Independent Predictors of Long-term Results After Balloon Pulmonary Valvuloplasty

Brian W. McCrindle, MD, MPH, FRCP(C), for the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators*

Background This study was performed to determine independent predictors of long-term outcome after percutaneous balloon dilation of congenital pulmonary valve stenosis. Smaller follow-up series of patients after balloon pulmonary valvuloplasty have shown inconsistent results regarding the independent relation between prognostic factors and long-term outcome, as many patient selection and technical factors are correlated.

Methods and Results Follow-up data were obtained for 533 patients from 22 institutions at up to 8.7 years after an initial balloon pulmonary valvuloplasty. Patients were grouped based on defined long-term outcomes, and the independent effects of patient selection and technical factors were sought in multivariate statistical analyses. At follow-up, 23% of patients were noted to have an outcome judged to be suboptimal because of either a residual right ventricle to pulmonary artery peak systolic gradient of ≥36 mm Hg or further treatment of pulmonary stenosis requiring repeat balloon pulmonary valvuloplasty or surgical therapy. Significant independent predictors of a suboptimal long-term outcome included an earlier study year of the initial valvuloplasty (adjusted odds ratio, 0.71 per consecutive year), a small valve hinge point diameter (0.81 per 1-mm increase), and a higher immediate residual gradient (1.32 per 10 mm Hg increase). A smaller ratio of balloon to valve hinge point diameter significantly predicted suboptimal outcomes for patients with valve morphologies classified as typical (0.52 per 0.1 increase in ratio) and complex (primarily postsurgical valvotomy, 0.43) but not for patients with dysplastic (0.95) or combined morphologies (dysplasia with commissural fusion, 1.01). Patient age, the presence of Noonan's syndrome or associated cardiac lesions, pre–balloon valvuloplasty hemodynamic parameters, and the use of a simultaneous double-balloon technique did not independently predict follow-up outcomes.

Conclusions Accurate prognostication after balloon pulmonary valvuloplasty depends on the careful determination of valvar anatomy. The use of an appropriate ratio of balloon to valve hinge point diameter in the setting of typical valve morphology will optimize the chance of long-term success. (***Circulation*. 1994;89:1751-1759.**)

Key Words • catheterization • valves • stenosis

Percutaneous balloon pulmonary valvuloplasty (BPV) is now the treatment of choice for congenital pulmonary valve stenosis. While many case series report immediate results and fewer series report intermediate or long-term results, large collaborative systematic studies of factors that predict the long-term outcome of pulmonary stenosis after BPV are lacking. One study that explored predictor variables systematically and in multivariate analyses concluded that the only significant independent risk factor of a suboptimal long-term outcome was a patient age <2 years at the initial BPV.[1] Small patient numbers did not allow the definition of other independent factors with which patient age could have been correlated. Rao et al[2] suggested that balloon to valve hinge point diameter ratio and the immediate residual gradient were independent predictors and that age was not. The purpose of the current study was to examine results from a large multi-institutional patient series and to determine independent patient selection and technical factors that impact on the long-term outcome and clinical course of pulmonary stenosis after BPV.

Received November 9, 1993; revision accepted December 20, 1993.

From the Division of Cardiology, Department of Pediatrics, University of Toronto Faculty of Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada.

Presented in part at the Scientific Sessions of the American Heart Association, Anaheim, Calif, November 11 through 14, 1991.

Correspondence to Brian W. McCrindle, MD, Division of Cardiology, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8.

*For the complete list of investigators, see "Appendix."

Methods

Study Population

Pediatric cardiologists at 26 member institutions of the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry reported data from 822 consecutive BPV procedures attempted between January 1981 and December 1986. The method of data collection and the acute results from this original database have been reported previously.[3]

Before starting the collection of follow-up data, the original database was examined for discrepancies, and duplicate reports for the same procedure were removed. Since the unit of measurement for the follow-up study was the individual patient who had undergone completed BPV, patients for whom the initial BPV was interrupted before completion or who had died at BPV were excluded. Data from subsequent repeat BPVs performed on the same patient were removed and kept as follow-up results for that patient; thus, data from 792 patients from the original database were eligible for inclusion in the current study. Two additional institutions joined the VACA Registry after the published report and submitted data retrospectively for initial BPVs performed in 43 patients. The final eligible study population thus consisted of 835 consecutive patients who had initial completed BPV at 28 institutions.

Follow-up Data Collection

Data from the initial BPV for each patient were duplicated and sent to the principal investigators at each institution. A

request was made for review of the original data and completion of a follow-up data collection form. To further specify patient selection factors, investigators were asked to specifically indicate for each patient the presence and type of associated cardiac defects, the presence of Noonan's syndrome, and the pulmonary valve morphology for which decisions concerning BPV were based. The pulmonary valve morphology was selected from one of four defined categories: (1) typical: mild to moderately thickened leaflets with evidence of commissural fusion and normal annular dimensions, (2) dysplastic: severely thickened leaflets with evidence of nodular hyperplasia or annular hypoplasia, (3) combined: dysplastic valve morphology as defined but with additional evidence of commissural fusion, and (4) complex: other morphologies including primarily post–surgical valvotomy valves and valves involved as part of complex congenital heart lesions.

Data concerning subsequent surgical or interventional catheterization procedures were requested. Data requested from the most recent follow-up assessment included the date and the right ventricle to pulmonary artery (RV-PA) systolic pressure gradient estimated at either cardiac catheterization (peak-to-peak systolic gradient) or by continuous-wave Doppler echocardiography (peak instantaneous systolic gradient). Pulmonary regurgitation was graded subjectively as none, trivial, mild, moderate, or severe, based on clinical, cardiac catheterization, or pulsed and color Doppler echocardiographic assessments. The follow-up data collection was begun in 1989 and closed on October 15, 1991. The original and follow-up data for each patient were linked after verification and correction.

Data Analysis

The distributions of values for predictor and outcome variables were determined, and frequencies are reported for categorical and ordinal variables and means (±1 SD) or medians (with ranges) for continuous variables, depending on their distributions.

