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Original Studies

Safety and Efficacy of Balloon Pulmonary Valvuloplasty: A Multicenter Experience

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Background: Balloon pulmonary valvuloplasty (BPV) is the treatment of choice for patients with pulmonary valve stenosis (PS); however, safety and efficacy outcomes are lacking in the current era. Methods: Demographic, procedural, and adverse event (AE) data were prospectively collected using a multicenter registry (C3PO) and cases performed between 02/07 and 06/10 at eight institutions. The registry was queried for cases of isolated BPV. Multivariable models were built to determine risk factors for procedure failure and adverse outcomes. Results: 211 cases were included (45%, <1 month). Procedural success was achieved in 91% procedures, being defined as one or more of the following: post-BPV peak systolic valvar gradient to < 25 mm Hg (88%), decrease in gradient by 50% (79%), or reduction of RV/systemic pressure ratio by 50% (45%). Procedural success was more common in neonates, when compared to older patients (96% vs. 87%, $P = 0.03$). Risk factors for procedural failure included moderate or severe pulmonary valve thickening (OR 2.9, CI 1–8.3), and presence of supravalve PS (OR 9.6, CI 2.7–33.8). Low severity AEs (levels 1–2) occurred in 9% of patients and higher severity AEs (levels 3–5) occurred in 3% of patient; there were no deaths. Risk factors for any AE (levels 1–5) were age below 1 month (OR 3.5, CI 1.3–8.9), as well as operator experience of less than 10 years (OR 3.8, CI 1.5–9.9). Conclusions: Procedural success is common and AEs, especially higher severity AEs, are rare for BPV in patients with isolated PS. Results have improved considerably when compared to historical data. © 2012 Wiley Periodicals Inc.

Key words: pCOMP, complications pediatric cath/intervention; PEDS, pediatric interventions; pulmonary valvuloplasty

INTRODUCTION

Since its introduction by Khan and colleagues in 1982, transcatheter balloon pulmonary valvuloplasty (BPV) has evolved as the accepted standard treatment modality for patients with pulmonary valve stenosis (PS). The largest registry to date (VACA) included the

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data of more than 680 procedures, documenting a low risk of procedure-related adverse events (AEs), with major AEs occurring in less than 1.3% of procedures, and a mortality of less than 0.2% [1]. However, while the risk for most patients is very low, the incidence of AEs in neonates with critical PS has been found to be significantly higher [2–4]. Reported AEs associated with this procedure include avulsion, annular tear or perforation (0.4%), tricuspid valve injury (0.9%), and arrhythmias (1%) [1].

Although the majority of studies have reported retrospectively on single-center institutional series, so far there is a lack of prospectively collected data specifically focusing on procedure-related AEs and intervention efficacy. Comparisons of procedural results as well as incidence of AEs are difficult due to a lack of standard definitions relating to AE severity and overall capture of these events. Bergersen et al. recently reported on the "Congenital Cardiac Catheterizations Outcome Project (C3PO)" [5], which is a multicenter registry devoted to prospectively collecting outcome data on all cardiac catheterization procedures, enabling an adjustment of center-specific variations in patient case mix [6,7], as well as using a comprehensive definitions for procedure-related AEs and efficacy. This study reports on the safety and efficacy outcomes related to BPV for patients with isolated pulmonary valve obstruction without atresia or history of valve intervention.

METHODS

Data were collected prospectively using the "Congenital Cardiac Catheterization Outcomes Project" (C3PO), which is a multicenter interventional registry with eight participating institutions. IRB approval was obtained for the prospective collection of patient and procedural characteristics and evaluation of the safety and efficacy of procedures. Details relating to registry design have been reported by Bergersen et al. [5]. All participating physicians reviewed and approved the content of this manuscript.

