Coronary Artery Pattern and Outcome of Arterial Switch Operation for Transposition of the Great Arteries
A Meta-Analysis

Sara K. Pasquali, MD; Vic Hasselblad, PhD; Jennifer S. Li, MD; David F. Kong, MD; Stephen P. Sanders, MD

Background—Prior studies of coronary pattern and outcome after arterial switch operation (ASO) for transposition of the great arteries (TGA) have been hindered by limited statistical power. This meta-analysis assesses the effect of coronary anatomy on post-ASO mortality, both overall and adjusted for time.

Methods and Results—A literature search revealed 9 independent series that reported post-ASO mortality by coronary pattern in a total of 1942 patients. Odds ratios comparing all-cause mortality in patients with usual versus variant coronary patterns were calculated and combined by use of an empirical Bayesian model. Single coronary patterns, both of which loop around the great vessels, were associated with significant mortality (OR 2.9, 95% CI 1.3 to 6.8), whereas looping patterns that arose from 2 separate ostia were not (OR 1.2, 95% CI 0.8 to 1.9). This latter group includes patients with the most common variant, circumflex from right coronary artery. Patients with an intramural coronary artery had the greatest mortality (OR 6.5, 95% CI 2.9 to 14.2). Overall, patients with any variant coronary pattern had nearly twice the mortality seen in those with the usual pattern (OR 1.7, 95% CI 1.3 to 2.4). Single ostium patterns and intramural coronary arteries remained associated with significant added mortality after adjustment for time-trend effects.

Conclusions—Over the past 2 decades, patients with common coronary variants have undergone ASO without added mortality compared with those with the usual coronary pattern. Those with intramural or single coronary arteries have significant added mortality that has persisted over time. (Circulation. 2002;106:2575-2580.)

Key Words: transposition of great vessels ▪ surgery ▪ meta-analysis ▪ arteries

The arterial switch operation (ASO) has become the procedure of choice for correction of transposition of the great arteries (TGA).1–4 Compared with atrial-level Mustard and Senning repairs, correction at the arterial level restores the left ventricle as the systemic pumping chamber and is associated with improved outcomes.5–7

Because of variations in coronary anatomy associated with TGA and the transfer of the coronary arteries during ASO, much attention has been paid to the relationship between the coronary anatomy pattern and outcome.8–10 Case series examining this relationship have reported mixed results. Some have indicated that coronary patterns such as a retropulmonary looping left coronary artery (LCA) or an intramural coronary artery predict increased morbidity and mortality, whereas others have not.11–19 In general, these studies have been limited by lack of statistical power to detect the impact of coronary anatomy on outcome. For example, in a 1999 study, Blume et al13 reported variant coronary patterns were not associated with increased mortality. However, that study had only 35% power to detect a 100% increase in mortality in a large group composed of several coronary patterns with a retropulmonary looping LCA and <20% power in more rare coronary patterns such as single or intramural coronary arteries. Even the largest series to date had <30% power to detect a doubling of mortality in these more rare coronary patterns.14 Finally, if a relationship exists between variant coronary patterns and adverse outcomes, the strength of this association may have diminished in more recent years owing to improvements in surgical techniques and increased operator experience.13

The present study combines the results of 9 case series in a meta-analysis to estimate the effect of coronary anatomy on mortality after ASO, both overall and adjusted for time.

Methods

Study Selection
A MEDLINE search using the MeSH term “transposition of the great vessels” and keyword “arterial switch” identified potential studies published from January 1966 to August 2001. This was supplemented by review of articles referenced in these studies, major surgical and cardiology textbooks, and relevant review articles. Abstracts from all 448 initially identified studies were examined for possible inclusion. Unique series of TGA patients that reported post-ASO mortality by coronary pattern were included. When overlapping series from a single institution were published, studies
were selected to provide data on the largest number of unique patients.\textsuperscript{13,14,20} A multicenter study was excluded in favor of studies from participating institutions that, taken together, provided data on more patients over a longer time period.\textsuperscript{14–16,21} After these criteria were applied, the present study included 9 independent case series\textsuperscript{11–19} (Table 1).

