Long-term Results After Balloon Pulmonary Valvuloplasty

Brian W. McCrindle, MD, MPH, and Jean S. Kan, MD

Background. The objective of this study was to determine the long-term outcome of patients after percutaneous balloon pulmonary valvuloplasty (BPV) treatment of congenital pulmonary valve stenosis.

Methods and Results. This study represents a case series with duration (mean±SD) of follow-up of 4.6±1.9 years. Forty-six patients with a median age of 4.6 years (range, 3 months to 56 years) had BPV at one academic institution between June 1981 and December 1986. Mean peak systolic pressure gradients from the right ventricle to the pulmonary artery were as follows: before BPV, 70±36 mm Hg; immediately after BPV, 23±14 mm Hg; at intermediate follow-up by cardiac catheterization or Doppler echocardiography at less than 2 years after BPV, 23±16 mm Hg (n=33); and at long-term follow-up by Doppler at more than 2 years after BPV, 20±13 mm Hg (n=42). BPV acutely reduced the gradient to less than 36 mm Hg for 41 of 46 (89%) patients. Available gradients at long-term follow-up were less than 36 mm Hg for 36 of 42 (86%) patients without additional procedures. A patient age of less than 2 years at the initial BPV was a significant risk factor for gradients over 36 mm Hg at follow-up.

Conclusions. BPV provides long-term relief of pulmonary valvular obstruction in the majority of patients. Close follow-up of patients who require BPV at less than 2 years of age is warranted. (Circulation 1991;83:1915–1922)

Growth in the field of cardiac surgery has been marked by several pioneering surgical innovations that were developed to relieve the obstruction caused by pulmonary valve stenosis.1 Likewise, percutaneous balloon pulmonary valvuloplasty (BPV) represents a major milestone in the field of interventional cardiology, and the technique has been applied with varying success to the dilatation of many other congenital and acquired cardiovascular lesions.2–6 Since its use was first reported in 1982,7 BPV has replaced surgery as the initial treatment of choice for patients of all ages with moderate to severe pulmonary valve stenosis and an intact ventricular septum. The procedure continues to be performed as originally described with few variations, including the use of double balloons or oversized balloons.8–12 Several case series report excellent acute and intermediate results,7–38 but data concerning the long-term outcome after BPV are lacking. The purpose of this study was to determine the long-term outcome for patients having BPV at one academic institution.

Methods

Study Population

Between June 1981 and December 1986, initial BPV was attempted in 49 consecutive patients at The Johns Hopkins Hospital. The procedure could not be performed in two patients (ages, 2 and 9 months) because of an inability to advance the balloon dilatation catheter across the pulmonary valve and in one patient (age, 16 months) because of cardiorespiratory instability during the procedure. All three patients had successful surgical valvotomy or valvectomy within 24 hours of the BPV attempt. The study population included the remaining 46 patients, which comprised 29 females and 17 males. Patient age at the initial BPV ranged from 3 months to 56 years, with a median age of 4.6 years. Fourteen patients were less than 2 years of age. Patient weight ranged from 5 to 65 kg, with a median weight of 16 kg. Seven patients weighed less than 10 kg. Thirty-nine patients had typical pulmonary valve stenosis, with a domed stenotic pulmonary valve evident on cineangiograms performed before BPV. Pulmonary valve dysplasia, which was defined as the presence of thick, immobile valve leaflets with the absence of poststenotic pulmonary
artery dilatation was evident in six patients. Five patients met criteria for the diagnosis of Noonan syndrome; pulmonary valve dysplasia was present in two of these patients. One patient with pulmonary atresia, an intact ventricular septum, and a hypoplastic right ventricle presented with persistent right ventricular outflow tract obstruction 1 year after a Brock surgical valvotomy performed in the neonatal period.