To determine independent factors that were predictive of the failure of the initial BPV to provide long-term relief of the obstruction, a suboptimal long-term outcome was defined. Patients who required surgery or a repeat BPV to relieve persistent or recurrent obstruction or who were found at the most recent follow-up assessment to have an RV-PA systolic pressure gradient of ≥36 mm Hg were defined as having had a suboptimal long-term outcome and were contrasted with the remainder. A gradient cut-point of 36 mm Hg was chosen arbitrarily because it represented a gradient above which closer medical follow-up or treatment might reasonably be considered to be necessary and because it corresponded to a Doppler echocardiographic peak systolic velocity of 3 m/s using a modified Bernoulli equation. After bivariate comparisons of characteristics, independent factors that were predictive of this suboptimal long-term result were sought in stepwise multiple logistic regression analyses with Hosmer and Lemeshow goodness-of-fit testing. In addition, for the subgroup of patients who had intervening procedures, the characteristics of patients who underwent surgery were compared with those who had repeat BPV. The subjective grade of pulmonary regurgitation at follow-up assessment was explored as a further outcome by contrasting the characteristics of patients with moderate or severe regurgitation with the characteristics of patients with lesser grades.

The clinical course for each individual patient was defined in relation to whether their initial BPV was successful in reducing the total RV-PA peak-to-peak systolic gradient <36 mm Hg. Total residual gradients were not routinely assessed as to the relative contributions of valvar versus infundibular components; therefore, this factor could not be analyzed. To determine risk factors for progression of obstruction, the group of patients with immediate residual gradients <36 mm Hg were divided into two subgroups. Characteristics at follow-up assessment of patients who continued to have gradients <36 mm Hg were contrasted with characteristics of patients whose gradients had either increased to ≥36 mm Hg or who required surgery or repeat BPV. Likewise, to determine risk factors for regression of important residual obstruction, the group of patients with immediate residual gradients of ≥36 mm Hg were divided into two subgroups. Characteristics at follow-up assessment of patients whose residual gradients regressed to <36 mm Hg were contrasted with characteristics of patients who either continued to have important gradients or who required surgery or repeat BPV.

Results

Of the eligible study population of 835 patients from 28 institutions, no response was obtained from 6 institutions, resulting in the exclusion of 177 patients from the final cohort. Of the 658 remaining patients from 22 institutions, completed follow-up data collection forms were returned for 533 patients (81%). The median follow-up interval was 33 months, with a range from 1 month to 8.7 years.

Given the final follow-up rate of 64% (533 of 835), concerns about response bias were addressed. The characteristics of the 533 patients for whom follow-up data were obtained were contrasted with the characteristics of the remaining 302 patients who were either lost to follow-up or who were from nonparticipating institutions. There were no significant differences between these two groups regarding patient age, valve hinge point diameter, the presence of Noonan's syndrome or dysplastic valve morphology, the ratio of balloon to valve hinge point diameter, or any hemodynamic parameters at BPV.

For patients with follow-up data, the median patient age at the initial BPV was 3.7 years (1 day to 55 years). Patient age was <2 years for 36% of patients, with 4% of patients being ≤28 days of age. The distribution of patients by age at BPV did not change significantly over time as the procedure was more widely adopted among the 22 participating institutions. Pulmonary valve morphology at BPV was categorized as typical for 82% of patients, dysplastic for 8%, combined for 5%, and complex for 5%. The mean valve hinge point diameter was 14.8±4.9 mm. Noonan's syndrome was noted for 5% of patients. Associated cardiac lesions were simple in 18% of patients, complex in 4%, and absent in 78%. A simultaneous double-balloon technique was used for 9% of patients. The effective dilating diameter for two simultaneous balloons was calculated using a previously reported formula.[4] The mean ratio of balloon effective–dilating diameter to valve hinge point diameter was 1.12±0.20. The mean peak systolic RV pressure decreased immediately after BPV from 92±35 to 52±24 mm Hg (paired t test, $P<.0001$), with a decrease in the mean ratio of RV to systemic artery peak systolic pressure from 0.90±0.35 to 0.49±0.24 ($P<.0001$). There was significant relief of mean peak RV to peak PA systolic pressure gradients (74±37 to 29±22 mm Hg, $P<.0001$). Immediate residual gradients of <36 mm Hg were noted for 74% of patients.

At follow-up assessment, an intervening surgical valvotomy or valvectomy had been performed in 44 patients (8%), 17 of whom also required an RV infundibular or transannular patch. A repeat BPV had been performed in 40 patients (8%). The remaining 449 patients (84%) were noted to be free from intervening

TABLE 1. Characteristics of Patients Related to Failure of the Initial Balloon Pulmonary Valvuloplasty to Provide Long-term Relief of Obstruction

Variable	Success (n=399)	Failure (n=120)	P
Median study time interval, y	4.5 (0.4-6.1)	4.3 (0-5.9)	<.005
Median patient age at initial BPV, y	4.0 (0-55)	1.9 (0-51)	<.0001
Valve morphology			
Typical	91%	52%	<.0001
Dysplastic	4%	22%	
Combined	2%	16%	
Complex	3%	10%	
Mean valve hinge point diameter, mm	15.5±4.7	12.1±4.5	<.0001
Noonan's syndrome	4%	12%	<.005
Associated cardiac lesions			
None	83%	62%	<.0001
Simple	14%	30%	
Complex	3%	8%	
Mean pre-BPV systolic pressure gradient, mm Hg	72.1±35.5	81.1±38.2	<.05
Mean pre-BPV ratio of RV to systemic artery systolic pressure	0.86±0.32	1.05±0.43	<.0001
Mean ratio of balloon to valve hinge point diameter at BPV	1.14±0.20	1.07±0.22	<.005
Double-balloon technique used	9%	8%	NS
Mean immediate residual post-BPV gradient, mm Hg	25.6±20.5	43.0±23.3	<.0001

BPV indicates balloon pulmonary valvuloplasty; RV, right ventricle.