Inclusion and Exclusion Criteria

Cases performed between 02/07 and 6/10 at eight institutions were queried for the intervention pulmonary valvuloplasty. To allow comparison of hemodynamic success criteria, and to facilitate a more uniform patient population, the following exclusion criteria were applied:

1 Any case that included other transcatheter intervention (such as atretic valve perforation, pulmonary artery rehabilitation, ASD closure, etc.), as these additional interventions would have led to difficulties in attributing an AE to pulmonary valvuloplasty.
2 Any patient that had either complex two-ventricle anatomy or single ventricle anatomy, due to the difficulty in defining uniform success criteria.
3 Cases with prior surgical or transcatheter interventions on the pulmonary valve (reinterventions), as the aim of the study was to include only patients undergoing valvuloplasty for the first time. Furthermore, the majority of reinterventions occurred in patients with complex two-ventricle anatomy.
4 Cases from one center that did not supply procedural efficacy data, as these cases would not have allowed us to evaluate the procedural efficacy.

Reports have suggested a difference in the incidence of AEs encountered as well as procedural success when comparing neonates to patients older than 1 month of age, and therefore data were analyzed separately for both age groups [1,8–10].

Data Collected

Collected data included demographic variables (age, weight), clinical variables (presence of genetic abnormality, use of prostaglandin, use of inotropes, history of surgical or transcatheter pulmonary valve procedure), pulmonary valve morphology (pulmonary valve annulus by angiography, pulmonary valve thickening, presence of supravalvar pulmonary stenosis), case data (admission type, type of anesthesia, procedure and fluoroscopy times, contrast used, blood transfusions), hemodynamic data before and after intervention (RV pressures, MPA pressures, aortic pressures, systemic ventricle pressure, RV to aortic ratio, RV to MPA systolic gradient, subpulmonary gradient, hemodynamic vulnerability score [7]), valvuloplasty data (maximum balloon diameter, balloon/annulus ratio, inflation pressure >8 atm), operator experience and volume, as well as data pertaining to AEs (type of AEs, seriousness, preventability).

Each AE was assigned a severity category from 1 to 5 (none, minor, moderate, major, catastrophic) and preventability designation (not preventable, possibly preventable, preventable), as defined previously [11]. All AEs were independently reviewed in a nonblinded fashion by two interventional cardiologists for appropriate and consistent application of seriousness and preventability criteria and where necessary adjusted. Hemodynamic vulnerability variables associated with an increased incidence of AE (subject of a separate manuscript) included for systolic main PA pressure $\geq$45 mm Hg, systemic ventricular end-diastolic pressure $\geq$18 mm Hg, mixed venous saturation $<$60%, and systemic saturation $<$95% [7]. A score was defined as none, 1, or 2 or more based on the total number of hemodynamic vulnerability variables present.

In this study, hemodynamic procedural success was arbitrarily defined as the presence of either a reduction of the peak systolic transvalvar gradient to less than 25 mm Hg (excluding any subpulmonary gradient), or a reduction of the RV/systemic pressure ratio by at least 50%, or a reduction of the RV/MPA gradient by at least 50%. All success criteria were based on hemodynamic measurements obtained in the catheterization laboratory and did not include echo Doppler measurements.

Although the majority of data were prospectively collected and entered into the database, an efficacy module was designed half way through the study period and institutions were asked to retrospectively enter the efficacy data for those cases that had already been completed. The efficacy module included valvar morphological data fields, as well as additional hemodynamic data fields. Pulmonary valve thickening was defined as either nonexisting to minor, if the pulmonary valve had a uniformly thin appearance without significant irregularities or nodular hyperplasia, or as moderately to severely thickened for any other morphology.

Completeness of case capture was evaluated and confirmed by each institution. A random independent audit of 10% of cases, performed at each institution after 15 months, documented a 92% capture rate of high severity (levels 3–5) AEs [5].

Statistical Analysis

Descriptive patient and case characteristics were provided for all cases, and also stratified by age ($<$1 month, $\geq$1 month). Because of procedural outcome being likely affected by previous surgical or transcatheter interventions on the pulmonary valve [9], all reinterventions were excluded from primary analysis. Median, range, and interquartile range were calculated for all continuous variables and frequency with percentages for categorical variables. Patient and case characteristics were compared between patients of less than 1 month of age and those equal to or above 1 month of age using the Wilcoxon rank sum test for continuous variables and the Fisher's exact test for categorical variables.

