retrospective nature of this study, it was not possible to re-create the decision-making that went into performing surgical arterioplasty versus surgical or percutaneous stent implantation. We can make some inferences, however the exact indication for intra-operative stent implantation was sometimes unknown, and, thus, selection bias could impact our results. Likewise, stent choice and size, as well as the indications for re-intervention are difficult to delineate retrospectively.

CONCLUSION

Intra-operative PA stent implantation is technically feasible with low procedural, stent-related complications. The rates of central vascular injury and stent embolization are lower than that reported for percutaneous stent implantation (17) and radiation exposure is eliminated. Similar to what is reported with percutaneous stent implantation, re-intervention is common. When utilized in younger patients and patients with MAPCA, re-intervention for either development of in-stent stenosis and/or somatic growth should be expected. This study expands the knowledge of intra-operative PA stent placement and the impact of stents placed largely during childhood on late outcomes.

Acknowledgements and Disclosures: None

Accepted Article

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Figure Legends:

1: Patient outcomes flow chart

2: Freedom from first re-intervention in the overall cohort stratified by the type of re-intervention (surgical versus percutaneous). The median time to re-intervention is 5.3 years for the overall cohort, as illustrated by the dotted line. The (*) indicates that no patient in any cohort was at risk after 10 years, and therefore, the figure was truncated to only include the first 10 years of follow-up.

3: Freedom from first re-intervention stratified by various clinical characteristics, including age (3A), body surface area (3B), cardiac diagnosis (3C), and cardiac diagnosis with presence of MAPCAs (3D). Median freedom from re-intervention is represented for each group by the dotted lines.

Abbreviations: BSA, body surface area; MAPCA, multiple aorto-pulmonary collateral arteries; non-TOF, diagnosis other than tetralogy of Fallot; TOF, tetralogy of Fallot.

4: Overall survival of the entire cohort (n=68)