The Ross Procedure
A Systematic Review and Meta-Analysis

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Background—Reports on outcome after the Ross procedure are limited by small study size and show variable durability results. A systematic review of evidence on outcome after the Ross procedure may improve insight into outcome and potential determinants.

Methods and Results—A systematic review of reports published from January 2000 to January 2008 on outcome after the Ross procedure was undertaken. Thirty-nine articles meeting the inclusion criteria were allocated to 3 categories: (1) consecutive series, (2) adult patient series, and (3) pediatric patient series. With the use of an inverse variance approach, pooled morbidity and mortality rates were obtained. Pooled early mortality for consecutive, adult, and pediatric patients series was 3.0% (95% confidence interval [CI], 1.8 to 4.9), 3.2% (95% CI, 1.5 to 6.6), and 4.2% (95% CI, 1.4 to 11.5). Autograft deterioration rates were 1.15% (95% CI, 1.06 to 2.06), 0.78% (95% CI, 0.43 to 1.40), and 1.38%/patient-year (95% CI, 0.68 to 2.80), respectively, and for right ventricular outflow tract conduit were 0.91% (95% CI, 0.56 to 1.47), 0.55% (95% CI, 0.26 to 1.17), and 1.60%/patient-year (95% CI, 0.84 to 3.05), respectively. For studies with mean patient age >18 years versus mean patient age ≤18 years, pooled autograft and right ventricular outflow tract deterioration rates were 1.14% (95% CI, 0.83 to 1.57) versus 1.69% (95% CI, 1.02 to 2.79) and 0.65% (95% CI, 0.41 to 1.02) versus 1.66%/patient-year (95% CI, 0.98 to 2.82), respectively.

Conclusions—The Ross procedure provides satisfactory results for both children and young adults. Durability limitations become apparent by the end of the first postoperative decade, in particular in younger patients. (Circulation. 2009;119:222-228.)

Key Words: epidemiology ■ prognosis ■ surgery ■ survival ■ valves

The potential advantages of the autograft or Ross procedure are the use of the patient’s own living valve with favorable hemodynamic characteristics, low endocarditis risk, low thrombogenicity, avoidance of anticoagulant therapy, and autograft size increase in children. However, the Ross procedure is a technically demanding operation, and both the autograft in aortic position and the valve substitute in the right ventricular outflow tract (RVOT) may develop structural failure over time.

Although survival of young adult patients after this procedure is almost uniformly excellent and comparable to that of the general population, autograft durability is in some centers clearly superior to other biological valve conduits, whereas other centers report worrisome autograft reoperation rates. The reason that these results diverge so much and whether keys to success exist remain unclear.

Systematic reviews allow for a more objective appraisal of evidence than traditional narrative reviews and thus may contribute to resolve uncertainty when original research, reviews, and editorials disagree. We hypothesize that systematic review of all available evidence on mortality and morbidity after the Ross procedure will improve insight into outcome. The goal of this study is to systematically review observational reports on mortality and morbidity after the Ross procedure to improve insight into potential determinants of success.
Methods

This systematic review and meta-analysis were done with the use of the Meta-analysis of Observational Studies in Epidemiology guidelines.1

Search Strategy

On January 11, 2008, a PubMed and EMBASE search of (aortic valve replacement AND autograft) OR (aortic valve replacement AND Ross procedure) OR (aortic valve replacement AND Ross operation) was conducted, limited to publications from 2000 until 2008 in humans. In addition, the entire Cochrane library was searched for (autograft aortic valve replacement) OR (Ross procedure) OR (Ross operation) in title, abstract, or key words of publications. One reviewer (J.M.T.) screened the titles and abstracts of identified studies. Inclusion criteria were observational studies reporting on mortality and/or morbidity after autograft aortic valve or root replacement, completeness of follow-up >90% (high quality), and study size n>30, reflecting the center’s experience. In case of multiple publications on the same patient population, the most recent report was selected. A second independent reviewer (L.M.A.K.) assessed whether inclusion and exclusion were performed correctly. In case of disagreement, an agreement was negotiated. References of selected articles were cross-checked for other relevant studies. Authors were contacted when a publication could not be obtained or not all required information could be retrieved from the publication.

