The Relationship Between Neo-Aortic Root Dilation, Insufficiency, and Reintervention Following the Ross Procedure in Infants, Children, and Young Adults

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Objectives The purpose of this study was to describe the relationship between neo-aortic root size, neo-aortic insufficiency (AI), and reintervention at mid-term follow-up.

Background Data on neo-aortic valve function and growth after the Ross procedure in children are limited.

Methods A total of 74 of 119 Ross patients from January 1995 to December 2003 had ≥2 follow-up echocardiograms at our institution and were included. Neo-aortic dimensions were converted to z-scores and modeled over time. Kaplan-Meier analysis was used to assess freedom from neo-aortic outcomes, and predictors were identified through multivariate analysis.

Results Median age at Ross was 9 years (range 3 days to 34 years). Over 4.7 years (range 3 months to 9.3 years) follow-up, there was disproportionate enlargement of the neo-aortic root (z-score increase of 0.75/year [p < 0.0001]). Neo-AI progressed ≥1 grade in 36% of patients and ≥2 grades in 15%. Nine patients (12%) had neo-aortic reintervention at 2.0 years (range 1.1 to 9.5 years) after the Ross procedure owing to severe neo-AI (n = 7), neo-aortic root dilation (n = 1), and neo-aortic pseudoaneurysm (n = 1). At 6 years after the Ross procedure, freedom from neo-aortic reintervention was 88%. Freedom from neo-aortic root z-score ≥4 was only 3% and from moderate or greater neo-AI was 60%. Longer follow-up time was associated with neo-aortic root dilation (p < 0.0001). Prior ventricular septal defect (VSD) repair predicted neo-AI (p = 0.02) and reintervention (p = 0.03). Prior aortic valve replacement (p = 0.002) also predicted neo-AI. Neo-aortic root dilation was not associated with neo-AI or reintervention.

Conclusions At mid-term follow-up after the Ross procedure, neo-aortic root size increases significantly out of proportion to somatic growth, and neo-AI is progressive. Prior VSD repair and aortic valve replacement were associated with neo-AI and reintervention. (J Am Coll Cardiol 2007;49:1806–12) © 2007 by the American College of Cardiology Foundation

The Ross procedure, first described in 1967 (1), is an attractive alternative to mechanical, porcine, and homograft valves in the treatment of aortic valve disease in infants, children, and young adults. Patients do not require anticoagulation, and early reports have suggested the potential for long-term durability and growth of the neo-aortic valve (2–4). However, there is also concern for neo-aortic root dilation out of proportion to somatic growth, in part because the pulmonary autograft is placed under systemic pressure (5,6). Neo-aortic root dilation has been shown to occur after other surgical interventions that use the pulmonary valve in the systemic circuit such as the arterial switch procedure and Norwood procedure for hypoplastic left heart syndrome (7–10). Studies have also shown dilation of the neo-aortic root out of proportion to somatic growth early in the postoperative period following the Ross procedure (2,5,6,11). Following the first 6 months after the Ross operation, data are conflicting, with some studies demonstrating stabilization of neo-aortic root dimensions and others suggesting continued dilation over the next 1 to 2 years (5,6,11–13). Serial echocardiographic measurements of neo-aortic root dimensions in pediatric patients beyond this time period are lacking.

The relationship among neo-aortic root dilation, neo-aortic insufficiency (AI), and reintervention is also unclear.

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Prior studies have documented 10-year freedom from significant neo-aortic regurgitation ranging from 75% to 90% following the Ross procedure, with reintervention rates of up to 10% at 10-year follow-up (14–16). It is not known whether neo-aortic root dilation is associated with neo-AI or reintervention after the Ross procedure (14,17).

The purpose of this study was to serially assess neo-aortic root size, insufficiency, and reintervention through midterm follow-up after the Ross procedure in a large population of infants, children, and young adults. A secondary aim was to identify predictors of neo-aortic root dilation, insufficiency, and reintervention.

**Methods**

**Study design and patient population.** This study was approved by our institutional review board. A retrospective analysis of patients who underwent the Ross procedure at our institution in isolation, or in combination with other procedures, between January 1995 and December 2003 was performed. Patients who had a discharge echocardiogram and at least 1 follow-up echocardiogram at our institution were included. Those who died (n = 5, 4.2%) were excluded from the analysis.