**Data Collection**

Included publications were abstracted for early, late, and total all-cause mortality associated with all coronary patterns they described, as visualized during intraoperative inspection. Three of the studies did not specifically report the method they used to visualize coronary anatomy.\textsuperscript{9,11,17} Because most of the studies used the Leiden classification and/or descriptive terminology to characterize coronary patterns, we chose to use this scheme as well.\textsuperscript{8,9} Data from studies that used the Yacoub classification were transformed into the appropriate Leiden class.\textsuperscript{8–10} Finally, characteristics of the study population, surgery, and follow-up were abstracted.

**Data Analysis**

On the basis of prior studies, as well as surgical techniques and complications, we hypothesized that certain coronary patterns would be associated with similar mortality rates and grouped them for analysis\textsuperscript{11–19} (Figure 1). The first group included coronary arteries that looped around the great vessels: either a portion or all of the LCA looped behind the pulmonary artery (circumflex from right coronary artery [RCA], single RCA), the RCA looped anterior to the aorta (single LCA), or both (inverted, inverted RCA and circumflex). This group corresponds to type III in the Marie Lannelongue classification.\textsuperscript{9} Cases in which the circumflex arose from the RCA, the most common coronary variant seen in TGA, were also analyzed separately.\textsuperscript{8} The second group consisted of coronary patterns in which both the left and right coronary systems arose from a single ostium (single RCA, single LCA). The third group was composed of intramural coronary artery patterns, or any coronary artery that arose and coursed between the great vessels, including those with commissural origins (Marie Lannelongue type II\textsuperscript{9}). The final group was

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**Table 1. Characteristics of Studies Included in Present Analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Period</th>
<th>Population Size, n</th>
<th>IVS, %</th>
<th>Single-Stage Repair, %</th>
<th>Mean Age at Surgery, d</th>
<th>Coronary Anatomy Known, %</th>
<th>Coronary Classification</th>
<th>Exclusion, n, Reason*</th>
<th>Follow-Up, %, Mean Length</th>
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<tbody>
<tr>
<td>Prêtre et al\textsuperscript{11}</td>
<td>1987–1999</td>
<td>432</td>
<td>71</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>Marie Lannelongue</td>
<td>...</td>
<td>95%, 4.9 y</td>
</tr>
<tr>
<td>Hutter et al\textsuperscript{12}</td>
<td>1977–1999</td>
<td>170</td>
<td>61</td>
<td>88</td>
<td>...</td>
<td>100</td>
<td>Descriptive</td>
<td>None</td>
<td>100%, 30 d</td>
</tr>
<tr>
<td>Blume et al\textsuperscript{13}</td>
<td>1992–1996</td>
<td>223</td>
<td>57</td>
<td>100</td>
<td>6</td>
<td>100</td>
<td>Descriptive</td>
<td>...</td>
<td>100%, 8 y</td>
</tr>
<tr>
<td>Wernovsky et al\textsuperscript{14}</td>
<td>1983–1991</td>
<td>470</td>
<td>60</td>
<td>100</td>
<td>6</td>
<td>100</td>
<td>Leiden</td>
<td>...</td>
<td>100%, 72 h</td>
</tr>
<tr>
<td>Lupinetti et al\textsuperscript{15}</td>
<td>1982–1991</td>
<td>126</td>
<td>72</td>
<td>100</td>
<td>6</td>
<td>60</td>
<td>Leiden</td>
<td>1, Tortuous LCA;</td>
<td>100%, In hospital,</td>
</tr>
<tr>
<td>Day et al\textsuperscript{16}</td>
<td>1987–1991</td>
<td>70</td>
<td>90</td>
<td>100</td>
<td>5.6</td>
<td>99</td>
<td>Leiden</td>
<td>1, distant origin;</td>
<td>97%, 27 mo</td>
</tr>
<tr>
<td>Yamaguchi et al\textsuperscript{17}</td>
<td>1982–1988</td>
<td>265</td>
<td>55</td>
<td>49</td>
<td>...</td>
<td>99</td>
<td>Yacoub</td>
<td>...</td>
<td>100%, 30 d and 3 y</td>
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<tr>
<td>Planché et al\textsuperscript{18}</td>
<td>1984–1987</td>
<td>120</td>
<td>92</td>
<td>100</td>
<td>7.8</td>
<td>100</td>
<td>Yacoub</td>
<td>...</td>
<td>100%, In hospital</td>
</tr>
<tr>
<td>Quaegebeur et al\textsuperscript{19}</td>
<td>1977–1985</td>
<td>66</td>
<td>35</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>Leiden</td>
<td>None</td>
<td>100%, In hospital and 13 mo</td>
</tr>
</tbody>
</table>

Ellipses indicate data not given; IVS, intact ventricular septum; IM, intramural. *Any exclusion from ASO in the study based on coronary pattern.