Patient and case characteristics were assessed in univariate analysis for a relationship with any AE, any high severity AE, and procedural success/failure. For demographic, clinical, hemodynamic, and procedural variables, Fisher's exact test was used for univariate comparisons. For institutional and operator variables, generalized estimating equations (GEE) models were used to account for the lack of independence among cases performed at the same institution or by the same operator. Predictors that were statistically significant in univariate analysis ($P < 0.1$) were retained for the multivariable analysis, which used GEE models with forward selection. Because of the low incidence of high severity AE, multivariable analysis was only performed for all AEs and for procedural success/failure. Variables significant at the 0.05 level based on the likelihood ratio test were retained in the final models. Odds ratios (OR) and 95% confidence intervals were provided. SAS 9.2 was used for statistical calculations.

RESULTS

Between February 1st, 2007 and June 30th, 2010, 487 patients were entered into the C3PO registry that underwent BPV. Excluded were patients with other transcatheter interventions ($n = 102$), patients with either single ventricle or complex two-ventricle anatomy ($n = 123$), patients with prior surgical or transcatheter interventions on the pulmonary valve ($n = 24$), as well as patients from one center that did not supply procedural efficacy data ($n = 27$). After applying these exclusion criteria, 211/487 (42%) patients who underwent BPV for isolated PS were included in the analysis. Just over half of the cases were performed in patients equal to or above 1 month of age, ($n = 115$, 55%), with the other half occurring in neonates below 1 month of age ($n = 96$, 45%). Eight patients (4%) underwent reinterventions during the study period, six of which were in patients who first underwent BPV during the neonatal period. Reinterventions were not included in the analysis.

Population Characteristics

The majority of patients were less than 1 year of age ($n = 172$, 82%), with adult patients ($\geq$ 18 years) accounting for very few procedures ($n = 7$, 3%). The median weight was 4.3 kg (0.7–102 kg). Noncardiac problems were present in 9% of patients and a genetic abnormality was present in 8% of patients. There was no significant difference when comparing the incidence of a genetic syndrome (7% vs. 8%, $P = 1$) or noncardiac problems (9% vs. 9%, $P = 1$) between neonates and patients above 1 month of age.

Pulmonary Valve Morphology

The median pulmonary valve annulus, as assessed by angiography, measured 6.9 mm (4–9.5 mm) for the neonatal group, and 9.8 mm (5.3–25 mm) for older patients. Presence of supravalvar pulmonary stenosis was notably less common in the neonatal group when compared to older patients (0% vs. 12%, $P < 0.001$). Subvalvar pulmonary stenosis was present in 70/211 (33%) patients, without any significant difference between the neonatal group and older patients (32% vs. 34%, $P = 0.74$). Moderate to severe pulmonary

TABLE I. Case Characteristics

Case characteristics	Total ($n = 211$), N (%) or median [IQR] (range)	<1 month ($n = 96$), N (%) or median [IQR] (range)	≥ 1 month ($n = 115$), N (%) or median [IQR] (range)	P value
Elective admission	133 (63)	22 (23)	111 (97)	<0.001
On PGE infusion	55 (26)	55 (57)	0 (0)	<0.001
Spontaneous respiration	51 (24)	16 (17)	35 (30)	0.02
Inotropic support at start	7 (3)	7 (7)	0 (0)	0.004
Case duration (min)	61 [49, 80], (23, 219)	59 [45, 79], (23, 185)	63 [55, 80], (25, 219)	0.03
Fluoroscopy time (min)	15 [11, 21], (5, 51)	15 [12, 21], (5, 51)	13 [11, 19], (6, 47)	0.13
Contrast dose (ml/kg)	2.5 [1.9, 3.7], (0.6, 15.6)	3.0 [2.3, 4.1], (0.6, 15.6)	2.3 [1.7, 3.1], (0.8, 6.8)	<0.001
Transfusion	7 (3)	3 (3)	4 (3)	1.0
Operator experience (since fellowship)				–
<10 years	111 (53)	50 (52)	61 (53)	
≥10 years	90 (43)	43 (45)	47 (41)	
Not reported	10 (5)	3 (3)	7 (6)	
Operator volume (all catheterizations)				–
<100 cases/year	25 (12)	7 (7)	18 (16)	
100–199 cases/year	103 (49)	45 (47)	58 (50)	
≥200 cases/year	83 (39)	44 (46)	39 (34)	
Balloon-to-annulus ratio (nondouble balloon)	1.25 [1.18, 1.32], (0.97, 1.54)	1.25 [1.21, 1.33], (1.00, 1.54)	1.23 [1.17, 1.32], (0.97, 1.49)	0.13
Max balloon/annulus ratio				0.04
<1.2	63 (30)	21 (22)	42 (37)	
≥1.2, <1.4	134 (63)	66 (69)	68 (59)	
≥1.4	14 (7)	9 (9)	5 (4)	
Balloon inflation ≥8 atm	19 (9)	2 (2)	17 (15)	<0.001
Double balloon technique	6 (3)	0 (0)	6 (5)	0.03

