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PEDIATRIC AND CONGENITAL HEART DISEASE

Original Studies

Balloon Valvuloplasty for Congenital Aortic Stenosis:
Multi-Center Safety and Efficacy Outcome Assessment

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Objective: To describe contemporary outcomes of balloon aortic valvuloplasty (BAVP) performed in 22 US centers. *Background*: BAVP constitutes first-line therapy for congenital aortic stenosis (cAS) in many centers. Methods: We used prospectively-collected data from two active, multi-institutional, pediatric cardiac catheterization registries. Acute procedural success was defined, for purposes of this review, as a residual peak systolic gradient $\leq$ 35 mm Hg and no more than mild aortic regurgitation (AR) for patients with isolated cAS. For patients with mixed aortic valve disease, a residual peak systolic gradient $\leq$ 35 mm Hg without worsening of AR was considered successful outcome. Results: In 373 patients with a median age of 8 months (1 day to 40 years of age) peak systolic gradient had a median of 59 [50, 71] mm Hg pre-BAVP and 22 [15, 30] mm Hg post-BAVP ($P < 0.001$). Procedural success was achieved in 160 patients (71%). The factors independently associated with procedural success were: first time intervention (OR = 2.0 (1.0, 4.0) $P = 0.04$), not-prostaglandin dependent, (OR=3.5 (1.5, 8.1); $P = 0.003$), and isolated cAS (absence of AR) (OR = 2.1 (1.1–3.9); $P = 0.03$). Twenty percent of patients experienced adverse events, half of which were of high severity. There was no procedural mortality. Neonatal status was the only factor associated with increased risk of high severity adverse events (OR 3.7; 95% CI 1.5–9.0). Conclusion: In the current era, BAVP results in procedural success (gradient reduction with minimal increase in AR) in 71% of patients treated at US centers where BAVP is considered first-line therapy relative to surgery.

Key words: congenital heart disease; aortic regurgitation; adverse events; bicuspid aortic valve

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INTRODUCTION

Transcatheter balloon aortic valvuloplasty (BAVP) was first reported nearly 30 years ago [1]. Randomized studies were never performed to compare the outcomes of BAVP to surgical aortic valvotomy. The steady adoption of the procedure has been supported mainly by several retrospective studies comparing historical and contemporaneous outcomes, and showing that the two procedures are comparable with respect to survival, relief of stenosis, and incidence of aortic regurgitation (AR) [2–7]. BAVP has since become the first line of therapy for congenital aortic stenosis (cAS) in neonates, children, and young adults in most centers [7–17].

Most reports describing rates of acute procedural success, and mid- or long- term outcomes, have described retrospective experiences at single centers [7,9,10,13,14,17–19]. One important exception is the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry, a multi-institutional experience that included data collected from 630 BAVPs performed at 22 institutions between 1984 and 1992 [13]. In the 20 years since the publication of this series, there have been important technological changes in the procedure and equipment; more recent data suggests that there has been a tendency toward improved outcomes, including a decrease in procedural mortality [14]. No report of a multi-institutional experience with BAVP in the current era exists.

The Congenital Cardiac Catheterization Outcome Project (C3PO) [20] and the Mid-Atlantic Group of Interventional Cardiology (MAGIC) [21] collected data on diagnostic and interventional catheterization procedures performed in patients with congenital heart disease at 22 centers (Appendix Table I). We examined the prospectively-collected data on BAVP for cAS from these two registries to assess the procedural efficacy and to estimate adverse event rates in the current era.

MATERIAL AND METHODS

Study Population and Data Collection

Data collection and reporting methodologies used within C3PO and MAGIC have been previously reported [20,21]. Institutional Review Board approval was obtained at all sites. Data for the C3PO patients was collected between February 2007 and June 2010. The data from the MAGIC registry was collected between November of 2003 and September of 2010.

The following populations were excluded: (1) patients with associated sub-valvar or supra-valvar aortic stenosis, (2) patients on extracorporeal circulatory support during BAVP, (3) elderly patients with calcific aortic valve stenosis, (4) patients who had undergone prenatal aortic valve modification, and (5) patients intended for single ventricle palliation at the time of the BAVP.

Indications for interventional referral were individual and institution dependent, and were not captured in the registries. Patient demographic data recorded included age, weight, gender, presence of genetic syndrome, cardiac anatomy (isolated defect or complex congenital heart disease), and history of previous BAVP or surgical aortic valve intervention. General procedure characteristics recorded included: clinical urgency (elective vs. non-elective), prostaglandin infusion, inotropic support, and airway management (spontaneous respirations vs. mechanical support). Baseline hemodynamic data included: aortic and left ventricular systolic pressures, left ventricle end diastolic pressure (LVEDp), and cardiac index (CI). Baseline and residual peak-to-peak systolic gradient across the aortic valve (PSG) were recorded (measured by simultaneous pressure tracings and/or catheter pullback before and after BAVP, respectively).

Grade of AR as assessed by aortic root angiography before and after BAVP and was graded at the time of the procedure by the operator based on Seller's criteria [22–24]:

- *Grade 1+ (mild): A small amount of contrast material enters the left ventricle in diastole; it is essentially cleared with each beat and never fills the entire ventricular chamber.*
- *Grade 2+ (moderate): contrast enters the left ventricle with each diastole resulting in faint opacification of the entire chamber.*
- *Grade 3+ (moderate to severe): The left ventricle is well opacified and equal in density with the ascending aorta.*
- *Grade 4+ (severe): Complete dense opacification of the left ventricle in one beat and appears more densely opacified than the ascending aorta.*

Patients were classified as having "*isolated cAS*" if aortic valve disease was purely obstructive. Patients with both obstructive and regurgitant valves before BAVP were classified as having "*mixed aortic valve disease*." In addition, neonates receiving prostaglandin infusion during the procedure were classified as having "*critical cAS.*"

The valve annulus diameter, as measured by the operator at the time of the procedure, was recorded as a single measurement in the registries. Based on this value, and the nominal diameter(s) of the balloon(s) used, minimal and maximal balloon to annulus ratio (BAR) was calculated. Echocardiographic data obtained from the

pre-procedure echocardiogram included: left ventricular shortening fraction and aortic valve annulus diameter and *Z*-score.

