

ORIGINAL RESEARCH

Native Bicuspid Pulmonary Valve in D-Loop Transposition of the Great Arteries: Outcomes of the Neo-Aortic Valve Function and Root Dilation After Arterial Switch Operation

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BACKGROUND: Neo-aortic root dilation and neo-aortic regurgitation (AR) are common after arterial switch operation for D-loop transposition of the great arteries. We sought to evaluate these outcomes in patients with bicuspid native pulmonary valve (BNPV).

METHODS AND RESULTS: A retrospective analysis of patients with transposition of the great arteries undergoing arterial switch operation at Boston Children's Hospital from 1989 to 2018 matched BNPV patients 1:3 with patients with tricuspid native pulmonary valve by year of arterial switch operation. Kaplan–Meier analyses with log-rank test compared groups for time to first neo-aortic valve reoperation, occurrence of \geq moderate AR, and neo-aortic root dilation (root z score \geq 4). A total of 83 patients with BNPV were matched with 217 patients with tricuspid native pulmonary valve. Patients with BNPV more often had ventricular septal defects (73% versus 43%; $P<0.001$). Hospital length of stay (11 versus 10 days) and 30-day surgical mortality (3.6% versus 2.8%) were similar. During median 11 years follow-up, neo-aortic valve reoperation occurred in 4 patients with BNPV (6.0%) versus 6 patients with tricuspid native pulmonary valve (2.8%), with no significant difference in time to reoperation. More BNPV had AR at discharge (4.9% versus 0%; $P=0.014$) and during follow-up (13.4% versus 4.3%; hazard ratio [HR], 3.9; $P=0.004$), with shorter time to first occurrence of AR; this remained significant after adjusting for ventricular septal defects. Similarly, neo-aortic root dilation was more common in BNPV (45% versus 38%; HR, 1.64; $P=0.026$) with shorter time to first occurrence.

CONCLUSIONS: While patients with BNPV have similar short-term arterial switch operation outcomes, AR and neo-aortic root dilation occur more frequently and earlier compared with patients with tricuspid native pulmonary valve. Further long-term studies are needed to determine whether this results in greater need for neo-aortic valve reoperation.

Key Words: aortic valve ■ congenital heart disease ■ transposition of the great arteries

Over the past 40 years since the first surgical case series were reported,^{1,2} the arterial switch operation (ASO) has achieved excellent outcomes for infants born with D-loop transposition of the great arteries (TGA) with or without ventricular septal defects (VSD). Because of the success of this surgical solution,

the ASO has been performed for patients with increasingly complex cardiovascular anatomy, including those with complex left ventricular outflow tract obstruction and pulmonary stenosis. Concerns have been raised about the success of using the native pulmonary valve in the operation, especially when patients

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CLINICAL PERSPECTIVE

What Is New?

- This article provides new insights on the differing outcomes of patients with D-loop transposition of the great arteries and differing native pulmonary valve morphology; namely, that while all patients have similarly excellent short-term outcomes post-arterial switch operation, subsequent neo-aortic regurgitation and neo-aortic root dilatation happen more frequently and earlier in patients with bicuspid native pulmonary valves.

What Are the Clinical Implications?

- Clinically, patients with bicuspid native pulmonary valves may merit more frequent imaging follow-up for surveillance for worsening neo-aortic root dilation and regurgitation.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
ARD	aortic root dilation
ASO	arterial switch operation
BNPV	bicuspid native pulmonary valve
TGA	transposition of the great arteries
TNPV	tricuspid native pulmonary valve

have bicuspid native pulmonary valves (BNPV) versus the normal tricuspid native pulmonary valves (TNPV).³ Given the known long-term risks of neo-aortic root dilation (ARD) and neo-aortic regurgitation (AR) in patients with TNPV,⁴ we sought to investigate the long-term outcomes after ASO for patients with BNPV with focus on AR, ARD, and incidence of surgical reoperation on the neo-aortic root.

METHODS

Patients

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a retrospective review of patients who had an ASO for D-loop TGA at Boston Children's Hospital from 1989 to 2018. Native pulmonary valve anatomy was determined by initial preoperative echocardiography. Patients with BNPV were frequency matched by year of ASO operation in a 1:3 ratio with patients with TNPV. Patients with greater than mild subpulmonary stenosis, formally diagnosed

systemic hypertension (defined by consistent blood pressure >90th percentile for age), or connective tissue disorders (such as Marfan, Ehler Danlos, etc) were excluded. Not all patients with BNPV without subpulmonary stenosis underwent the ASO operation, and not another operation, in the time period outlined. The study was approved by the Boston Children's Hospital Institutional Review Board, and individual patient consent was waived.

