Cardiol Young 2004; 14: 315–321

ISSN 1047-9511

Original Article

Outcomes after balloon dilation of congenital aortic stenosis in children and adolescents

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Abstract *Objectives:* To determine the long-term outcomes and risk factors for, reintervention after balloon dilation of congenital aortic stenosis in children aged 6 months or older. *Background:* Although balloon dilation of congenital aortic stenosis has become a primary therapeutic strategy, few data are available regarding long-term outcomes. *Methods:* We carried out a retrospective review of 87 children who had undergone balloon dilation of the aortic valve at median age of 6.9 years. *Results:* The procedure was completed in 98% of the children, with an average reduction in the gradient across the valve of 64 ± 28%, and without mortality. Of the children, 76 had been followed for a mean of 6.3 ± 4.2 years. Reintervention on the aortic valve was required in 32 children, with 12 undergoing reintervention within 6 months, with 1 death. Another patient had died over the period of follow-up due to a non-cardiac event. Estimated freedom from reintervention was 86% at 1 year, 67% at 5 years, and 46% at 12 years. Parametric modeling of the hazard function showed a brief early phase of increased risk, superimposed on an ongoing constant risk. The only incremental risk factor for the early phase was a residual gradient immediately subsequent to the procedure greater than 30 mmHg. Incremental risk factors for the constant phase included the presence of symmetric valvar opening, and greater than moderate regurgitation immediately after dilation. *Conclusion:* Long-term survival was excellent, albeit that the need for further reintervention was high due to the palliative nature of the procedure.

Keywords: Interventional catheterization; congenital heart disease; pediatric cardiology; aortic valvar stenosis; outcomes

CONGENITAL AORTIC STENOSIS ACCOUNTS FOR 5–6% of all congenital cardiac lesions, with predominance in males.[1] Since its introduction over 20 years ago, balloon dilation of the stenotic aortic valve has proven to be an effective means for providing initial palliation in neonates, children and young adults.[2–10] Of the studies, however, few with large numbers have addressed outcomes over the longer term, greater than 4 years, after the application of this strategy for management.[11–17] In this paper, therefore, we sought to determine the outcomes over a period of more than 6 years, seeking to establish risk factors for reintervention after the use of the technique in children aged 6 months or older.

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Accepted for publication 16 February 2004

Materials and methods

Study design: Within the computer database from the Division of Cardiology at the Hospital for Sick Children, Toronto, Ontario, Canada, we identified 113 children who had undergone dilation of the aortic valve for congenital stenosis between April 1985 and December 1993. Due to the unique nature of the disease in the neonate and young infant,[18,19] our review focused on children aged 6 months or older, permitting us to establish for final analysis a population of 87 children and adolescents with a potential duration of follow-up of greater than 4 years. Data were abstracted from the medical records, including clinic

visits, electrocardiographic tracings, echocardiograms, catheterization and surgical notes, and death or autopsy reports. Data were classified into four time periods:

- Prior to dilation, including in this period studies and assessments conducted nearest to the date of the procedure, within a maximum period of 6 months.
- The index period, including data collected at the time of the procedure.
- The post-dilation period, including studies and assessments performed nearest to and after the procedure, within a maximum of 6 months.
- The period of follow-up, including studies and assessments conducted at least 6 months after dilation, or immediately before death, repeated dilation, or aortic valvar surgery. If no intervention or death occurred in the period of follow-up, we used the most recent available data for analysis.

Informed consent for balloon dilation was obtained from parents following the guidelines of the Human Subject Protection Committee of the Hospital for Sick Children, University of Toronto.

Indications for intervention: The indication for dilation was the presence of a measured peak-to-peak systolic pressure gradient of greater than 60 mmHg, irrespective of symptoms, or a gradient of 50 mmHg or more in the presence of symptoms or electrocardiographic ST-T wave changes at rest or after exercise. The procedure was also performed on children with symptomatic heart failure with "borderline" gradients. Significant aortic regurgitation greater than moderate was considered a contraindication for balloon dilation.

