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Long-term outcomes up to 25 years following balloon pulmonary valvuloplasty: A multicenter study

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Abstract

Objective: Evaluate long-term outcomes following balloon pulmonary valvuloplasty (BPV) for pulmonary stenosis (PS).

Background: Long-term data following BPV is limited to small, single center studies.

Methods: BPV from April 12, 1985 to January 7, 2015 from three centers were included. Outcomes studied were ≥ moderate PI by echocardiogram and residual PS ≥ 40 mm Hg. Risk factors for ≥ moderate PI, residual PS, and repeat intervention were assessed by univariate and multivariate analysis.

Results: Among 254 patients, mean age at BPV was 3.8 years (range 1 day-67 years), initial PS catheter gradient was 56 mm Hg (IQR 40-70), 19% had critical PS, and 9% had genetic syndromes. Mean follow-up duration was 7.5 years (maximum 25 years). Sixty-nine (29%) had ≥ moderate PI, 41 patients (17%) had residual PS > 40 mm Hg, and 31 (13%) had re-intervention. In univariate analysis, younger age, lower weight, greater initial PS gradient, greater initial RV/systemic pressure ratio, critical PS, and longer follow-up duration were associated with ≥ moderate PI. Greater initial PS gradient was associated with long-term residual PS or repeat intervention. In multivariate analysis, greater initial gradient and lower weight were independently associated with > moderate PI and greater initial PS gradient and genetic abnormality were independently associated with residual PS and repeat intervention.

Conclusion: Smaller patients with greater initial PS were more likely to develop significant long-term PI. Patients with greater initial PS and genetic abnormalities were more likely to have residual PS or require repeat intervention following BPV.

KEYWORDS
balloon pulmonary valvuloplasty, percutaneous intervention, pulmonary insufficiency, pulmonary valve stenosis

Abbreviations: BPV, balloon pulmonary valvuloplasty; MRI, magnetic resonance imaging; PA, pulmonary artery; PI, pulmonary insufficiency; PS, pulmonary stenosis; PSEG, peak systolic ejection gradient; RV, right ventricular; TR, tricuspid regurgitation.

1 | INTRODUCTION

Pulmonary stenosis (PS) is found in 8-10% of patients with congenital heart disease.[1] Prior to the first description of balloon pulmonary valvuloplasty (BPV) in 1982 by Kan et al, the only treatment for PS was surgical valvotomy or valvectomy.[2] Since that time, multicenter studies have demonstrated excellent early and intermediate term outcomes following BPV.[3,4] Consequently, BPV has replaced surgical intervention as the initial treatment for moderate and severe PS.[5] However, there remains limited data from larger, multicenter cohort studies regarding risk factors for residual PS in long-term follow-up and the long-term incidence and progression of pulmonary insufficiency (PI).[5-8]

The main objective of this study was to evaluate the long-term incidence of and risk factors for moderate or severe PI following BPV in a large, multicenter cohort. The secondary objective was to evaluate the long-term efficacy of BPV in reducing PS by evaluating the incidence and risk factors for poor outcome, defined as a composite variable of residual PS ≥ 40 mm Hg or requirement for repeat intervention by repeat BPV or surgical intervention to relieve residual PS.

2 | METHODS

2.1 | Patient population

Patients who underwent BPV from April 12, 1985 to January 7, 2015 for isolated PS from three separate centers in Syracuse, Buffalo, and Rochester comprising the Pediatric Cardiac Consortium of Upstate New York were included in this study. Patients included in the study had isolated PS diagnosed by echocardiogram and were identified by chart review of catheterization log books. Patients with critical PS, defined as a requirement for prostaglandins to maintain patency of the ductus arteriosus prior to BPV, were included in the study. Patients with minor additional cardiac lesions such as small atrial septal defects, patent ductus arteriosus, or small ventricular septal defects not requiring surgical intervention were also included in the study. Patients with additional complex congenital cardiac defects including pulmonary atresia with intact ventricular septum or severely hypoplastic right ventricle were excluded. Additionally, patients with surgical relief of PS, such as pulmonary valvotomy or valvectomy, transannular patch, or augmentation of pulmonary blood flow with modified Blalock-Taussig shunt prior to initial BPV were excluded. The study was approved and the requirement for informed consent was waived by the Institutional Review Boards at the participating centers.

2.2 | Data collection

Baseline demographic data, including gender, age, and weight at time of initial BPV were collected from the medical record. Baseline echocardiographic and catheterization data as well as follow-up echocardiographic and clinical data were also collected from available echocardiogram and catheterization reports, and outpatient medical records. Individual echocardiogram and catheterization images were not independently reviewed for this study. There is no standardized method for quantifying degree of valvar regurgitation or ventricular dysfunction by echocardiogram between the three centers included in this study. Data regarding these variables were exclusively obtained from written reports. There was no attempt to contact patients who were lost to follow-up; these patients were excluded from the final statistical analysis.