Data Collection

Baseline and clinical characteristics were extracted from the clinical records including demographic information, gestational age and weight, age at time of surgery, weight and body surface area at time of ASO, and associated anomalies. The following anatomic variables were recorded: native pulmonary valve morphology, presence or absence of VSD, and VSD location. Native pulmonary valve morphology for the patients with BNPV was confirmed in both the preoperative echocardiogram report and the operative note, with the surgical report considered the criterion standard. Notably, 79/83 (95%) of patients had their valve morphology identified in their preoperative echocardiograms, with all of the missed diagnoses in the first decade of the study. Preoperative data included balloon atrial septostomy, prior cardiac surgical procedures, as well as echocardiogram data before ASO. In all instances, the data collected from each echocardiogram report included descriptive data on ventricular dilation, ventricular dysfunction, and valve regurgitation, as well as measurements and z scores for pulmonary and aortic valve annuli, aortic root, and ascending aorta. Intraoperative procedural data recorded included surgical techniques such as the Lecompte maneuver, VSD closure, atrial septal defect closure, and repair of coarctation. Postoperative data included hospital length of stay, the need for early reoperation, mortality, and discharge echocardiogram. Follow-up data were collected at 1, 3, 5, 10, and 15 years, as well as data from the most recent follow-up documentation, including echocardiogram data. Documented cardiac reoperation, stroke, thromboembolism, endocarditis, heart failure requiring hospitalization, or arrhythmia were recorded if they occurred any time after ASO. If aortic root measurements were not documented in the echocardiogram report, measurements were made directly on the echocardiogram images (n=69).

Statistical Analysis

Patient and surgical characteristics are summarized using frequencies and percentages for categorical variables and compared for patients with BNPV versus patients with TNPV using Fisher exact test. Continuous variables are summarized using medians

with 25th and 75th percentiles and compared using the Wilcoxon rank sum test. For patients surviving to hospital discharge following ASO surgery with follow-up information available, time from discharge to first cardiac reoperation on the neo-aortic root was estimated using the Kaplan–Meier method, and compared between groups using the log-rank test. Similar analyses were performed for time from discharge to first occurrence of \geq moderate AR, and time from discharge to first occurrence of ARD (defined as neo-aortic root z score ≥ 4). Hazard ratios for patients with BNPV versus patients with TNPV were estimated based on the Cox proportional hazards model. Because of the small number of outcome events, relationships between type of pulmonary valve and outcomes were adjusted for age at ASO and presence of VSD in separate models. Neo-aortic root z-scores for patients with $<$ moderate versus \geq moderate AR were compared using the Wilcoxon rank sum test. Associations between neo-aortic root z score and degree of AR were evaluated using Spearman correlation coefficients. Additional analyses collapsed degree of AR into the 2 groups $<$ moderate and \geq moderate, and compared z scores between groups using the Wilcoxon rank sum test. Analyses were performed using Stata version 15.

RESULTS

Patient Characteristics

During the study period 1989 to 2018, 83 patients with BNPV met anatomic inclusion criteria and underwent ASO. Early surgical outcomes in this group were similar to a contemporaneous group of 217 matched patients with TNPV, including hospital length of stay (11 days BNPV versus 10 days TNPV, $P=0.99$) and 30-day mortality (3.6% BNPV versus 2.8% TNPV, $P=0.71$). A total of 67 patients with BNPV who survived to hospital discharge had adequate follow-up data to be included in the long-term outcomes analysis. These were matched in a 1:3 fashion with 211 patients with TNPV as described for a total analysis cohort of 278 patients. Patient characteristics are shown in Table 1, with no significant differences in sex, race/ethnicity, or birth weight between groups; patients with BNPV more commonly had VSD versus those with TNPV (73% versus 43%, $P<0.001$).

Before ASO, the majority of both BNPV and TNPV underwent balloon atrial septostomy (69% and 72%, respectively, Table 1). Notably, age (median 5 days BNPV versus 4 days TNPV) and weight (3.5 kg versus 3.4 kg) at ASO were statistically different, although clinically comparable between the 2 groups. Hospital length of stay after ASO was similar between the 2 groups.