valve thickening was present in 84/211 (40%) patients, again without significant difference between neonatal and older patients (41% vs. 39%, $P = 0.96$).

Case Characteristics

Case characteristics are listed in Table I. Elective admissions for BPV were significantly more common in older patients, when compared to the neonatal group (97% vs. 23%, $P < 0.001$). Fifty-seven percent of neonates had ductal patency maintained on Prostaglandin infusion prior to the procedure. Slightly more procedures were performed by operators with less than 10 years experience when compared to those with more than 10-years experience since completing fellowship (53% vs. 43%).

In the majority of cases ($n = 134$, 63%), a maximum balloon diameter to pulmonary valve annulus ratio of equal to or above 1.2 but less than 1.4 was chosen. Larger balloon-to-annulus ratios (≥1.4) were more common in the neonatal group (9% vs. 4%), while smaller ratios (<1.2) were more common in older patients (37% vs. 22%, $P = 0.04$). High-pressure balloon inflation of equal to or above eight atmospheres was more common in older patients when compared to the neonatal group (15% vs. 2%, $P = 0.001$). A double-balloon technique was only used in 6/115 (5%) patients older than 1 month.

Hemodynamic Data

Parameters of hemodynamic vulnerability were significantly more common in the neonatal group when compared to older patients (one parameter: 57% vs. 24%, two or more parameters: 10% vs. 3%, $P < 0.001$). Systemic saturations below 95% were more common in the neonatal group (55% vs. 23%, $P < 0.001$), as were MPA systolic pressures >45 mm Hg (6% vs. 0%, $P = 0.008$). Mixed venous saturations below 60% were seen in 16% of neonates and 9% of older patients ($P = 0.14$), while an elevated end-diastolic pressure (≥18 mm Hg) was only recorded in one single patient.

Prevalvuloplasty and postvalvuloplasty data are listed in Table II. There were significant improvements in the RV/MPA gradient and the RV/systemic pressure ratio for both, neonates and older patients. A large percentage of neonates had no prevalvuloplasty pulmonary artery pressure recorded ($n = 61$, 64%). Suprasystemic right ventricular pressures were seen in 10% of neonates and none of the older patients, but no patient left the catheterization laboratory after valvuloplasty still having suprasystemic pressures. The median RV/systemic pressure ratio prior to valvuloplasty was 1.4 (0.6–2.6) for the neonatal group and 0.8 (0.3–1.7) for older patients. Postvalvuloplasty, subvalvar gradients of 10 mm Hg or more were seen in 17% of neonates, and 14% of older patients.