Technique: General anesthesia was employed in the majority of cases. The technique of balloon dilation has not change significantly since its introduction, and has been described in previous published protocols.[2–17] All procedures were performed from a retrograde approach, except one, which was done antegradely.[20] Administration of adenosine, or rapid ventricular pacing, was not used to stabilize the balloon across the aortic valvar orifice. Successful relief was defined as a residual peak-to-peak systolic gradient less than 50 mmHg, or a reduction in gradient of at least 40%. If the gradient remained greater than 50 mmHg, or fell less than 40%, and the degree of aortic regurgitation was unchanged, the balloon diameter was increased to the next size of the balloon. Angiograms and ventriculograms before and after the procedure were reviewed by one of the authors (C.A.C.P.) and, acutely, the degree of aortic regurgitation was assessed according to the classification described by Moore and colleagues.[11] Morphological characteristics of the valve were analyzed and classified as to the thickness of the leaflets and the pattern of opening. Thick leaflets were defined as being of 2 mm or more, and asymmetric valvar opening as unequal doming leaflets.

Follow-up: Follow-up visits were made at the discretion of the referring cardiologist, but were generally scheduled within 6 months of the procedure, and then every 12 months with electrocardiographic and echocardiographic evaluation. Echocardiographic tapes before and after the procedure were reviewed by one of the authors (R.N.J.). The degree of aortic regurgitation was assessed by determining the ratio of the diameter of the width of the regurgitant aortic jet to the diameter of the orifice of the aortic valve according to previous published protocols.[13] Restenosis was defined as the presence of an echo-Doppler-derived[21] or measured peak-to-peak systolic pressure gradient of greater than 60 mmHg. These children were referred either for a surgical procedure or, in the absence of significant aortic regurgitation, a repeat dilation. Patients with severe aortic regurgitation were followed clinically and referred for further procedures at the discretion of the cardiologist.

Statistical analysis: All values are described as frequencies, mean plus or minus one standard deviation, or median with range as applicable. A paired Student's t-test was used to compare changes in pressures before and after the procedure. A Mann–Whitney Rank Sum test, or a Wilcoxon Signed Rank test, was used to compare the degree of aortic regurgitation before and after the procedure. Time-related freedom from reintervention on the aortic valve, either surgery or repeat balloon dilation, was initially estimated using the Kaplan–Meier method. Children who died during follow-up before a reintevention were censored at the date of death. Parametric modeling of the phases of the hazard function was performed as described by Blackstone et al.[22] Incremental risk factors were sought using automated techniques, with transformations of continuous variables, additionally to calibrate the relationship of the variable to risk. Bootstrap bagging was used to determine the reliability of variable selection. Sigmastat 2.0 (Jandel Corporation) and SAS Version 8 (SAS Institute, Inc, Cary, NC) statistical software, set to default settings, were used to perform the statistical analyses. The level of statistical significance was set at a p value of less than 0.05.

Results

Population studied: From April 1985 to December 1993, 87 children 6 months of age or older had undergone balloon dilation of the aortic valve, with 71 children (82%) being male. The median age at the time of the procedure was 6.9 years, with a range from 6 months

https://doi.org/10.1017/S1047951104003105 Published online by Cambridge University Press

to 17.9 years. Median weight and height were 25 kg, with a range of 5–106 kg, and 123 cm, with a range of 65–184 cm, respectively. Associated cardiac abnormalities were present in 25 children (29%), including 9 with Shone's complex; 4 with coarctation of the aorta; 2 children each with supravalvar stenosis or mitral valvar stenosis, and 1 child each with Shone's complex with a non-hemodynamically significant ventricular septal defect; a single left coronary artery; pulmonary atresia and intact ventricular septum, significant mitral valvar regurgitation, and an isolated coronary arterial fistula. Extracardiac conditions in 3 children each included Turner's syndrome or miscellaneous neurological disorders and a non-defined somatic syndrome in 1 child.