Table 1. Patient Characteristics

	Bicuspid PV (n=67)	Tricuspid PV (n=211)	P value
Male sex	41 (61%)	133 (63%)	0.88
Race			
White	43 (64%)	150 (71%)	0.58
Black	2 (3%)	11 (5%)	
Asian	1 (1%)	3 (1%)	
Other	8 (12%)	18 (9%)	
Not reported	13 (19%)	29 (14%)	
Birth weight, kg	3.4 (3.0, 3.7) (n=62)	3.3 (3.0, 3.6) (n=204)	0.52
Any VSD	49 (73%)	90 (43%)	<0.001
None	18	121	
Conoventricular	25	31	
Muscular	14	40	
Membranous	14	31	
Atrioventricular canal	3	2	
Other	1	0	
Balloon atrial septostomy	46 (69%)	150 (72%)	0.64
Age at surgery, d	5 (3, 20)	4 (3, 6)	0.062
Weight at surgery, kg	3.5 (3.2, 4.1) (n=66)	3.4 (3.0, 3.7) (n=211)	0.012
Hospital length of stay, d	12 (8, 17) (n=66)	10 (8, 16) (n=211)	0.23

Data presented as number (%), or median (25-75 percentile).

PV indicates pulmonary valve; and VSD, ventricular septal defect.

Subsequent Clinical Outcomes

Over a median follow-up of 11.3 years (range 0.02–30.3 years), there was no late mortality, defined as death >30 days post ASO, in patients with BNPV. Two patients with TNPV had late mortality, 1 patient with death after 1.7 years (death caused by underlying mitochondrial disease) and the other with death after 1.3 years (death caused by pulmonary hypertension). A total of 10 patients underwent any cardiac surgical reintervention on the neo-aortic root, 4 patients with BNPV and 6 patients with TNPV (6.0% and 2.8%, respectively; $P=0.16$). There was no significant difference in time to cardiac reoperation on the neo-aortic root among patients with BNPV versus patients with TNPV (Figure 1, log-rank test $P=0.16$).

Neo-Aortic Regurgitation

The development of \geq moderate AR over follow-up was more common in patients with BNPV ($n=9$, 13.4%) than patients with TNPV ($n=9$, 4.3%), hazard ratio 3.9 for BNPV ($P=0.004$). At time of initial surgical discharge, 3 patients with BNPV (4.9%) already had \geq moderate AR versus 0 for TNPV ($P=0.014$). Freedom from first