**Data collection.** Charts were reviewed for age at surgery, gender, original anatomic diagnoses, prior interventions, indication for surgery, postoperative complications, and mortality. Patients were defined as having “isolated” aortic valve disease if they had aortic stenosis, AI, or both, with no other significant left-sided heart disease present. Patients were defined as having “complex” left heart disease if they had aortic valve disease in association with multiple levels of obstruction or additional hemodynamic or structural abnormalities that required surgical intervention. Information on additional procedures performed at the time of the Ross procedure, and the duration of cardiopulmonary bypass, myocardial ischemia, and circulatory arrest (if used) was obtained from operative notes. Follow-up data, including reintervention, were obtained from clinic charts and our institutional cardiac database.

Discharge and follow-up transthoracic echocardiographic data were obtained from our echocardiography database. Measurements of the neo-aortic root complex (at the level of the annulus, root, and sinotubular junction) (Fig. 1), were evaluated as previously described (18). A second echocardiographer independently reviewed 10% of the echocardiograms. The degree of neo-AI and measurements of left ventricular (LV) size and function were also assessed. Neo-aortic valve regurgitation was graded utilizing the quantitative criteria for children described by Tani et al. (19). The primary method was the ratio of neo-AI jet width to neo-aortic annulus width. A ratio of <0.25 was considered mild, 0.25 to 0.5 moderate, and >0.5 severe neo-AI. However, because of the potential to underestimate the grade of neo-AI due to dilation of the neo-aortic root, the Doppler flow pattern in the descending aorta was also evaluated. If holodiastolic flow reversal in the descending aorta was present, neo-AI was judged to be moderate or greater.

Normal LV shortening was defined as ≥28%. For patients who underwent neo-aortic root reintervention, their most recent echocardiogram was defined as the last echocardiogram before reintervention.

**Statistical analysis.** Summary statistics are expressed as means and standard deviation, or medians and ranges where appropriate. Baseline characteristics of our study population were compared with the cohort of patients who underwent the Ross procedure at our institution but did not meet inclusion criteria for our study using the Wilcoxon rank-sum test and Fisher exact test. Raw neo-aortic root complex measurements were normalized to the patient’s body surface area and converted to z-scores based on normal aortic valve measurements (20). A mixed-effects linear regression model was used to assess the relationship between neo-aortic raw and z-score dimensions, and time, due to the repeated measurements in the study and variable follow-up time. Kaplan-Meier analysis was performed to assess freedom from neo-aortic root dilation, moderate or greater neo-AI, and neo-aortic root reintervention. Univariate and multivariate analyses were performed to identify predictors of neo-aortic root outcomes. Neo-aortic root dilation was defined as change in neo-aortic root z-score from discharge to most recent echocardiogram. Progressive neo-AI was defined as change in grade of neo-AI from discharge to most recent echocardiogram. Neo-aortic reintervention included surgical or catheter-based reintervention. Stepwise linear regression was used to identify predictors of neo-aortic root dilation and neo-AI, while a Cox proportional hazard model was used to identify predictors of neo-aortic root reintervention owing to the variation in follow-up time. Neo-aortic root
the Ross procedure was a combination of aortic stenosis and aortic insufficiency in the majority of patients (n = 51, 69%) (Table 1). The Ross procedure was performed using the root replacement technique and a running suture for the proximal and distal neo-aortic anastomosis in all cases (21). Only 1 patient, who had longstanding AI, had an annuloplasty performed utilizing pledged suture to create an adequate size match between the autograft and aortic valve annulus. Of the 74 patients, 55 (74%) had reinforcement of the proximal suture line with oversewing of the proximal native aorta (n = 45), a felt strip (n = 8), or Dacron strip (n = 2). Eight of the 74 patients (11%) had the distal suture line reinforced with felt. The indication for surgery for all of the patients who had reinforcement of the distal or proximal suture lines was AI or combined AI and aortic stenosis. In 8 patients (11%), the ascending aorta was larger than the pulmonary autograft and a wedge of tissue was excised from the ascending aorta before anastomosis of the distal autograft. In 3 patients (4%), the ascending aorta was smaller that the pulmonary autograft, and an incision was made in the anterior portion of the ascending aorta to accommodate the larger pulmonary autograft.