Analysis of Procedure Efficacy

Efficacy was assessed using a composite outcome that reflected both the residual gradient and the degree of AR at the end of the procedure. The thresholds determining the outcome classification were based on expert consensus, and also in part on recently published data by Brown et al.[25] which suggests that there is an interaction between the residual PSG and degree of AR immediately following BAVP, and the need for aortic valve replacement on follow-up.

- ***Optimal outcome***: Residual PSG $\leq$ 35 mm Hg and trivial or no AR.
- ***Adequate outcome***: for patients with *isolated cAS*, residual PSG $\leq$ 35 mm Hg and mild AR. For patients with *mixed aortic valve disease*, residual PSG $\leq$ 35 mm Hg and no/trivial change in AR.
- ***Inadequate outcome***: for patients with *isolated cAS*, residual PSG$>$ 35 mm Hg or $>$ mild AR. For patients with *mixed aortic valve disease*, residual PSG$>$ 35 mm Hg or change in AR $\geq$ 1 angiographic grade.

For purposes of our analysis, an ***acute procedural success*** was defined as achievement of an optimal or adequate result.

Analysis of factors associated with outcomes could only be performed on the subset of patients in the C3PO registry, as the MAGIC registry did not fully capture some data related to technical and patient factors.

Sub-populations of interest were further analyzed with the objective of finding factors associated with inadequate outcomes within each sub-population. Patients with *mixed aortic valve disease* were compared to patients with *isolated cAS* and patients undergoing BAVP as a reintervention were compared to those undergoing BAVP for the first time. Similarly, patients undergoing BAVP during the first month of life were sub-analyzed separately from those undergoing the procedure after the first month of life.

Analysis of Adverse Events

Analysis of adverse events (AE) was performed on the C3PO cohort only, due to the confirmed accuracy and completeness of the C3PO database, which has undergone independent event review, validation, and audits for event capture and completeness [20]. An AE was defined as any complication that occurred during or as a consequence of the procedure. AE were categorized as related to vascular/cardiac trauma, technical issues, arrhythmias, hemodynamic complications, vascular entry site complications, and sedation/anesthesia/airway related. An increase of $>$2+ on the degree of AR was defined as vascular/cardiac trauma AE. Information on each AE included timing, symptoms, interventions or management, and seriousness classified according to a 5 level severity scale and grouped according to *low severity* (level 1 and 2) and *high severity* (level 3, 4, and 5) (Appendix Table II) [20]. In addition, each event was classified as preventable, possibly preventable, or not preventable.

Statistical Analysis

Data are presented as frequency (%), or median [interquartile range](range). For comparisons between groups, Chi-square or Wilcoxon rank sum test were used for categorical and continuous variables, respectively. Wilcoxon signed-rank test was used for comparison of paired continuous variables. A P value of <0.05 was considered statistically significant. Logistic regression models were built for both (1) high severity AE and (2) procedural success. The models were built using stepwise forward inclusion of variables significant at $P < 0.1$. A P value of <0.05 was necessary for a variable to be retained in the final model. Odds ratios are presented with 95% confidence intervals.

RESULTS

Patient and Procedural Characteristics

A total of 373 patients were included in this study, of whom 233 (62%) were in the C3PO group and 140 (38%) were in the MAGIC group. The median age at the time of BAVP was 8 months (1 day to 40 years of age), with one-third of the patients being under 1 month of age, over half the patients under 1 year of age, and only 9% of patients $\geq$18 years of age. The cohort included 77 patients (21%) with a history of prior BAVP and 25 patients (7%) with a history of prior surgical valvotomy.

Efficacy of BAVP

Table I summarizes the outcome measures for the entire cohort. The median BAR for the first dilation was 0.88 (0.52–1.18) and for the last dilation was 0.94 (0.50–1.27) (Fig. 1). Eighty-five percent of the patients had a residual PSG $\leq$ 35 mm Hg, and 7% had a residual PSG $\geq$ 45 mm Hg. The majority of patients had no AR before BAVP (71%), with only 4% of the cohort having 2+ AR and a single patient having 3+ AR before BAVP. After BAVP, 43% of the cohort had no AR and 6 patients ($<$ 4%) had $\geq$ 3+ AR.

TABLE I. Outcome Measures

	Number or value ($n = 373$)
Baseline PSG (mm Hg) ($n = 369$)	59 [50, 71]
Residual PSG (mm Hg) ($n = 371$)	22 [15, 30]
≤35 mm Hg	314 (85%)
>35 <45 mm Hg	31 (8%)
≥45 mm Hg	26 (7%)
AR Angiographic grade before BAVP ($n = 371$)	
None	262 (71%)
1+	93 (25%)
2+	15 (4%)
3+	1 (<1%)
4+	0 (0%)
AR Angiographic grade after BAVP ($n = 367$)	
None	156 (43%)
1+	141 (38%)
2+	58 (16%)
3+	11 (3%)
4+	1 (<1%)
Increase in AR ($n = 366$)	
None	235 (64%)
+1 grade	94 (26%)
+2 grades	31 (8%)
+3 grades	5 (1%)
+4 grades	1 (<1%)
Acute procedural success ($n = 366$)	260 (71%)
Outcome category ($n = 366$)	
Optimal	136 (37%)
Adequate	124 (34%)
Inadequate	106 (29%)

Values shown are number (percent) or median [interquartile range]. AR: aortic regurgitation; BAVP: balloon aortic valvuloplasty; PSG: peak-to-peak systolic gradient across the aortic valve.

Although gradient relief was almost universally accomplished, only 71% of BAVP procedures achieved acute procedural success according to our definition, with an optimal result achieved in 37% of the patients. The result was categorized as inadequate in 29% of the patients.