Data Extraction

Microsoft Excel and Review Manager version 4.2 for Windows (The Cochrane Collaboration, 2003) were used for data extraction and statistical analysis. To control for potential heterogeneity caused by patient age, publications were allocated to 3 categories: (1) consecutive series in both children and adults; (2) adult patient series (adults and/or children aged ≥10 years at the time of the procedure); and (3) pediatric patients series. Study design was documented. Outcome events were registered according to the 2008 American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery guidelines.2 Structural valve deterioration and nonstructural valve deterioration were defined as diagnosed either at reoperation or autopsy and were combined to 1 end point. Bleeding, thromboembolism, and valve thrombosis were combined to 1 end point. If the total number of patient-years was not provided, we calculated it by multiplying the number of patients with the mean follow-up duration of that study.

Statistical Analysis

Early mortality risk and linearized occurrence rates of valve-related complications were calculated (number of events/number of patient-years)×100 for each individual study and pooled on a logarithmic scale with the use of the inverse variance method in a fixed-effects model. In case a particular event was reported not to occur in an individual study, then for the analyses it was assumed that 0.5 patient experienced the event. When an included study did not specify a particular valve-related event in the Methods section, did not mention it in the Results section, or omitted it from both sections, then the study was excluded from analysis of that event. Funnel plots were used to study publication bias. Heterogeneity was assessed with the use of the Cochran Q statistic and the I2 test. Study size, patient age, mean follow-up duration, and retrospective versus prospective study design were explored as potential causes for heterogeneity through subgroup analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 268 studies were identified; 229 studies were excluded for the following reasons: other subject (n=54), case report or <30 patients in study (n=47), review (n=33), exercise or imaging study (n=27), overlap with other studies (n=25), (invited) comment (n=12), surgical/technical article (n=7), experimental/histopathological study (n=5), irretrievable Polish, Spanish, or Japanese articles (n=5), Ross-Konno procedure only (n=5), follow-up completeness <90% (n=5), focus on endocarditis (n=2), and focus on reoperative procedure (n=2). Thirty-nine publications were included: 17 consecutive series with both children and adults1-19 (n=2610; 11 604 patient years); 12 adult patient series20-31 (n=1749; 7458 patient-years); and 10 pediatric patient series32-41 (n=672; 3374 patient-years).

Study Characteristics

Table 1 provides an overview of the publications obtained by the systematic review.

Study Outcomes

Tables 2, 3, and 4 display pooled morbidity and mortality after the Ross procedure by category, including heterogeneity test results.

Publication Bias and Subgroup Analyses

No significant publication bias was found, but a tendency toward higher outcome estimates in small studies was observed. Study design did not cause heterogeneity, and thus outcomes of retrospective and prospective studies were combined. To further study patient age effects on autograft and RVOT durability, we divided all 39 studies into 2 age groups. For studies with a mean patient age >18 years versus studies with a mean patient age ≤18 years, pooled autograft and RVOT structural valvular deterioration/nonstructural valvular deterioration rates were 1.14% (95% confidence interval [CI], 0.83 to 1.57) versus 1.69% (95% CI, 1.02 to 2.79) and 0.65% (95% CI, 0.41 to 1.02) versus 1.66%/patient-year (95% CI, 0.98 to 2.82), respectively. Follow-up duration did not influence study outcomes.

Discussion

This study shows that a considerable experience with the Ross procedure has accumulated worldwide. It also illustrates that it is almost exclusively employed in children and young adults, in an age range in which its advantages of avoidance of anticoagulant therapy, superior hemodynamics, and size increase are most important. Late mortality rates are low and resemble the adult series age-matched general population mortality. Occurrence of thromboembolic complications, bleeding, nonstructural valve failure, and endocarditis is low compared with other aortic valve substitutes.52 With time, both the autograft and the valve substitute in the RVOT show limited durability, and autograft reoperation and RVOT reintervention for valve deterioration are the most common valve-related complications. Noteworthy is the variability between studies in autograft and RVOT structural and nonstructural valve deterioration rates, causing increasing variability in reported freedom from these events by the end of the first postoperative decade.

Patient Factors

Patient age, valve disease pathogenesis, and preoperative aortic regurgitation and dilatation are the most commonly
reported patient-related determinants of durability of the autograft valve. Younger patient age was previously implicated to be associated with increased autograft dilatation but not with late autograft dysfunction.\textsuperscript{14} The results from the present review indicate that younger patient age may indeed be associated with decreased autograft durability. The accumulating evidence on autograft performance in the second decade after the Ross procedure will eventually reveal whether patient age is indeed a determinant of autograft durability.