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**Figure 1.** Coronary artery patterns seen in TGA. Upper panels show coronary artery distribution as visualized by 2D echocardiography and caudally angulated aortography. Lower panels show same coronary artery distribution as viewed from front. Ant indicates anterior; Post, posterior; R, right; L, left; Sup, superior; Inf, inferior; LAD, left anterior descending artery; and Cx, circumflex coronary artery. Reproduced with permission from Wernovsky and Sanders.\textsuperscript{8}
a composite of all variant coronary patterns. After the initial analysis with these groupings, an additional group was examined that consisted of group 1 but excluded coronaries that arose from a single ostium (ie, group 2). In other words, this group consisted of patients with coronary arteries that looped around the great vessels but arose from 2 separate ostia. All variant coronary patterns were compared with the usual pattern in TGA in which the RCA arises from the right and posterior facing sinus and the LCA arises from the left and anterior facing sinus before branching into the left anterior descending and left circumflex coronary arteries (Figure 1).

**Statistical Analysis**

For each study, Fast*Pro version 1.81 software was used to calculate ORs estimating mortality in patients with usual versus variant coronary anatomy patterns; these were then combined by use of an empirical Bayesian model.22,23 This widely used random-effects model described by Hedges and Olkin accounts for differences among studies (heterogeneity) by including a measure of the variation between studies in computation of the total uncertainty used to compute weights for each estimate. As a result, the random-effects weighted average of the studies generally has a larger CI than a comparable fixed-effects estimate. The empirical Bayesian model approaches a fixed-effects estimate when the variation between studies is small. Because the test for heterogeneity was not significant for any of the coronary groups (P=0.22 to 0.79), indicating little variation between combined studies, our estimates approach those of a fixed-effects model.

**Time-Trend Analysis**

To assess possible changes in mortality associated with variant coronary patterns over time, 2 analyses based on year of surgery were performed. In a subgroup analysis, studies were divided into those in which infants underwent surgery before 1992 versus 1992 or later (Table 1). Because the study by Pretre et al reported data for both subgroups, data from this study were split. The study by Hutter et al reported over a 22-year period that spanned both eras and was excluded. ORs were calculated and combined for studies conducted before 1992 and during 1992 or later. We compared these ORs by computing their ratio and testing whether it was different from 1. In a second analysis of time-trend effects, we used the methods of Hasselblad24 to fit a generalized random-effects meta-analysis (meta-regression). This multivariate logistic normal model, implemented in EGRET software (Cytel Software Corp), included terms for the separate study results and a time-dependent covariate (study mid-point). A likelihood ratio test was used to test the significance of the time-trend covariate. The ORs from random-effects meta-regression models differ slightly from the ORs that describe treatment effects for an individual trial in that they are actually “odds ratios of odds ratios” that describe the relations between trials.

**Results**

The 9 studies included in the present analysis are summarized in Table 1.11-19 Each study represents the experience of a single center over a time period of 3 to 22 years. The sample sizes ranged from 66 to 470 patients, for a total of 1942 patients in our combined analysis. In 8 of the 9 studies, >50% of infants had TGA with an intact ventricular septum, and in all but 2 studies, 100% of patients underwent a single-stage repair at ≤1 week of life.12,17,19 The coronary anatomy was recorded and known in 99% to 100% of the patients with TGA undergoing ASO, and most studies used the Leiden and/or a descriptive classification scheme.8,9 During the time period in which these studies were conducted, a total of 4 TGA patients were deemed ineligible for ASO because of their coronary pattern and were excluded by the publications that described them: 2 patients had an intramural LCA, 1 had a tortuous LCA, and 1 had a coronary origin too distant for reimplantation.12,15,16 These patients underwent atrial-level repairs in lieu of ASO and were not included in the analysis of the individual study or the present combined analysis. Follow-up was 95% to 100% complete, and studies reported either early (in hospital or 30-day) or midterm to long-term (13 months to 8 years) mortality, or both.