2.3 | Echocardiographic data

Baseline echocardiographic data, including baseline peak PS gradient, were collected from the echocardiogram reports. Data collected from the most recent echocardiogram reports included age, time since initial BPV, peak PS gradient, degree of PI and TR, RV size, RV hypertrophy and RV function.

2.4 | Balloon pulmonary valvuloplasty and cardiac catheterization data

Cardiac catheterization and BPV were performed using techniques described previously.[2,9] Procedures were performed at University of Rochester Medical Center for patients from Rochester, New York and Buffalo, New York by individual pediatric interventional cardiologists from the patients' respective institution where follow-up continued. Procedures for patients from Syracuse, New York were performed at Crouse Hospital. There were no specified requirements for balloon/annulus ratio among any of the study centers. Pulmonary valve annulus diameter, baseline and post-valvuloplasty RV (right ventricular) to PA (pulmonary artery) PSEG (peak systolic ejection gradient), baseline and post-valvuloplasty RV/systemic pressure ratio, degree of PI and tricuspid regurgitation (TR) were obtained from the cardiac catheterization reports. Maximum balloon diameter used during the procedure was used to calculate the balloon/annulus ratio. For patients with repeat cardiac catheterizations, the same data elements were collected for all subsequent BPV procedures.

2.5 | Statistical analysis

The Wilcoxon Rank Sum Test was used to compare the continuous variables between groups with good outcome and poor outcome. The chi-square or Fisher's exact test was used to compare the categorical variables. Logistic regression analysis was performed to evaluate the association of various risk factors with the outcomes of interest while adjusting for potential confounding variables. Patient weight and age at initial BPV, balloon size, balloon/annulus ratio, initial PS catheter gradient, initial RV to systemic pressure ratio, presence of critical PS, and presence of genetic syndrome were included as predictors of both primary and secondary outcomes. Odds ratios and 95% confidence intervals were obtained for the included variables. Additionally, an era effect was analyzed by comparing outcomes of patients who underwent BPV prior to January 1, 2000 to those who underwent BPV after that date. The analysis of era effect

was separate from the total length of follow-up as total length of follow-up was defined by the time between the initial BPV and the most recent follow-up echocardiogram. The main outcome of interest was the degree of PI on most recent echo report. The secondary outcome of interest was a residual PS gradient ≥ 40 mm Hg or requirement for a repeat intervention for residual PS. A stepwise model selection procedure was used to build the final model in order to avoid collinearity and to improve the analysis efficiency. Statistical significance was defined by a *P* value < .05. Statistical analysis was performed using Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Baseline population characteristics

Of the 254 patients included in the study with baseline data, follow-up echocardiogram data were available for 248 patients. All follow-up echocardiogram reports included information regarding residual PS; however, six of the available echocardiogram reports were missing data regarding PI. Mean age at initial BPV was 3.8 years (median 7 months, IQR 12.7 days-4 years, range 1 day-67 years), mean weight at initial BPV was 15.3 kg (median 7.25 kg, IQR 3.9-16.2 kg, range 2-135 kg), mean initial peak echocardiographic PS gradient was 68 mm Hg (median 65 mm Hg, IQR 55-81), mean initial RV to PA PSEG was 56 mm Hg (median 57 mm Hg, IQR 40-70), initial RV/systemic pressure ratio was 1.06 (median 0.95, IQR 0.7-1.4, range 0.33-2.29). Mean RV to PA PSEG post-valvuloplasty was 23 mm Hg (median 18 mm Hg, IQR 12-27 mm Hg) and mean RV/systemic pressure ratio was 0.6 (median 0.55, IQR 0.4-0.8). Mean balloon/annulus ratio was 1.25 (median 1.25, IQR 1.2-1.33). Critical PS was present in 19%. Twenty-one patients (9%) had a genetic syndrome; 13 had Noonan syndrome. Other genetic diagnoses included Williams syndrome and Alagille syndrome. Eighty-one (32%) underwent initial BPV prior to January 1, 2000. Of the patients who underwent initial BPV prior to January 1, 2000, 54 (67%) had ≥ 10 years follow-up. BPV prior to January 1, 2000 was used as a surrogate for remote length of time since initial BPV (Table 1, Figure 1**).**

TABLE 1 Baseline patient characteristics

Variable	Mean (IQR)
Age (years)	3.8 (0.04-4.1)
Weight (kg)	15.3 (3.9-16.2)
Pulmonary annulus diameter (mm)	11.4 (8-14)
Balloon/annulus ratio	1.25 (1.2-1.33)
Peak pulmonary valve echocardiographic gradient (mm Hg)	68.5 (55-81)
RV to MPA peak catheter gradient (mm Hg)	55.9 (40-70)
RV/systemic pressure ratio	1.06 (0.7-1.4)
	N (%)
Male gender	117 (47%)
Critical PS	37 (19%)
Genetic syndrome	19 (8%)
BPV prior to January 1, 2000	78 (31%)

Notes: *N* = 248 patients. Data are presented as mean (interquartile range) for continuous variables and number of patients (percentage) for categorical variables.