Congenital aortic valve disease was previously suggested to be associated with increased autograft root dilatation risk.\textsuperscript{43} Although in our systematic review several reports studied the association between bicuspid valve disease and autograft durability, only 1 study found a possible association between bicuspid aortic valve and an increased occurrence of aortic regurgitation.\textsuperscript{27} A recent prospective serial echocardiography study failed to find an association between bicuspid valve disease and (increase in) aortic regurgitation or neoaortic dimensions over time.\textsuperscript{44} Therefore, the influence of bicuspid valve disease on autograft durability remains debatable.

Rheumatic valve disease is another cause reported to be associated with impaired autograft durability. Two overlapping reports in the systematic review showed an association between rheumatic valve disease in young patients and increased autograft dysfunction.\textsuperscript{13,28} With increasing patient age, recurrence of rheumatic fever (and risk of subsequent...
The allograft is used to reconstruct the RVOT in most patients in this review. Only a few patients received a bioprosthesis, primarily a bovine jugular vein conduit. It appears from this review that structural and nonstructural valve deterioration of the valve substitute in the RVOT is more common in children than in adults. Besides degeneration of the RVOT conduit, young children may outgrow their pulmonary valve substitute. Measures to improve RVOT allograft durability are the use of pulmonary allografts and prescription of anti-inflammatory drugs to suppress the specific immune response to the allograft. It is hoped that, with further development of tissue-engineered valved conduits, a more durable solution will be found for RVOT reconstruction.

### Table 3. Pooled Outcome Estimates for Adult Series

<table>
<thead>
<tr>
<th>Early Mortality, %</th>
<th>Late Mortality, %/y</th>
<th>SUUD, %/y</th>
<th>Autograft SVDNSVD, %/y</th>
<th>RVOT SVD/NSVD, %/y</th>
<th>TE/BLVT, %/y</th>
<th>Autograft Endocarditis, %/y</th>
<th>RVOT Endocarditis, %/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knott-Craig 2000</td>
<td>5.80 (5.52–11.14)</td>
<td>1.31 (1.20–2.87)</td>
<td>0.44 (0.33–1.61)</td>
<td>0.66 (0.55–1.94)</td>
<td>1.09 (0.98–2.57)</td>
<td>0.22 (0.11–1.25)</td>
<td>0.22 (0.11–1.25)</td>
</tr>
<tr>
<td>Paparella 2001</td>
<td>0.60 (0.33–3.70)</td>
<td>0.17 (0.09–0.97)</td>
<td>0.08 (0.00–0.83)</td>
<td>0.85 (0.77–2.00)</td>
<td>0.17 (0.08–0.97)</td>
<td>0.34 (0.26–1.25)</td>
<td>0.08 (0.00–0.83)</td>
</tr>
<tr>
<td>Fullerton 2003</td>
<td>6.80 (5.70–28.18)</td>
<td>0.35 (0.00–3.45)</td>
<td>0.35 (0.01–3.45)</td>
<td>0.35 (0.01–3.45)</td>
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<tr>
<td>Matalanis 2004</td>
<td>3.20 (1.65–18.49)</td>
<td>0.94 (0.48–5.41)</td>
<td>0.94 (0.48–5.41)</td>
<td>0.47 (0.00–4.59)</td>
<td>0.47 (0.00–4.59)</td>
<td>0.47 (0.00–4.59)</td>
<td>0.47 (0.00–4.59)</td>
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<tr>
<td>Kumar 2005</td>
<td>5.64 (6.22–12.07)</td>
<td>0.87 (0.82–1.73)</td>
<td>0.05 (0.00–0.53)</td>
<td>0.87 (0.82–1.73)</td>
<td>0.05 (0.00–0.53)</td>
<td>0.44 (0.38–1.16)</td>
<td>0.05 (0.00–0.53)</td>
</tr>
<tr>
<td>Alphonso 2004</td>
<td>3.52 (3.31–6.98)</td>
<td>0.58 (0.52–3.18)</td>
<td>0.46 (0.41–1.20)</td>
<td>0.46 (0.41–1.20)</td>
<td>0.46 (0.41–1.20)</td>
<td>0.46 (0.41–1.20)</td>
<td>0.46 (0.41–1.20)</td>
</tr>
<tr>
<td>Brown 2007</td>
<td>1.20 (0.90–4.40)</td>
<td>0.12 (0.06–0.67)</td>
<td>0.06 (0.00–0.57)</td>
<td>1.41 (1.35–2.47)</td>
<td>0.82 (0.76–1.70)</td>
<td>0.82 (0.76–1.70)</td>
<td>0.82 (0.76–1.70)</td>
</tr>
<tr>
<td>Chippini 2007</td>
<td>1.80 (1.60–4.72)</td>
<td>0.10 (0.05–0.58)</td>
<td>0.05 (0.00–0.50)</td>
<td>0.10 (0.05–0.58)</td>
<td>0.05 (0.00–0.50)</td>
<td>0.05 (0.00–0.50)</td>
<td>0.05 (0.00–0.50)</td>
</tr>
<tr>
<td>Kleverik 2007</td>
<td>2.70 (2.40–7.08)</td>
<td>0.32 (0.28–0.82)</td>
<td>0.04 (0.00–0.38)</td>
<td>1.81 (1.77–2.72)</td>
<td>0.63 (0.59–1.25)</td>
<td>0.08 (0.04–0.45)</td>
<td>0.16 (0.10–0.58)</td>
</tr>
<tr>
<td>Pasquali 2007</td>
<td>2.50 (2.07–7.34)</td>
<td>0.09 (0.09–1.00)</td>
<td>0.09 (0.09–1.00)</td>
<td>1.93 (1.84–3.46)</td>
<td>0.18 (0.09–1.00)</td>
<td>0.09 (0.09–1.00)</td>
<td>0.09 (0.09–1.00)</td>
</tr>
<tr>
<td>Pooled total</td>
<td>3.04 (1.78–4.87)</td>
<td>0.28 (0.27–0.93)</td>
<td>0.28 (0.27–0.93)</td>
<td>1.15 (1.06–2.06)</td>
<td>0.91 (0.56–1.47)</td>
<td>0.16 (0.03–0.92)</td>
<td>0.32 (0.10–1.02)</td>
</tr>
</tbody>
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**Heterogeneity test**

