Long-Term Predictors of Aortic Root Dilation and Aortic Regurgitation After Arterial Switch Operation

Marcy L. Schwartz, MD; Kimberlee Gauvreau, ScD; Pedro del Nido, MD; John E. Mayer, MD; Steven D. Colan, MD

Background—Neo-aortic root dilation (ARD) and neo-aortic regurgitation (AR) may be progressive after arterial switch operation (ASO) for d-loop transposition of the great arteries (dTGA). We sought to identify predictors of ARD and AR after ASO.

Methods and Results—335 patients were identified who underwent ASO for dTGA with intact ventricular septum or ventricular septal defect (VSD), including double-outlet right ventricle (DORV), before 2001 with at least 1 postoperative echocardiogram at our institution, at least 1 year after ASO, and no previous atrial switch procedure (median follow-up of 5.0 years). Probability of freedom from AR was 97%, 92%, 82%, and 51%, from at least moderate AR was 98%, 97%, 96%, and 93%, and from neo-aortic valve or root surgery was 100%, 100%, 99%, and 95%, at 1, 2, 5, and 10 years, respectively. For patients in whom AR developed, progressive dilation was not observed during late follow-up. By Kaplan–Meier method, independent predictors of ARD, with neo-aortic root z-score of ≥3.0, were previous pulmonary artery band (PAB) (P=0.002, hazard ratio [HR]=2.4) and later time period when ASO was performed (P<0.002, HR=19.0). Risk factor for at least moderate AR was age ≥1 year at ASO (P=0.002, HR=5.8), which was closely related to VSD repair at ASO (P<0.001) and previous PAB.

Conclusions—Significant ARD and AR continue to develop over time after ASO, but ARD does not tend to be progressive during late follow-up. Previous PAB was a significant risk factor for ARD. Older age at time of ASO, presence of VSD, and previous PAB were risk factors for AR. (Circulation. 2004;110[suppl II]:II-128–II-132.)

Key Words: transposition of great vessels ♦ aorta ♦ heart defects ♦ congenital ♦ pediatrics ♦ echocardiography

Since first successfully performed by Fontan et al, the arterial switch operation (ASO) has become the preferred technique for repair of d-loop transposition of the great arteries (dTGA).1–4 Although the long-term complications of atrial switch procedures, including venous baffle obstructions and systemic right ventricular failure, are avoided, other complications may arise after the ASO. Neo-aortic root dilation (ARD) and neo-aortic regurgitation (AR) have been reported to occur during short-term and medium-term follow-up.5–7 With long-term follow-up, it seems that some of these patients have progressive ARD and/or AR develop and may require neo-aortic root or valve surgery.2,8 Preoperative factors may place some patients at higher risk for these outcomes after ASO. The goal of this study was to identify risk factors associated with the development of ARD and AR and to describe the frequency and time course of ARD after ASO.

Methods

Patients

The cardiology database at Children’s Hospital was searched for all patients with dTGA with or without a ventricular septal defect (VSD), or with double-outlet right ventricle and subpulmonary VSD (DORV), who underwent an ASO between January 1981 and December 2000, and had at least 1 postoperative echocardiogram at Children’s Hospital. Patients with at least 1 year of echocardiographic follow-up at our institution were included in risk factor analysis. Patients were excluded who had undergone a Senning or Mustard procedure before ASO.

To describe the time course for progression of ARD, we also examined a subset of those patients who underwent an ASO at Children’s Hospital between January 1981 and December 1994 and had at least 1 preoperative and 2 postoperative echocardiograms at this institution with at least 5 years of echocardiographic follow-up.

Outcomes

Potential risk factors were analyzed for each of 3 separate outcomes after ASO: (1) development of at least moderate AR; (2) development of ARD, defined by a neo-aortic root z-score ≥3.0; and (3) neo-aortic valve or root surgery. Severity of AR was assessed by the proximal regurgitation jet width in parasternal long-axis, presence of diastolic flow reversal in the aortic arch or descending aorta, and degree of left ventricular dilation. The maximum systolic neo-aortic root diameters at the sinuses of Valsalva and annulus diameters at the valve hinge points were measured from parasternal long-axis. Z-scores for the neo-aortic root and annulus size relative to body surface area were derived from our institutional normal database.
Body surface area was calculated according to the formula of Haycock et al.9

Potential Risk Factors
Variables examined for each of the 3 outcomes included a previous Blalock–Taussig shunt, a previous pulmonary artery band (PAB), age at ASO, and surgeon. Preoperative native pulmonary valve Z-score, presence of a bicommissural native pulmonary valve, coronary anatomy, presence of a VSD, DORV as a subset of VSD, presence of left ventricular outflow obstruction, and presence of aortic arch obstruction were based on the preoperative echocardiogram. Coronary anatomy was also confirmed by the operative report. Repair of VSD or left ventricular outflow tract obstruction at the time of the ASO was recorded, as was the presence of subaortic left ventricular outflow tract obstruction (LVOTO) or subaortic LVOTO surgery after ASO. Time period when ASO was performed, divided into 3 similarly sized groups (1981 to 1988, 1989 to 1992, 1993 to 2000), was examined as a potential predictor of outcomes. In addition, the trends of the other potential risk factors were examined by time period.