Study excludes 14 patients who were noted at follow-up to have had no intervening procedures but whose gradient was unknown. Success refers to patients who had no intervening procedures and were noted at follow-up assessment to have gradients <36 mm Hg; failure refers to patients who either had subsequent surgery or repeat BPV or who were noted to have follow-up gradients of ≥36 mm Hg.

procedures. Follow-up RV-PA gradients were obtained at cardiac catheterization (peak to peak) for 67 patients and by Doppler echocardiography (peak instantaneous) for 368 patients, with no follow-up gradient reported for 14 patients. Follow-up gradients of <36 mm Hg were noted for 399 patients and ≥36 mm Hg for 36 patients. Thus, 449 patients (84%) were noted at follow-up to be free from intervening procedures, 399 of whom were also known to have gradients of <36 mm Hg (75%).

To determine factors that predicted failure of the initial BPV to provide long-term relief of obstruction, the characteristics of patients who had a suboptimal long-term outcome were contrasted with the characteristics of the remaining patients (Table 1). A study time interval was calculated for each patient by subtracting the date of the initial BPV from the date of the first attempted BPV that was reported to the VACA Registry. The median time interval was shorter for patients who had a suboptimal long-term outcome. Patients with a suboptimal outcome were significantly younger at the initial BPV, were more likely to have valve morphologies other than typical, had smaller mean valve hinge point diameters, were more likely to have Noonan's syndrome or associated cardiac lesions, had higher mean predilation gradients or RV to systemic artery systolic pressure ratios, and had higher mean immediate residual gradients. A suboptimal long-term result was significantly associated with the use of a lower mean ratio of balloon to valve hinge point diameter but not with the use of a double-balloon technique.

To explore the independent relation between the significant predictor variables and a suboptimal long-term outcome, stepwise multiple logistic regression analyses were performed. All variables explored in bivariate analyses were entered into the regression model-building with one notable exception. Normalization of angiographically determined valve hinge point diameters was not possible because data regarding patient weight or body surface area were not collected. Normalization for age was not considered valid, although age and valve hinge point diameter were highly correlated (Spearman's correlation coefficient, .84; $P<.0001$). In the initial stages of model building, age could not be entered significantly in the presence of other factors, whereas valve dimension consistently was shown to be a significant independent predictor. The relation between age, valve hinge point diameter, and annular hypoplasia appeared to be complex, and given the inability to determine appropriate normalized scores for annulus size, it was decided to enter valve hinge point diameter into the final models as the proxy variable for the correlated effects of age and annulus characteristics.

Significant variables and calculated adjusted odds ratios were derived from the final multivariate model (Table 2). A longer study time interval, a larger valve

TABLE 2. Independent Predictors of Failure of the Initial Balloon Pulmonary Valvuloplasty to Provide Long-term Relief of Obstruction

Variable	Adjusted Odds Ratio*	95% Confidence Interval
Study time interval (per consecutive year)	0.71	0.54, 0.93
Valve hinge point diameter (per 1-mm increase)	0.81	0.75, 0.88
RV-PA gradient immediately after initial BPV (per 10 mm Hg increase)	1.32	1.16, 1.50
Balloon to valve hinge point diameter ratio for patients with the following valve morphology (per 0.1 increase)		
Typical	0.52	0.40, 0.68
Dysplastic	0.95	0.60, 1.50
Combined	1.01	0.52, 1.98
Complex	0.43	0.21, 0.88

BPV indicates balloon pulmonary valvuloplasty; RV, right ventricle; and PA, pulmonary artery.
Failure is defined as an intervening surgical procedure or repeat BPV having been performed or a follow-up gradient of ≥36 mm Hg.
*From multiple logistic regression analyses; nonsignificant variables not included in the final model are the presence of Noonan's syndrome or associated cardiac lesions, pre-BPV hemodynamic parameters, and the use of a double-balloon technique.

hinge point diameter, a lower immediate residual gradient, typical valve morphology, and a larger ratio of balloon to valve hinge point diameter all were shown to be significant independent predictors of improved long-term results after BPV. The presence of Noonan's syndrome or associated cardiac lesions, hemodynamic parameters before the initial BPV, and the use of a double-balloon technique were not significant independent predictors after controlling for the effects of the variables included in the final model. The effect of balloon to valve hinge point diameter ratio depended on the patient's valve morphology. Patients with typical and complex morphologies had improved results with larger ratios, whereas there was no significant effect of ratio on the results for patients with dysplastic or combined valve morphologies. Patients with other than typical valve morphologies showed consistently higher adjusted odds of a suboptimal long-term result over the usual range of values of balloon to valve hinge point diameter ratios.

Of the patients who required an intervening procedure, those who underwent surgery (n=44) were significantly different from those who underwent a repeat BPV (n=40) (Table 3). Surgical patients were less likely to have a typical valve morphology and were more likely to have Noonan's syndrome or associated cardiac lesions. They did not differ regarding study time interval, age, valve hinge point diameter or hemodynamic characteristics at BPV, or the gradient before the intervening procedure. Patients who underwent a repeat BPV were more likely to have technical failures secondary to the use of lower balloon to valve hinge point diameter ratios. Surgery was associated with a lower follow-up gradient but higher grades of pulmonary regurgitation.