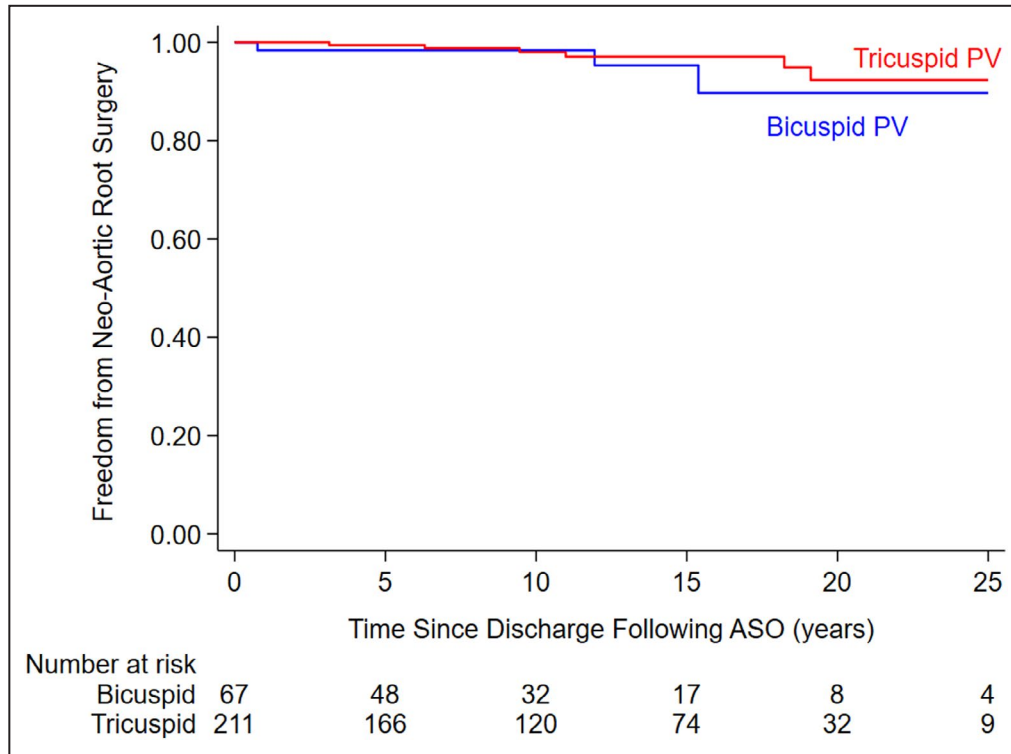


Figure 1. Freedom from neo-aortic root surgery.

The Kaplan–Meier estimate of freedom from cardiac reoperation on the neo-aortic valve and root was found for 278 patients who had D-loop transposition of the great arteries and who had undergone ASO and survived to hospital discharge. A total of 10 patients underwent reoperation, with no significant difference between patients with BNPV (n=67, blue line) and those with TNPV (n=211, red line), $P=0.16$. ASO indicates arterial switch operation; BNPV, bicuspid native pulmonary valves; PV, pulmonary valve; and TNPV, tricuspid native pulmonary valves.

occurrence of \geq moderate AR, excluding the patients with BNPV with AR at discharge, differs between groups and is shorter for BNPV (Figure 2, log-rank test $P=0.002$). Freedom from \geq moderate AR for patients with BNPV at 5, 10, 15, and 20 years was 91.4, 86, 80.6, and 80.6% versus 97, 97, 94.8, and 90.5% for patients with TNPV. Moreover, the relationship between first occurrence of \geq moderate AR and BNPV remains statistically significant after adjusting for either the presence of VSD (hazard ratio, 3.3; $P=0.014$) or age at ASO (hazard ratio, 3.8; $P=0.006$).

Neo-Aortic Root Dilatation

The development of \geq moderate ARD over follow-up was more common in patients with BNPV (n=30, 45%) than in patients with TNPV (n=80, 38%; hazard ratio 1.6 for BNPV; $P=0.02$). Excluding those patients with \geq moderate ARD at discharge (2 patients with BNPV and 6 patients with TNPV), the freedom from occurrence of \geq moderate ARD differs between groups and is a shorter period of time for patients with BNPV (Figure 3, $P=0.024$). Freedom from \geq moderate ARD for patients with BNPV at 5,

10, 15, and 20 years was 57.2, 41.7, 38.7, and 38.7% versus 65.7, 58.9, 55.2, and 52.1% for patients with TNPV. The association between first occurrence of \geq moderate ARD and BNPV remains statistically significant even after adjusting for age ($P=0.048$), but only trends towards significance after adjusting for VSD ($P=0.085$).

Relationship of Neo-Aortic Regurgitation and Neo-Aortic Root Dilatation

An analysis of the correlation between \geq moderate AR and \geq moderate ARD performed at 5, 10, and 15 years follow-up for the entire cohort showed a positive correlation between increasing AR and increasing neo-aortic root Z score (Table 2; Spearman correlation 0.31–0.46; $P=0.001$ for all comparisons).

Neo-Aortic Surgical Interventions

For the 10 patients in the cohort who underwent reoperation on the neo-aortic valve/root, procedures included the following: 2 with neo-aortic valve repair alone; 2 with neo-aortic root reduction alone; 2 with neo-aortic valve repair and root