Factors Associated With Acute Procedural Success

Data from the C3PO registry were further analyzed to identify factors associated with acute procedural success (Table II). Factors independently associated with acute procedural success were: first aortic valve intervention, non-critical cAS, and isolated cAS.

Outcomes did not differ significantly by institution within the C3PO registry and are summarized in Fig. 2 (for patients undergoing BAVP for the first time only) and Appendix Table III (for all patients in the C3PO cohort).

BAVP in neonates. Table III summarizes the factors associated with outcome in the 76 patients in the C3PO cohort undergoing BAVP in the first month of life. Acute outcomes were evenly distributed, with one-third of these patients having optimal, adequate, and inadequate results. In this age group, factors associated with an inadequate result were lower aortic valve diameter *z*-score and critical cAS. Notably, weight, presence of complex congenital heart disease, left ventricular function, baseline PSG, and maximum BAR were not associated with outcome in this age group. AR before BAVP was also not associated with outcome, but very few patients had AR before BAVP in this age group.

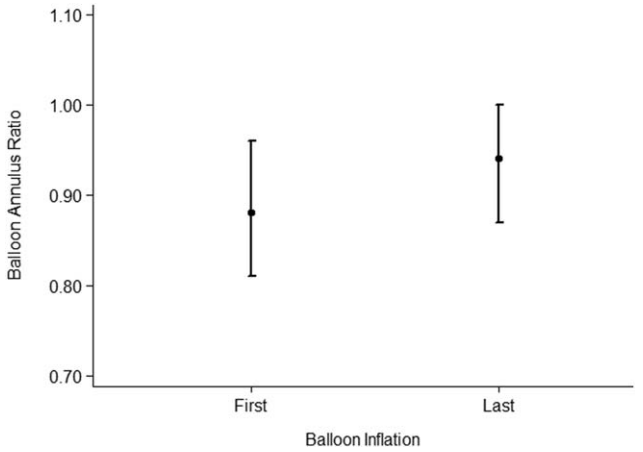

Fig. 1. Balloon annulus ratio. Figure shows the balloon-to-annulus ratio for the first last dilation. The median is represented by the dot and the interquartile range by the whiskers.

BAVP in patients ≥ 1 month of age. Table IV summarizes the factors associated with outcome in the 155 patients in the C3PO cohort undergoing BAVP after the first month of life. Older age, history of prior BAVP, and presence of ≥ 1 + AR before BAVP were associated with inadequate outcome, whereas baseline PSG and aortic valve diameter *z*-score were not.

History of prior aortic valve intervention. History of a prior aortic valve intervention was associated with inadequate outcome by univariate analysis (odds ratio = 2.0 (1.0–4.0); $P = 0.04$). Almost half of these patients had an inadequate result from BAVP (44%). Importantly, these patients tended to be older, more commonly had complex congenital heart disease, had higher LVEDp before BAVP, and had a higher degree of AR before BAVP (63% of them had mixed aortic valve disease, compared to 24% of the patients with no prior aortic valve intervention; $P < 0.001$)(Appendix Table IV). The change in degree of AR after BAVP did not differ between patients undergoing the procedure for the first time and those undergoing BAVP as a re-intervention, but the re-intervention group had a higher degree of AR pre- and post-BAVP. Despite having similar gradients pre BAVP as patients undergoing the procedure for the

TABLE II. Factors Associated With Acute Procedural Success in C3PO Cohort

	Number	Acute procedural success		Multivariable model	
		N (%)	Odds ratio (95% CI)	Odds ratio (95% CI)	*P* value
Age					
<1 month	75	50 (67%)	1.0		
≥ 1 month	154	107 (69%)	1.1 (0.7, 2.0)		
Diagnosis					
Isolated defects	175	122 (70%)	1.3 (0.7, 2.4)		
Complex CHD	54	35 (65%)	1.0		
First aortic valve intervention					
No	62	35 (56%)	1.0	1.0	
Yes	167	122 (73%)	2.1 (1.1, 3.9)	2.0 (1.0, 4.0)	0.04
Aortic valve *z*-score					
<−1	54	32 (59%)	1.0		
≥−1	118	92 (78%)	2.4 (1.2, 4.8)		
Critical AS (prostaglandin infusion)					
Yes	32	17 (53%)	1.0	1.0	
No	197	140 (71%)	2.2 (1.0, 4.6)	3.5 (1.5, 8.1)	0.003
Left ventricular end diastolic pressure					
≥18	54	36 (67%)	1.0		
<18	175	121 (69%)	1.1 (0.6, 2.1)		
Cardiac index					
<2.8 l/min/m^2	18	14 (78%)	1.7 (0.5, 5.3)		
≥2.8 l/min/m^2	211	143 (68%)	1.0		
Baseline PSG					
<50	53	41 (77%)	2.3 (0.9, 5.6)		
50–74	129	88 (68%)	1.4 (0.7, 2.9)		
≥75	45	27 (60%)	1.0		
AR present pre-BAVP					
None (isolated AS)	153	113 (74%)	2.1 (1.1, 3.7)	2.1 (1.1, 3.9)	0.03
≥ Mild (mixed aortic valve disease)	76	44 (58%)	1.0	1.0	

AR: aortic regurgitation; AS: aortic stenosis; BAVP: balloon aortic valvuloplasty; CHD: congenital heart disease; PSG: peak-to-peak systolic gradient across the aortic valve.

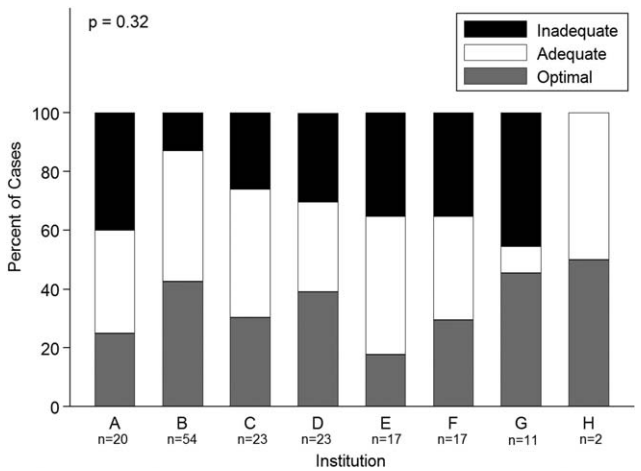

Fig. 2. Outcomes by institution: first procedure only. Stacked bar graph showing outcome categories by institution for patients undergoing BAVP for the first time.

first time, the post intervention gradient was higher in the re-intervention group.