The subjective grade of pulmonary regurgitation noted at follow-up was none for 26% of patients, trivial for 22%, mild for 45%, and moderate for 7%, with no patients having severe regurgitation. The characteristics of patients with moderate pulmonary regurgitation did not differ significantly from the characteristics of patients with lesser grades regarding study time interval, age, presence of Noonan's syndrome, predilation hemodynamic parameters, use of double-balloon technique, or whether a subsequent repeat BPV had been performed. Patients with moderate pulmonary regurgitation, however, were significantly more likely to have a valve morphology other than typical (54% versus 13%, $P<.0001$), smaller median valve hinge point diameter (12 mm, 8 to 20 versus 14.7 mm, 5 to 30; $P<.005$), associated cardiac lesions (51% versus 17%, $P<.0001$), higher mean immediate residual gradients (39.4±30.9 versus 27.5±20.9 mm Hg, $P<.005$), and higher balloon to valve hinge point diameter ratios (1.25±0.32 versus 1.12±0.18, $P<.005$). They also were more likely to have had an intervening surgical procedure (30% versus 4%, $P<.0001$). From multiple logistic regression analyses, significant independent predictors of the presence of moderate pulmonary regurgitation included a complex valve morphology (includes many postsurgical valves) (adjusted odds ratio [OR], 5.5; 95% confidence interval [CI], 1.7, 17.8; $P<.005$), an intervening surgical procedure (OR, 9.1; CI, 3.4, 24.6; $P<.0001$), and an increasing ratio of balloon to valve hinge point diameter (1.3 for each 0.1 increment; CI, 1.1, 1.5; $P<.005$). A more detailed bivariate analysis of the effect of balloon to valve hinge point diameter ratio on the grade of pulmonary regurgitation confirmed a significant trend ($P<.005$) toward greater regurgitation with use of ratios of ≥1.4 (Fig 1).

Given that the immediate residual gradient was a significant independent predictor of long-term outcome after BPV, the clinical course for individual patients was determined by dividing the study population into two groups, based on their immediate outcome (Fig 2). One group included 133 patients with immediate residual gradients of ≥36 mm Hg after their initial BPV. At follow-up assessment, 25 patients were found to have had subsequent surgery and 23 a repeat BPV. No intervening procedure had been performed in 85 patients whose gradients were noted at follow-up to be

TABLE 3. Comparison of Patients Who Required Surgery Versus Repeat Balloon Valvuloplasty for Relief of Persistent or Recurrent Obstruction

Variable	Intervening Procedure		P
	Surgery (n=44)	Repeat BPV (n=40)	
Median study time interval, y	4.4 (0-5.9)	3.6 (1.3-5.9)	NS
Median patient age at initial BPV, y	1.1 (0-16)	2.1 (0-23)	NS
Valve morphology			
Typical	21%	72%	<.0001
Dysplastic	40%	8%	
Combined	18%	17%	
Complex	21%	3%	
Mean valve hinge point diameter, mm	10.7±3.7	12.3±5.1	NS
Noonan's syndrome	18%	3%	<.05
Associated anomalies			
None	42%	80%	<.0001
Simple	42%	20%	
Complex	16%	0	
Mean pre-BPV gradient, mm Hg	79.0±35.0	91.1±46.3	NS
Mean pre-BPV ratio of RV to systemic artery systolic pressure	1.09±0.46	1.15±0.46	NS
Mean immediate residual post-BPV gradient, mm Hg	49.0±29.7	45.5±21.6	NS
Mean ratio of balloon to valve hinge diameter at BPV	1.16±0.18	0.94±0.22	<.005
Double-balloon technique used	5%	11%	NS
Mean gradient before any intervening procedure, mm Hg	67.2±27.6	67.8±31.8	NS
Median gradient at recent follow-up, mm Hg	15 (0-68)	23 (0-165)	<.005
Subjective grade of pulmonary regurgitation			
None	7%	8%	<.0001
Trivial	15%	30%	
Mild	41%	54%	
Moderate	37%	8%	

BPV indicates balloon pulmonary valvuloplasty; RV, right ventricle.

≥36 mm Hg for 14 patients, <36 mm Hg for 69 patients, and not available for 2 patients. Thus, 47% of patients who had significant immediate residual gradients had a suboptimal long-term outcome, with the remainder (53%) showing spontaneous regression of gradients to <36 mm Hg.

The second group included 383 patients who had an optimal immediate result from their initial BPV, ie, an immediate residual gradient of <36 mm Hg; 9 were found at follow-up to have had subsequent surgery and 16 a repeat BPV. Of the 358 patients who had no intervening procedures, 20 were found at follow-up to have a gradient of ≥36 mm Hg, with a gradient not available for 12 patients. Thus, for patients with optimal immediate results, only 12% had progressed to require intervening procedures or were noted to have a significant follow-up gradient. The residual gradient immediately after BPV was not reported for 17 patients. At follow-up, 10 of these patients had subsequent surgery, 1 a repeat BPV, and 2 had no intervening procedures but were noted to have gradients of ≥36 mm Hg.

Given the immediate results after BPV, risk factors were sought that predicted the clinical course for each group. Of the patients who had successful procedures

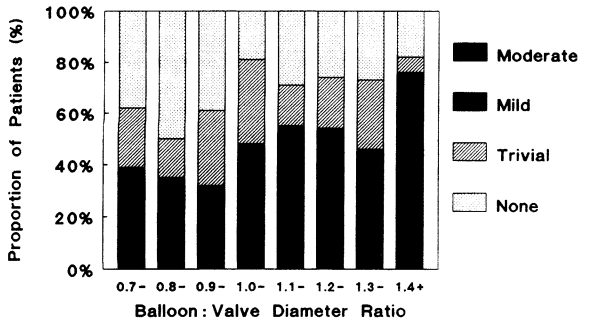

FIG 1. Effect of the ratio of balloon to valve hinge point diameter on the grade of pulmonary regurgitation at long-term follow-up assessment. Patients who had valve morphologies other than typical or who had intervening surgical procedures were excluded.

with immediate residual gradients <36 mm Hg, progression to surgery or repeat BPV or a follow-up gradient of ≥36 mm Hg was noted for 12% of this group. In bivariate analyses, significant risk factors for progression included shorter study time interval, young patient age, valve morphologies other than typical, smaller valve hinge point diameter, the presence of Noonan's syndrome or associated cardiac lesions, higher pre-BPV ratio of RV to systemic artery systolic pressure, higher immediate residual gradient, and lower balloon to valve hinge point diameter ratio. Significant independent predictors of progression in multiple logistic regression analyses included dysplastic valve morphology, lower balloon to valve hinge point diameter ratio, and smaller valve hinge point diameter (Table 4).