Echocardiographic Measurements
Postoperative neo-aortic annulus and root measurements and assessment of AR were taken from the original echocardiographic reports. For the subset of patients examined to describe time course of ARD, diameters of the neo-aortic annulus and root were retrospectively remeasured off-line from the echocardiographic recording using a Hewlett Packard ultrasound system (Sonos 5500) by a single observer blinded to outcome.

Statistical Analysis
For each of the 3 outcome variables (ARD, moderate or severe AR, and neo-aortic valve or root surgery), times from the ASO to outcome for patients with at least 1 year of echocardiographic follow-up were estimated using the Kaplan–Meier method. Patients who did not reach the outcome were censored at the time of last follow-up. The Kaplan–Meier method was also used to obtain survival estimates according to each potential risk factor; subgroups were compared using the log-rank test. For continuous risk factors such as age, cutpoints were explored. Multivariate analyses were performed using the Cox proportional hazards model. Subaortic LVOTO surgery, which could occur either at the time of ASO or after the ASO, was treated as a time-varying covariate. The relationships between neo-aortic root z-score and both degree of AR and neo-aortic annulus z-score were assessed using the Spearman rank correlation coefficient. Changes in risk factors over time were evaluated using Fisher exact test.

Results
Patients
There were 884 patients identified from our database who underwent an ASO for dTGA or DORV before December 2000, who had no previous Senning or Mustard operation, and who had at least 1 postoperative echocardiogram. Patient characteristics are listed in Table 1a.

From the total cohort, 335 patients had at least 1 year of echocardiographic follow-up at our institution. For these patients, a total of 1748 echocardiograms were reviewed from this institution, with a median of 4 echocardiograms performed per patient (range, 1 to 20 echocardiograms). The median age at ASO was 6 days, ranging from 0 days to 7.8 years (56% ≤7 days and 5.4% ≥1 year). The median echocardiographic follow-up from ASO was 5.0 years (range, 1 to 17.7 years). This patient subset cohort is described in Table 1b. No statistical difference was found between the study cohort and the excluded patients of the total cohort for the characteristics listed with the exception of coarctation surgery at time of ASO (11.6% for the study cohort versus 7.6% for the remainder of the total, P=0.05). Of the 33 patients with previous PAB, 19 were performed within 1 month of ASO or did not have a VSD, consistent with 2-stage ASO. No patient had obvious manifestations of a connective tissue disorder.

Time Course for Outcomes
Probability of freedom from AR was 97%, 92%, 82%, and 51%, from at least moderate AR was 98%, 97%, 96%, and 93%, and from aortic valve or root surgery was 100%, 100%, 99%, and 95%, at 1, 2, 5, and 10 years, respectively (Figure 1). The median time from ASO to ARD for the patients in whom it developed was 6.0 years (range, 7 days to 16.4 years), from ASO to at least moderate AR was 1.6 years (range, 3 days to 10.8
years), and from ASO to neo-aortic valve or root surgery was 6.7 years (range, 3.3 to 14.6 years). For patients with at least 5 years of echocardiographic follow-up after ASO (N=1100), the mean neo-aortic root z-score initially after ASO was 2.6, at 5 years after ASO it was 3.6, and at 10 years after ASO it was 4.6. No significant change was seen after 10 years (Figure 2a). After the development of ARD, with a neo-aortic root z-score ≥3.0, the mean z-score change over time was 0.05 per year (95% CI: −0.02, 0.12) with a range of −0.65 per year to +0.51 per year and a mean z-score of 4.6 (N=51). Although rare patients continued to dilate, this suggests stabilization of ARD for the majority of patients (Figure 2b). Of the study cohort, 6 patients had neo-aortic root z-scores of ≥8.0. For all 6 patients, ARD was already severe (z-score 5.5 to 16.8) by the first postoperative echocardiogram at our institution (range, 9 months to 11.7 years since ASO). Three of these patients stabilized at a z-score of ≥8.0 and 3 underwent neo-aortic root surgery.