Isolated cAS vs. mixed aortic valve disease. Among patients ≥ 1 month of age, acute procedural success was achieved in 58% of patients with mixed aortic valve disease, compared to 78% of patients with isolated cAS ($P = 0.005$). The isolated cAS group was also younger, while patients in the mixed aortic valve disease group had undergone prior aortic valve intervention more commonly (Appendix Table V). As expected, patients in the mixed aortic valve disease group had worse composite outcomes, since the presence of aortic regurgitation automatically excludes these patients from an optimal result category. However, the inferior outcomes were not attributable to AR grade at the end of the procedure only. While the baseline PSG did not differ between the two groups, residual PSG was higher in the mixed aortic valve disease group, and this group had a lower proportion of patients with a residual gradient ≤ 35 mm Hg. The majority of the patients in both groups had no change in AR; however, the proportion of patients with no change in AR was higher in the mixed aortic valve disease group. In fact, the majority of patients in this group (78%) did not have a change in angiographic degree of AR. Also, the proportion of patients with a change in AR of two or more angiographic grades was higher in the isolated AS group.

TABLE III. Outcome Analysis—Patients <1 Month of Age

	Acute procedural success			
Patient characteristics	Optimal ($n=25$)	Adequate ($n=25$)	Inadequate ($n=25$)	P value*
Weight (kg)	3.5 [3.4, 3.7]	3.5 [3.2, 3.7]	3.4 [3.0, 3.7]	0.32
Diagnosis				0.76
Isolated defects	17 (68%)	23 (92%)	19 (76%)	
Complex CHD	8 (32%)	2 (8%)	6 (24%)	
Critical AS	9 (36%)	8 (32%)	15 (60%)	**0.047**
Inotropic support during case	9 (36%)	7 (28%)	9 (36%)	0.80
Maximum balloon to annulus ratio ($n=24,25,25$)	0.92 [0.87, 1.01]	0.95 [0.87,1.03]	0.93 [0.88, 1.00]	0.97
Aortic valve diameter z-score ($n=17,22,18$)	−0.8 [−2.0, −0.3]	−0.4 [−1.3, −0.2]	−1.7 [−2.5, −0.9]	**0.02**
Baseline PSG ($n=25,24,25$)	61 [50, 71]	60 [52, 67]	70 [58, 78]	0.09
AR before BAVP				0.73
None	25 (100%)	22 (88%)	23 (92%)	
1+	0 (0%)	2 (8%)	2 (8%)	
2+	0 (0%)	1 (4%)	0 (0%)	

*P values compare values for optimal + adequate (acute procedural success) versus inadequate.
AR: aortic regurgitation; AS: aortic stenosis; BAVP: balloon aortic valvuloplasty; CHD: congenital heart disease; PSG: peak-to-peak systolic gradient across the aortic valve.

TABLE IV. Outcome Analysis—Patients ≥ 1 Month of Age

	Acute procedural success			
Patient characteristics	Optimal ($n=41$)	Adequate ($n=66$)	Inadequate ($n=47$)	P value*
Age (years)	0.8 [0.2, 8.4]	8.7 [3.3, 15.0]	12.1 [3.0, 18.4]	**0.002**
1–11 months	21 (51%)	14 (21%)	8 (17%)	**0.02**
1–5 years	7 (17%)	10 (15%)	6 (13%)	
6–10 years	8 (20%)	15 (23%)	6 (13%)	
11–17 years	3 (7%)	19 (29%)	15 (32%)	
≥18 years	2 (5%)	8 (12%)	12 (26%)	
Weight (kg)	8.9 [5.0, 27.2]	27.2 [14.0, 60.8]	42.8 [13.7, 62.6]	**0.006**
Diagnosis				0.69
Isolated defects	28 (68%)	54 (82%)	34 (72%)	
Complex CHD	13 (32%)	12 (18%)	13 (28%)	
History of BAVP	5 (13%)	20 (31%)	24 (55%)	**<0.001**
History of surgical valvotomy	4 (10%)	7 (11%)	6(13%)	0.59
Any prior aortic valve intervention	7 (18%)	24 (38%)	27 (61%)	**<0.001**
Maximum balloon to annulus ratio ($n=39,64,44$)	0.96 [0.89, 1.01]	0.94 [0.87, 1.00]	0.92 [0.84, 1.03]	0.58
Valve diameter z-score ($n=35,50,30$)	0.00 [−0.80, 1.10]	−0.15 [−1.00, 1.40]	−0.45 [−1.40, 0.60]	0.13
Baseline PSG($n=41,66,46$)	52 [48, 65]	57 [45, 65]	60 [50, 71]	0.19
AR before BAVP				**<0.001**
None	41 (100%)	25 (38%)	17 (36%)	
1+	0 (0%)	40 (61%)	22 (47%)	
2+	0 (0%)	1 (2%)	7 (15%)	
3+	0 (0%)	0 (0%)	1 (2%)	
4+	0 (0%)	0 (0%)	0 (0%)	

*P values compare values for optimal + adequate (acute procedural success) versus inadequate.
AR: aortic regurgitation; BAVP: balloon aortic valvuloplasty; CHD: congenital heart disease; PSG: peak-to-peak systolic gradient across the aortic valve.

Within the group of patients with isolated cAS, older age at the time of BAVP was associated with an inadequate result (11.7 [7.0, 14.7] years for patients with inadequate results vs. 3.5 [0.2, 8.7] years for those with optimal or adequate result; $P=0.01$).