**Intervention**

BPV was performed as previously reported. Informed consent was obtained for all patients. After initial hemodynamic assessment right ventricular angiography was performed, and the maximum internal diameter of the pulmonary valve from hinge point to hinge point during systole was measured from the lateral projection cineangiogram and corrected for magnification. This dimension corresponds to the pulmonary root proximal diameter as described by Sievers et al and will hereafter be called the pulmonary valve diameter. The mean pulmonary valve diameter was 16.1±4.5 mm, with a range from 7 to 30 mm. Two patients with valve dysplasia and one with typical valve stenosis had some degree of pulmonary valve diameter hypoplasia, which was arbitrarily defined as a ratio of measured to predicted pulmonary valve diameter of less than 0.8 mm. Predicted valve diameters were derived from normative angiographic data related to body surface area. A single dilatation balloon ranging from 6 to 25 mm in diameter on a 6F to 9F catheter was selected (based on measured pulmonary valve diameter) to correspond to a mean balloon:valve diameter ratio of 1.01±0.11 with a range from 0.67 to 1.22. The balloon was positioned straddling the pulmonary valve orifice and rapidly inflated by hand with diluted contrast material a median of three times to peak pressures corresponding with maximum disappearance of “waisting” of the balloon, as seen on fluoroscopy. Initial suboptimum response in five patients necessitated the use of larger balloons. Hemodynamic assessment was repeated after valve dilatation.

**Data Collection and Analysis**

Data on each patient were collected at three time points: the initial BPV (acute results); the first follow-up visit, occurring less than 2 years after the initial BPV (intermediate results); and the longest interval follow-up visit, occurring more than 2 years after the initial BPV (long-term results). Data were retrospectively collected by review of medical records, cardiac catheterization reports, and noninvasive studies to obtain acute and intermediate results; the majority of data on long-term results were prospectively obtained at scheduled patient visits. Data on patients who were no longer followed at The Johns Hopkins Hospital were obtained from their current sources of cardiac care.

Hemodynamic data were collected at the initial BPV both immediately before and after balloon dilatation. Hemodynamic assessment of right ventricle-to-pulmonary artery peak systolic pressure gradients and subjective grading of pulmonary regurgitation was determined at intermediate follow-up by either repeat cardiac catheterization or Doppler echocardiography and at long-term follow-up by Doppler echocardiography only. Doppler estimates of gradients were calculated by application of the modified Bernoulli equation to maximum continuous-wave Doppler systolic peak flow velocities across the right ventricular outflow tract and main pulmonary artery obtained from multiple transducer positions. Color Doppler assessments of the breadth, area, and duration of evident pulmonary regurgitation were graded subjectively as absent, trivial, mild, moderate, or severe. Intermediate and long-term follow-up data were collected by an investigator (B.W.M.) blinded to the results of the patient’s initial BPV.

Clinical and electrocardiographic findings were reviewed at each of the three study points. Twelve-lead electrocardiograms were recorded in a standardized manner. Available electrocardiographic tracings were assessed for the presence of right ventricular hypertrophy based on measurements related to age-specific normative data as reported by Davignon et al. Measurements of the mean QRS axis, the amplitude of the R wave in leads V1 and V2, the amplitude of the S wave in V5 and V6, the ratio of the R to S wave in V2, and the amplitude of the T wave in V1 were recorded.

Data were analyzed on an IBM mainframe computer. Normally distributed continuous data are presented as mean±SD. Pooled data from each time period were compared using χ² test, Fisher’s exact tests, Student’s t tests, paired t tests, and analyses of variance. In addition, a right ventricle-to-pulmonary artery peak systolic pressure gradient of less than 36 mm Hg was used as a cut point to define success at both initial BPV and follow-up for each individual patient. This cut point value was chosen because it corresponded to a continuous-wave Doppler peak velocity of 3 m/sec and also represented a reasonable gradient above which repeat BPV or surgical intervention might be considered. Patients requiring repeat BPV were defined as long-term failures regardless of the acute or long-term results of the repeat BPV. Risk factors for persistent obstruction (gradients≥36 mm Hg) at the initial BPV and recurrent or persistent obstruction at follow-up were sought using stepwise multiple logistic regression. The level of statistical significance was set at p<0.05.

**Results**

Immediately after initial BPV, right ventricular peak systolic pressures decreased from 88±35 to 42±14 mm Hg (p<0.0001). Right ventricular end-diastolic pressures also slightly decreased from 7±3 to 6±3 mm Hg (p<0.005). There were no significant changes in both pulmonary artery peak systolic (18±5 versus 19±5 mm Hg, p=NS) and diastolic pressures (9±2 versus 9±3 mm Hg, p=NS). Arterial
systolic pressures measured by femoral artery monitoring also did not significantly change (109±16 versus 112±13 mm Hg, p=NS). Both the ratio of right ventricle-to-femoral artery peak systolic pressure (0.81±0.34 versus 0.37±0.12, p<0.0001) and the right ventricle-to-pulmonary artery peak systolic gradient (70±36 versus 23±14, p<0.0001) were significantly decreased immediately after BPV.