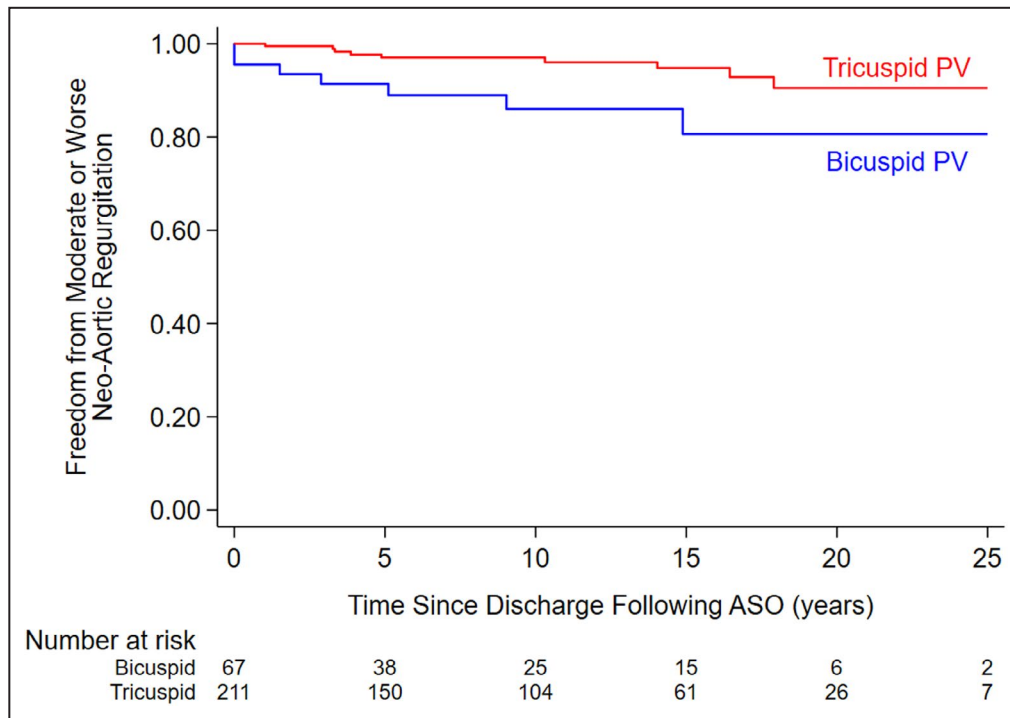


Figure 2. Freedom from neo-aortic valve regurgitation.

The Kaplan–Meier estimate of freedom from ≥moderate neo-aortic valve regurgitation was found for 278 patients who had D-loop transposition of the great arteries and who had undergone ASO and survived to hospital discharge. Patients with BNPV (n=67, blue line) had reduced freedom from neo-aortic regurgitation and shorter time to first occurrence than those with TNPV (n=211, red line), *P*=0.002. ASO indicates arterial switch operation; BNPV, bicuspid native pulmonary valves; PV, pulmonary valve; and TNPV, tricuspid native pulmonary valves.

reduction; 2 with neo-aortic valve-sparing root replacement; and 2 with neo-aortic valve repair and neo-aortic valve-sparing root replacement. Two patients went on to have subsequent neo-aortic valve replacement surgeries: 1 patient with BNPV and 1 patient with TNPV. Those who underwent reoperation had higher median neo-aortic root Z scores than those who did not (4.1 versus 2.7; *P*=0.016), with no difference between groups. This was true for patients with BNPV (median Z score 6.8 versus 3.3; *P*=0.08) and patients with TNPV (3.9 versus 2.5; *P*=0.13), although these differences were not statistically significant potentially because of the small number of patients who underwent reoperation.

DISCUSSION

Given the excellent survival and long-term outcomes after ASO for the surgical management of simple TGA,^{5,6} this operation has been increasingly performed for patients with more complex anatomy, including those with left ventricular outflow tract obstruction and native pulmonary valve abnormalities. In the present study, we sought to evaluate the short- and long-term

outcomes among patients with BNPV compared with those with normal TNPV.

Early Postoperative Outcomes

Previous studies have identified lower birth weight, aortic root repair before ASO, and overall cardiopulmonary bypass time as risk factors for early mortality post-ASO within the TGA population.^{7,8} This is the first study to show that there is no difference in early mortality between infants born with D-TGA with a bicuspid NPV compared with infants with D-TGA and a normal tricuspid NPV. This study also showed no difference in postsurgery length of stay between these 2 populations as a surrogate for other early postoperative clinical outcomes.