3.2 | Follow-up data

3.2.1 | Long-term echocardiographic data

Of the 254 study patients, 248 had follow-up echocardiogram data available for review. Certain data of interest were missing from some of the older, archived echo reports. The mean follow-up duration was 7.5 years, (median 5.4 years, IQR 2-11.8) with a maximum duration of 25 years. There were 128 patients with follow-up echocardiogram data <5 years from initial BPV; of these patients, 34 had <1 year follow-up. There were a total of 78 patients (32%) with follow-up echocardiogram data >10 years after initial BPV; 33 of these patients had follow-up >15 years and 6 had follow-up >20 years. On most recent echocardiogram report, 21% of patients had no TR, 78% had trivial to mild TR, 1% had moderate TR, and no patients had severe TR. Decreased RV systolic function was present in 2% of patients on most recent echo and 98% had normal RV function. A mildly hypoplastic RV was present in 3% of patients, 20% had RV dilation, and 77% had a normal RV size by most recent echocardiographic data. Patients with a severely hypoplastic right ventricle were excluded from the study. Right ventricular hypertrophy (RVH) was present in 18% of patients. There was some variability in echo interpretation, particularly with regard to subjective data such as degree of valvar regurgitation, RV size, and RV function (Table 2).

3.2.2 | *Risk factors for ≥ moderate pulmonary insufficiency*

Of the 248 patients with available echocardiographic studies post-initial BPV, data regarding the degree of PI were reported in 242 of the echocardiogram reports. The mean follow-up duration was 7.5 years with a maximum follow-up time of 25 years (IQR 2-11.8). Of these 242 patients, 69 (29%), had moderate to severe PI on most recent echo (26% moderate PI, 3% severe PI). In the group with ≥ moderate PI, 22/69 (31.9%) had critical PS compared with 25/173 (14.5%) in the group with < moderate PI. In the group of patients with ≥ moderate PI, 29/69 (42%) underwent initial BPV prior to January 1, 2000 whereas 49/173 (28%) had initial BPV prior to January 1, 2000 in the group with < moderate PI.

By univariate analysis, patients who developed ≥ moderate PI in long-term follow-up were younger in age and lower in weight at the time of initial BPV ($P < .05$). Additionally, the group of patients with ≥ moderate PI were found to have greater baseline RV to PA PSEG and greater baseline RV/systemic pressure ratio ($P < .05$). Presence of critical PS was found to be a statistically significant risk