Of patients who had important immediate residual gradients of ≥36 mm Hg at the initial BPV, 53% had regression of these gradients to <36 mm Hg at follow-up without the need for any intervening procedure. In bivariate analyses, significant predictors of regression included typical valve morphology, larger valve hinge point diameter, and higher pre-BPV gradient. In multiple logistic regression analyses, significant independent predictors of regression included only typical valve morphology and a shorter study time interval (Table 5).

Discussion

This study clearly defines the independent contribution made by several patient selection and technical factors to the prediction for patients of the long-term effectiveness of BPV. There are several potential threats to the validity of these findings. The patient cohort whose results are reported represents an early and evolving experience with pediatric interventional cardiology in general and BPV specifically and may not represent the current status of the procedure. This assertion may be supported by the finding in this study that the study time interval was a significant and independent predictor of gradually improved results. However, this effect was small, and the majority of patients whose procedures were reported to the VACA Registry were performed after any potential "learning curve" effect may have been operating. It could be debated that for BPV, the indications and techniques had become quickly standardized and disseminated.

Additional sources of potential bias relate to the representativeness of the patient population and the reliability with which the data were collected and reported. The lack of complete follow-up on all patients has the potential to introduce response bias, but this was evaluated and was not evident in this study. While this type of analysis cannot uncover differences in outcomes related to response status, there were no

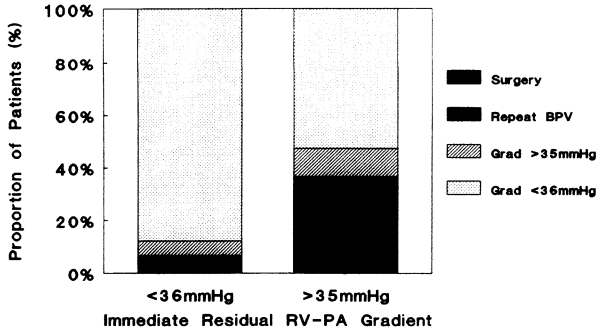

FIG 2. Effect of the immediate results of the initial balloon pulmonary valvuloplasty (BPV) on the patient's status at long-term follow-up. Grad indicates gradient; surgery, surgical pulmonary valvotomy or valvectomy; RV, right ventricle; and PA, pulmonary artery.

TABLE 4. Independent Predictors of Progression to a Suboptimal Outcome After Successful Initial Balloon Pulmonary Valvuloplasty

Variable	Adjusted Odds Ratio*	95% Confidence Interval
Valve morphology (relative to typical morphology)		
Dysplastic	9.61	2.80,33.0
Combined	4.73	0.96,23.3
Complex	3.81	0.77,18.8
Valve hinge point diameter (per 1-mm increase)	0.79	0.72,0.88
Balloon to valve hinge point diameter ratio (per 0.1 increase)	0.48	0.36,0.64

Suboptimal outcome is defined as either an intervening surgical or repeat balloon valvuloplasty having been performed or a follow-up gradient of ≥36 mm Hg; successful balloon pulmonary valvuloplasty is defined as a reduction in immediate gradient to <36 mm Hg.

*Derived from multiple logistic regression analyses.

TABLE 5. Independent Predictors of Regression of Important Immediate Residual Gradients After Balloon Pulmonary Valvuloplasty

Variable	Adjusted Odds Ratio	95% Confidence Interval
Study time interval (per consecutive year)	1.61	1.10,2.38
Valve morphology (relative to typical morphology)		
Dysplastic	0.04	0.008,0.20
Combined	0.04	0.005,0.33
Complex	0.33	0.09,1.24

Regression is defined as the resolution of an immediate residual gradient of ≥36 mm Hg to <36 mm Hg at follow-up without the need for an intervening procedure.

differences between respondents and nonrespondents regarding any of the variables that were subsequently shown to be significant predictors of outcomes. The multi-institutional nature of our data raises issues of reliability regarding how patients were selected for BPV, how the procedure was performed, and the degree of rigor with which measurement were made and reported. The "pooled" nature of this large patient series tends to negate significant biases that may have been introduced by any single institution and provides for more generalizable prognostic information across patient populations.

In terms of the intermediate and long-term reduction in RV-PA systolic pressure gradient at follow-up, the current series is comparable in results to other series that report follow-up data.[1,2,5-15] However, patients may be more interested in whether they might need further therapy or closer follow-up than in the actual value of their gradient. The analyses of follow-up data should reflect the importance of clinical course and prognosis. Meaningful cut-points for continuously measured outcomes such as gradient therefore become relevant. While many factors may contribute to patient selection, increasingly the echocardiographically derived RV-PA peak instantaneous systolic pressure gradient is the pivotal clinical study that affects decisions regarding the need for BPV. Rao[16] and Wang et al[17] have advocated that a gradient cut-point of 50 mm Hg be used to determine candidacy for BPV, but patients with gradients less than this have frequently undergone BPV[3] or may be considered to be at risk for progression, especially those patients requiring treatment at less than 2 years of age.[18-20] In the current series, 6.5% of patients with immediate gradient reductions to <36 mm Hg after their initial BPV progressed to require additional therapy, with another 5.8% noted to have gradients of ≥36 mm Hg at follow-up. Clearly, the 50 mm Hg gradient cut-point should be reconsidered.

The new contribution from this series is the definition of several independent predictor variables that impact on the long-term result after BPV; these variables increase the ability to define the long-term prognosis for individual patients. In previous follow-up studies, valve morphologies other than typical, valve cusp thickness, young patient age, poor immediate hemodynamic result, and the use of undersized balloons have been variably related to persistent follow-up gradients.[1,14,21-26] Two follow-up studies have sought independent predictors of long-term results using multivariate analyses. Rao concluded that the ratio of balloon to valve hinge point diameter and the immediate residual gradient were significant independent predictors,[2] whereas McCrindle and Kan[1] concluded that only patient age <2 years was a significant independent predictor. Both studies were limited by small patient numbers. The large patient numbers in the current series allowed the detection of a significant independent association between long-term outcome and valve morphology, valve hinge point diameter, balloon to valve dimension ratio, immediate hemodynamic results, and study time interval. Patient age, the presence of Noonan's syndrome or associated cardiac anomalies, pre-BPV hemodynamic parameters, and double-balloon technique did not independently predict long-term outcome after controlling for the significant predictors.