Safety of BAVP

There were no deaths attributed to the procedure. In 233 BAVP procedures in the C3PO cohort, there were 53 AE in 47 patients (20%). The highest level of severity was level 1 in 3 patients (1%), level 2 in 21 patients (9%), level 3 in 11 patients (5%), and level

TABLE V. Summary of Adverse Event Severity, Preventability, and Timing

	All adverse events ($n = 53$)
Severity	
1—none	5 (9%)
2—minor	25 (47%)
3—moderate	11 (21%)
4—major	12 (23%)
5—catastrophic	0 (0%)
Preventability	
Preventable	5 (10%)
Possibly preventable	17 (32%)
Not preventable	31 (58%)
Timing of Identification	
After catheters inserted, before removal	39 (74%)

4 in 12 patients (5%). There was no significant difference in the occurrence of high severity AE between institutions (Appendix Table III, $P = 0.08$). Table V summarizes the AE by severity category, preventability, and timing of identification. Age less than 1 month at the time of BAVP was the only factor independently associated with increased risk of high severity AE (odds ratio 3.7; 95% confidence interval 1.5–9.0). Appendix Table VI summarizes the reported adverse events, as well as a comparison of their frequency by age. Patients under 1 month of age experienced vascular or cardiac trauma more frequently (15% vs. 5%; $P = 0.03$). Hemodynamic compromise, vascular entry site issues, and AE related to sedation or airway were also more common in patients < 1 month of age. Of the patients that experienced AE, there was no significant difference in the AE severity between the patients < 1 month of age and those ≥ 1 month of age. Appendix Table VII summarizes the level 3/4/5 AE, with pertinent clinical details.

DISCUSSION

In this prospective, multi-institutional study we report current outcomes and incidence of AE for patients undergoing BAVP for cAS. There is currently no widely accepted definition of acute procedural success for BAVP. Some authors have focused on the residual PSG, the ratio of left ventricular to aortic pressure, or on the percent reduction in the PSG [7,13,17]. Others have also included a lack of "significant AR" as part of the definition of procedural success, defining significant AR as at least moderate [10,25], moderate-to-severe [16], or severe AR or an increase of two AR grades or more [13]. We categorized procedural outcome as optimal, adequate, or inadequate based on the interventional result with regard to BOTH residual obstruction, and resultant regurgitation. These outcome categories were designed to reflect the overall impact of BAVP on longer-term patient management, recognizing that gradient reduction is often accompanied by acute increase in regurgitation, and that, in fact, progression of AR is often the precipitant of surgical referral [26].

Using our unique classification, we find that over 70% of the patients in the study had an optimal or adequate outcome. The correlation of these acute outcome categories with long-term outcomes for this patient population is yet to be substantiated in a prospective manner.

As more data becomes available, the definitions of acute procedural success may very well require adjustment. One limitation of these definitions becomes apparent when applying it to a population of patients with mixed aortic valve disease. By definition, none can have an optimal outcome from BAVP (because AR exists even before the intervention), but they can still have what would be considered an adequate outcome, and therefore, *procedural success*. Despite its limitations, we believe that this represents a reasonable starting point in the understanding of what constitutes a desirable outcome after BAVP.

The efficacy of BAVP as a palliative procedure for cAS has been well documented [3,8,10,13,15,17]. The reduction in PSG reported in the present study is comparable to other reports in the literature, with 85% of patients with residual PSG ≤ 35 mm Hg and 93% < 45 mm Hg. The residual AR is also comparable to other reports, with 43% of patients having no AR at the end of the procedure and 81% having mild or less AR. AR $\geq$ moderate ($\geq 2+$) continues to be seen relatively frequently. We found that 19% of the patients had at least moderate AR immediately after BAVP, which is similar to reported rates by other investigators (7–22%) [4,7,14,26,27]. Only one patient ($<1\%$) in the series had severe AR immediately after BAVP. Earlier series have reported rates of severe AR immediately after BAVP between 1 and 2% [4,7,9].

Our data suggests that BAVP has become safer over the last 30 years. In 373 patients, there were no reports of procedure-related deaths, despite 33% of the patients being under one month of age at the time of the procedure. Prior reports that include a similar proportion of neonates report early mortality after the procedure between 2 and 4% [2,9,13,16,17,27]. Neonatal BAVP is associated with a higher early mortality, ranging between 9 and 14% [4,5,10,14,28]. Other reports have also suggested that BAVP has become safer over time. McElhinney et al. reported a decrease in the incidence of early deaths ($\leq$ 30 days after the procedure) in patients undergoing BAVP in the neonatal period ($\leq$ 60 days of life) when comparing the outcomes of patients undergoing the procedure between 1985 and 1993 (22%) to those undergoing the procedure between 1994 and 2002 (4%) [14]. It is important to note, however, that within the neonatal group, patients with

small left sided structures have been shown to be at increased risk of early mortality after BAVP or surgical valvotomy [4,18,29–31]. The absence of early mortality in our series may be explained, at least in part, by the exclusion of patients that were not felt to be candidates for a biventricular circulation.

Catastrophic complications in patients older than 1 month of age undergoing BAVP are uncommon, with reported rates under 1% [7,15,32]. In fact, even in the early experience of BAVP, no deaths were reported in over 400 patients undergoing the procedure after infancy [3].

McCrindle et al. reported an incidence of major morbidity of 7.1% in a multi-institutional study of over 700 patients undergoing BAVP for cAS during childhood, including neonates [13]. They defined major morbidity as the development of severe AR, aortic valve avulsion, severe arterial disruption, cardiac or vascular perforation, cardiac tamponade, or stroke. Our definition of high severity AE is broader, and includes not only major events, but also what would be considered moderate (level 3) events. Using this broader definition we observed high severity AE in approximately 10% of the procedures. If all AE are taken into account, 20% of the patients had an AE. Using similar criteria in a population with similar age distribution, Justo et al. reported complication rates for BAVP of ~40% during the early experience with BAVP [2]. To our knowledge, this is the only report of BAVP in the current era that includes AE data from multiple institutions that has been collected and analyzed prospectively, and has undergone independent event review, validation, and audits for event capture and completeness.