Previous cardiac surgery had been performed in 25 children (23%), including 9 children having an aortic valvotomy, 4 children having two previous valvotomies, 4 a repair of coarctation, 3 children having an aortic valvotomy combined with mitral surgery and/or enlargement of the sub or supra aortic areas and/or coarctation repair, 1 child having three surgeries, and 1 child each having resection of a subaortic shelf, repair of coarctation combined with mitral valvar surgery or enlargement of the supravalvar area, and placement of a left modified Blalock–Taussig shunt followed by tricuspid valvar excision.

At the time of dilation, 25 children (29%) presented with chest pain, syncope, or exercise intolerance, 5 children (6%) were in mild clinical heart failure, and 9 (10%) were on digitalis and/or diuretics. Although all children were clinically stable before the procedure, 1 was deeply cyanosed, having associated pulmonary atresia with an intact ventricular septum, with an arterial oxygen saturation of 70–75%. The electrocardiogram demonstrated ST segment or T wave changes in 29 of 84 children (35%; three missing values). On echocardiography, 72 of 78 (92%; nine missing values) children were considered to have a bicuspid aortic valve, and 6 of 78 (8%) had tricuspid aortic valves. The ratio of the width of the regurgitant jet to the diameter of the aortic valve was assessed in 65 children, and graded as 0–0.28, with a median of 0 (confidence intervals 25%: 0; 75%: 0.1, 22 missing values). The peak instantaneous gradient, at 77 ± 20 mmHg, was measured in 79 children.

Acute results after dilation: The procedure was completed in 85 of 87 (98%) children. Although there was no mortality, 33 children (39%) had significant complications related to the procedure. The most frequent was arterial damage (29 of 33; 88%), with most cases (20 of 29) occurring in the first 5 years of our experience. After the administration of heparin or a thrombolytic agent, the distal pulse was restored in 18 of 29 children (62%). Vascular surgery was needed in 10 children (35%) for resolution of the arterial occlusion. Severe aortic regurgitation developed in 4 children (5%) due to tears of the leaflets of the aortic valve, prolapse, or perforation requiring surgical aortic valvuloplasty, performed at the same admission in 2, and within 4 months in the other 2 children.

The measured diameters of the aortic valve varied from 1.0 to 3.0 cm, with a mean of 1.9 ± 0.5 cm. In 23 children (27%), a double balloon technique was employed. The mean ratio of the diameter of the balloon to that of the aortic valve was 0.97 ± 0.08.

Left ventricular systolic pressure decreased from a mean of 158 ± 26 to 127 ± 21 mmHg ($p < 0.001$). Mean left ventricular end-diastolic pressure, 12 ± 7 before and 11 ± 6 mmHg after dilation, showed no significant change ($p = 0.141$). The mean aortic systolic pressure increased from a mean of 102 ± 17 to 107 ± 16 mmHg ($p = 0.032$), while the mean aortic diastolic pressure, 70 ± 13 before and 68 ± 17 mmHg after dilation, showed no significant change ($p = 0.57$). The mean peak-to-peak systolic gradient across the aortic valve decreased from 56 ± 23 to 21 ± 18 mmHg ($p < 0.001$), a mean reduction in gradient of 64 ± 28%. Despite an overall reduction in the peak-to-peak gradient, the hemodynamic criterions for success were not met in 10 children (12%). Angiographically, the degree of aortic regurgitation increased from a median of one to a median of two ($p < 0.001$, one missing value) after dilation, with 38 of 85 children (45%) having an increase of the degree of aortic regurgitation.

Post-dilation period: Assessments were performed at a median of 1 day, with a range from 0 to 180 days, after the procedure. On Doppler echocardiography, the peak instantaneous gradient, assessed in 78 children, decreased to a mean of 47 ± 18 mmHg ($p < 0.001$), and the ratio of the width of the regurgitant jet relative to that of the aortic valve increased to a median of 0.05, with a range of 0–0.52; confidence intervals 25%: 0; 75%: 0.28, $p < 0.001$, 20 missing values.