Gradients at intermediate follow-up were available for 33 (72%) patients at a mean interval of 0.8±0.6 years after the initial BPV. The gradients were obtained at repeat cardiac catheterization for 18 patients and by Doppler echocardiography for 15. The mean gradient of 23±16 mm Hg was not significantly different from that obtained immediately after BPV (Figure 1). Gradients at long-term follow-up were available for 42 (91%) patients at a mean interval of 4.9±1.6 years (range, 2.2–7.9 years) after the initial BPV. All gradients were obtained by Doppler echocardiography. The mean gradient of 20±13 mm Hg was not significantly different from that obtained immediately after initial BPV or at intermediate follow-up (Figure 1). However, this analysis of the pooled data includes three patients with residual or recurrent gradients of 58, 59, and 77 mm Hg at 3 months, 5 months, and 3 years after initial BPV who had had repeat BPV with gradients at long-term follow-up of 21, 19, and 21 mm Hg, respectively. In addition, the patient with pulmonary atresia and an intact ventricular septum had progression of a residual gradient of 40 mm Hg immediately after BPV to a gradient of 74 mm Hg at cardiac catheterization 8 months later. She had pulmonary valvotomy with right ventricular infundibular resection and patching 9 months after initial BPV and had a gradient of 6 mm Hg at long-term follow-up.

To determine factors that predicted failure of BPV, two groups of patients were defined based on the acute results of the initial BPV. Group 1 consisted of 41 (89%) patients who had successful initial procedures, in whom the residual gradient was 35 mm Hg or less immediately after BPV. The mean residual gradient was 20±8 mm Hg, with a right ventricle-to-systemic artery peak systolic pressure ratio of 0.35±0.08. Group 2 consisted of the five remaining patients who had failed initial procedures, with residual gradients of greater than 35 mm Hg immediately after BPV. The mean residual gradient was 53±18 mm Hg with a right ventricle-to-systemic artery peak systolic pressure ratio of 0.60±0.16. There were no statistically significant differences between groups 1 and 2 at the initial BPV regarding age (median, 4.8 versus 2.0 years), weight (median, 16 versus 13 kg), and sex (37% males versus 40% males). All of the five patients with Noonan syndrome and five of the six (83%) patients with pulmonary valve dysplasia had successful initial BPV. The patient with pulmonary atresia and an intact ventricular septum had a residual gradient of 40 mm Hg immediately after BPV. Patients in group 1 had lower gradients before BPV (63±28 versus 124±52 mm Hg, p=0.06) and lower ratios of right ventricle-to-systemic artery peak systolic pressure before BPV (0.74±0.24 versus 1.40±0.46, p=0.03). There was a success rate of 88% for 24 initial procedures performed in the first half of the intervention period versus 91% for 22 initial procedures performed in the second half (p=NS). The ratio of measured to predicted pulmonary valve diameter (0.99±0.13 versus 0.89±0.16, p=NS) and the ratio of balloon diameter to pulmonary valve diameter (1.01±0.11 versus 1.01±0.11, p=NS) were not significantly different between groups 1 and 2. With stepwise multiple logistic regression to determine which variables were predictive of failure of initial BPV, the only variable that could be entered significantly into the model was the ratio of right ventricle-to-systemic artery peak systolic pressure before BPV (β coefficient, 4.92; standard error, 1.77; p<0.005). All other variables and interaction terms did not reach the level of significance (p<0.05) for inclusion in the model. This model predicted that the higher the ratio of right ventricle-to-systemic artery peak systolic pressure before BPV, the greater the odds of failure versus the odds of success. No other variable significantly predicted acute results after controlling for this ratio.