Patients that undergo BAVP during the neonatal period are generally considered to be at higher risk for complications, death, and suboptimal results. We found that the only factor associated with increased risk of a high severity AE was age < 1 month. Within this group of patients, a lower aortic valve annulus z-score and infusion of prostaglandins during the procedure (critical cAS) were associated with an inadequate outcome, whereas weight, baseline PSG, and maximum BAR were not. Lower aortic valve annulus z-score has been identified previously as a risk factor for poor acute [14] and long-term outcomes [28].

Among patients undergoing BAVP after 1 month of age, older age was one of the factors associated with inadequate outcome, as has been observed in other series [13]. History of any prior aortic valve intervention was also found to be a risk factor within this group.

Patients with mixed aortic valve disease were also at increased risk for inadequate outcome. This association is to be expected, given our outcomes categorization system. However, it is interesting to note that 58% of these patients achieved a result characterized by post-dilation gradient ≤ 35 mm Hg and no increase in the degree of AR. Also, as a group, the patients with mixed aortic valve disease had less of a change in AR grade associated with BAVP than patients with isolated cAS. Taken together with the higher residual PSG in this group, these findings would suggest that the approach of the operators tended to be more conservative in patients with mixed aortic valve disease, and that further resolution of the gradient was not sought because of the existing degree of AR. Presence of pre-existing AR has been found to be an independent predictor of the development of significant AR after BAVP by other investigators [7,13].

There are several limitations to this study. The source databases were based on an intervention being performed at the time of catheterization. Our study does not attempt to identify appropriate thresholds for catheterization referral or for BAVP. Another important limitation is that the assessment of the degree of AR used to determine the acute outcome category was based on a qualitative assessment by the operator, and was not performed by a single blinded reviewer, as would be ideal in order to minimize potential bias and inter-rater variability that has been shown to occur in other studies [25]. Also, although data were prospectively collected from the time of catheterization, some important information could only be inferred retrospectively. For example, we excluded all patients who were not felt to have an adequate left ventricle for a biventricular circulation, though how providers arrived at this exclusion is unknown. The population of patients with borderline left heart structures is at particularly high risk for poor outcomes, and excluding them may make our outcomes appear overly optimistic when compared to studies that include this sub-population. Similarly, patients recorded to be receiving PGE infusion during the catheterization procedure were understood to have critical aortic stenosis, though we are unable to know whether all were truly prostaglandin dependent, or whether practice among centers varied with regard to administration of PGE. Finally, the pooling of data from multiple institutions may dilute potential institutional biases and therefore make it more difficult to identify certain procedural factors that may be associated with outcome.

CONCLUSION

We find that when BAVP is performed in patients with cAS, it results in a favorable outcome in over 70% of patients, and that serious AE are relatively uncommon. Although patients undergoing the procedure during the first month of life continue to be at a higher risk for complications, the safety and efficacy profile of the procedure appears to be relatively consistent across institutions of varying sizes and practice models.

APPENDIX

TABLE A1. Institutions Participating in C3PO and MAGIC Cohorts

C3PO	MAGIC
Boston Children's Hospital	Children's Hospital of Central California
Children's Hospital of Pittsburgh	Children's Hospital of the Kings Daughters
Cincinnati Children's Hospital Medical Center	Children's Hospital of Wisconsin
Morgan Stanley Children's Hospital of New York Presbyterian	Duke University
Nationwide Children's Hospital	Johns Hopkins
Oregon Health Sciences University	Medical University of South Carolina
Rady Children's Hospital—San Diego	Northwestern Children's Memorial Hospital
St. Louis Children's Hospital	Nemours Children's Hospital
	Riley Children's Hospital/University of Indiana
	University of Mississippi
	University of Virginia
	Vanderbilt University Children's Hospital
	Wake Forest University
	Yale University

TABLE A2. Definitions for Adverse Event Severity, With Examples

Severity group	Severity level	Definition	Examples
Low	1. None	No harm, no change in condition, may have required monitoring to assess for potential change in condition with no intervention indicated.	Balloon rupture Equipment problem
	2. Minor	Transient change in condition, not life threatening, condition returns to baseline, required monitoring, required minor intervention such as holding a medication, or obtaining lab test.	Groin hematoma Self resolving arrhythmia
High	3. Moderate	Transient change in condition may be life threatening if not treated, condition returns to baseline, required monitoring, required intervention such as reversal agent, additional medication, transfer to the intensive care unit for monitoring, or moderate trans-catheter intervention to correct condition.	Unstable arrhythmia with preserved blood pressure requiring intervention Vascular damage not life-threatening but requiring intervention
	4. Major	Change in condition, life threatening if not treated, change in condition may be permanent, may have required an intensive care unit admission or emergent readmit to hospital, may have required invasive monitoring, required interventions such as electrical cardioversion or unanticipated intubation or required major invasive procedures or trans-catheter interventions to correct condition.	Event requiring cardiopulmonary resuscitation Event leading to surgery or repeat catheterization Stroke
	5. Catastrophic	Any death, and emergent surgery or heart lung bypass support (ECMO) to prevent death with failure to wean from bypass support.	Event resulting in death