Our study clearly identified valve morphology and valve hinge point diameter as significant independent predictors of long-term results. Pathologically, these two characteristics represent the contribution of anatomy to the definition of the "balloon-dilatable" valve. Valve morphology probably represents the contribution of valve cusp thickness or deformity, whereas valve hinge point diameter represents the contribution of hypoplasia or narrowing of the valve annulus itself. Studies of pulmonary valve dysplasia have relied on various qualitative observations of valve morphology and make distinctions at inconsistent points along a continuum of anatomic changes.[27-31] Thus, reported results of BPV for atypical valve morphologies have been variable and confusing.[22,26,30,32-34] Adding to this confusion are case reports of spontaneous regression of pulmonary valve dysplasia.[35,36] Perhaps the most practical solution is to define a dysplastic pulmonary valve as one that fails to respond to balloon dilation. Further evidence from our analyses supporting this approach is the finding that the effect of the ratio of balloon to valve hinge point diameter interacted with or was dependent on the valve morphology, with little effect of increasing ratios when the valve morphology was atypical. This effect has not been previously described and is in conflict with results reported by Rao,[33] who suggested that improved results for dysplastic valves occurred when oversized balloons were used. The inability of the presence of Noonan's syndrome and associated cardiac anomalies to independently predict long-term results is best explained by their effects being due primarily to their association with an increased incidence of valve dysplasia.[37] The observation that the immediate residual gradient was a significant independent predictor of long-term results represents a further dimension of the definition of the balloon-dilatable valve. Our clinical course analyses indicated that important immediate residual gradients frequently persisted; this may distinguish a subgroup of patients with factors affecting valvar anatomy who were not accounted for by the variables valve morphology or valve hinge point diameter.

Patient age at the initial BPV was not shown to be a significant independent predictor of long-term results in this study, even when this variable was categorized to distinguish neonates and infants. The age at which BPV is performed may be more of a function of factors that impact on early clinical presentation and disease severity rather than patient size and maturity. The independent effect of patient size and maturity is probably small and would require a much larger patient series with greater numbers of neonates and infants in order to have sufficient statistical power to differentiate it from the effect of anatomy and its relation to disease severity. Our study suggests that most of the age effect is due to anatomy, since valve morphology and valve dimension were independent predictors whereas pre-BPV hemodynamic indicators of the severity of obstruction, such as RV-PA systolic pressure gradient and the ratio of RV to systemic arterial systolic pressure, were not. Follow-up studies have suggested that infants are more likely to demonstrate progression of obstruction over time.[18-20] Our study suggests that after controlling for the effects of anatomy and technique, age is not an independent risk factor for progression after BPV.

The ratio of balloon to valve hinge point diameter is perhaps the single most significant technical factor impacting on therapeutic alterations of valve anatomy, provided that an adequate inflation of the balloon at the appropriate anatomic position is achieved. Our study clearly shows an independent linear improvement in long-term results with increasing ratios but that this relation is dependent on the valve morphology. For patients with typical valve morphology, there appeared to be no upper limit regarding the maximum ratio that would give improved results; however, the number of patients whose valves were dilated with oversized balloons was small. We did observe a significant rise in the incidence of important pulmonary regurgitation with the use of ratios of ≥ 1.4, and we would suggest that the optimal ratio for BPV is between 1.2 and 1.4, ensuring maximal relief of obstruction while avoiding the production of important pulmonary regurgitation.

Our results indicate that patients who failed initial BPV and underwent surgery were probably patients with valves that were not balloon dilatable, since these patients differed from patients who underwent repeat BPV for initial failure in that they were more likely to have an atypical valve morphology, Noonan's syndrome, and associated cardiac anomalies. Surgical patients had lower residual gradients at follow-up but higher grades of pulmonary regurgitation. O'Connor et al,[15] in a case-control study, showed that surgical patients also had a higher incidence of ventricular ectopic activity. Given concerns about potential patient selection bias, the degree to which surgical technique versus anatomic substrate contributed to this observation is unknown.

Many patient series have reported some evidence of regression of significant residual gradients during follow-up, and this has been attributed to the regression of secondary RV infundibular hypertrophy.[8-11,13,38-42] The two factors predicting regression in our study were typical valve morphology and longer study time interval. Regression of residual gradients is unlikely to occur in patients whose residual obstruction continues to be valvar in nature, as would be expected in patients with valve morphologies other than typical. The association with study time interval is best explained by the fact that early in the experience with BPV, the role of infundibular hypertrophy and its potential for regression were not known, and therefore these patients were sent for surgery after BPV failed to adequately relieve the obstruction. Although our study showed the immediate residual gradient to be a significant independent predictor of long-term results, we did not distinguish valvar from infundibular gradients. It might be suggested that the prognostic residual gradient for a suboptimal long-term outcome is the gradient at the valvar level. It is therefore recommended that for prognostication, every attempt should be made after BPV to delineate the relative contributions of valvar versus infundibular obstruction in the assessment of significant residual gradients.

BPV is effective in the long-term relief of obstruction secondary to congenital pulmonary valve stenosis. Accurate prognostication depends on the careful determination of valvar anatomy, and future studies should focus on more detailed and quantitative assessments of valve characteristics. The use of a ratio of balloon to valve hinge point diameter of 1.2 to 1.4 in the setting of typical valve morphology will ensure long-term success.