The natural history of each patient in both groups was studied. Of the 41 patients in group 1 (Figure 2), gradients at intermediate follow-up were not known for 13 patients, all of whom had gradients that remained less than 36 mm Hg at long-term follow-up. Twenty-four patients had gradients of less than 36 mm Hg at intermediate follow-up. Long-term follow-up gradients were unknown for two of these patients and 20 continued to have gradients of less than 36 mm Hg, but two patients who had gradients of 26 and 29 mm Hg by cardiac catheterization at intermediate follow-up had gradients of 81 and 58 mm Hg by Doppler echocardiography at a long-term follow-up of 5.5 and 7.5 years, respectively, after the initial BPV. Both of these patients were less than 2
Thus, after an acute success rate of 89%, 36 (86%) of 42 patients for whom long-term gradients were known had gradients of less than 36 mm Hg without having had repeat BPV or surgery. After successful initial BPV in 41 patients, six (15%) of these patients developed recurrent gradients over 36 mm Hg, four at intermediate follow-up and two at long-term follow-up only. Of the five patients with significant residual gradients over 36 mm Hg immediately after BPV, three had spontaneous regression of their gradients to less than 36 mm Hg at both intermediate and long-term follow-up.

On the basis of the gradient at long-term follow-up available in 42 patients, two further groups were defined using the cut point of a residual right ventricle to pulmonary artery peak systolic gradient of 36 mm Hg. Group 3 consisted of 36 (86%) patients with gradients of less than 36 mm Hg without further interventions. Group 4 consisted of two patients with gradients over 36 mm Hg and four who required additional interventions for persistent or recurrent obstruction. At the initial BPV, group 3 patients were significantly older (median, 5.2 versus 2.0 years, \( p<0.05 \)) but did not weigh more (median, 17 versus 12 kg, \( p=NS \)) than group 4 patients. The proportion of male patients was not significantly different between groups 3 and 4 (31% versus 67%, \( p=NS \)). Four of the five patients with Noonan syndrome (\( p=NS \)) and four of the six with pulmonary valve dysplasia (\( p=NS \)) had good long-term results. There were no statistically significant differences between groups 3 and 4 regarding gradients before BPV (70±38 versus 77±37 mm Hg, \( p=NS \)) and gradients immediately after BPV (21±11 versus 38±23 mm Hg, \( p=NS \)). Likewise, there were no statistically significant differences between the groups regarding the ratio of right ventricle-to-systemic artery systolic pressure either before initial BPV (0.81±0.33 versus 0.97±0.41, \( p=NS \)) or after BPV (0.36±0.11 versus 0.52±0.13, \( p=NS \)). The ratio of measured to predicted pulmonary valve diameter was significantly less in group 4 than in group 3 (0.87±0.16% versus 1.00±0.13%, \( p<0.05 \)). The ratio of balloon diameter to pulmonary valve diameter (1.02±0.12 versus 0.96±0.09, \( p=NS \)) at the initial BPV was not significantly different between groups 3 and 4.

By means of multiple logistic regression to determine which variables were predictive of failure at long-term follow-up, the only variable that could be entered significantly into the model was the ratio of right ventricle-to-systemic artery peak systolic pressure immediately after BPV (\( \beta \) coefficient, 9.89; standard error, 4.19; \( p=0.02 \)). However, when age at the initial BPV was recoded from being a continuous variable to an ordinal variable with two levels—those patients below versus those above 2 years of age—this variable eliminated any significant effect of any other variable or interaction term in the model (\( \beta \) coefficient, 3.03; standard error, 1.17; \( p<0.01 \)). This model predicted that there was a 21-fold greater odds
of failure at long-term follow-up for patients having an initial BPV at less than 2 years of age versus more than 2 years of age and that no other variable was significantly predictive of failure after controlling for the effect of age category. Nonetheless, the success rate for patients less than 2 years of age was 79% immediately after initial BPV and 58% at long-term follow-up, without further intervention.