Late Outcomes: Neo-Aortic Valve Regurgitation

Many studies have demonstrated that patients with isolated bicuspid aortic valve are at risk for progressive AR and aortic root and ascending aorta dilation.⁹ In the ASO population for TGA, AR is a known long-term complication and may progress over time, with previously identified independent risk factors including the

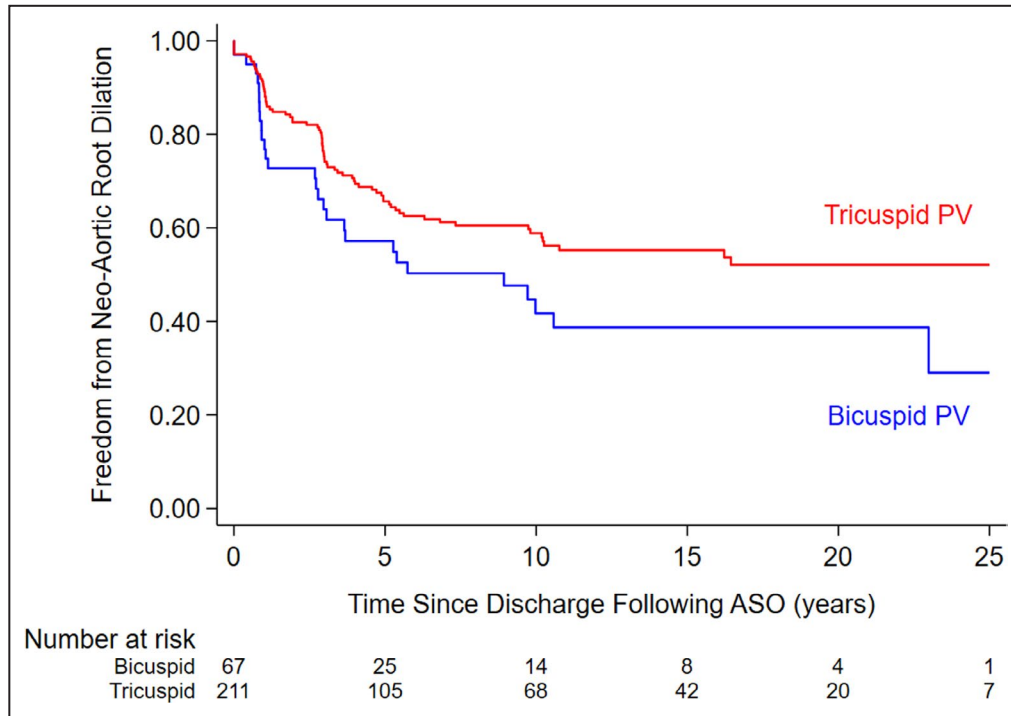


Figure 3. Freedom from neo-aortic root dilation.

The Kaplan–Meier estimate of freedom from cardiac reoperation on the neo-aortic valve and root was found for 278 patients who had D-loop transposition of the great arteries and who had undergone ASO and survived to hospital discharge. Patients with BNPV (n=67, blue line) had reduced freedom from neo-aortic root dilation (defined as Z score ≥4) and shorter time to first occurrence than those with TNPV (n=211, red line), P=0.024. ASO indicates arterial switch operation; BNPV, bicuspid native pulmonary valves; PV, pulmonary valve; and TNPV, tricuspid native pulmonary valves.

presence of a VSD, AR at ASO hospital discharge, and residual left ventricular outflow tract obstruction.^{10–13} In our study we found that patients with BNPV develop significant AR more frequently, and earlier, than patients with TNPV. Notably this relationship remained the case even when adjusted for AR at ASO discharge, age at ASO, or presence of VSD, which are variables that differed in the bicuspid cohort (who more frequently had significant AR at discharge, and more commonly had

VSDs). The rate and time course for the development of AR in patients with BNPV in our study is similar to a prior study that focused on a smaller cohort of patients with BNPV alone.³ The mechanism for the development of AR in this setting is not entirely clear; in past studies, it has been speculated that AR post ASO may be related to high pressure and flow in the pulmonary artery before ASO.^{10,14} Bicuspid valves by nature may develop higher pressure given their propensity to have smaller annulus sizes and more turbulent blood flow,^{9,15} and may be more sensitive to ARD. Moreover, surgical techniques, in particular VSD repair, have been thought to be another risk factor.^{10,14} However, our study showed no association between VSD, and thus by extrapolation VSD closure, and the development of AR.