TABLE II. Preprocedural and Postprocedural Hemodynamic Data (< 1 month)

	Preintervention med [IQR], (range)	Postintervention med [IQR], (range)	*P* value
All patients			
RV/MPA gradient (mm Hg)	46 [36, 60], (18, 108)	14 [7, 22], (−6, 69)	<0.001
RV (2V)/Ao ratio	1.08 [0.79, 1.43], (0.34, 2.57)	0.57 [0.42, 0.82], (0.18, 1.44)	<0.001
Subvalvar gradient (mm Hg)	–	10 [6, 20], (1, 55)	–
Age <1 month			
RV/MPA gradient (mm Hg)	58 [44, 73], (25, 108)	12 [6, 20], (−6, 40)	<0.001
RV (2V)/Ao ratio	1.44 [1.18, 1.80], (0.58, 2.57)	0.74 [0.60, 0.92], (0.32, 1.44)	<0.001
Subvalvar gradient (mm Hg)	–	10 [8, 20], (1, 35)	–
Age ≥1 month			
RV/MPA gradient (mm Hg)	43 [34, 55], (18, 104)	15 [8, 24], (1, 69)	<0.001
RV (2V)/Ao ratio	0.83 [0.68, 1.07], (0.34, 1.70)	0.46 [0.37, 0.57], (0.18, 1.19)	<0.001
Subvalvar gradient (mm Hg)	–	10 [6, 20], (1, 55)	–

TABLE III. Procedural Success

Case characteristics	Total ($n = 211$), *N* (%)	<1 month ($n = 96$), *N* (%)	≥1 month ($n = 115$), *N* (%)	*P* value
Procedural success[a]	192 (91)	92 (96)	100 (87)	0.03
Individual success criteria				
Transvalvar gradient ≤25 ($n = 93, 115$)	184 (88)	87 (94)	97 (84)	0.05
RV/MPA gradient reduction ≥50% ($n = 35, 101$)	108 (79)	33 (94)	75 (74)	0.01
RV/systemic ratio reduction ≥50% ($n = 75, 98$)	77 (45)	36 (48)	41 (42)	0.44

[a]Procedural success defined as either reduction of transvalvar gradient to ≤25 mm Hg (after deduction of any subvalvar gradient), reduction of RV/MPA gradient by at least 50%, or reduction of RV/systemic pressure ratio by at least 50%. The RV/systemic pressure ratio was defined as the ratio between RV systolic pressure and aortic systolic pressure.

Procedural Success

Procedural success parameters are listed in Table III. At least one out of the three acute procedural success criteria was present in 192/211 (91%) patients. Procedural success was slightly more common in neonates, when compared to older patients (96% vs. 87%, $P = 0.03$), mainly due to a higher percentage of neonates that achieved a gradient reduction of 50% or more (94% vs. 74%, $P = 0.01$). A reduction of the transvalvar systolic gradient to 25 mm Hg or less was achieved in 88% of patients, and a reduction of the RV/systemic pressure ratio by 50% or more was achieved in 45% of patients. However, due to the fact that MPA pressures were often not measured prior to valvuloplasty, only 27% of neonates and 73% of older patients had all three measures documented for evaluation.

Predictors of procedural failure. There were multiple variables associated with procedural failure by univariate analysis (Table IV). However, in multivariable analysis the only independent risk factors for procedural failure were moderate or severe pulmonary valve thickening (OR 2.9, CI 1–8.3), and the presence of supravalvar pulmonary stenosis (OR 9.6, CI 2.7–33.8).

Adverse Events

In total, 28 AEs were observed in 25/211 (12%) cases, with 22/28 (79%) being of low severity (levels 1–2), and 6/28 (21%) being high severity (levels 3–5) AEs (Table V). There were significantly more patients who encountered AEs in the neonatal group, when compared to older patients (19% vs. 6%, $P = 0.02$). There were no deaths (level 5 AEs) and only one level 4 AEs, which was an episode of ventricular fibrillation during valvuloplasty requiring electrical defibrillation.

There was no significant difference in the distribution of the severity of AEs between the neonatal group and older patients. The majority of AEs were classified as not preventable ($n = 17$, 61%), and only 6/28 (21%) AEs were classified as preventable (Table V). Preventable AEs were mainly sedation and airway-related and included, air leak in the ventilator, unrecognized right main stem bronchus intubation, self-extubation, and corneal abrasion. Other preventable adverse vents included a power injection in an inappropriate location, as well as femoral arterial pulse loss.

The most common types of AEs were arrhythmias and conduction anomalies seen in 10/211 (5%) procedures, sedation, anesthesia, or airway-related AEs in 8/211 (4%) procedures, and hemodynamic AEs in 5/211 (2%) procedures. Vascular entry site AEs were seen in 4/211 (2%) procedures, while technical AEs were seen in only one procedure. Vascular or cardiac trauma, such as heart perforation, was not observed in any patient.

