Optimal timing of Ross operation in children: A moving target?

Igor E. Konstantinov, MD, PhD, FRACS, a Emile Bacha, MD, b David Barron, MD, FRCS, c Tirone David, MD, d Joseph Dearani, MD, e Yves d’Udekem, MD, PhD, FRACS, f Ismail El-Hamamsy, MD, PhD, g Hani K. Najm, MD, MSc, h Pedro J. del Nido, MD, i Christian Pizarro, MD, j Peter Skillington, MBBS, FRACS, k Vaughn A. Starnes, MD, l and David Winlaw, MBBS, FRACSm

Supplemental material is available online.

The optimal age for Ross operation in children is not defined. One may believe that the Ross operation may recreate an aortic valve as close to normal as possible, and, therefore, should be done early in childhood, so that the autograft will grow together with a child and will become a normal natural substitute for the aortic valve. In contrast, it may appear logical to perform aortic valve repair first and postpone the Ross operation until the child is sufficiently grown, so that the autograft can be stabilized at an adult size and a larger right ventricle-to-pulmonary artery conduit can be placed. This approach would aim at delaying the Ross operation until adolescence or, ideally, early adulthood. As there are no data to support or refute either opinion regarding the optimal timing of Ross operation in children, herein we put together the expert opinions on the topic and support our opinions with the best evidence currently available.

ROSS OPERATION IN NEONATES AND INFANTS

It should be taken into consideration that Ross operation, and more so the Ross–Konno operation, is often performed in neonates and infants, when it is perceived that no other option is available. Thus, the neonates and infants undergoing Ross operation may have significant concomitant cardiovascular anomalies, including endocardial fibroelastosis. Therefore, the current literature does not allow a direct comparison of the outcomes in neonates and infants with isolated aortic stenosis (AS).

Although a wide range of mortality rates have been reported1-10 (Table 1), good results with Ross and Ross–Konno operation can be achieved in neonates and infants.2,3,6 In a recent study of 58 children who underwent the Ross operation between 1993 and 2020 and were younger than 1 year of age, which appears to be the largest single-institutional study, the authors reported operative mortality of 19% (11/58) in overall cohort and of 39%
TABLE 1. Ross outcomes in neonates and infants

<table>
<thead>
<tr>
<th>Study</th>
<th>Era</th>
<th>Follow-up</th>
<th>No. of patients</th>
<th>Associated Konno, n (%)</th>
<th>Isolated AS, n (%)</th>
<th>Associated pathologies, n (%)</th>
<th>Survival</th>
<th>Autograft reintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland et al¹</td>
<td>1993-2020</td>
<td>Mean 6.7 y (range, 2.1-13.1)</td>
<td>58</td>
<td>33 (57%)</td>
<td>26 (45%)</td>
<td>9 (16%) hypoplastic arch</td>
<td>19% (11/58) hospital mortality</td>
<td>Freedom from 98%, 96%, 96% at 5, 10, and 15 y</td>
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<td></td>
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<td></td>
<td></td>
<td>15 (26%) Shone complex</td>
<td>4% (1/26) isolated AS hospital mortality</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>8 (14%) IAA/VSD</td>
<td>4.3% (2/47) late mortality</td>
<td></td>
</tr>
<tr>
<td>Luxford et al²</td>
<td>1995-2018</td>
<td>Median 4.1 y (IQR, 3.4-5.2)</td>
<td>35</td>
<td>30 (86%)</td>
<td>Unknown</td>
<td>11 (31%) arch obstruction</td>
<td>0% hospital mortality</td>
<td>No patients</td>
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<td></td>
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<td></td>
<td></td>
<td>7 (20%) mitral valve dysplasia</td>
<td>100% survival at 1 y</td>
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<td>97% survival at 5 and 10 y</td>
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<tr>
<td>Sames-Dolzer et al³</td>
<td>2008-2017</td>
<td>Mean 5.9 y (range, 0.5-16.7)</td>
<td>44</td>
<td>44 (100%)</td>
<td>Unknown</td>
<td>21 (48%) arch obstruction</td>
<td>7% (3/44) hospital mortality</td>
<td>No patients</td>
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<td></td>
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<td></td>
<td></td>
<td>2% (1/41) late mortality</td>
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</tr>
<tr>
<td>Lo Rito et al⁴</td>
<td>1991-2011</td>
<td>Median 10.8 y (range, 0.96-21) for entire group</td>
<td>140, 22 less than 18 mo of age</td>
<td>8 (36%)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>14% (3/22) hospital mortality</td>
<td>18% mortality at 2.5 y</td>
</tr>
<tr>
<td>Elder et al⁵</td>
<td>1991-2010</td>
<td>Median 10.6 y (range, 1.4-20.4)</td>
<td>34</td>
<td>26 (76%)</td>
<td>12 (35%)</td>
<td>12 (35%) subvalvar AS</td>
<td>12% (4/34) hospital mortality</td>
<td>Freedom from 96% at 10 y</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>10 (29%) arch obstruction</td>
<td>88% survival at 10 y</td>
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<td></td>
<td>6 (18%) endocardial fibroelastosis</td>
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<td></td>
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<td>3 (9%) mitral stenosis</td>
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<tr>
<td>Maeda et al⁶</td>
<td>1994-2010</td>
<td>Median 81 mo (range, 1-173)</td>
<td>24</td>
<td>2 (8%)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>4% (1/24) hospital mortality</td>
<td>No late mortality</td>
</tr>
</tbody>
</table>