A total of 78 concurrent procedures were performed in 40 patients (54%). Of the 41 patients with isolated aortic valve disease, 7 (17%) required a concurrent aortic annulus enlargement procedure to accommodate the size of the larger pulmonary autograft (21). A concurrent Konno procedure was performed in 26 of the 33 patients (79%) with complex left heart disease. Other concurrent procedures in patients with complex left heart disease included subaortic membrane resection (n = 11), mitral valve replacement or repair (n = 7), ventricular septal defect (VSD) repair (n = 6), arch augmentation (n = 4), apical aortic conduit division (n = 3), and other procedures (n = 14).

At the time of the Ross procedure, a valved pulmonary homograft was used in 69 patients (93%) to reconstruct the right ventricular outflow tract. In the other 5 patients, an aortic homograft was used.

**Follow-up.** Median follow-up was 4.7 years (range 3 months to 9.3 years). All patients had a discharge echocardiogram. The median number of follow-up echocardiograms was 3 (range 1–18). Table 1 shows the population characteristics. No statistical difference was found between our study cohort of 74 patients and the patients who were excluded from our analysis, for the characteristics listed in Table 1. Our study population included a significant number of neonates and infants (15% < 1 year of age at the time of Ross) and patients with complex left heart disease (n = 33, 45%). The Ross procedure was the first intervention in a minority of patients (n = 19, 26%). Table 2 displays the 110 procedures performed before the Ross operation. The most common prior procedure was balloon valvotomy in 24 patients (32%).

**Results**

**Population characteristics.** Between January 1995 and December 2003, 119 patients underwent the Ross procedure at our institution. Early mortality (< 30 days) was 2.5% (n = 3). Two patients with complex disease died in hospital; one patient had severe postoperative ventricular dysfunction and the other had ventricular tachycardia and cardiac arrest. The third patient had isolated aortic valve disease and died soon after hospital discharge. Dehiscence of the neo-aortic root was identified at autopsy. There were 2 late deaths (1.7%). Both patients had complex left heart disease with LV and/or mitral valve hypoplasia, resulting in pulmonary hypertension and severe right ventricular dysfunction. Of the 114 survivors, 74 (65%) had a discharge echocardiogram and at least 1 follow-up echocardiogram at our institution during the follow-up period and constitute our study population. Patients referred for surgery who did not receive follow-up care at our institution (n = 30) were not included.

Patient characteristics are shown in Table 1. No statistical difference was found between our study cohort of 74 patients and the patients who were excluded from our analysis, for the characteristics listed in Table 1. Our study population included a significant number of neonates and infants (15% < 1 year of age at the time of Ross) and patients with complex left heart disease (n = 33, 45%). The Ross procedure was the first intervention in a minority of patients (n = 19, 26%). Table 2 displays the 110 procedures performed before the Ross operation. The most common prior procedure was balloon valvotomy in 24 patients (32%).

**Surgical indications and technique.** The indication for the Ross procedure was a combination of aortic stenosis and neo-AI, along with other variables with a p value ≤ 0.1 in univariate analysis, were used for multivariate analysis (Table 1). Of note, neo-AI was not used as a variable in the multivariate model for reintervention, because it was believed to be an indication for reintervention. Paired t test and Fisher exact test were used to compare LV size and function before and after the Ross procedure, respectively. A p value < 0.05 was considered statistically significant.