Predictors of adverse events. Because of the low incidence of levels 3–5 AE, uni-and multivariable analysis was only performed for any AE (levels 1–5; Table VI).

TABLE IV. Risk Factors for Procedural Failure

	Procedural failure			Multivariable model	
Risk factor	Number	Procedural failure (%)	Univariate *P* value	*P* value	Odds ratio (95% CI)
Demographic/clinical predictors					
Age			0.03		
<1 month	96	4 (4)			
≥1 month	115	15 (13)			
Genetic syndrome			0.16		
Yes	16	3 (19)			
No	195	16 (8)			
PGE infusion			0.31		
Yes	55	2 (4)			
No	154	17 (11)			
Unknown	2	0 (0)			
Pulmonary valve thickening			0.03		
None or minor	123	6 (5)		–	1.0
Moderate or severe	84	13 (15)		0.05	2.9 (1.0, 8.3)
Unknown	4	0 (0)			
Supravalvar PS			<0.001		
Yes	14	6 (43)		<0.001	9.6 (2.7, 33.8)
No	197	13 (7)		–	1.0
Subvalvar PS			0.71		
Yes	70	5 (7)			
No	138	14 (10)			
Unknown	3	0 (0)			
Hemodynamic predictors					
RV/Ao ratio			0.90		
≤1	170	15 (9)			
>1	10	1 (10)			
Unknown	31	3 (10)			
Baseline RV/MPA gradient			0.36		
≥60 mm Hg	35	4 (11)			
<60 mm Hg	101	11 (11)			
Unknown	75	4 (5)			
Hemodynamic vulnerability			0.93		
0	114	11 (10)			
1	83	7 (8)			
2+	14	1 (7)			
Procedural predictors					
Maximum balloon/annulus ratio			0.03		
<1.2	63	10 (16)			
≥1.2	148	9 (6)			
Inflation ≥8 atm			0.16		
Yes	19	4 (21)			
No	174	14 (8)			
Unknown	18	1 (6)			

Even though many variables were significantly associated with a higher incidence of any AE in univariate analysis, the only independent risk factors for any AE (levels 1–5) were age below 1 month (OR 3.5, CI 1.3–8.9), as well as operator experience of less than 10 years (OR 3.8, CI 1.5–9.9).

Institutional Comparison

The number of BPV procedures performed per year ranged between 6 and 14, accounting for 1–3.1% of the total caseload of individual institutions. Reported AEs ranged from 0 to 21% with procedural success ranging from 86 to 97%. The percentage of procedures that were either unsuccessful or had a levels 3–5 AE ranged from 7 to 17%.

DISCUSSION

In this population of patients with isolated pulmonary valve obstruction, AEs occurred in 12%, with 3% of patients encountering higher severity (levels 3–5) AEs. Life threatening AEs occurred only in a single patient who required defibrillation for ventricular fibrillation. This is notably less frequent than the number of life threatening AEs reported in the VACA

TABLE V. All Adverse Events: Severity and Preventability

All adverse events	Total ($n = 28$), N (%)	<1 month ($n = 20$), N (%)	≥1month ($n = 8$), N (%)	P value
Severity				0.62
1—none	5 (18)	4 (20)	1 (12)	
2—minor	17 (61)	12 (60)	5 (63)	
3—moderate	5 (18)	4 (20)	1 (12)	
4—major	1 (4)	0 (0)	1 (12)	
5—catastrophic	0 (0)	0 (0)	0 (0)	
Preventability				0.85
Preventable	6 (21)	5 (25)	1 (12)	
Possibly preventable	5 (18)	3 (15)	2 (25)	
Not preventable	17 (61)	12 (60)	5 (63)	

registry [1]. In contrast to earlier studies [1,4], catastrophic complications such as death or annular avulsion/tear were not observed in this study, likely related to operators having learned from past experiences and more frequently avoiding larger balloon-to-annulus ratios [10,12]. However, while improved when compared to historical data, balloon-to-annulus ratios in excess of 1.4 were still used in 7% of patients, which was somewhat surprising, given not only the potential for vascular disruption but also the risk for more significant pulmonary insufficiency.