Clinical and electrocardiographic correlates of long-term results were explored. No patient was symptomatic at any point in the study period. Clinical findings were recorded for 45 patients immediately before initial BPV, for 35 at intermediate follow-up, and for 41 at long-term follow-up. A right ventricular heave was felt to be palpable in 89% of patients before initial BPV, in 23% at intermediate follow-up, and in only 12% at long-term follow-up \( (p<0.005) \); the second heart sound was diminished during auscultation in 62%, 34%, and 32% of patients \( (p<0.01) \), and pulmonary ejection clicks were evident in 80%, 43%, and 59%, respectively \( (p<0.005) \). The intensity of systolic ejection murmurs decreased from 93% of patients having murmurs of grade 3 or more after initial BPV to 49% at intermediate and 32% at long-term follow-up \( (p<0.0001) \). Diastolic murmurs were audible in only one patient before initial BPV, in 14% of patients at intermediate follow-up, and in 34% at long-term follow-up \( (p<0.0005) \). Pulmonary regurgitation was evident by color Doppler echocardiography at follow-up in 89% of patients. In only one patient was the degree of the pulmonary regurgitation felt to be more than mild.

Evidence of regression of right ventricular hypertrophy was noted on standard 12-lead electrocardiograms (Table 1). There were statistically significant decreases noted in the proportion of patients with a rightward QRS axis, an increased and anterior T wave in V1, and increased rightward ventricular forces (S wave in V3 or V4). No statistically significant decreases in the amount of anterior forces (an R wave in V1 or V2 and a ratio of R to S wave in V1) were noted.

**Discussion**

The present study provides evidence that BPV affords both acute and long-term relief of valvular obstruction in patients with moderate to severe pulmonary valve stenosis. Our patient population was similar to that of most other institutions that have reported acute and intermediate results, with comparable distributions regarding patient demographics and hemodynamic parameters before BPV.\(^8,9,13,14,16–24,26–29,31,36,37\) The proportion of patients with associated Noonan syndrome and/or pulmonary valve dysplasia was higher in the current series than that reported in the large multi-institutional case series of the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry,\(^1,3\) for which uniform definitions of valve dysplasia were not specified.

The benign natural history of pulmonary valve stenosis for most patients lends controversy concerning the indications for intervention.\(^42,43\) The rationale for intervention has included the prevention and relief of symptoms, the prevention of secondary changes in the right ventricle and pulmonary artery, and the prevention of progression to more severe degrees of obstruction.\(^44–46\) The vast majority of patients are asymptomatic, including most patients with severe grades of obstruction.\(^46,47\) Young children are more likely to have severe obstruction and present with cyanosis; older patients are more likely to have symptoms, predominantly fatigue and diminished exercise tolerance, occurring with lesser degrees of obstruction.\(^46\) Unpredictable progression to more severe grades of obstruction has been well documented to occur more frequently in children less than 2 years of age.\(^45,46,48\) The successful relief of obstruction has been associated with an improved clinical outcome.\(^46,49\) Therefore, the indications for intervention based on natural history study data might include any patient with moderate or severe obstruction, any patient with significant symptoms, and children less than 2 years of age with mild degrees of obstruction who have shown any evidence of progression at follow-up evaluations. Criteria for intervention in the BPV era should be based on proof of alteration of the natural history, just as during the surgical era.\(^46,50,51\) When hemodynamic parameters only are considered, variability caused by measurement inconsistencies\(^33,52,53\) and physiological state...
changes33,54,55 blur strict criteria, and clinical parameters must contribute to management decisions as well.43 Therefore, it is not unreasonable that patients with gradients of less than 50 mm Hg (mild stenosis) might be treated by BPV, as was evident in our series and many others.5,10,12–18,21,22,24,26–29,31,32,34–37

BPV is very effective in producing significant hemodynamic alterations indicative of the relief of pulmonary valvular obstruction. In 32 published case series, statistically significant reductions in the right ventricle systolic pressure, right ventricle–to-femoral artery systolic pressure ratio, and/or right ventricle–to-pulmonary artery peak systolic pressure gradient occurred immediately after BPV in their patient populations.7–38 In only some of these studies are results for individual patients included in addition to pooled study population data. Gradients immediately after BPV available for 353 individual patients from 15 studies were extracted.8–11,14–16,18,21–24,26,32,37 When the criterion used in our series for defining successful procedures (i.e., a gradient of less than 36 mm Hg immediately after BPV) was applied to this data, acute success rates for individual series ranged from 37% to 100%, with 283 patients overall (80%) having had successful procedures. The acute success rate of 89% in the current series is comparable.