TABLE A3. Outcomes and Adverse Events by Institution Within the C3PO Cohort

	Total $n=233$, n (%)	Institution—n (%)							
		A ($n=33$)	B ($n=82$)	C ($n=31$)	D ($n=27$)	E ($n=21$)	F ($n=21$)	G ($n=14$)	H ($n=4$)
Acute procedural success	157 (69)	20 (60)	62 (78)	21 (68)	18 (70)	15 (71)	12 (57)	7 (50)	2 (50)
Outcome category									
Optimal	66 (29)	8 (24)	27 (34)	8 (26)	9 (35)	3 (14)	5 (24)	5 (36)	1 (25)
Adequate	91 (40)	12 (36)	35 (44)	13 (42)	9 (35)	12 (57)	7 (33)	2 (14)	1 (25)
Inadequate	72 (31)	13 (39)	17 (22)	10 (32)	8 (31)	6 (29)	9 (43)	7 (50)	2 (50)
Residual PSG $\geq$35	42 (18)	8 (24)	13 (26)	3 (10)	5 (19)	2 (10)	5 (24)	6 (43)	0 (0)
2+ or more AR after BAVP	47 (20)	10 (30)	9 (11)	8 (26)	4 (15)	4 (20)	7 (33)	3 (21)	2 (50)
Age									
<1 month	76 (33)	13 (39)	17 (21)	12 (39)	11 (41)	10 (48)	7 (33)	5 (36)	1 (25)
1–11 months	45 (19)	6 (18)	18 (22)	3 (10)	5 (19)	5 (24)	4 (19)	2 (14)	2 (50)
1–5 years	23 (10)	2 (6)	9 (11)	5 (16)	4 (15)	0 (0)	1 (5)	1 (7)	1 (25)
6–10 years	30 (13)	3 (9)	12 (15)	5 (16)	2 (7)	3 (14)	3 (14)	2 (14)	0 (0)
11–17 years	37 (16)	5 (15)	17 (21)	3 (10)	2 (7)	2 (10)	4 (19)	4 (29)	0 (0)
$\geq$18 years	22 (9)	4 (12)	9 (11)	3 (10)	3 (11)	1 (5)	2 (10)	0 (0)	0 (0)
Any level 3/4/5 event	23 (10)	2 (6)	5 (6)	5 (16)	1 (4)	6 (29)	3 (14)	1 (7)	0 (0)

AR: aortic regurgitation; BAVP: balloon aortic valvuloplasty; PSG: peak-to-peak systolic gradient across the aortic valve.

TABLE A4. C3PO Cohort Comparison: First Time Intervention Versus Reintervention

	First Time BAV ($n=169$)	Re-intervention ($n=64$)	P value
Age			
<1 month	72 (43%)	4 (6%)	<0.001
1–11 months	32 (19%)	13 (20%)	
1–5 years	17 (10%)	6 (9%)	
6–10 years	19 (11%)	11 (17%)	
1117 years	22 (13%)	15 (23%)	
$\geq$ 18 years	7 (4%)	15 (23%)	
Weight (kg)	5.0 [3.5, 25.6]	35.8 [8.2, 62.0]	<0.001
Diagnosis			0.02
Isolated defects	135 (80%)	41 (64%)	
Complex CHD	34 (20%)	23 (36%)	
Genetic syndrome	5 (3%)	6 (9%)	0.08
Non-cardiac problem	23 (14%)	8 (13%)	1.0
Left ventricular end diastolic pressure $\geq$ 18	32 (19%)	23 (36%)	0.009
Aortic valve diameter z-score ($n=126$, 49)	−0.3 [−1.2, 0.7]	−0.8 [−1.6, 0.1]	0.13
Baseline PSG (n=167, 64)	58 [50, 70]	60 [50, 70]	0.70
Residual PSG ($n=168$, 63)	22 [15, 30]	30 [20, 40]	<0.001
AR Before BAVP ($n=168$, 63)			<0.001
None	131 (78%)	23 (37%)	
1+	35 (21%)	31 (49%)	
2+	1 (1%)	9 (14%)	
3+	1 (1%)	0 (0%)	
4+	0 (0%)	0 (0%)	
AR after BAVP ($n=168$, 63)			0.003
None	66 (39%)	10 (16%)	
1+	74 (44%)	34 (54%)	
2+	21 (13%)	14 (22%)	
3+	6 (4%)	5 (8%)	
4+	1 (1%)	0 (0%)	
Increase in AR ($n=167$, 63)			0.63
None	96 (57%)	39 (62%)	
+1 grade	51 (31%)	21 (33%)	
+2 grades	15 (9%)	2 (3%)	
+3 grades	4 (2%)	1 (2%)	
+4 grades	1 (1%)	0 (0%)	
Acute procedural success ($n=167$, 62)	122 (73%)	35 (56%)	0.02
Composite outcome ($n=167$, 62)			0.002
Optimal	58 (35%)	8 (13%)	
Adequate	64 (38%)	27 (44%)	
Inadequate	45 (27%)	27 (44%)	

[a]AR: aortic regurgitation; BAVP: balloon aortic valvuloplasty; CHD: congenital heart disease; PSG: peak-to-peak systolic gradient across the aortic valve.

TABLE A5. C3PO Cohort Comparison: Aortic Stenosis vs. Mixed Aortic Valve Disease, Age >1 Month

Variable	Isolated AS: AS, no AR ($n=84$)	Mixed aortic valve disease: AS, 1+ or greater AR ($n=72$)	*P* value
Age (years)	5.5 [0.2, 10.9]	11.8 [3.5, 17.5]	**<0.001**
Age category			
1–11 months	32 (38%)	12 (17%)	**<0.001**
1–5 years	10 (12%)	13 (18%)	
6–10 years	21 (25%)	9 (13%)	
11–17 years	14 (17%)	23 (32%)	
≥18 years	7 (8%)	15 (21%)	
Associated cardiovascular anomalies			
Isolated defects	62 (74%)	55 (76)	0.85
Complex CHD	22 (26%)	17 (24)	
Weight (kg)	19.6 [5.6, 46.3]	39.2 [15.9, 63.0]	**<0.001**
History of BAV ($n=81$, 70)	15 (19%)	35 (50)	**<0.001**
History of surgical valvotomy($n=82$, 70)	10 (12%)	7 (10)	0.80
Left ventricular end diastolic pressure (mm Hg) ($n=82$, 67)	12 [9, 17]	14 [11, 18]	0.06
Aortic valve diameter *z*-score ($n=64$, 52)	-0.2 [-0.9,0.8]	-0.1 [-1.3, 1.1]	0.87
Baseline PSG ($n=83$, 72)	55 [50, 70]	57 [47, 66]	0.52
Residual PSG ($n=84$, 71)	23 [15, 30]	29 [19, 38]	**0.007**
Percent change in gradient ($n=83$, 71)	60 [50, 72]	47 [33, 67]	**0.002**
Residual PSG category($n=84$, 71)			
<35 mm Hg	75 (89%)	51 (72%)	**0.004**
≥35 mm Hg	9 (11%)	20 (28%)	
≥35 < 45 mm Hg	7 (8%)	8 (11%)	
≥45 mm Hg	2 (2%)	12 (17%)	
AR after BAVP ($n=83$, 72)			
None/trivial	48 (58%)	0 (0%)	**<0.001**
1+	27 (33%)	(69%)	
2+	7 (8%)	16 (22%)	
3+	1 (1%)	(8%)	
4+	0 (0%)	0 (0%)	
Increase in AR			
None	48 (58%)	56 (78%)	**0.01**
1+	27 (33%)	(21%)	
≥2+	8 (10%)	1 (1%)	
Acute procedural success ($n=83$, 71)	66 (79%)	41 (58%)	**0.005**
Outcome category ($n=83$, 71)			**<0.001**
Optimal	41 (49%)	0 (0%)	
Adequate	25 (30%)	41 (58%)	
Inadequate	17 (20%)	30 (42%)	