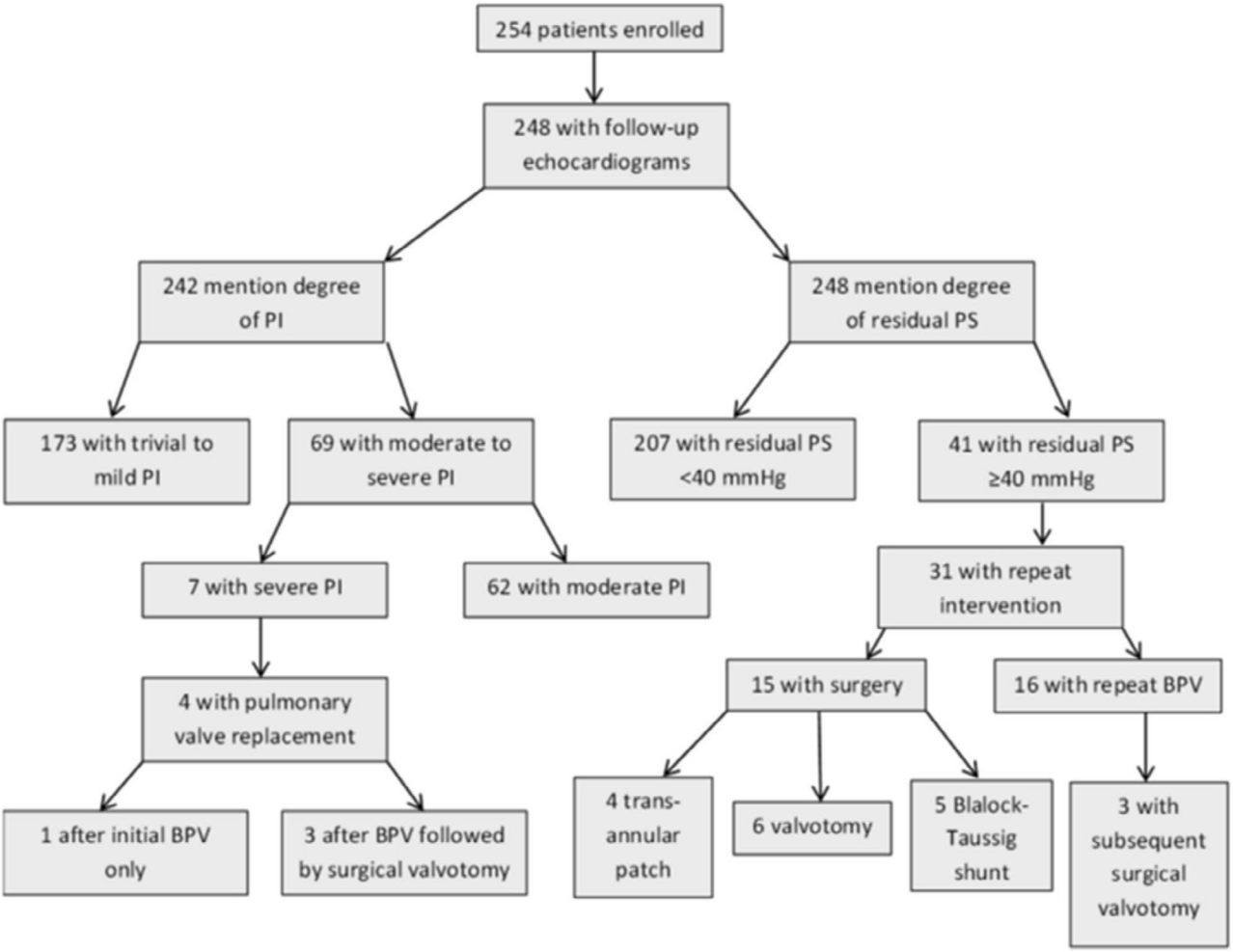

FIGURE 1 Flow diagram of BPV patient outcomes
Notes: Of 254 patients, 248 had available follow-up echocardiograms, 41 patients had residual PS ≥ 40 mm Hg, 31 had repeat intervention—16 repeat BPV, 15 had surgery, 69 had ≥ moderate PI, 4 had pulmonary valve replacement.

factor for ≥ moderate PI by univariate analysis ($P < .05$). Earlier initial intervention, defined as having initial BPV prior to January 1, 2000, was also found to be a statistically significant risk factor associated with ≥ moderate PI ($P < .05$). Of patients who underwent BPV prior to January 1, 2000, 67% had ≥ 10 years follow-up. BPV prior to January 1, 2000 was used as a surrogate remote time since initial procedure as most of these patients achieved ≥ 10 years follow-up (Table 3).

Of the patients with ≥ moderate PI, five of the 69 (7%) were diagnosed with a genetic syndrome; this was not found to be statistically significant in predicting development of ≥ moderate PI. Genetic syndromes included Noonan syndrome, Williams syndrome, and Alagille syndrome. There was no statistically significant association between balloon/annulus ratio and presence of ≥ moderate PI ($P = .94$). The mean balloon/annulus ratio was the same compared between the group with ≥ moderate PI and the group with < moderate PI (mean 1.25).

In multivariate analysis, lower weight (OR 0.8, 95% CI 0.67-0.96) and greater initial RV to PA PSEG (OR 1.021, 95% CI 1.001-1.041) remained independent risk factors for ≥ moderate PI ($P < .05$) (Table 4).

Four patients (1.7%) required pulmonary valve replacement for severe PI ranging 8-18 years after initial BPV. Of these four patients, one had initial BPV only prior to pulmonary valve replacement. Three had initial BPV followed by a surgical pulmonary valvotomy for residual PS. None of the patients received pulmonary valve replacement for residual PS.

3.2.3 | Residual pulmonary valve stenosis and repeat intervention

Follow-up data regarding degree of residual pulmonary valve stenosis after initial BPV were available on follow-up echocardiogram reports BPV for 248 (98%) patients. Mean follow-up duration was 7.5 years (maximum 25 years, IQR 2-11.8). The mean initial peak catheter gradient was 56 mm Hg (IQR 40-70 mm Hg). Two hundred seven patients (83%) with a mean initial peak catheter gradient of 53 mm Hg (IQR 38-68 mm Hg) had relief from initial BPV with a

TABLE 2 Follow-up echocardiographic data

Variable	*N* (%)
Pulmonary insufficiency	
None to mild	173 (71%)
Moderate	62 (26%)
Severe	7 (3%)
Tricuspid regurgitation	
None	51 (21%)
Trivial to mild	190 (78%)
Moderate	2 (1%)
Severe	0 (0%)
RV size	
Small	7 (3%)
Normal	189 (77%)
Dilated	49 (20%)
RV hypertrophy	
None	203 (82%)
Present	44 (18%)
RV function	
Normal	243 (98%)
Decreased	5 (2%)

Notes: *N* = 248 patients. Data are presented as number of patients (percentage) for categorical variables.

residual echocardiographic peak pulmonary gradient of <40 mm Hg and no repeat intervention, either surgical or by repeat BPV. Forty-one patients (17%) with mean initial peak catheter gradient of 71 mm Hg (IQR 48-90 mm Hg) had residual or recurrent PS ≥ 40 mm Hg by echocardiogram; 33 patients had repeat intervention, either repeat BPV or surgery for relief of residual or recurrent stenosis. The patients with residual or recurrent PS ≥ 40 mm Hg without repeat intervention were followed clinically for evidence of right ventricular dysfunction or further progression of PS. Subsequent intervention was deferred by the primary cardiologists as these patients were clinically well. Four patients (1.7%) required pulmonary valve replacement for PI; none required pulmonary valve replacement for residual PS (Figure 2).