The only significant factors predictive of a poor acute result were hemodynamic indicators of more severe degrees of obstruction. Data from the large VACA Registry study13 suggest that the majority of these significant residual gradients are at the infundibular level and that the higher the degree of total obstruction before BPV the higher the infundibular gradient immediately after BPV. Regression of infundibular hypertrophy has been associated with resolution of residual gradients in some patients.25 Although separate infundibular gradients were not measured in our study population, this hypothetically is the mechanism of spontaneous resolution of residual gradients observed in three patients.

Our acute success in five of six patients with pulmonary valve dysplasia suggests that BPV might still be indicated for this group. Results with BPV and the dysplastic pulmonary valve are variable and may depend on the relative contributions to the degree of obstruction made by thickened, immobile leaflets; nodular tissue in the leaflet sinuses; and commissural fusion, all of which may form a continuum with typical pulmonary stenosis. When strict definitions of dysplasia56–58 are applied, commissural fusion is probably not present and the results of BPV are poor.18,36,59–61 When milder forms of dysplasia are included or criteria are not specified, acute results of BPV are more encouraging.13,28,29 The degree of valve dysplasia should determine the applicability of BPV for these patients.

The most frequent technical consideration purported to affect acute results is the size of the dilatation balloon relative to the pulmonary valve diameter. Excellent results in the current series were obtained using balloon diameters equal to valve diameters, and the balloon:valve diameters were not significantly predictive of acute results. This observation has been confirmed in two large series.13,31 Although undersized balloons may be associated with a poor acute result, especially in neonates and infants, the use of oversized balloons probably offers no clear improvement in long-term results and may increase the risk of valve disruption, outflow tract damage, and vascular complications.62–64 Our association of young age with less optimum long-term results is probably a reflection of the natural history of progression of severity observed in this age group rather than a result of the failure to use oversized balloons. Khan et al.38 have reported a similar significant restenosis rate in infants after BPV. Long-term follow-up comparisons of the use of oversized balloons in neonates and infants are needed.

The new data from this series concerns the intermediate and long-term follow-up of patients after initial BPV. We found no significant change in mean gradient at follow-up from that immediately after initial BPV. In addition, when individual patients were tracked a long-term success rate of 86% was noted, confirming the long-term effectiveness of BPV in relieving pulmonary valvular obstruction. Other reports of intermediate follow-up (range, 1 month to 3 years) have similarly shown continued relief of obstruction, with further decreases in gradients attributed to the regression of infundibular hypertrophy and narrowing.8,11,14,17–19,21–32,34–36,38

Electrocardiographic evidence of regression of right ventricular hypertrophy provides further confirmation of the success of BPV in relieving the excessive work load imposed on the right ventricle. The current series reports evidence of such regression on standard 12-lead electrocardiograms. Kveselis et al.64 documented reductions in vectorcardiographic evidence of right ventricular hypertrophy at follow-up after successful BPV. More acute changes such as T wave normalization have reportedly occurred immediately after BPV.65

The majority of our patients showed echocardiographic evidence of pulmonary regurgitation at follow-up, though usually trivial to mild in severity, which has been observed after surgical valvotomy as well.66 The significance of mild degrees of regurgitation regarding its tolerance and natural history is unknown, although no impairments were noted in our population. Patients with moderate to severe pulmonary regurgitation after surgical correction of pulmonary outflow obstruction have had diminished exercise capacities and abnormal hemodynamic responses.67 Such patients may require closer follow-up.

In our series, six patients developed recurrences of significant gradients at varying intervals after a successful initial BPV. Progression of residual gradients has been documented to occur infrequently at intermediate follow-up in several series.14,21,22,27,29,31,36 Longer follow-up similar to the current series may reveal additional patients with long-term recurrences of significant gradients. The excellent success in our
series of repeat BPV in relieving residual or recurrent obstruction is similar to the findings at other institutions.9,14,18,21,22,25—29,38

Thus, BPV is safe and effective for both the immediate and long-term relief of obstruction caused by pulmonary valve stenosis. Increased severity of obstruction before BPV is associated with significant immediate residual gradients that resolve over time with regression of infundibular hypertrophy and narrowing. Initial BPV performed in patients less than 2 years of age is associated with an increased incidence of persistence or recurrence of significant obstruction; therefore, these patients require close follow-up.

References

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KEY WORDS • pulmonary valve stenosis • interventional catheterization