[a]AR: aortic regurgitation; AS: aortic stenosis; BAVP: balloon aortic valvuloplasty; CHD: congenital heart disease; PSG: peak-to-peak systolic gradient across the aortic valve.

TABLE A6. Distribution of Adverse Events by Age

	Total ($n=233$)	Age < 1 month ($n=76$)	Age ≥ 1 month ($n=157$)	*P* value
Vascular/cardiac trauma	18 (8)	11 (14)	7 (4)	**0.02**
Confined tear	1 (<1)	1 (1)	0 (0)	
Aneurysm/pseudo-aneurysm	1 (<1)	0 (0)	1 (1)	
Heart perforation	3 (1)	2 (3)	1 (1)	
Other vessel trauma	13 (6)	8 (11)	5 (3)	
Technical	3 (1)	1 (1)	2 (1)	1.0
Balloon rupture	2 (1)	1 (1)	1 (1)	
Valvuloplasty problem	1 (<1)	0 (0)	1 (1)	
Arrhythmias	15 (6)	6 (8)	9 (6)	0.57
Atrial arrhythmia	2 (1)	0 (0)	2 (1)	
Heart block, resolved	3 (1)	1 (1)	2 (1)	
Ventricular arrhythmia	10 (4)	5 (7)	5 (3)	
Hemodynamic	5 (2)	4 (5)	1 (1)	**0.04**
Hypotension	3 (1)	3 (4)	0 (0)	
Hypoxia	1 (<1)	0 (0)	1 (1)	
Non-specific ST/T-wave changes	1 (<1)	1 (1)	0 (0)	
Vascular Entry Site	8 (3)	6 (8)	2 (1)	**0.02**
Pulse loss	6 (3)	5 (7)	1 (1)	
Re-bleed	1 (<1)	0 (0)	1 (1)	
Other problem	1 (<1)	1 (1)	0 (0)	
Sedation/Anesthesia/Airway	7 (3)	5 (7)	2 (1)	**0.04**
Respiratory acidosis	1 (<1)	0 (0)	1 (1)	
Other	6 (3)	5 (7)	1 (1)	

TABLE A7. Description of High Severity Adverse Events

Description	*n*	Comments
>2 grade increase in angiographic aortic regurgitation	6	
Heart perforation	2	1. Wire perforated LV apex, causing hemopericardium which was evacuated and auto-transfused immediately. Patient did well. Procedure continued with good result 2. While probing the atrial septum with a catheter, the stiff end of a torque wire was used to puncture the atrial septum in an attempt to enter the LA. The guide wire was inadvertently advanced into the pericardial space and then withdrawn without complication.
Post extubation stridor	1	Patient with history of prior surgical procedures and intubations. Remained intubated for 3 days after the procedure while hemodynamics recovering post valvuloplasty. After extubation stridor and respiratory distress prominent. ORL evaluation revealed left vocal cord paralysis and granulation tissue below the cords. Granulation tissue laser resection performed.
Atrial arrhythmia	1	Atrial fibrillation during atrial catheter manipulation. Required cardioversion. Well tolerated.
Ventricular arrhythmia	6	4 patients had ventricular fibrillation and 2 had ventricular tachycardia. Only 1 patient had spontaneous resolution. The rest required CPR and/or cardioversion/defibrillation.
Apnea/Hypoxia	2	1. Patient sedated with versed and fentanyl and became apneic and hypoxic. Managed without intubation. 2. At the beginning of the case, patient was sedated and spontaneously breathing. Developed bilateral upper lobe atelectasis with desaturation to the low 90s. Patient intubated.
Thrombosis/embolism	1	Following aortic angiography (post 3rd aortic valve balloon dilation) became hypotensive and bradycardic with ST segment changes, then developed 2:1 heart block. Resuscitated and paced with temporary wire and heart block fully resolved within 5 minutes. Post-catheterization ECG morning after the procedure showed ST segment changes and echocardiogram showed decreased wall motion of the posterior LV free wall. Filling defect in the distal posterior circumflex artery identified by angiography, consistent with thromboembolism. Patient was treated with intra-coronary TPA and started on a nitroglycerine drip with improvement of flow into the distal circumflex.
Heart Block Resolved	1	2 day old with severe AS. Developed complete heart block with retrograde wire entry into LV. Resolved after wire withdrawal, epinephrine boluses and 1 minute of chest compressions. Procedure completed after resolution of heart block and patient did well.
ST-T wave changes	1	Post dilation angiogram demonstrated one to two plus AI with marked ST segment changes and hypotension requiring resuscitation. Patient observed in ICU overnight, recovered well.
Mitral Regurgitation	1	Balloon was not stable across aortic valve annulus during initial inflation and there was concern about possible mitral valve trauma. Echo documented mild but new mitral regurgitation. No treatment needed.
Access problem	1	Decreased pulse noted, prophylactic heparin drip increased to therapeutic.

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