Table 2. Correlation Between Neo-Aortic Regurgitation and Neo-Aortic Root Dilation

Follow-up period	Neo-aortic regurgitation	No. of patients (n)	Neo-aortic root Z score (25th–75th percentiles)
5 y (n=147)	<Moderate	142	3.0 (2.1–4.2)
	≥Moderate	5	3.7 (1.4–4.8)*
10 y (n=123)	<Moderate	120	2.7 (1.8–3.5)
	≥Moderate	3	3.7 (3.4–4.4)†
15 y (n=95)	<Moderate	91	2.2 (1.2–3.3)
	≥Moderate	4	4.6 (2.9–5.4)‡

*Wilcoxon rank sum P value 0.81, Spearman correlation: r_s 0.31, P<0.001.

†Wilcoxon rank sum P value 0.09, Spearman correlation: r_s 0.30, P<0.001.

‡Wilcoxon rank sum P value 0.05, Spearman correlation: r_s 0.46, P<0.001.

Late Outcomes: Neo-Aortic Root Dilation

The current study also demonstrated that ARD happens more frequently and earlier in patients with BNPV than in those with TNPV. This association remained significant when adjusted for age at time of ASO and was borderline significant when adjusted for presence of VSD. The time course to significant ARD in our study was similar to a prior smaller cohort study of patients with BNPV,

although ARD was more common in our cohort and to a greater degree of severity (we used a more stringent definition of z score ≥ 4).³ Because the neo-aortic root is embryologically pulmonary artery and not aorta, this likely creates the substrate for ARD under systemic pressures in patients with BNPV as well as patients with TNPV. The hemodynamic differences of a bicuspid valve versus a tricuspid variant, with increased tensile and shear stressors, most likely plays a role in the pathogenesis of worse ARD in the setting of a BNPV. Blood flow is more likely to be turbulent through bicuspid valves, and this turbulent blood flow may cause an uneven burden of force on the convex wall of the ascending aorta. Moreover, given that BNPVs are more likely to have regurgitant flow, the higher stroke volume also leads to higher wall tension in the ascending neo-aorta.^{9,16} There is also a positive feedback loop-type effect between dilation and regurgitation: the increase in ARD leads to reduced valve leaflet coaptation and thus leads to further AR.⁹ Prior studies into ASO outcomes have shown significant overlap in patients displaying AR and ARD.⁴ In the present study, we also found a positive correlation between greater degrees of ARD and presence of AR (Table 2), which supports this mechanism for the development of worsening AR.

In previous studies, it has been noted that the AR and ARD post ASO rarely lead to reoperation.^{10,14} In this study, we have also found that there was a low incidence of reoperation on the aortic root post ASO in both groups.

Limitations

This study was retrospective in nature and because follow-up data were obtained for clinical purposes and not standardized, this may have resulted in ascertainment bias for some patients over others regarding valve function outcomes. We attempted to limit this potential issue by choosing TNPV controls with as much echocardiographic follow-up data as possible, although because patients with BNPV were much less common they could not be easily replaced; we did ensure that all patients with BNPV in our analysis had initial, post-operative, and then a most recent echocardiogram. However, it should be noted that follow-up was obtained in only 80% of bicuspid patients. Additionally, given that we were studying a specific population within a relatively small population of patients with d-TGA, the sample sizes were small enough that there was low statistical power, which prevented us from adjusting some of the analyses for potential confounders. Moreover, given the >30-year time span of this study, the improvement of surgical techniques and medical care over time may influence the differing outcomes of patients born in different eras. In addition, some technical surgical considerations that theoretically might

impact subsequent valve function, such as the potential differences in coronary implantation site on the neo-aortic root in patients with BNPV versus patients with TNPV, could not be ascertained in this retrospective case series. Lastly, there are also limits to using echocardiograms for measurement data, given suboptimal images and user dependence; this may have impacted the assessment of neo-AR, although this would likely be true for both BNPV and TNPV cohorts equally.

CONCLUSIONS

This study demonstrates that while bicuspid and tricuspid NPV patients have similarly excellent short-term outcomes post-ASO, subsequent AR and ARD happen more frequently and earlier in BNPV patients. BNPV patients may merit more frequent imaging follow-up over time as surveillance for AR and ARD. Further long-term studies are needed to determine whether this results in greater need for neo-aortic valve reoperation.