Temporary arrhythmias and conduction anomalies were the most common AEs seen in this study (5% of patients), which is not surprising, especially related to wire manipulation and balloon inflation. It was interesting to see that sedation, anesthesia, and airway-related AEs were the second most common AEs, many of which were preventable or possibly preventable AEs such as self-extubation or corneal abrasion. Neonates were more likely to encounter AEs (19% vs. 6%), which can be partially explained by higher hemodynamic vulnerability scores, higher use of vasoactive drugs, and also by the fact that patients undergoing valvuloplasty early in the neonatal period often have a more severe degree of PS. In our study, this was reflected in a higher incidence of patients with suprasystemic RV pressures in the neonatal group. Other independent risk factors for any AE included operator experience of less than 10 years, which suggests that operators with less experience may benefit from guidance and mentoring even for so-called "routine" procedures of lower risk category [6].

Because of the lack of established guidelines, procedural success criteria were somewhat arbitrarily defined. Most studies though have defined a successful immediate procedural outcome through a residual systolic gradient of less than 20–35 mm Hg [1,3,8,13–15], or a 50% or more reduction in valvar gradient or RV/systemic pressure ratio [2,3]. The VACA registry, dating back more than 15 years, defined a gradient on follow-up of equal to or above 35 mm Hg as procedural failure [9]. In contrast, one of the success criteria used in this study was a gradient reduction to less than 25 mm Hg. Despite this lower gradient threshold, hemodynamic procedural success was seen in 91% of procedures, which is an improvement to what was reported in the original VACA registry where a suboptimal outcome was seen in 15% of patients with typical valve morphology and 65% of patients with a dysplastic pulmonary valve. However, the VACA registry did include reinterventions and was not solely limited to isolated PS, which may explain some of the less optimal outcome of that registry. Some of the improved results in this study can be explained as a result of the VACA registry representing a fairly early experience with operators since having gained a better understanding of the technique and balloon size required for achieving a successful result. Furthermore, available equipment such as balloon catheters and guidewires has improved that is likely to have contributed to improved results seen in our patient population. Interestingly though, the acute procedural success was slightly higher in the neonatal group (96% vs. 87%), which may be related to the fact that in neonates with critical PS often a large PDA is present that may have associated increased pulmonary artery pressures and as a result a reduced transvalvar gradient after the procedure (which was used as one of the success criteria). However, acute procedural success is not necessarily related to medium and long-term procedural success, as highlighted by the fact that 6% of neonates underwent reinterventions during the study period, compared to just 2% of the older patients. In most reported series, the need for reintervention for a residual obstruction, using either a transcatheter or a surgical approach has been reported to vary between 10 and 20% [2,3,8,9,14,16]. However, exact comparisons are difficult as many of the historical series included patients with atretic valve perforation or patients with complex two-ventricular anatomy.

Independent predictors of procedural failure were similar to what has been described in other reports and included moderate or severe pulmonary valve thickening as well as the presence of supravalvar pulmonary stenosis. Supravalvar pulmonary stenosis was found to have a higher incidence in older patients when compared to those undergoing valvuloplasty in the neonatal period. Whether this is an incidental finding, or whether this would suggest that supravalvar pulmonary stenosis develops more gradually after birth is unclear. Although not analyzed individually in this study, previous reports have suggested a strong correlation of procedural failure with Noonan's syndrome, which are patients that have frequently supravalvar pulmonary