**Predictors of Neo-aortic Root Dilation**

Of the 335 patients who met entry criteria, 112 (33.4%) had ARD with a neo-aortic root z-score ≥3.0 at some point during follow-up. By both univariate and multivariate analyses, risk factors predictive of a shorter time to ARD were a previous PAB (P=0.006, hazard ratio [HR]=2.2) and later time periods when ASO was performed (1989 to 1992, HR=4.5, P<0.001; and 1993 to 2000, HR=18.8, P<0.001) (Table 2). Time to ARD was also significantly shorter for the most recent time period ASO performed (1993 to 2000) compared directly with the second time period 1989 to 1992 as a baseline (HR=4.2, P<0.001). The Kaplan–Meier curves for previous PAB and time period of ASO are shown in Figures 3 and 4, respectively. Two of the surgeons who performed the ASO had lower risk for ARD, and primarily operated in the first time period with decreasing number of ASO procedures performed by these surgeons in the second time period and only 1 ASO in the last time period. The median number of postoperative echocardiograms per patient was similar in each time period (5 in 1981 to 1988, 4 in 1989 to 1992, and 4 in 1993 to 2000), and the median time to first postoperative echocardiogram was ≈1 week in the 3 time periods. The age at ASO was slightly younger in the recent

**Table 2. Multivariate Predictors of Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazards Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root dilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAB</td>
<td>2.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Time period of ASO compared with earliest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989–1992</td>
<td>4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1993–2000</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥Moderate aortic regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 1 year or older at ASO</td>
<td>5.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic valve or root surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD surgery at ASO, all patients</td>
<td>17.0</td>
<td>0.008</td>
</tr>
<tr>
<td>VSD surgery at ASO, patients younger than 1 year at ASO</td>
<td>13.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD surgery at ASO</td>
<td>12.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Subaortic LVOTO after ASO</td>
<td>10.9</td>
<td>0.006</td>
</tr>
</tbody>
</table>

PAB indicates pulmonary artery band; ASO, arterial switch operation; VSD, ventricular septal defect; LVOTO, left ventricular outflow tract obstruction.
time period but was the same in the earlier time periods (median age 5 days for 1993 to 2000 and 8 days in 1981 to 1988 and in 1989 to 1992). Previous PAB was less frequent during each subsequent time period (14% for 1981 to 1988, 11% for 1989 to 1992, and 4% for 1993 to 2000, \( P=0.02 \)). No other preoperative variable significantly changed with time period. If PAB patients were excluded from the analysis, only the time period in which ASO was performed is a significant predictor of time to ARD. Initial postoperative neo-aortic root z-score (within 3 months of ASO) did not correlate with preoperative native pulmonary root z-score (within 1 month of ASO) (\( N=20 \)).

**Predictors of Severe Neo-aortic Root Dilation**

For the 6 patients in whom severe ARD developed with neo-aortic root z-scores \( \geq 8.0 \), significant risk factors by univariate analysis for shorter time to severe ARD were previous PAB (\( P<0.001 \)), VSD surgery at time of ASO (\( P=0.01 \)), presence of DORV (\( P<0.001 \)), coarctation (\( P=0.02 \)), age 1 year or older at time of ASO (\( P<0.001 \)), subaortic LVOTO surgery at ASO (\( P<0.001 \)), and later time period of ASO (\( P=0.03 \)). By multivariate analysis, only DORV and last time period of ASO were significant (\( P<0.001 \), HR 40.1, and \( P=0.04 \), HR 23.6, respectively).

**Predictors of at Least Moderate Neo-aortic Regurgitation**

There were 17 patients (5.1%) in whom at least moderate AR developed during follow-up. By univariate analysis, the variables that were associated with shorter time to at least moderate AR were age 1 year or older at time of ASO (\( P=0.005 \)), previous PAB (\( P=0.006 \)), presence of VSD (\( P=0.03 \)), VSD surgery at the time of ASO (\( P=0.01 \)), DORV (\( P=0.04 \)), and subaortic LVOTO surgery at time of ASO (\( P<0.001 \)). By multivariate analysis, the only independent predictor of at least moderate AR was age 1 year or older at time of ASO (HR = 5.8, \( P=0.002 \)) (Figure 5, Table 2). This risk factor was closely related to VSD repair at ASO (\( P=0.001 \)) and previous PAB. Subaortic LVOTO surgery at the time of ASO was not included in the multivariate model because of the small number of patients in this group (\( N=4 \)).

Neo-aortic root z-score tended to be higher with increasing degree of AR (\( r_s=0.39, P<0.001 \)), but significant overlap in neo-aortic root z-scores was seen between all degrees of AR (Figure 6). Postoperative neo-aortic annulus z-score correlated with neo-aortic root z-score (\( r_s=0.63, P<0.001 \)).

**Predictors of Neo-aortic Valve or Root Surgery**

Eight patients (2.4%) underwent neo-aortic valve or root surgery during follow-up. Indications for surgery were AR in 4 patients, ARD in 2 patients, subaortic LVOTO in 1 patient, and subaortic LVOTO with AR and ARD in 1 patient.