### Table 1 Population Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 yr</td>
<td>9 yrs (3 days–34 yrs)</td>
</tr>
<tr>
<td>Male</td>
<td>55 (74%)</td>
</tr>
<tr>
<td>Complex left heart disease vs. isolated aortic valve disease</td>
<td>33 (45%)</td>
</tr>
<tr>
<td>Patients with procedures prior to Ross</td>
<td>55 (74%)</td>
</tr>
<tr>
<td>Primary indication for Ross</td>
<td></td>
</tr>
<tr>
<td>Combined AS/AI</td>
<td>51 (69%)</td>
</tr>
<tr>
<td>AI</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>AS</td>
<td>10 (13%)</td>
</tr>
</tbody>
</table>

AI = aortic insufficiency; AS = aortic stenosis.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>110 in 55 Patients</th>
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</thead>
<tbody>
<tr>
<td>Balloon valvotomy</td>
<td>24</td>
</tr>
<tr>
<td>Surgical valvotomy</td>
<td>20</td>
</tr>
<tr>
<td>VSD repair</td>
<td>10</td>
</tr>
<tr>
<td>Coarctation repair/dilation</td>
<td>10</td>
</tr>
<tr>
<td>Surgical valvuloplasty</td>
<td>7</td>
</tr>
<tr>
<td>Subaortic membrane resection</td>
<td>7</td>
</tr>
<tr>
<td>Recoarctation repair/dilation</td>
<td>5</td>
</tr>
<tr>
<td>Apical aortic conduit</td>
<td>3</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>2</td>
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<tr>
<td>Interrupted aortic arch repair</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
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VSD = ventricular septal defect.
grams was 5 (range 1 to 10). Median age at most recent follow-up was 14.8 years (range 1.1 to 42.3 years).

Neo-aortic root dilation. Results from an independent review of neo-aortic root measurements by a second echocardiographer showed an intra-class correlation coefficient of 0.81. Dimensions of the neo-aortic root complex increased significantly throughout the follow-up period: annulus 0.09 cm/year, root 0.18 cm/year, and sinotubular junction 0.18 cm/year (p < 0.0001 for all). As shown in Figure 2, this enlargement was out of proportion to changes in body surface area, as there was also a significant increase in z-scores over time for all 3 measurements: annulus 0.31/year, root 0.75/year, and sinotubular junction 0.59/year (p < 0.0001 for all). At 6 years after the Ross procedure, freedom from neo-aortic root z-score >4 was 3%, and root z-score >8 was 35% (Fig. 3). Predictors of neo-aortic root dilation are displayed in Table 3. In multivariate analysis, longer follow-up time (p < 0.0001) and isolated aortic valve disease (vs. complex left heart disease, p = 0.035) were significant predictors of neo-aortic root dilation.

Neo-AI. Figure 4 displays progression of neo-AI from discharge to most recent follow-up echocardiogram. During the follow-up period, 27 (36%) patients had progression of ≥1 grade of neo-AI, and 11 (15%) patients ≥2 grades. At most recent echocardiogram 18 (24%) patients had moderate or greater neo-AI compared with 1 patient at discharge (p < 0.0001). At 6 years after the Ross procedure, freedom from moderate or greater neo-AI was 60% (Fig. 3). Predictors of progressive neo-AI are shown in Table 3. In multivariate analysis, prior aortic valve replacement (p = 0.002) and prior VSD repair (p = 0.02) were significant predictors of progressive neo-AI. Neo-aortic root dilation was not a significant predictor in univariate or multivariate analysis.

Neo-aortic reintervention. Nine patients underwent neo-aortic reintervention at median 2.8 years (range 1.1 to 9.5 years) following the Ross procedure (Table 4). Seven patients with severe neo-AI underwent neo-aortic valve replacement: mechanical valve (n = 4) and homograft (n = 2) or neo-aortic valvuloplasty (n = 1). One patient had only mild neo-AI but progressive dilation of the neo-aortic root (sinus dimension 6.4 cm at the time of reintervention) and underwent valve sparing root replacement 9.5 years after the Ross procedure. Finally, there was 1 patient who developed a pseudoaneurysm at the proximal suture line of pulmonary autograft and underwent pseudoaneurysm resection. At 6 years after the Ross procedure,
freedom from neo-aortic reintervention was 88% (Fig. 3). Predictors of neo-aortic reintervention are displayed in Table 3. In multivariate analysis, VSD repair before the Ross procedure (p = 0.03) was a significant predictor of neo-aortic reintervention. Trends were seen for patients with an original diagnosis of AI (p = 0.06), and longer cardiopulmonary bypass time (p = 0.06).