TABLE VI. Risk Factors for Any AE

	Incidence of any AE			Multivariable model	
Risk factor	Total procedures, *n*	Procedures with any AE, *n* (%)	Univariate *P* value	*P* value	Odds ratio (95% CI)
Demographic/clinical predictors					
Age			0.005		
<1 month	96	18 (19)		0.01	3.5 (1.3, 8.9)
≥1 month	115	7 (6)		–	1.0
Genetic syndrome			0.41		
Yes	16	3 (19)			
No	195	22 (11)			
PGE infusion			0.10		
Yes	55	11 (20)			
No	154	14 (9)			
Unknown	2	0 (0)			
Pulmonary valve thickening			0.63		
None or minor	123	17 (14)			
Moderate or severe	84	8 (10)			
Unknown	4	0 (0)			
Supravalvar PS			1.0		
Yes	14	1 (7)			
No	197	24 (12)			
Hemodynamic predictors					
RV/Ao ratio			0.04		
≤1	170	18 (11)			
>1	10	4 (40)			
Unknown	31	3 (10)			
Baseline RV/MPA gradient			0.02		
≥60 mm Hg	35	4 (11)			
<60 mm Hg	101	6 (6)			
Unknown	75	15 (20)			
Hemodynamic vulnerability			0.20		
0	114	10 (9)			
1	83	14 (17)			
2+	14	1 (7)			
Procedural predictors					
Maximum balloon/annulus ratio			1.0		
<1.4	197	24 (12)			
≥1.4	14	1 (7)			
Inflation ≥8 atm			0.02		
Yes	19	2 (11)			
No	174	17 (10)			
Unknown	18	6 (33)			
Operator predictors					
Operator experience			0.01		
<10 years	111	19 (17)		0.007	3.8 (1.5, 9.9)
≥10 years	90	5 (6)		–	1.0
Not reported	10	1 (10)			
Operator volume			0.38		
<200 cases/year	128	17 (13)			
≥200 cases/year	83	8 (10)			

stenosis as well as a dysplastic pulmonary valve [1,8]. A dysplastic valve has been shown in other studies to be associated with reduced procedural efficacy [1,9,17].

There was considerable variation between centers with regards to incidence of AEs ranging from 0 to 21% as well as procedural success, ranging from 86 to 97%. However, with the limited number of AEs, these data are difficult to interpret and differences may have occurred by chance.

Limitations

The study is limited by the lack of long-term follow-up data. It reports only acute procedural efficacy and does not evaluate some parameters, such as pulmonary

insufficiency, which may be potentially important with regards to long-term morbidity and potential need for surgical intervention. With echo criteria for pulmonary insufficiency being not well established [18,19], and only very few studies having looked at long-term impact of pulmonary insufficiency after BPV [8,10], it was decided not to include echo parameters of pulmonary valve insufficient within this acute outcome data of C3PO. However, ultimately a composite outcome measure using both, degree of pulmonary insufficiency as well as residual gradient will be required to better judge the result of these procedures.

Even though a best effort was made to report all AEs, it is likely that some AEs, especially those of lesser significance (levels 1–2) may not have been captured completely. In addition, due to the retrospective collection of some efficacy data, not all studies had a complete dataset available for analysis. Furthermore, the limited number of high severity AEs may not have been sufficient to identify all potential predictor variables associated with these events. Some other potentially important data such as pulmonary annulus *z*-score, acute echocardiographic data, incidence of Noonan's syndrome, and others, were not collected and other parameters, such as supravalvar pulmonary stenosis, were left to the interpretation of individual operators. A corelab functionality was not included in this study.

The data in this study only applies to isolated PS and cannot be extended to patients with previous surgical or transcatheter procedures, or patients with single or complex two-ventricle anatomy. These patients may have a different risk profile and differences in procedural success. However, due to the great variability in anatomy, comparisons would have been impossible to make, especially regarding hemodynamic procedural success. Therefore, it was decided to solely focus on isolated PS.

CONCLUSIONS

This study has documented a low rate of high severity AEs for patients undergoing BPV for isolated valvar stenosis. These results are derived from procedures performed in the last 4 years and as such represent the current operator era, based on a multicenter registry. Death or catastrophic AEs such as annular tear or disruption, which have been described in earlier series, were not seen in this study. The acute procedural success was 91% with up to 6% of neonates requiring early reinterventions. This study has identified characteristics associated with AEs and procedural failure, which are crucial data during preprocedural planning, and when counseling patients and parents. Although this small dataset suggests that operator experience may be related to outcome, further analysis is required to better understand this relationship.

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