Follow-up: Of the 85 children in whom the procedure was completed, 9 were lost to follow-up. In the remaining 76 children, follow-up had continued for a mean of 6.3 ± 4.2 years, ranging up to 12.7 years. In 12 children (16%), some type of intervention to the aortic valve had been needed within 6 months, with 4 children having an uneventful surgical valvoplasty because of significant aortic regurgitation, as noted above. Out of the 10 children in whom the hemodynamic criterions for successful relief of the gradient were not met, 6 underwent surgery within 6 months, with 1 death, and 2 had valvar replacement 21 and 72 months after the procedure. The remaining 2 children were followed clinically, with derived peak-to-peak gradients of less than 50 mmHg on

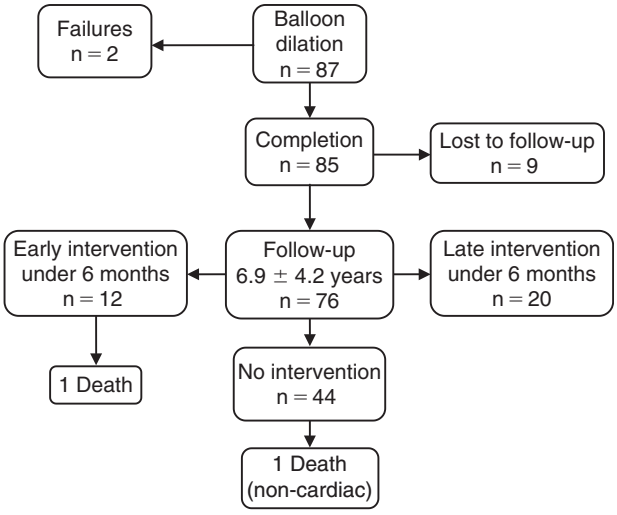

Figure 1.
Outcomes after balloon aortic valvoplasty.

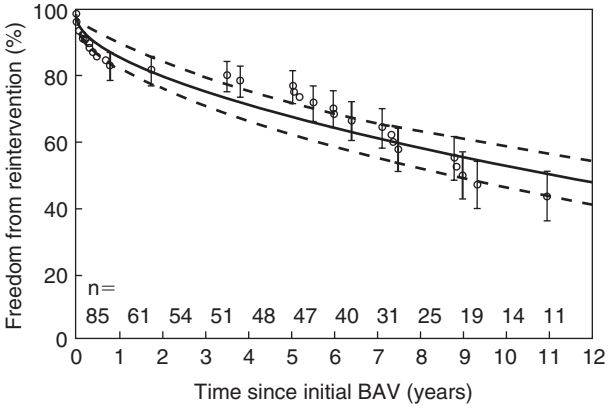

Figure 2.
Time-related freedom from reintervention to the aortic valve. Circles with error bars represent Kaplan–Meier estimates. The solid line represents the parametric model, with dashed lines enclosing the 70% confidence interval. Numbers above the horizontal axis represent the number of children remaining at risk. BAV: balloon aortic valvotomy.

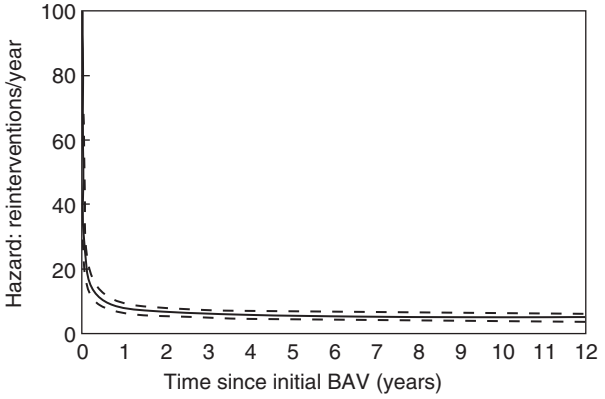

Figure 3.
Time-related hazard of reintervention for aortic valvar disease. BAV: balloon aortic valvotomy.

echocardiography at late follow-up. The child with pulmonary atresia and intact ventricular septum underwent an uneventful bidirectional cavopulmonary anastomosis 1 month after a successful aortic valvar dilation. In two children in whom the procedure was successful, restenosis developed early, at less than 6 months, requiring surgical valvotomy. Of these, 1 underwent an unsuccessful second dilation before surgery.