Appendix

Participating VACA Registry Investigators

L. Benson, B. McCrindle: The Hospital for Sick Children, Toronto, Canada; V. Fontes: Instituto "Dante Pazzanese" de Cardiologia, Sao Paolo, Brazil; J. Kan: The Johns Hopkins Hospital, Baltimore, Md; C. Mullins, J. Slack: Texas Children's Hospital, Houston, Tex; S. Shapiro, J. Cockerham: Georgetown University Hospital, Washington, DC; P.S. Rao: University of Wisconsin Medical School, Madison; R. Beekman, A. Andes: University of Michigan, Ann Arbor; V. Zales, A. Muster: Children's Memorial Hospital, Chicago, Ill; J. Murphy, D. Donnelly: Children's Hospital of Philadelphia (Pa); P. Stanger: University of California at San Francisco; T. Lloyd: University of Arizona, Tucson; G. Ben Shachar: Rainbow Babies and Childrens Hospital, Cleveland, Ohio; J. Hess: Sophia Children's Hospital, Rotterdam, The Netherlands; R. Morrow, E. Colvin: University of Alabama Medical College Birmingham; L. Latson: University of Nebraska Medical Center, Omaha; R. Collins-Nakai: University of Alberta, Edmonton, Canada; D. Fischer: Children's Hospital of Pittsburgh (Pa); A. Rocchini: University of Minnesota Hospital, Minneapolis; D. Hagler: The Mayo Clinic, Rochester, Minn; J. Morriss: University of Iowa Hospitals and Clinics, Iowa City; J. Finley, D. Human: I.W. Killam Hospital for Children, Halifax, Canada; D. Girod: Riley Hospital for Children, Indianapolis, Ind; H. Allen: Children's Hospital—Columbus, Columbus, Ohio.

Acknowledgment

This study was supported in part by a grant from the Children's Hospital Research Foundation, Winnipeg, Manitoba, Canada.

References

1. McCrindle BW, Kan JS. Long-term results after balloon pulmonary valvuloplasty. *Circulation.* 1991;83:1915-1922.
2. Rao PS, Thapar MK, Kutayli F. Causes of restenosis after balloon valvuloplasty for valvular pulmonary stenosis. *Am J Cardiol.* 1988; 62:979-982.
3. Stanger P, Cassidy SC, Girod DA, Kan JS, Lababidi Z, Shapiro SR. Balloon pulmonary valvuloplasty: results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *Am J Cardiol.* 1990;65:775-783.
4. Rao PS. Influence of balloon size on short-term and long-term results of balloon pulmonary valvuloplasty. *Tex Heart Inst J.* 1987; 14:57-61.
5. Kan JS, White RI, Mitchell SE, Anderson JH, Gardner TJ. Percutaneous transluminal balloon valvuloplasty for pulmonary valve stenosis. *Circulation.* 1984;69:554-560.
6. Kveselis DA, Rocchini AP, Snider AR, Rosenthal A, Crowley DC, Dick M. Results of balloon valvuloplasty in the treatment of congenital valvar pulmonary stenosis in children. *Am J Cardiol.* 1985; 56:527-532.
7. Shrivastava S, Sundar AS, Mukhopadhyaya S, Rajani M. Percutaneous transluminal balloon pulmonary valvoplasty: long-term results. *Int J Cardiol.* 1987;17:303-314.
8. Robertson M, Benson LN, Smallhorn JS, Musewe N, Freedom RM, Moes CA, Burrows P, Johnston AE, Burrows FA, Rowe RD. The morphology of the right ventricular outflow tract after percutaneous pulmonary valvotomy: long-term follow-up. *Br Heart J.* 1987;58:239-244.
9. Fontes VF, Sousa JE, Esteves CA, Silva MV, Cano MN, Maldonado G. Pulmonary valvoplasty: experience of 100 cases. *Int J Cardiol.* 1988;21:335-342.
10. Rey C, Marache P, Francart C, Dupuis C. Percutaneous transluminal balloon valvuloplasty of congenital pulmonary valve stenosis, with a special report on infants and neonates. *J Am Coll Cardiol.* 1988;11: 815-820.
11. Rao PS, Fawzy ME, Solymar L, Mardini MK. Long-term results of balloon pulmonary valvuloplasty of valvar pulmonic stenosis. *Am Heart J.* 1988;115:1291-1296.