ARTICLE INFORMATION

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REFERENCES

1. Castaneda AR, Trusler GA, Paul MH, Blackstone EH, Kirklin JW. The early results of treatment of simple transposition in the current era. *J Thorac Cardiovasc Surg*. 1988;95:14–28. doi: 10.1016/S0022-5223(19)35382-6
2. Quaegebeur JM, Rohmer J, Ottenkamp J, Buis T, Kirklin JW, Blackstone EH, Brom AG. The arterial switch operation. an eight-year experience. *J Thorac Cardiovasc Surg*. 1986;92:361–384. doi: 10.1016/S0022-5223(19)35789-7
3. Angeli E, Gerelli S, Beyler C, Lamerain M, Rochas B, Bonnet D, Vouhe P, Raisky O. Bicuspid pulmonary valve in transposition of the great arteries: impact on outcome. *Eur J Cardiothorac Surg*. 2012;41:248–255. doi: 10.1016/j.ejcts.2011.03.063
4. Schwartz ML, Gauvreau K, del Nido P, Mayer JE, Colan SD. Long-term predictors of aortic root dilation and aortic regurgitation after arterial switch operation. *Circulation*. 2004;110:1128–1132. doi: 10.1161/01.CIR.0000138392.68841.d3
5. Shim MS, Jun TG, Yang JH, Park PW, Kang IS, Huh J, Song JY. Current expectations of the arterial switch operation in a small volume center: a 20-year, single-center experience. *J Cardiothorac Surg*. 2016;11:34. doi: 10.1186/s13019-016-0428-9
6. Pretre R, Tamisier D, Bonhoeffer P, Mauriat P, Pouard P, Sidi D, Vouhe P. Results of the arterial switch operation in neonates with transposed great arteries. *Lancet*. 2001;357:1826–1830. doi: 10.1016/S0140-6736(00)04957-6
7. Blume ED, Altmann K, Mayer JE, Colan SD, Gauvreau K, Geva T. Evolution of risk factors influencing early mortality of the arterial switch operation.

- J Am Coll Cardiol.* 1999;33:1702–1709. doi: 10.1016/S0735-1097(99)00071-6
8. Fricke TA, Bulstra AE, Loyer BR, Weintraub RG, d'Udekem Y, Brizard CP, Konstantinov IE. Outcomes of the arterial switch operation in children less than 2.5 kilograms. *Ann Thorac Surg.* 2017;103:840–844. doi: 10.1016/j.athoracsur.2016.11.079
 9. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. *Circulation.* 2009;119:880–890. doi: 10.1161/CIRCULATIONAHA.108.795401
 10. Losay J, Touchot A, Capderou A, Piot JD, Belli E, Planche C, Serraf A. Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. *J Am Coll Cardiol.* 2006;47:2057–2062. doi: 10.1016/j.jacc.2005.12.061
 11. Lange R, Cleuziou J, Horer J, Holper K, Vogt M, Tassani-Prell P, Schreiber C. Risk factors for aortic insufficiency and aortic valve replacement after the arterial switch operation. *Eur J Cardiothorac Surg.* 2008;34:711–717. doi: 10.1016/j.ejcts.2008.06.019
 12. Fraser CD Jr, Chacon-Portillo MA, Well A, Zea-Vera R, Binsalamah Z, Adachi I, Mery CM, Heinle JS. Twenty-three-year experience with the arterial switch operation: expectations and long-term outcomes. *Semin Thorac Cardiovasc Surg.* 2020;32:292–299. doi: 10.1053/j.semthor.2020.01.004
 13. Nakayama Y, Shinkawa T, Matsumura G, Hoki R, Kobayashi K, Niinami H. Late neo-aortic valve regurgitation long after arterial switch operation. *Ann Thorac Surg.* 2019;108:1210–1216. doi: 10.1016/j.athoracsur.2019.04.009
 14. del Nido PJ, Schwartz ML. Aortic regurgitation after arterial switch operation. *J Am Coll Cardiol.* 2006;47:2063–2064.
 15. Park CS, Seo DM, Park JJ, Kim YH, Park IS. The significance of pulmonary annulus size in the surgical management of transposition of the great arteries with ventricular septal defect and pulmonary stenosis. *J Thorac Cardiovasc Surg.* 2010;139:135–138. doi: 10.1016/j.jtcvs.2009.07.011
 16. Novaro GM, Tiong IY, Pearce GL, Grimm RA, Smedira N, Griffin BP. Features and predictors of ascending aortic dilatation in association with a congenital bicuspid aortic valve. *Am J Cardiol.* 2003;92:99–101. doi: 10.1016/S0002-9149(03)00480-6