Absolute mortality rates and ORs and 95% CIs for total all-cause mortality associated with coronary patterns from each individual study, as well as combined ORs calculated in the present analysis, are displayed in Figures 2 through 4. Because data for early and total mortality were similar, only total mortality data are displayed. Individually, 5 of the 9 studies failed to show a significant association of coronary artery anatomy with mortality. When data were combined, the presence of a coronary artery that looped around either of the great vessels was associated with a 40% increase in mortality (OR 1.4, 95% CI 1.0 to 2.1; Figure 2A). Patients with a single coronary ostium had a 3-fold mortality increase (OR 2.9, 95% CI 1.3 to 6.8; Figure 2B). As displayed in Figure 1, both single RCA and single LCA were also associated with looping around the great arteries (retropulmonary LCA and anterior looping RCA, respectively). When we excluded single RCA and single LCA patterns and analyzed only coronary patterns that arose from 2 separate ostia and looped around the great vessels, coronary looping was no longer associated with a significant mortality risk (OR 1.2, 95% CI 0.8 to 1.9; Figure 2C).

The presence of an intramural coronary artery was associated with the highest mortality of any coronary pattern, with more than a 6-fold increase compared with the usual coronary arrangement (OR 6.5, 95% CI 2.9 to 14.2; Figure 3). Overall, patients with any variant coronary pattern had nearly twice the mortality seen in those with the usual pattern (OR 1.7, 95% CI 1.3 to 2.4; Figure 4).

Subgroup analysis of mortality associated with variant coronary patterns over time suggested decreased mortality rates for infants who underwent surgery during 1992 or later compared with before 1992 (Figure 5). Mortality rates decreased in both the usual and variant anatomy groups, such that none of these differences between time periods were statistically significant (all P>0.05). Patients with variant anatomy continued to have higher mortality risk than patients with the usual anatomy, although those with an intramural coronary artery were the only group of patients with a significant mortality risk detected in the post-1992 subgroup (OR 4.6, 95% CI 1.2 to 18.3). In the random-effects regression model, no significant time-trend effects were detected (Table 2). The presence of a single coronary ostium or an intramural coronary artery contributed significant additional mortality risk after adjustment for time-trend effects (P=0.039 and 0.006, respectively).

**Discussion**

Although the superiority of ASO over atrial-level TGA repairs has been established, the present meta-analysis clarifies the relationship between coronary pattern and outcome of
this surgical approach. Our findings support the results of prior case series that have suggested certain coronary patterns are associated with adverse outcomes. The presence of an intramural coronary artery has been shown to be a predictor of increased post-ASO morbidity and mortality. The present analysis quantifies this relationship, demonstrating a >6-fold increase in mortality in patients undergoing surgery during the past 2 decades. This added mortality may reflect...
the risk of inadvertently damaging a coronary artery during surgery when its intramural origin was unknown preoperatively or technical difficulties with the transfer of a known intramural coronary artery. Improvements in preoperative imaging and increased operator experience have likely played a role in the trend toward decreased mortality associated with this coronary pattern over time. However, despite these advances, those with an intramural coronary artery have a significant mortality risk even in recent years, with nearly a 5-fold increase over those with the usual pattern.

Previous studies have also associated patterns that include looping of a coronary artery around the great arteries with adverse outcomes. Because this group includes both single coronary patterns (single RCA and single LCA), we divided it into 2 categories: looping coronary arteries that arise from 2 ostia and those arising from 1 ostium. When these 2 groups were analyzed separately, the presence of looping in the setting of a single ostium was associated with a 3-fold increase in mortality, whereas coronary looping with 2 ostia in separate sinuses of Valsalva was not associated with a significantly increased mortality risk.