(Continued)
Age younger than 3 months was an independent risk factor for mortality. Children younger than 3 months of age had an operative mortality of 31% (10/32) as compared with 4% (1/26) in the rest of the group. In-hospital mortality for children older than 3 months of age was 4% (1/26). As expected, the younger age was inter-related with severity of the condition. Children with concomitant Shone complex had an operative mortality of 40% (6/15), and those with interrupted aortic arch and ventricular septal defect had an operative mortality of 38% (3/8). In-hospital mortality of Ross operation for isolated AS in this series was 4% (1/26). Freedom from autograft reintervention was 96% at 15 years. The authors concluded that Ross operation is effective in children less than 1 year of age with isolated AS and/or aortic arch obstruction. Although encouraging results of both aortic valve repair and Ross operation in neonates and infants can be achieved in some institutions, the overall results are of concern, as indicated by recent meta-analyses. A recent meta-analysis of Ross operations performed in the neonatal period demonstrated an operative mortality up to 30%. Pooled early mortality after the Ross operation in infants was substantially greater (16.3%) than in older children (3.7%) in the recent meta-analysis of 3468 children, who underwent Ross operation. Similarly, pooled early mortality after aortic valve repair for aortic valve stenosis was 10.7% in neonates, 7% in infants, and 3.5% in older children in a recent meta-analysis of 2623 children who underwent aortic valve repair. Yet, it should be remembered that many of these operations would have been emergent procedures after failed balloon aortic valvuloplasty and/or many children may have had concomitant cardiac lesions, including endocardial fibroelastosis. Ideally, it would be important to study the outcomes in neonates and infants with isolated aortic valve disease in whom both aortic valve repair and Ross operation are equally feasible, so that the proper comparison of these aortic valve surgical interventions can be performed. Unfortunately, such comparison is not possible in the current literature. For this group, the appropriate comparison may be a stage I palliation versus a Ross–Konno procedure, as they typically are on the spectrum of hypoplastic left heart structures. Many of the neonates and infants who died might have been better served initially with a stage I approach, to be either reconverted to a 2-ventricle repair later or not.

Much better results for both Ross operation and aortic valve repair can be achieved in some institutions with significant expertise. Thus, much improved results of Ross operation have been recently reported in 35 infants, including 13 neonates, operated from 1995 to 2018, with no operative mortality and 62% freedom from reoperation in 10 years. None required reoperation on the autograft at 10 years, albeit with only 10 patients at risk at this point of time. Although 14% (5/35) had concomitant aortic arch repair, neoaortic dimensions appear to be stable over medium-term follow-up.

Because of heterogeneity of reported patients, it is not possible to separate the outcomes of Ross operation in patients with isolated AS in most studies. Good results with
aortic valve repair can be achieved in neonates, which may be temporizing, yet a much simpler procedure, compared with Ross operation. The operative mortality for neonatal isolated AS was reported to be 0% in a group of 43 neonates undergoing aortic valve repair between 1980 and 2021, even in those with reduced preoperative left ventricle function. However, neonates who underwent aortic valve repair had freedom from reoperation on the aortic valve of 32% at 10 years, yet 60% retained their own aortic valve by 10 years. It also appears that freedom from autograft reoperation was significantly lower if Ross operation was performed in infancy, as compared with that in patients who had Ross operation beyond infancy.9

Recent meta-analysis of 587 patients younger than 1 year of age demonstrated that Ross operation in neonates and infants still carries significant risk of both early and late mortality as well as autograft reintervention.10 Ross operation in neonates and infants is rarely performed, as aortic valve repair generally appears to be a safer alternative in this subgroup of children with consistently lower mortality.