12. Mullins CE, Ludomirsky A, O'Laughlin MP, Vick GW, Murphy DJJ, Huhta JC, Nihill MR. Balloon valvuloplasty for pulmonic valve stenosis—two-year follow-up: hemodynamic and Doppler evaluation. *Cathet Cardiovasc Diagn.* 1988;14:76-81.
13. Sievert H, Kober G, Bussman WD, Reuhl J, Cieslinski G, Satter P, Kaltenbach M. Long-term results of percutaneous pulmonary valvuloplasty in adults. *Eur Heart J.* 1989;10:712-717.
14. Schmaltz AA, Bein G, Gravinghoff L, Hagel K, Hentrich F, Hofstetter R, Lindinger A, Kallfelz HC, Kramer HH, Mennicken U, Mocellin R, Pfefferkorn JR, Redel D, Rupprath G, Sandhage K, Singer H, Sebening W, Ulmer H, Vogt J, Wessel A. Balloon valvuloplasty of pulmonary stenosis in infants and children: co-operative study of the German Society of Pediatric Cardiology. *Eur Heart J.* 1989;10:967-971.
15. O'Connor BK, Beekman RH, Lindauer A, Rocchini A. Intermediate-term outcome after pulmonary balloon valvuloplasty: comparison with a matched surgical control group. *J Am Coll Cardiol.* 1992;20:169-173.
16. Rao PS. Indications for balloon pulmonary valvuloplasty. *Am Heart J.* 1988;116:1661-1662.
17. Wang JK, Lue HC, Wu MH, Young ML. Efficacy of balloon valvuloplasty in treating mild pulmonary stenosis. *Acta Cardiol.* 1992;47:349-355.
18. Mody MR. The natural history of uncomplicated valvular pulmonic stenosis. *Am Heart J.* 1975;90:317-321.
19. Nugent EW, Freedom RM, Nora JJ, Ellison RC, Rowe RD, Nadas AS. Clinical course in pulmonary stenosis. *Circulation.* 1977; 56(suppl I):I-38-I-47.
20. Wennevold A, Jacobsen JR. Natural history of valvular pulmonary stenosis in children below the age of two years: long-term follow-up with serial heart catheterizations. *Eur J Cardiol.* 1978;8:371-378.
21. Rao PS. Further observations on the effect of balloon size on the short term and intermediate term results of balloon dilatation of the pulmonary valve. *Br Heart J.* 1988;60:507-511.
22. Ballerini L, Mullins CE, Cifarelli A, Pasquini L, De Simone G, Giannico S, Guccione P, Di Donato R, di Carlo D. Percutaneous balloon valvuloplasty of pulmonary valve stenosis, dysplasia, and residual stenosis after surgical valvotomy for pulmonary atresia with intact ventricular septum: long-term results. *Cathet Cardiovasc Diagn.* 1990;19:165-169.
23. Tynan M, Baker EJ, Rohmer J, Jones ODH, Reidy JF, Joseph MC, Ottenkamp J. Percutaneous balloon pulmonary valvuloplasty. *Br Heart J.* 1985;53:520-524.
24. Kopecky SL, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM, McGoon DC, Kirklin JW, Danielson GK. Long-term outcome of patients undergoing surgical repair of isolated pulmonary valve stenosis: follow-up at 20-30 years. *Circulation.* 1988; 78:1150-1156.
25. Melgares R, Prieto JA, Azpitarte J. Success determining factors in percutaneous transluminal balloon valvuloplasty of pulmonary valve stenosis. *Eur Heart J.* 1991;12:15-23.
26. Masura J, Burch M, Deanfield JE, Sullivan ID. Five-year follow-up after balloon pulmonary valvuloplasty. *J Am Coll Cardiol.* 1993;21: 132-136.
27. Koretzky ED, Moller JH, Korns ME, Schwartz C, Edwards JE. Congenital pulmonary stenosis resulting from dysplasia of valve. *Circulation.* 1969;40:43-53.
28. Jeffrey RF, Moller JH, Amplatz K. The dysplastic pulmonary valve: a new roentgenographic entity: with a discussion of the anatomy and radiology of other types of valvular pulmonary stenosis. *Am J Roentgenol.* 1972;114:322-339.
29. Schneeweiss A, Blieden LC, Shem-Tov A, Goor D, Milo S, Neufeld HN. Diagnostic angiocardiographic criteria in dysplastic stenotic pulmonic valve. *Am Heart J.* 1983;106:761-762.
30. Musewe NN, Robertson MA, Benson LN, Smallhorn JF, Burrows PE, Freedom RM, Moes CA, Rowe RD. The dysplastic pulmonary valve: echocardiographic features and results of balloon dilatation. *Br Heart J.* 1987;57:364-370.
31. Cazzaniga M, Vagnola O, Alday L, Spillman A, Sciegata A, Faella H, Kurlat I. Balloon pulmonary valvuloplasty in infants: a quantitative analysis of pulmonary valve-anulus-trunk structure. *J Am Coll Cardiol.* 1992;20:345-349.
32. DiSessa TG, Alpert BS, Chase NA, Birnbaum SE, Watson DC. Balloon valvuloplasty in children with dysplastic pulmonary valves. *Am J Cardiol.* 1987;60:405-407.
33. Rao PS. Balloon dilatation in infants and children with dysplastic pulmonary valves: short-term and intermediate-term results. *Am Heart J.* 1988;116:1168-1173.
34. Marantz PM, Huhta JC, Mullins CE, Murphy DJJ, Nihill MR, Ludomirsky A, Yoon GY. Results of balloon valvuloplasty in typical and dysplastic pulmonary valve stenosis: Doppler echocardiographic follow-up. *J Am Coll Cardiol.* 1988;12:476-479.
35. Kirk CR, Wilkinson JL, Qureshi SA. Regression of pulmonary valve stenosis due to a dysplastic valve presenting in the neonatal period. *Eur Heart J.* 1988;9:1027-1029.
36. Chan KC, Clark D, Gibbs JL. Spontaneous resolution of pulmonary stenosis. *Int J Cardiol.* 1989;24:375-377.
37. Noonan JA. Hypertelorism with Turner phenotype: a new syndrome associated with congenital heart disease. *Am J Dis Child.* 1968;116:373-380.
38. Griffith BP, Hardesty RL, Siewers RD, Lerberg DB, Ferson PF, Bahnson HT. Pulmonary valvulotomy alone for pulmonary stenosis: results in children with and without muscular infundibulary hypertrophy. *J Thorac Cardiovasc Surg.* 1982;83:577-583.
39. Fontes VF, Esteves CA, Sousa JE, Silva MV, Bembom MC. Regression of infundibular hypertrophy after pulmonary valvuloplasty for pulmonic stenosis. *Am J Cardiol.* 1988;62:977-979.
40. Thapar MK, Rao PS. Significance of infundibular obstruction following balloon valvuloplasty for valvar pulmonic stenosis. *Am Heart J.* 1989;118:99-103.
41. Fawzy ME, Galal O, Dunn B, Shaikh A, Sriram R, Duran CM. Regression of infundibular pulmonary stenosis after successful balloon pulmonary valvuloplasty in adults. *Cathet Cardiovasc Diagn.* 1990;21:77-81.
42. Ben-Shachar G, Cohen MH, Sivakoff MC, Portman MA, Riemenschneider TA, Van Heeckeren DW. Development of infundibular obstruction after percutaneous pulmonary balloon valvuloplasty. *J Am Coll Cardiol.* 1985;5:754-756.

Independent predictors of long-term results after balloon pulmonary valvuloplasty. Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators.

B W McCrindle

Circulation. 1994;89:1751-1759
doi: 10.1161/01.CIR.89.4.1751
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539