- $\chi^2$ for Early Mortality: 2.67 ($P=NS$)
- $\chi^2$ for Late Mortality: 2.63 ($P=NS$)
- $\chi^2$ for SUUD: 1.82 ($P=NS$)
- $\chi^2$ for Autograft SVD/NSVD: 6.34 ($P=NS$)
- $\chi^2$ for RVOT SVD/NSVD: 5.10 ($P=NS$)
- $\chi^2$ for TE/BLVT: 3.21 ($P=NS$)
- $\chi^2$ for Autograft Endocarditis: 2.16 ($P=NS$)
- $\chi^2$ for RVOT Endocarditis: 1.47 ($P=NS$)

95% CIs are provided in parentheses. SUUD indicates sudden unexpected unexpected death; SVD, structural valvular deterioration; NSVD, nonstructural valvular deterioration; and TE/BLVT, thromboembolism, bleeding, and valve thrombosis.

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Surgical/Technical Considerations

The variable durability results of the autograft procedure may also partly be explained by the surgical technique and by individual variation of the application of the root replacement technique.

The subcoronary implantation technique was abandoned by most centers for multiple reasons, including its technical complexity and the attractive option of the root replacement technique that preserves the geometry of the autograft valve apparatus. In the systematic review, only 1 series reports solely on results with the subcoronary implantation technique. Thus far, these results are excellent and offer hope for those surgeons who are willing and able to master this technique.

Most patients in the systematic review received an autograft with the use of the freestanding root replacement technique with coronary artery reimplantation. This surgical technique can be applied in a variety of ways. The autograft can be inserted on the annulus or below the annulus, and scalloping of the muscle rim can be done to a minimum below the valve cusps. In addition, either continuous or interrupted sutures can be used for the proximal suture line. Another option is to employ support to the proximal suture line with antihypertensive drugs defeats the purpose of the Ross operation when indicated. In patients with ascending aorta aneurysm, the replacing Dacron graft may have a stabilizing effect on the aorta-pulmonary junction. In addition, the convexity of the autograft (anterior pulmonary root) should preferably come on the right side in aortic position (former ascending aortic convexity). The unsupported facing sinus of the pulmonary valve should be placed in the left coronary position, where it derives support from surrounding tissues.