Historically, a study comparing pulmonary autograft of 8 infants who underwent Ross operation to 12 normal children demonstrated accelerated annular growth and dilatation in the first 1 to 2 years after Ross operation in infancy suggests that the autograft is not as well supported at the annulus as the native pulmonary root when exposed to systemic pressures. Whether this results in the late regurgitation is not clear. In contrast, other studies demonstrated lack of autograft dilatation in neonates and infants, suggesting that pulmonary autograft in neonates and infants may be able to differentiate into a more histologically aortic valve compared to the pulmonary autograft of an older child or adult. It appears that operative mortality after Ross operation or aortic valve repair in neonates and infants occurs mainly in children with concomitant cardiovascular anomalies or severe acute aortic insufficiency after failed balloon dilatation. Aortic valve repair in acute aortic insufficiency after failed balloon dilatation could be an easier and safer operation compared with urgent Ross operation.17 Provided that the operative mortality is controlled, Ross and modified Ross–Konno operation may provide an excellent autograft durability in neonates and infants.

Finally, a recent study showed that patients with a history of aortic valve balloon dilatation for critical AS before the Ross operation and who present with either aortic insufficiency or mixed disease behave like patients with AS, as far as Ross operation outcomes are concerned. These patients have a low rate of autograft reintervention or dilation. This suggests that in critical patients with AS, the Ross operation may be delayed by balloon dilatation. Although primary aortic valve repair may provide better long-term durability of the aortic valve, a good-quality repair can be still achieved after previous successful balloon valve dilatation. In contrast, failed aortic valve dilatation that causes severe aortic valve insufficiency is more problematic. Urgent aortic valve repair for severe aortic valve insufficiency after failed balloon dilatation could be a much safer and easier operation compared with urgent Ross operation in a neonate or infant.

ROSS OPERATION IN OLDER CHILDREN

In older children, it appears from the current literature that primary aortic valve repair is associated with better survival than the Ross operation, whereas overall freedom from reintervention was similar (Table 2). Optimal aortic valve repair (ie, peak systolic pressure gradient of <35 mm Hg and trivial or less aortic insufficiency) and the Ross operation has similar freedom from aortic valve reoperation at 15 years, whereas suboptimal aortic valve repair showed worse results. The optimal aortic valve repair can be achieved in about one half of children with isolated aortic valve stenosis. In these children with an optimal aortic valve repair, freedom from aortic valve replacement at 10 years was 92% compared with 58% in those who had suboptimal repair. The importance of optimal repair must be emphasized, as some children with mixed AS and insufficiency may have deleterious effect on the left ventricular function long term. In contrast, the Ross operation in older children has been associated with approximately 20% to 25% reoperation rate at 15 years, when the Ross operation was performed after 1 year of age. Interestingly, in one institution, secondary Ross operation performed after initial aortic valve surgery achieved superior long-term survival and freedom from autograft reoperation compared to primary Ross operation in children. A recent study of 140 children (most were beyond infancy, median age 8.6; interquartile range, 3.1-14 years) demonstrated overall incidence of autograft reintervention at 15 years was 26% for those who underwent primary Ross operation and 3% for those who underwent secondary Ross operation after prior aortic valve surgery. Thus, a strategy of initial aortic valve repair followed by delayed Ross operation may provide better long-term survival and freedom from autograft reoperation.

Similarly, in a recent study of 125 children between ages 1 and 18 years (excluded infants; median, age 10.7 years) (interquartile range, 6.8-14.8 years) who underwent Ross operation the authors described the overall incidence of severe autograft insufficiency or autograft reintervention of 24% at 15 years; notably, it was much greater in children who underwent Ross operation for aortic insufficiency (39%) as compared with those who underwent Ross operation for AS (8.8%). The overall rate of autograft reintervention was 17.1% at 15 years. At reintervention, most patients had autograft replacement with mechanical pros thesis, and autograft-sparing root replacement was performed rarely. Therefore, it appears that akin to adults, stabilization of the autograft is important in children aged...
that over a median follow-up of 5 years after the Ross operation in patients with median age of 9 years at the time of Ross operation, the neoaortic root size increases significantly out of proportion to somatic growth, and neo-aortic insufficiency is progressive, with nearly one-quarter of patients developing moderate-to-greater neoaortic insufficiency.\cite{E6,E7} Neoaortic reintervention was required in approximately 10% of patients.\cite{E6,E7} A modified Ross–Konno procedure with a small or no patch material\cite{E5} may provide good results in older children. The autograft stabilization after Ross operation in older children appeared to be important, particularly in those with preoperative aortic valve insufficiency.