The risk associated with looping coronaries demonstrated in other studies was believed to be due to kinking or stretching of these coronary arteries after their transfer. Although this may play a role, the present analysis suggests that the majority of the risk may be attributable to the inclusion of the single coronary patterns in this group. The mortality risk associated with a single coronary ostium may result from it being the sole source of myocardial blood supply, so that any kinking, stretching, or thrombosis will have a profound effect on cardiac function. In addition, the fact that the branches arise from a common origin and extend in opposite directions may increase the likelihood of their stretching or kinking. To the best of our knowledge, outside the context of coronary looping, the presence of a single coronary artery has not been demonstrated to be a predictor of mortality after ASO previously. This is likely because of the limited power of earlier studies to detect mortality differences associated with this rare coronary pattern.

The present data suggest that patients with coronary looping in association with 2 separate ostia undergo the ASO without a significant increase in risk compared with those with usual coronary anatomy. This is important because this group includes patients in whom the circumflex arises from the RCA, by far the most common coronary variant in patients with TGA. On the other hand, those with looping associated with a single coronary ostium may represent a separate high-risk category. Although the absolute risk for these patients may have decreased in recent years, as demonstrated for other coronary patterns, the elevated relative mortality risk for this subgroup has persisted over time.

**Study Limitations**

Because information on patient clinical and surgical variables in relation to the different coronary patterns was not given in the individual studies, we were unable to adjust for these in our analysis. However, it is likely that these factors were distributed relatively evenly across groups. In addition, our analysis was limited to all-cause mortality, as in the individual studies, which did not report on cardiac-specific death in relation to the different coronary patterns. On the other hand, because determination of cause of death is often somewhat subjective and imprecise, the use of all-cause mortality avoids this subjectivity. Finally, this study is subject to the limitations associated with all meta-analyses. However, these were minimized by our extensive literature search to ensure
relevant studies were not missed, the thorough and complete ascertainment of coronary patterns and follow-up across studies, and the homogeneity between patient and surgical variables, as well as study results. Publication bias can also be a limitation in that trials with positive results may be more likely to be published. Because the majority of trials used in the present analysis showed no statistically significant association between coronary pattern and mortality, a substantial publication bias is unlikely.

Conclusions
Over the past 2 decades, patients with common coronary variants have undergone ASO without added mortality compared with those with the usual pattern. However, the combined experience indicates that patients with certain more rare coronary patterns, including those with an intramural or single coronary artery, have a significantly increased mortality risk that has persisted over time. Adequately powered contemporary studies of TGA patients undergoing ASO are needed to more thoroughly examine mortality trends over time. In addition, further study of long-term coronary patency and cardiac function is needed to fully assess the impact of coronary artery transfer associated with ASO. The creation of an international congenital heart surgery registry may be the best way to provide the extensive amount of data needed to answer questions such as these.

References

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<th>Coronary Pattern</th>
<th>95% CI</th>
<th></th>
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<tbody>
<tr>
<td>Any coronary looping</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Time-trend effect</td>
<td>0.59</td>
<td>1.03</td>
<td>0.93</td>
</tr>
<tr>
<td>Adjusted variant effect</td>
<td>0.63</td>
<td>1.23</td>
<td>0.53</td>
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<tr>
<td>Single coronary ostium</td>
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<td></td>
<td></td>
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<tr>
<td>Time-trend effect</td>
<td>0.19</td>
<td>0.83</td>
<td>0.63</td>
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<tr>
<td>Adjusted variant effect</td>
<td>0.039*</td>
<td>9.35</td>
<td>1.12</td>
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<td>1.60</td>
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<td>0.95</td>
<td>0.80</td>
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<tr>
<td>Adjusted variant effect</td>
<td>0.006*</td>
<td>9.67</td>
<td>1.92</td>
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<tr>
<td>Any variant coronary pattern</td>
<td></td>
<td></td>
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<tr>
<td>Time-trend effect</td>
<td>0.67</td>
<td>1.02</td>
<td>0.93</td>
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<tr>
<td>Adjusted variant effect</td>
<td>0.19</td>
<td>1.64</td>
<td>0.78</td>
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</table>

Adjusted variant effect indicates effect of coronary variant adjusted for time trend.

*P<0.05.
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Circulation. 2002;106:2575-2580
doi: 10.1161/01.CIR.0000036745.19310.BB
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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