Of the remaining 64 children who did not require reintervention to the aortic valve within 6 months of the procedure, 44 (58%) were followed clinically, with 32 having greater than 4 years of follow-up. One child died from gastroenteritis 21 months after dilation. In the remaining 43 children, the mean peak instantaneous gradient assessed by Doppler echocardiography was 53 ± 22 mmHg at follow-up, with two missing values, this being similar to the mean peak instantaneous gradient of 47 ± 18 mmHg measured in the post-dilation period ($p = 0.55$). On echocardiography, the ratio of the width of the regurgitant jet relative to that of the aortic valve increased to a median of 0.10, with a range from 0 to 0.52; confidence intervals 25%: 0.05; 75%: 0.40, 10 missing values, $p < 0.001$. Reintervention at periods of less than 6 months was needed in 20 children (26%) due to restenosis, significant aortic regurgitation, or both. There was no late mortality due to cardiac events (Fig. 1).

Reinterventions: Overall, early or late reintervention on the aortic valve was performed in 32 children during the period of follow-up. Of these 32 children, 17 required reintervention due to restenosis, with 12 children undergoing surgical repair and 5 repeat dilation. Of the 12 children who underwent surgery, 7 required some technique to enlarge the diameter of the aortic valve, the subvalvar region, or the supravalvar area. Late surgical procedures were needed in 12 children due to significant aortic regurgitation. Surgical procedures were needed in 3 children due to restenosis associated with either significant aortic regurgitation or severe mitral regurgitation. The estimated freedom from reintervention was 86% at 1 year, 67% at 5 years, and 46% at 12 years after dilation (Fig. 2). Parametric modeling of the hazard function showed a brief early phase of increased risk superimposed on an ongoing constant risk (Fig. 3). The only incremental risk factor for reintervention during the early phase was a higher gradient immediately after dilation, with a p value of 0.10 after logarithmic transformation, and reliability from bootstrapping 45%. As shown in Figure 4a, the risk of

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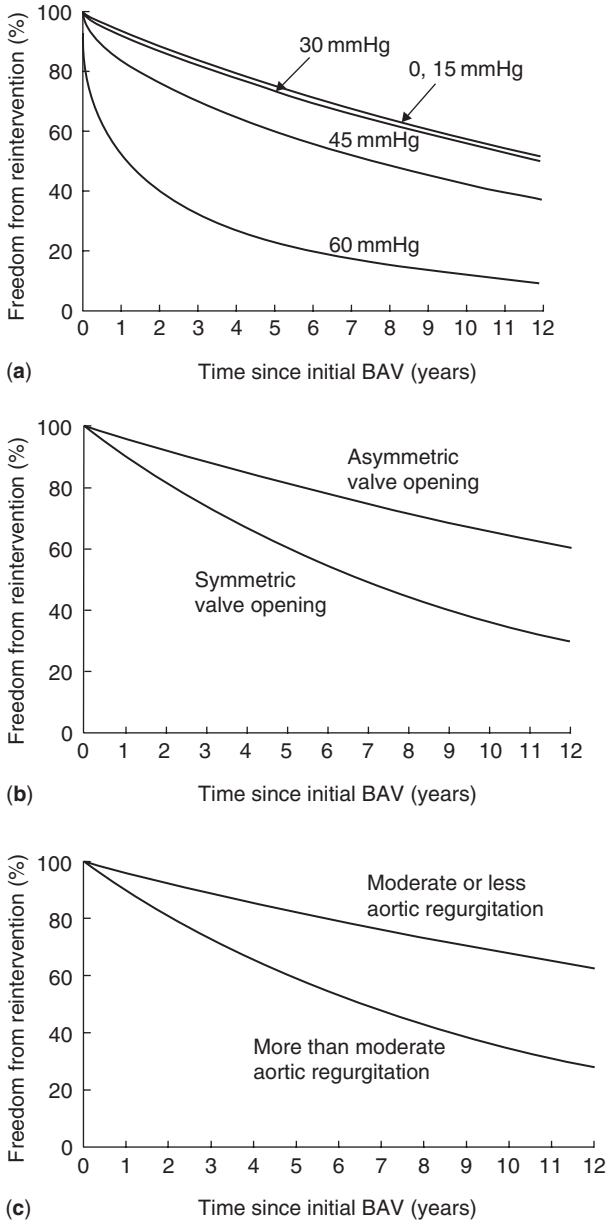