**THE VALUE AND FEASIBILITY OF AUTOGRAPH STABILIZATION DURING ROSS OPERATION IN CHILDREN**

Ross operation is associated with excellent long-term outcomes in young adults,\cite{E9} and in this group an excellent autograft durability has been attributed to autograft stabilization technique.\cite{E10,E11} In adults the autograft can be calibrated and stabilized at the aortic annulus and at the sinotubular junction. Generally, the aortic annulus after aortic valve repair is stabilized according to the body surface area using Hegar dilator for sizing (at 21 mm for <1.8 m², at 23 mm for 1.8-2.0 m², and at 25 mm for >2.0 m²) with excellent long-term results.\cite{E12} Similar numbers would be applicable to the autograft stabilization.
Excellent results with autograft stabilization in adults have been described. Accordingly, in older children aged 10 to 18 years of age, an effective stabilization can often be achieved during Ross operation, especially if the aortic root dimensions would reach adult size. It appears logical to conclude that if autograft stabilization is important in adults to achieve long-term durability of the autograft, it is also important in children. Yet, stabilization of the 18-mm autograft, although appropriate for some children, may become too restrictive when somatic growth is completed, not to speak of a smaller size autografts. Stabilization of the autograft in smaller children becomes even more problematic and is limited to various modifications of the root inclusion technique and is hardly feasible in infants and very small children. This has been one argument for delaying the Ross procedure in infants and young children, although the clinical evidence for this approach is limited. Most surgeons would be somewhat reluctant to use any foreign material in a child <12 years of age, who are yet to complete somatic growth, unless the aortic root has already reached adult size. The challenge is to stabilize the root and yet allow somatic growth of the child. This requires a “living” support for the autograft to prevent late aortic root dilatation and autograft failure, which can reach very high rates as children grow into adulthood.

It was recently demonstrated that Ross operation in children with previous aortic valve surgery may provide better freedom from autograft dilatation and failure. Thus, in a growing child it appears to be beneficial to perform Ross operation after initial aortic valve repair as durability of the autograft may be better after redo surgery and additional options for stabilization may become feasible.

**WILL AORTIC VALVE REPAIR IN CHILDHOOD ALWAYS RESULT IN SUBSEQUENT AORTIC VALVE REPLACEMENT?**

With increasing experience with aortic valve repair in neonates and infants, excellent results of aortic valve repair have been reported for isolated AS, especially, if the aortic valve was repaired without the use of a patch. When the patch was not required, freedom from aortic valve replacement was 75% at 10 years. If optimal repair can be achieved during primary aortic valve repair for isolated AS, freedom from aortic valve reoperation was 80% at 10 years. Interestingly, bicuspid morphology was associated with better freedom from reoperation. Such delay, would, of course, allow implantation of adult-size pulmonary conduit, should Ross operation be performed at a later stage, but, most importantly, this would question a need for the aortic valve replacement. Although it is not clear whether congenital aortic valve disease can be cured, a good quality, durable, and long-lasting aortic valve repair with additional aortic root stabilization can be achieved in teenagers, who will come back for reoperation after primary valve repair. Should these patients require Ross operation rather than redo aortic valve repair? Could the need for Ross operation be avoided entirely in some children with isolated AS? The entire aortic root can be stabilized in older children at adult dimensions during redo aortic valve repair. Could these patients keep their native aortic valve for life? These questions remain to be answered.

**CURRENT CLINICAL IMPLICATIONS**

Herein, we state the key clinical implications of the current expert opinion review:

1. Low mortality and good long-term outcomes for both aortic valve repair and Ross operation have been reported and can be achieved at the units with significant expertise.
2. Direct comparison of Ross operation and aortic valve repair in identical groups of patients is not possible currently.
3. It is possible that if Ross or Ross–Konno operation is performed in infancy, the pulmonary autograft may grow proportionally with somatic growth.
4. Autograft stabilization in older children appears as important as autograft stabilization in adults, especially for children with significant preoperative aortic insufficiency.
5. Primary aortic valve repair or percutaneous aortic balloon valvuloplasty does not prevent the Ross operation from being done, and results with the Ross operation after these procedures are excellent in experienced units.
6. Mortality after both aortic valve repair and Ross operation is mainly driven by concomitant anomalies in institutions with significant expertise.
7. Mortality after both aortic valve repair and Ross operation remains high in neonates and infants if these procedures are performed outside the institutions with significant expertise.

**CONCLUSIONS**

Good results with Ross and Ross–Konno operations can be achieved in small children, including neonates and infants in institution with significant expertise. Stabilization of the autograft during Ross operation in children beyond infancy appears to be important to achieve lasting long-term results. Good results can also be achieved with primary aortic valve repair or percutaneous balloon aortic valvuloplasty, followed by a delayed Ross if needed. Although limited, some emerging data suggest that autograft implanted in infancy may allow normal growth of the neo-aortic root without need of subsequent stabilization.
Conflict of Interest Statement

The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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