Sixteen of the 31 patients who had repeat intervention for residual or recurrent PS underwent subsequent BPV ranging 3 months to 17 years (mean 4.8 years) after initial procedure. Of the 16 patients who required repeat BPV, 3 went on to require surgical relief of ongoing PS unable to be relieved by second BPV (two surgical valvotomy, one infundibular muscle resection with placement of 23 mm RV to PA conduit). These three patients had repeat BPV 5 months to 5 years after initial BPV and went on to surgery 2 weeks to 1.25 years after second BPV.

Of the 16 patients requiring repeat BPV, 7 were for recurrent PS with an end peak RV to PA PSEG of <40 mm Hg after initial BPV. Nine patients required repeat BPV for residual PS with an

TABLE 3 Univariate comparison of baseline characteristics based on degree of PI

Variable	Trivial to Mild PI (*N* = 173)	Moderate to severe PI (*N* = 69)	*P* value
Age (years)	4.6 (0.08-4.33)	1.3 (0.01-2.4)	<.001
Weight (kg)	17.5 (4.3-18)	8.2 (3.7-13.2)	<.001
Pulmonary annulus diameter (mm)	11.8 (8-15)	9.7 (7.75-11.5)	.0149
Balloon: Annulus ratio	1.245 (1.20-1.33)	1.252 (1.16-1.32)	.77
RV to MPA peak catheter gradient (mm Hg)	53 (37-64.5)	64.5 (46-76.5)	<.001
RV/systolic pressure ratio	0.99 (0.67-1.33)	1.27 (0.84-1.54)	<.001
Critical PS	25 (14%)	22 (32%)	.002
Genetic syndrome	14 (8%)	5 (7%)	.83
BPV prior to January 1, 2000	49 (28%)	29 (42%)	.0394

Notes: *N* = 242 patients. Data are presented as mean (interquartile range) for continuous variables and number of patients (percentage) for categorical variables.

TABLE 4 Multivariate analysis identifying independent risk factors for ≥ moderate PI

Variable	Odds Ratio	95% Confidence Limits	*P* value
Weight (kg)	0.8	0.67-0.96	.015
RV to MPA peak catheter gradient (mm Hg)	1.02	1.001-1.04	.04
Pulmonary annulus diameter (mm)	1.37	0.998-1.88	.0514
BPV prior to January 1, 2000	2.27	0.86-5.99	.098

Notes: Age, RV/systolic pressure ratio, critical PS were not included in the final multiple logistic regression model due to collinearity between variables.

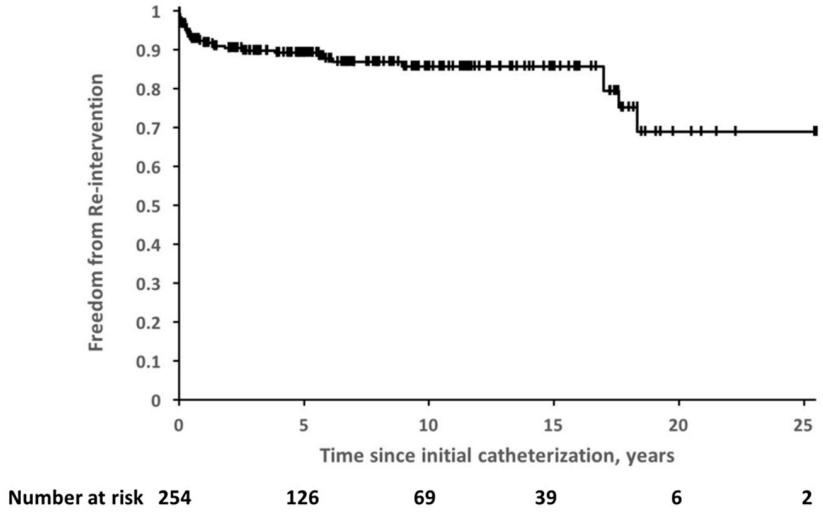

FIGURE 2 Kaplan-Meier curve demonstrating freedom from repeat intervention. Repeat intervention includes patients with a repeat BPV, surgery for residual PS, or pulmonary valve replacement for PI

end peak RV to PA PSEG ≥ 40 mm Hg after initial BPV. Among patients with repeat BPV for recurrent or residual PS, mean balloon/annulus ratio on initial procedure was 1.2 (median 1.2, IQR 1.09-1.03) compared to a mean balloon/annulus ration on repeat procedure of 1.26 (median 1.26, IQR 1.2-1.33). The mean RV to PA PSEG for initial BPV was 92 mm Hg pre-procedure (median 95 mm Hg, IQR 72-100) and 44 mm Hg post-procedure (median 41 mm Hg, IQR 18-67). On repeat BPV, the mean RV to PA PSEG pre-procedure was 60 mm Hg (median 55 mm Hg, IQR 45-65) and 35 mm Hg post-procedure (median 25 mm Hg, IQR 19-42). Mean RV/systemic pressure ratio prior to initial BPV was 1.44 (median 1.54, IQR 1.14-1.65) compared to the mean RV/systemic pressure ratio prior to repeat BPV of 0.89 (median 0.75, IQR 0.71-1.07). Critical PS was present in two patients in both the residual PS and recurrent PS groups (22% and 29%, respectively).