Figure 4.
*(**a**) Time-related freedom from reintervention for aortic valvar disease stratified by immediate after balloon dilation residual peak-to-peak systolic gradient by catheterization. (**b**) Time-related freedom from reintervention for aortic valvar disease stratified by aortic valvar morphology. (**c**) Time-related freedom from reintervention for aortic valvar disease stratified by the presence of more than moderate aortic valvar regurgitation by angiography immediately after balloon dilation. BAV: balloon aortic valvotomy.*

reintervention increases logarithmically for gradients above 30 mmHg. Incremental risk factors for constant phase reintervention included angiographically determined symmetrical opening of the valve ($p < 0.05$; reliability 42%; Fig. 4b) prior to dilation, and the presence of more than moderate angiographic aortic regurgitation on or immediately after dilation ($p < 0.03$; reliability 46%; Fig. 4c).

Discussion

Immediate results: Although our study was confined to the assessment of long-term clinical outcomes in children 6 months of age or more after balloon dilation of the aortic valve, it also confirms the findings of previous studies in regards to the immediate results.[2–10] Balloon dilation was completed in 98% of children, and was effective in reducing the gradient across the aortic valve, with haemodynamic success in 88%. Although the procedural mortality was low, there was significant morbidity associated with dilation, due to the use of the high profile balloons available during the period of study producing arterial damage. Evolving catheter technology, and the availability of larger diameter balloons mounted on lower profile catheter shafts, has reduced the issue of vascular injury,[23] as observed in the last years of this series.

An increase in the degree of aortic regurgitation occurred in 45% of children, and was generally well tolerated. Significant aortic regurgitation due to either prolapse or perforation of an aortic leaflet was observed in 5%, requiring early surgical intervention. Although it is not clear what factors may predict this occurrence, attention to technical details is of paramount importance when manipulating wires and catheters to gain access to the left ventricle. Data from the VACA registry demonstrated that three factors independently predicted the development of significant aortic regurgitation, specifically an increased ratio of the diameter of the balloon to that of the aortic valve of more than 1, the presence of pre-existing aortic regurgitation graded at mild or greater, and valves greater than 16 mm in diameter. Previous surgical valvotomy was not considered a risk factor.[24] It has been speculated that the presence of previous aortic regurgitation may signify valves with morphological abnormalities that would be exacerbated by the dilation. Larger valves in older children may also exhibit signs of secondary degenerative changes, which may predispose them to insufficiency. In addition, stabilization of the balloon across the valve is generally difficult in the older child with normal ventricular function, which may damage the leaflets during the inflation, inducing regurgitation.[25]

Late outcomes: Series with large numbers of children with follow-up of more than 4 years are scarce in the literature. This series was designed to address such follow-up, and had a follow-up duration of 6.3 ± 4.2 years in 76 children. Although late mortality was uncommon, the need for repeat intervention to the aortic valve was high, being seen in 32 of 76 children (42%). Time-related freedom from repeat intervention was 86% at 1 year, 67% at 5 years, and 46% at 12 years after dilation. Furthermore, we found that the only incremental risk factor for reintervention

https://doi.org/10.1017/S1047951104003105 Published online by Cambridge University Press

in the early phase was a higher immediate gradient after dilation, the risk increasing logarithmically for values of greater than 30 mmHg. Not surprisingly, most of the reinterventions, specifically eight of 12, performed on the aortic valve within 6 months were due to restenosis or persistent residual gradients. Restenosis was also observed at late follow-up, with 5 children being successfully managed by a repeat dilation, in accordance with the results reported in the literature.[26,27] Interestingly, of the 12 children who underwent surgery, mainly for restenosis, 7 required some technique to deal with a hypoplastic valvar orifice, concomitant with significant subvalvar or supravalvar stenosis. These findings suggest that, when successful relief of the gradient is not achieved, it is likely that other sites in the left ventricular outflow tract are participating in perpetuating the obstruction.