Left ventricular dimensions and function. Although mean shortening fraction was slightly less after the Ross procedure (37 ± 10% vs. 35 ± 7%, p = 0.04), there was no difference in the proportion of patients with a shortening fraction <28% before and after the Ross procedure (12% vs. 12%, p = NS). Before the Ross procedure, mean LV end-diastolic dimension was 4.9 ± 1.6 cm with a mean z-score of 1.5 ± 1.4. The proportion of patients with a LV end-diastolic dimension z-score >2 was 43%. At follow-up, LV end-diastolic dimension was 4.9 ± 1.1 cm. Mean LV end-diastolic dimension z-score (0.8 ± 0.9), and the proportion of patients with a z-score >2 (18%) had significantly decreased (p < 0.01).

Discussion

After the Ross procedure, neo-aortic root size increases significantly out of proportion to somatic growth. Neo-AI is also progressive, with nearly one-quarter of patients developing moderate or greater neo-AI during the follow-up period. Thus far, neo-aortic reintervention has been performed in 12% of patients. Neo-aortic root dilation is not associated with significant neo-AI or reintervention at mid-term follow-up. Prior interventions such as aortic valve replacement and VSD repair predicted neo-AI and reintervention after the Ross procedure.

Prior studies of the pediatric Ross population have shown dilation of the neo-aortic root at the level of both the neo-aortic annulus and sinus in the early postoperative period (3,5,6,12). Our study is the first to evaluate pediatric Ross patients through midterm follow-up and shows progressive dilation, out of proportion to somatic growth, at the...
level of neo-aortic root annulus, root, and sinotubular junction; with the change in the neo-aortic sinus being most prominent. Our findings are similar to data in adults, with a prior study showing freedom from neo-aortic root dilation of only 45% at 7-year follow up (17).

In multivariate analysis, we found that longer follow-up time was the strongest predictor of neo-aortic root dilation. Age at the time of the Ross procedure and the presence of pre- or postoperative aortic or neo-AI were not predictors of neo-aortic root dilation. Although some studies have suggested that early postoperative dilation of the neo-aortic root stabilizes over time, our data show continued dilation throughout the follow-up period (5,13). Progressive dilation over time may be explained by the histologic findings of early damage and granulation tissue found in the walls of explanted autograft specimens, which progresses to scarring and focal loss of normal muscle cells, elastin, and collagen 3 to 6 years after the Ross operation (22).

Interestingly, we also found that isolated aortic valve disease (vs. complex left heart disease) was a significant predictor of neo-aortic sinus dilation in multivariate analysis. We hypothesize that the presence of multiple left-sided obstructive lesions or shunt lesions in those with complex left heart disease may result in elevated pulmonary artery pressures before the Ross operation, such that the native pulmonary valve may be better adapted to higher pressures when it is transitioned to the pulmonary circulation at the time of the Ross operation, and that the cellular level changes in wall structure of the pulmonary autograft may not be as pronounced.

Our study also showed progressive neo-AI following the Ross procedure. At 6 years after the Ross procedure, freedom from moderate or greater neo-AI was 60% and from neo-aortic reintervention was 88%. The majority of neo-aortic reinterventions were performed because of severe neo-AI. Other studies have documented 10-year freedom from significant neo-aortic regurgitation ranging from 75% to 90% following the Ross procedure, with re-intervention rates of up to 10% at 10-year follow-up (14–16). In multivariate analysis, we found aortic valve replacement and VSD repair before the Ross procedure were significant predictors of progressive neo-AI. The VSD repair before the Ross operation was also a significant predictor of neo-aortic reintervention, and a trend toward greater risk of reintervention was seen for patients with an original diagnosis of AI. We hypothesize that VSD repair (particularly when the VSD is close to the native pulmonary valve) may result in subtle abnormalities of the pulmonary valve apparatus that manifest when the pulmonary autograft is transitioned to the systemic circulation. In one of our patients who underwent VSD repair before the Ross procedure, a suture in the pulmonary valve annulus was noted at the time of Ross, with no pulmonary insufficiency. After the Ross procedure, he developed progressive neo-AI and underwent early reintervention.