Of the 31 patients who required repeat intervention for residual or recurrent PS, 15 went on to surgery following initial BPV 1 day to 1.5 years later (mean 3.5 months). Six of the 15 patients underwent surgical pulmonary valvotomy, 5 patients had a modified right Blalock-Taussig shunt, and 4 had transannular patch. Among the patients who required surgical relief of residual or recurrent PS, all have sustained two ventricle repairs with no patients going on to require single ventricle palliation. Patients with pulmonary atresia or severely hypoplastic right ventricle were not included in the study; therefore, valvar atresia or ventricular hypoplasia was less likely to influence choice of surgical intervention. It is possible that surgical technique was influenced based on patient size, presence of a dysplastic valve, or multilevel right ventricular outflow obstruction based on direct surgical observation.

3.2.4 | Risk factors for residual stenosis or repeat intervention

In the group of patients with residual or recurrent PS ≥ 40 mm Hg or requiring repeat intervention, 10 patients (24.4%) had critical PS and 7 patients (17%) had a genetic syndrome. In the group of patients with good result from initial BPV defined as residual stenosis <40 mm Hg and no repeat intervention, 37 patients (17.9%) had critical PS and 14 patients (6.8%) had a genetic syndrome.

Five of the patients with a genetic syndrome who required repeat intervention carried a diagnosis of Noonan Syndrome. The repeat interventions required in the group of patients with Noonan Syndrome included one repeat BPV, one transannular patch, one pulmonary valvectomy, one pulmonary valvotomy with main pulmonary artery patch, and one pulmonary valvotomy with right ventricular muscle bundle resection.

By univariate analysis, increased baseline RV to PA PSEG and increased baseline RV/systemic pressure ratio were associated with peak echocardiographic gradient of ≥ 40 mm Hg at most recent follow-up or requirement for repeat intervention ($P < .05$). Presence of a genetic syndrome approached statistical significance as a predictor for increased residual PS or repeat intervention ($P = .0576$). Critical PS was not associated with residual PS or repeat intervention ($P = .33$) (Table 5).

In multivariate analysis, greater initial RV to PA PSEG (OR = 1.022, 95% CI 1.004-1.04), and presence of genetic abnormality (OR = 5.26, 95% CI 1.67-16.6) were significant independent risk factors for residual or recurrent echocardiographic PS gradient ≥ 40 mm Hg or repeat intervention ($P < .05$) (Table 6).

3.2.5 | Loss of follow-up

Patients who were considered lost to follow-up were defined by having no follow-up echocardiogram data available following initial procedure. Of the 254 patients who underwent BPV, follow-up echo data were available for 248. Six patients had no echocardiogram data available following initial BPV. Some of these patients may have been referred from surrounding smaller private cardiology groups where they returned for their follow-up care. There were no patient deaths noted in the medical record of patients with available follow-up data.

TABLE 5 Univariate comparison of baseline characteristics based on degree of residual PS and repeat intervention

Variable	Residual PS gradient <40 mm Hg (*N* = 207)	Residual PS gradient ≥40 mm Hg or repeat intervention (*N* = 41)	*P* value
Age (years)	3.7 (0.04-4.1)	3.9 (0.02-1.8)	.3
Weight (kg)	15 (3.9-17)	14.3 (3.6-12.5)	.54
Pulmonary annulus diameter (mm)	11.3 (8-13.8)	11 (7.2-14.4)	.46
Balloon: Annulus ratio	1.24 (1.2-1.32)	1.27 (1.2-1.4)	.58
RV to MPA peak catheter gradient (mm Hg)	68 (54-81)	75 (55-91)	.006
RV/systolic pressure ratio	1.04 (0.7-1.4)	1.2 (0.8-1.6)	.017
Critical PS	37 (18%)	10 (24%)	.33
Genetic syndrome	14 (7%)	7 (17%)	.058

Notes: *N* = 248 patients. Data are presented as mean (interquartile range) for continuous variables and number of patients (percentage) for categorical variables.

TABLE 6 Multivariate analysis identifying independent risk factors for residual PS gradient ≥40 mm Hg or repeat intervention

Variable	Odds ratio	95% confidence limits	*P* value
RV to MPA peak catheter gradient (mm Hg)	1.022	1.004-1.04	.017
Genetic syndrome	5.26	1.67-16.6	.005

4 | DISCUSSION

In the largest, multicenter cohort with longest follow-up of 25 years and mean follow-up of 7.5 years after initial BPV for isolated PS, we found that initial BPV is highly successful in relieving PS with a low rate of significant residual PS (echocardiographic gradient ≥ 40 mm Hg) or repeat intervention. In our study, 83% of patients (*n* = 207) had relief of PS from initial BPV; only 17% had repeat intervention. There were 78 patients with ≥ 10 years follow-up (range 10-25 years follow-up). Risk factors predicting significant residual PS or repeat intervention included greater initial peak catheter gradient and presence of a genetic syndrome (usually Noonan syndrome). Our study adds to existing literature demonstrating efficacy of BPV for relief of PS.