The third surgical technique used to insert the autograft is the inclusion cylinder technique. It is infrequently used in the series in this review. It prevents dilatation of the neoaortic root, but its application requires an intact anatomy of the ascending aorta and aortic root and is limited by several technical challenges, including distortion of the reinserted coronary arteries.

Postoperative antihypertensive treatment may potentially increase autograft root durability. It was reported that the physical properties of the pulmonary root change after being in the aortic position for a short time. Because the autograft will be subject to significantly increased mechanical stress, blood pressure control may result in improved valve longevity. Whether this treatment is effective and whether it should be restricted to the early postoperative period or for a prolonged period of time have not yet been studied systematically. One can argue that prolonged use of beta-blockers or other antihypertensive drugs defeat the purpose of the Ross operation and may impair quality of life in these young patients.

Histological Aspects

Rabkin-Aikawa et al. reported that explanted autografts are viable and have a near-normal trilaminar cuspal structure and collagen architecture, but autograft walls are damaged, with focal loss of normal smooth muscle cells, elastin, and collagen. Another recent histological study found that compared with normal pulmonary and aortic valves, explanted autograft valves also have an intact laminar architecture and cellularity, but apposition of fibrous tissue on the ventricular surface increases overall valve thickness, as can be seen in longstanding valvular insufficiency. The autograft wall typi-
cally shows severe aneurysm formation with intimal hyperplasia and medial degeneration characterized by elastin loss and fragmentation, hypertrophy of smooth muscle cells, and adventitial fibrosis containing functional vasa vasorum.\(^{50}\) An important question arising from the observed histological features is as follows: Do they represent appropriate repair with the adapted neoorta as a functional and stable end product? The majority of explants was removed for clinical failure and thus proved unstable. Therefore, one can argue that the observed changes, the result of adaptive remodeling, are pathological and should be classified as degenerative. The mode of adaptation conceivably differs between normal aorta and pulmonary root, with each having their own typical functional design. Consequently, the pulmonary root has a different stress-strain curve than the aortic root, with a greater extensibility at lower strain levels. One can therefore expect the neoaortic root to stretch beyond its normal transitional point of high to low extensibility. This is supported by in vitro analysis of pulmonary root dynamics.\(^{51}\) The theoretical consequence of this stretch is compliance loss and root stiffening, a mechanism supported by clinical magnetic resonance imaging study, confirming distensibility loss of the pulmonary autograft in adult patients.\(^{52}\) When one adds to this the thin-walled and dilated neoaortic root, it is plausible that the autograft is subject to significantly elevated stresses and that observed histological changes of elastin loss (distensibility) and collagen increase (integrity) are conceivable modes of adaptation in which functional priority is shifted to integrity maintenance. Despite this adaptation, as in any aneurysm, excess wall stress may induce intimal tearing, causing a localized chronic dissection.

**Limitations**

Selection bias is likely because of the selection criteria employed and because unpublished data, abstracts, and presentations were not included. Valve-related event occurrence is probably underestimated because most studies had a retrospective design. Valve degeneration has an increasing hazard with time since implantation and may better be described by a Weibull distribution. However, because follow-up duration of most studies is limited to the first postoperative decade, and no increasing hazard was yet observed, we chose to depict only linearized rates. We did not study echocardiographic valve performance in this review; it is extremely difficult to obtain this information because it is infrequently, incompletely, and inconsistently reported in most included studies.

**Conclusions**

The Ross procedure provides both children and young adults an adequate biological solution in the first decade after the operation. Durability limitations become apparent by the end of the first postoperative decade, in particular in younger patients. Whether these limitations may be addressed at least in part by surgical details and postoperative measures discussed in this article remains to be determined.

**Disclosures**

None.

**References**


When pediatric and young adult patients require aortic valve replacement, the choice for a particular valve prosthesis has a major impact on their lives. A mechanical prosthetic comes with lifelong anticoagulation and increased risk of bleeding and thromboembolic complications. The choice for a biological valve substitute, on the other hand, implies 1 or more reoperations during the remainder of life because of limited durability. The concept of the Ross procedure provides the patient factors, histological aspects, and surgical technique details. In addition, the potential measures to optimize durability small reports, this systematic review and meta-analysis gives an objective overview of outcome after the Ross procedure, discussion on the value of this operation. By systematically compiling and weighing evidence on outcome from multiple pulmonary autograft. The Ross procedure is the procedure of choice for congenital aortic valve disease. J Thorac Cardiovasc Surg. 2002;123:437–441.