By univariate analysis, the risk factors found to be significant for a shorter time to neo-aortic valve or root surgery were age \( \geq 7 \) days.
at ASO (P=0.001), a previous PAB (P=0.008), presence of VSD (P=0.001), VSD surgery at the time of ASO (P<0.001), DORV (P<0.001), history of coarctation (P=0.009), native pulmonary valve z-score ≥2.0 at ASO (P=0.02), and subaortic LVOTO surgery at the time of ASO (P<0.001). By multivariate analysis, VSD surgery at the time of ASO was the only independent predictor of neo-aortic valve or root surgery after ASO for all patients (HR=17, P=0.008) and for patients younger than age 1 year at time of ASO (HR=13.9, P=0.02) (Table 2). If subaortic LVOTO surgery after ASO (N=11) is included in the multivariate model, patients with VSD surgery at the time of ASO and those with subaortic LVOTO surgery after ASO had a shorter time to neo-aortic valve or root surgery (HR=12.9, P=0.02, and HR=10.9, P=0.006, respectively, Table 2).

Discussion

In this study we identified independent risk factors associated with the development of ARD, at least moderate AR, and neo-aortic root or valve surgery after ASO for dTGA.

The development of ARD was common relative to at least moderate AR and aortic valve or root surgery. Although ARD continued to develop during late follow-up, for most patients, root dimensions tended to stabilize without significant progression over time.

A risk factor for development of ARD after ASO in our study and others3,6 was a previous PAB. The mechanism of the association of previous PAB with ARD is not clear. One series found a large increase in native pulmonary root immediately after PAB placement as part of 2-stage ASO.10 Of the patients with a previous PAB, 58% were part of a 2-stage ASO and the risk of ARD was not significantly different from those performed for VSD. Although previous PAB is now rarely performed, additional risk factors for ARD were not evident by univariate or multivariate analysis when PAB patients were excluded. In addition, ARD was seen sooner in each subsequent time period ASO was performed. This finding may be attributable to a change in surgical technique, perhaps using larger buttons for coronary transfer. Initial neo-aortic root z-score after ASO was not measured consistently enough to support this speculation. The median age at time of ASO was the same for the first 2 time periods and only 3 days younger for the most recent time period. Therefore, age at time of ASO does not appear to explain earlier ARD in each subsequent time period. Although DORV was not significant for ARD with neo-aortic root z-score ≥3.0, it was a significant risk factor for severe ARD with root z-score ≥8.0.

We found that age 1 year or older at time of ASO was predictive of at least moderate AR. Because of the high degree of covariance between older age at ASO, presence of VSD, and previous PAB, it is not possible to distinguish which of these factors was the most influential. Several series also reported the association of previous PAB with mild AR in short-term and medium-term follow-up.3,6,7 We found by both univariate and multivariate analysis that subaortic LVOTO surgery at the time of ASO was another significant factor for at least moderate AR and a predictor of earlier time to neo-aortic valve or root surgery. However, with only 4 patients in this group, the broader significance of this association is uncertain.

Several variables were not found to be associated with ARD, AR, or neo-aortic valve or root surgery after ASO. Although higher mortality has been found at some centers to be related to intramural coronary pattern,2,11 this has not been consistently observed.12 Similarly coronary anatomy was not associated with the development of ARD or AR in this report. A higher incidence of ARD and AR has been found in patients with isolated bicommissural aortic valve,13 but bicommissural native pulmonary valve was not associated with progressive AR or ARD in patients with dTGA during childhood in our study or in others.14

In summary, ARD and AR continue to develop over time after ASO, but ARD does not tend to be progressive during late follow-up. We examined anatomic and hemodynamic variables associated with development of significant AR and ARD after ASO. Previous PAB was a significant risk factor for ARD. Older age at time of ASO, presence of VSD, and previous PAB were risk factors for AR. VSD surgery at the time of ASO was associated with subsequent neo-aortic valve or root surgery, although this outcome is infrequent with varied surgical indications. Likely other factors also play an important role in the outcome of the neo-aortic valve and root after ASO, including histologic variables (intracellular matrix) and surgical technique, and should be investigated further.

Acknowledgments

We thank Ruthanne Pepin for assistance with data collection and Emily Harris for artwork.

References

Long-Term Predictors of Aortic Root Dilation and Aortic Regurgitation After Arterial Switch Operation
Marcy L. Schwartz, Kimberlee Gauvreau, Pedro del Nido, John E. Mayer and Steven D. Colan

Circulation. 2004;110:II-128-II-132
doi: 10.1161/01.CIR.0000138392.68841.d3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/11_suppl_1/II-128

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/