In a prior multicenter study by McCrindle et al, which included 519 patients with median follow-up 4.5 years (range 0.4-6.1 years), 23% of patients had a significant residual PS (defined as gradient ≥ 36 mm Hg) or repeat intervention. The mean balloon/annulus ratio was 1.12 ± 0.20. A lower balloon/annulus ratio was a significant risk factor for suboptimal outcome and a balloon/annulus ratio between 1.2 and 1.4 was suggested.[4] In our study, only 17% of patients had suboptimal outcome with a mean balloon/annulus ratio of 1.2 (IQR 1.2-1.33). Balloon/annulus ratio was not a significant risk factor for residual PS or repeat intervention suggesting improved relief of PS with an optimal balloon/annulus ratio, supporting the findings of McCrindle et al.

There have been few prior studies reporting risk degree of PI in long-term follow-up. In a prior study by Merino-Ingelmo et al, which included follow-up data for 48 patients who underwent BPV, no patients were free of PI. Moderate PI was noted in 31.2% of patients and severe PI was present in 10.4% of patients ranging 10-24 years after initial BPV. PI was noted to increase over time.[5] A recent study by Devanagondi et al described a larger population (*n* = 103) in which 62 patients had greater than 10 years follow-up (range 10.1-26.3 years). Sixty percent of patients had ≥ moderate PI. There was significant loss to follow-up in the study by Devanagondi et al with data available for only 103 of 211 eligible patients. This likely led to selection bias as the study included a larger number of patients with more severe baseline PS.[8] In our study, 29% of the total number of patients had ≥ moderate PI. Of patients with ≥ 10 years follow-up (32% of the study population, *n* = 78), 42% (*n* = 33) had ≥ moderate PI. Patients who had BPV prior to and after January 1, 2000 were compared to observe for era effect in degree of PI. In review of procedure documentation, there was no apparent difference in techniques during BPV between the early and late era; however, there was an increased length of follow-up time for most patients who underwent BPV prior to January 1, 2000. Patients more remote from initial BPV were more likely to have ≥ moderate PI or have undergone pulmonary valve replacement for severe PI. This likely reflects an increase in PI over time as there was no difference in BPV technique or balloon/annulus ratio prior to January 1, 2000. This is clinically significant because it suggests that patients may be at risk for worsening PI over time and should not be discharged from follow-up.

Similar to prior studies, our study showed that younger age, lower weight, greater baseline RV to PA PSEG, greater baseline RV/systemic pressure ratio, and presence of critical PS were statistically significant risk factors for increased PI. Our study adds to existing data regarding risk factors for PI after BPV.

In a prior study by Berman et al, balloon/annulus ratio >1.4 was found to be a statistically significant risk factor for increased PI and pulmonary valve replacement. The study by Berman et al advised against oversized balloon sizes to avoid such complications.[7] In our study, there was no statistical evidence for balloon/annulus ratio as a risk factor for increased PI. This may be because oversized balloons were used with caution based on historical data. The mean balloon/

annulus ratio for patients with < moderate PI was equal to the mean for patients with ≥ moderate PI at 1.25. There were oversized balloon/annulus ratios used in both the groups with a maximum balloon size of 1.66 in the group with < moderate PI and 1.75 in the group with ≥ moderate PI. The use of these increased balloon/annulus ratios did not affect the outcomes of degree of PI.

The prior study by Pathak, et al suggested use of smaller balloon/annulus ratio ≤1.2 could achieve similar results in relief of PS while preventing significant PI. Sixty-seven patients underwent BPV with balloon/annulus ratio ≤1.2 compared with 31 patients with balloon/annulus ratio >1.2. In patients with a smaller balloon/annulus ratio, there was statistically significant decreased PI and no increase in need for repeat intervention for residual PS.[10] In our study, smaller balloon/annulus ratio ≤1.2 was utilized in both the group with < moderate PI and the group with ≥ moderate PI with minimum balloon annulus ratios of 0.62 and 0.7, respectively. However, balloon/annulus ratio was not found to be a statistically significant risk factor for residual PS or increased PI. Mean balloon/annulus ratio was 1.25 for both groups.