Factors affecting the structure and dimensions of the neo-aortic root (original diagnosis of AI and aortic valve replacement before the Ross operation) were also significant predictors of neo-AI or reintervention in our study. Elkins et al. (16) also showed that those with a diagnosis of AI are at increased risk for neo-aortic reintervention following the Ross procedure. The relationship between the dimensions of the native aortic root and pulmonary autograft has been shown to be important in patients undergoing the Ross procedure; a mismatch may lead to pulmonary autograft failure (23–25). Long-standing AI or aortic valve replacement before the Ross procedure likely affects the dimensions of the aortic root and may make a subsequent Ross procedure more challenging.

Neo-aortic valvuloplasty and valve replacement with homograft or mechanical valve were utilized in our study for neo-aortic reintervention. At our center, neo-aortic valvuloplasty is generally considered as the first option. If this is not possible, mechanical valve replacement is performed. In females, a homograft may be used in order to avoid anticoagulation during childbearing years.

Neo-aortic root dilation was not associated with neo-AI or reintervention in our study, suggesting that the mechanisms of neo-AI and neo-aortic root dilation after the Ross procedure may be different. Although prior studies have shown structural damage to the wall of the pulmonary autograft, the structure of pulmonary autograft leaflets appears to evolve toward that of normal aortic valve leaflets, with thickening of autograft cusps due to cell proliferation and/or progenitor cell recruitment, change in the expression pattern of endothelial cells to resemble a normal aortic valve phenotype, and remodeling of the extracellular matrix (22). Thus, the structural damage of the autograft walls may lead to neo-aortic root dilation, without significant neo-AI owing to adaptation of the leaflets to the systemic circulation. However, it is possible that continued neo-aortic root dilation may lead to coaptation defects and more significant neo-aortic root insufficiency as patients are followed over longer periods of time.

Reintervention after the Ross procedure because of neo-aortic root dilation in association with significant neo-AI has been reported (26,27), including valve sparing root replacement, prosthetic valve replacement, and reduction of the neo-aortic root. However, less is known concerning the appropriate indications for reintervention because of neo-aortic root dilation alone and the associated risk of rupture or dissection. In adults with Marfan syndrome, an aortic root diameter of >5 cm and progressive increase in root size have been found to be risk factors for aortic dissection and rupture, and are used as indications for surgical intervention (28). Similar guidelines have yet to be developed in Ross patients. The patient who underwent reintervention at our institution had progressive neo-aortic root dilation and a dimension of 6.4 cm at the time of reintervention. In adults, different operative techniques, such as the inclusion cylinder technique where the autograft is implanted inside the native aortic root, have been reported to be associated with less neo-aortic root dilation after the Ross operation (29). This technique has limited applicability in pediatric patients, where the pulmonary autograft is larger than the native
aortic annulus in many cases and the use of an inclusion technique may compromise valve function.  

**Study limitations.** This was a single-center study, and results may not be applicable to all patients undergoing the Ross procedure. Only the subset of patients with serial echocardiographic data available at our institution was included in this study. However, selection bias is likely minimal, given similar baseline characteristics to the Ross patients who were excluded. Although there may have been some variation in the echocardiographic measurements of the neo-aortic root, an independent review of measurements showed good correlation. Our study did not assess native aortic and pulmonary root sizes to evaluate for mismatch. Finally, given the relatively low prevalence of reintervention, it is possible that additional risk factors may be identified as the prevalence increases.

**Conclusions**

The Ross operation remains a palliative procedure for aortic valve disease. Over a median follow-up of nearly 5 years after the Ross procedure, neo-aortic root size increases significantly out of proportion to somatic growth, and neo-AI is progressive, with nearly one-quarter of patients developing moderate or greater neo-AI. Neo-aortic reintervention was required in 12% of patients. We did not identify an association between neo-aortic root dilation and neo-AI or reintervention at mid-term follow-up. Prior anatomic alteration of the aortic root because of aortic valve replacement or AI and VSD repair before the Ross procedure were associated with neo-AI and reintervention. Longer follow-up may reveal different risk factors and a higher incidence of reintervention.

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**REFERENCES**