We identified the presence of more than moderate aortic regurgitation on angiography immediately after the procedure as an incremental risk factor for constant phase reintervention. Additionally, while the valvar gradients in the 43 children who did not require reintervention was unchanged over the period of follow-up, the degree of aortic regurgitation increased significantly, reflecting its progressive nature. The observation that the degree of aortic regurgitation increases over time is universal, and is common to all case series, be they are related to catheter or surgical intervention. Although risk factors for increasing aortic regurgitation have not been fully defined, it has been speculated that this is an inevitable occurrence due to the intrinsically abnormal morphology of the aortic valve, reflecting the modified natural history of this disorder. This is not surprising, considering that either the balloon of the interventionist, or the scalpel of the surgeon, causes variable splitting of the fused zones of apposition of the leaflets, this being the primary mechanism for valvar obstruction.[28] The observation that the presence of a symmetric valvar opening also emerged as an incremental risk factors for constant phase reintervention in this series is intriguing.[11] Such valves may be more prone to tear through the leaflet, rather than along or parallel to the zones of apposition between the leaflets. Whether an asymmetric valvar opening represents a subset of valves torn along the zones of apposition, or those less prone to malfunction over time, is speculative.

Other studies have shown similar outcomes and risk factors, although with fewer numbers of children and/or shorter periods of follow-up.[11,12,14–17] Repeat intervention for restenosis, or significant aortic regurgitation, was not uncommon, with time-related freedom from repeat intervention on the valve of 40–76% at 8 years after the procedure. Additionally, as in our series, the prevalence of significant aortic regurgitation increased over the period of follow-up. In the study from Boston,[11] a similar effect of valvar morphology, as seen on angiography, was observed on late outcomes, with higher rates of intervention associated with the presence of symmetrically thin or thick aortic valvar leaflets. Furthermore, most series identified the degree of aortic regurgitation and higher residual gradients as predictors for reintervention. In the study by Galal et al.,[14] multivariable stepwise logistic regression analysis also identified age less than 3 years and an immediate aortic valvar gradient of greater than 30 mmHg as predictors of restenosis. Logistic regression analysis further suggested that the degree of echo-Doppler estimated aortic regurgitation the day following dilation predicted aortic regurgitation at late follow-up. In the study by Demkow et al.,[16] a residual gradient of greater than 40 mmHg after the procedure carried a six-fold increase in relative risk for reintervention for restenosis. The immediate degree of aortic regurgitation after the dilation was the only risk factor for reintervention for regurgitation, with grades greater than two carrying a 10-fold increase in relative risk.

Although these studies have demonstrated similar outcomes and associated risk factors, systematic comparison of different series and to historical surgical series are of limited value because of heterogeneous populations, non-contemporary timeframes, lack of uniformity in defining restenosis and significant aortic regurgitation, inconsistent and variable techniques to assess aortic regurgitation, and variable criterions to determine the need of reintervention, either by repeated balloon dilation or surgery. While it has been suggested that aortic regurgitation may be more frequent after balloon dilation than surgical valvotomy, data from our institution does not support this view.[13] At late follow-up, aortic regurgitation increased significantly in both surgically and balloon dilated cohorts, with no difference in the degree of progression. Similarly, freedom from reintervention was the same in both groups.

There have been no prospective and randomized trials comparing the results of surgical valvotomy and balloon dilation for congenital non-calcific aortic stenosis. Nonetheless, this longitudinal observational study suggests that balloon dilation is a safe and effective procedure to provide sustained gradient relief across the aortic valve when applied to children 6 months of age or more. Due to its palliative nature, the incidence of repeat intervention is high. Because dilation avoids cardiopulmonary bypass, it may have a beneficial effect on subsequent neurological development and outcomes. Also, dilation is associated with shorter hospital stays and recovery periods, and lower costs. Avoiding an early median sternotomy may also be advantageous, considering that these

children are likely to have some future surgical procedure on their valve.

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