There is limited data regarding pulmonary valve replacement for severe PI and RV dysfunction in this patient population. The study by Berman et al in 1999 identified one patient with pulmonary valve replacement and five more who were predicted to undergo pulmonary valve replacement in the near future.[7] In the study by Devanagondi et al, three patients (3%) required pulmonary valve replacement for severe, symptomatic PI.[8] In our study, only four patients (1.7%) had pulmonary valve replacement ranging 8-18 years following initial BPV. It is important to note that three of the patients who required pulmonary valve replacement underwent surgical pulmonary valvotomy after initial BPV. Only one patient who underwent pulmonary valve replacement had a BPV only. As 75% of patients requiring pulmonary valve replacement for PI underwent a subsequent surgical valvotomy following initial BPV and 25% underwent initial BPV only, it is possible that having undergone only BPV indicates a decreased risk for pulmonary valve replacement secondary to PI; however, due to the small cohort of patients requiring pulmonary valve replacement in our study, this conclusion requires further study. None of the patients required pulmonary valve replacement for residual PS. These patient populations requiring pulmonary valve replacement will likely increase over time as there are multiple patients with severe PI who are nearing clinical criteria for pulmonary valve replacement. We did not examine specific risk factors for pulmonary valve replacement as this percentage of patients comprised a small number of the total patient population. Our study did show that patients with increased PI and pulmonary valve replacements underwent BPV in the earlier era studied, prior to January 1, 2000. As there did not appear to be a difference in technique for BPV or in balloon/annulus ratio, this suggests a possibility of worsening PI over time even if initial degree of PI was < moderate. Lifelong follow-up is warranted in this patient population to monitor increasing PI over time which may lead to pulmonary valve replacement.

There were several limitations to this study. Long-term follow-up data are not available for our entire patient population as we included patients with BPV until January 7, 2015. Only 32% of our patients (n = 78) had ≥ 10 years follow-up. Despite this, we have a large retention of patients who continue to be followed at our centers which will add to future data sets. There was no significant loss to follow-up after initial BPV with a total of 248/254 (98%) of our patients having at least one outpatient echocardiogram following initial BPV. This extensive patient retention helps to eliminate selection bias toward patients with more severe initial pulmonary valve disease and more risk factors for significant residual PS or increased PI, which was likely a problem in previous studies. However, echo data for our patients with more recent BPV is limited in some cases to an echocardiogram as soon as one day following initial BPV. Thirty-four patients had follow-up echocardiogram data <1 year after initial BPV. This is in part due to the fact that the University of Rochester Pediatric Cardiology department preferentially performs sedated echocardiograms between the ages of 6 months and 3 years with physicians primarily relying on examination findings during this time period. These patients did have clinic notes available and have not been lost to follow-up. Due to this, future studies of this population will include longer-term echocardiographic data. We discovered that patients who underwent BPV more remotely, prior to January 1, 2000, were more likely to be discharged from follow-up if they had < mild PI and trivial residual PS after reaching adult age (18 years). This further limited the length of time of available follow-up data. Those patients from the earlier era, prior to January 1, 2000, did show a propensity for increased PI over time, so now patients have ongoing follow-up. This will improve the number of patients with long-term follow-up from our centers and improve future data sets. With regard to progression of PI over time, only data from the most recent echocardiogram were collected. In future studies, more data points regarding degree of PI could be collected to better understand evolution of PI related to time since initial BPV. This type of data would help guide expectations and workup for future pulmonary valve replacement in this population.

There were additional limitations in the data collection from echocardiogram reports as some archived reports were lost or incomplete. The manner in which the echocardiographic data were obtained was a significant study limitation; the echocardiographic data were obtained from echocardiogram reports rather than by direct review of the images. A large portion of the angiograms and echocardiograms were not available for individual review as they were completed prior to our current electronic imaging systems. There were multiple attending reviewers from each of our three study institutions which allowed for a wide range of variability in interpretation. Interobserver variability would have been minimized if we had designated one research team member to review the available echocardiogram images; however, the imaging prior to the current electronic medical records would still have been unavailable for review.

In our study, we determined that critical PS was a statistically significant risk factor for increased pulmonary regurgitation following initial BPV; however, we did not specifically compare risk factors for

repeat intervention or significant PI between patients with critical PS and the remainder of the study population. Our study only examined critical PS as a risk factor rather than as a separate group. This comparison could be examined in future studies.

Finally, cardiac MRI (magnetic resonance imaging) would augment the follow-up data, particularly with regard to objectively analyzing RV size, RV function, and degree of PI. At the time of data collection, only one patient had a cardiac MRI; therefore, this was not included in the final analysis. Future studies are needed to define the role of MRI in evaluating PI, RV function, and RV dilation in long-term follow-up. We predict that MRI will serve as an important tool in assessing patients with severe PI to guide timing for pulmonary valve replacement.

5 | CONCLUSIONS

While BPV has been shown to be effective in relieving PS with a low risk for significant residual PS and repeat intervention,[3-6] little was previously known about the risk factors for PI following the procedure.[5,7,8] This study adds to existing data by demonstrating a higher incidence of ≥ moderate PI in patients with longer follow-up after BPV. Lifelong follow-up of this patient population should be considered as this study suggests that pulmonary regurgitation may be progressive over time. Further studies are needed to investigate the progression of PI over time and risk factors for pulmonary valve replacement.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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