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Patient Age at the Ross Operation in Children Influences Aortic Root Dimensions and Aortic Regurgitation

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Abstract

Background: The Ross operation provides the advantage of growth potential of the pulmonary autograft in the aortic position. However, development of autograft dilatation and regurgitation may occur. We sought to assess the progression of autograft diameters and aortic regurgitation (AR) with regard to patient age at the time of the Ross operation. **Methods:** Autograft echo dimensions from 48 children <16 years of age at the time of the Ross operation, who had follow-up echocardiograms at <20 years of age, were analyzed using hierarchical multilevel modeling. The z values of autograft dimensions were calculated according to the normal aortic dimensions. Mean follow-up was 5.1 $\pm$ 3.3 years. The mean age at the time of the Ross operation was 10.0 $\pm$ 4.3 years. **Results:** The mean *z* values of all patients showed a significant increase with follow-up time at the sinus (0.5 $\pm$ 0.1/year, $P <$ .001) and the sinotubular junction (0.7 $\pm$ 0.2/year, $P <$ .001) but not at the annulus (0.1 $\pm$ 0.1/year, $P =$ .59). There was no significant difference in the *z* values of sinus and the sinotubular junction between younger and older children at implantation and with time. The initial annulus *z* value was significantly larger in younger children ($P <$ .0001), whereas the annual increase was significantly higher in older children ($P =$ .021). Age at operation has no impact on the initial AR grade ($P =$ .60). The AR tends to increase more quickly in older patients ($P =$ .040). Sinus and sinotubular junction dilate with time, regardless of patient age. **Conclusions:** Young children show larger initial annulus sizes than older children. However, annulus diameters tend to normalize in young children, whereas they increase in older children. Autograft regurgitation develops slowly, but significantly, and predominantly in older children. Stabilizing measures to prevent autograft root dilatation are warranted in adolescents, but they are not required in young children.

Keywords

aortic root, aortic valve replacement, valve lesions, heart valve, autograft, pediatric

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Introduction

The autograft pulmonary valve may be the ideal substitute for the aortic valve in children because of its alleged growth potential.[1,2] Therefore, it is the procedure of choice for aortic valve replacement in children presenting with congenital heart disease[3] and rheumatic valve disease.[4] However, there may also be pathologic autograft dilatation in children, that is dilatation out of proportion to somatic growth.[5-9] In a previously published study, we analyzed longitudinal echocardiographic data of a pediatric Ross-operated population. We were able to show that the annulus matches somatic growth; however, the diameters of the sinus and the sinotubular junction increase significantly relative to somatic growth.[8] In adolescents and adults,

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stabilizing measures are required to prevent autograft dilatation and regurgitation.[10-12] In small children, stabilizing the root is unfavorable since it prevents growth and may lead to stenosis. The present study was conducted to reveal the impact of age at the time of the Ross operation on autograft diameters and regurgitation in children.

Patients and Methods

Study Population and Operative Data

Data from the Dutch–German Ross Registry database were analyzed. The data set of the present analyses has been previously evaluated to determine regression equations for the development of autograft dimensions and autograft regurgitation with time.[8] Now we allowed for the intercept and the slope to vary with patient age at the time of the Ross operation. All patients <16 years of age at the time of the Ross operation, who had follow-up echocardiograms were included into the study. Echocardiographic data from patients >20 years of age at the time of the examination were excluded. The study population included patient data from four departments of cardiac surgery in Germany and one department of cardiac surgery in the Netherlands. The Ross operations were performed between October 1988 and October 2006. The follow-up data from each center were taken into the database and subsequently a common systematic, prospective registry was started in January 2002. The responsible surgeon at each center determined the surgical technique. Root replacement was performed in 44 patients, and the subcoronary technique was applied in 4 patients. Nine patients underwent modifications of the autograft implantation technique for size matching purpose. Patients'characteristics and operative data are listed in Tables 1, 2, and 3. Details of the operative techniques have been described elsewhere.[13-15] Institutional review board approval was obtained to conduct this prospective follow-up study for which a need for patients to provide their informed consent was waived. The authors had full access to the data and took full responsibility for the integrity of the data.

Clinical Follow-Up

All hospital survivors were enrolled in this ongoing follow-up assessment by means of physical examination in conjunction with echocardiographic evaluation. Follow-up investigations were scheduled at discharge and on a yearly basis thereafter. Due to the widespread origin of the patients and to support the adherence to the program, complete clinical and echocardiographic examinations (documented on videotapes) from the referring cardiologists were also accepted.

Echocardiographic Data Acquisition and Measurements

Autograft dimensions were measured as described by Roman et al[16] at three different levels: annulus at the level of the autograft leaflet hinges, sinus of Valsalva at the largest anteroposterior diameter, and sinotubular junction (supraaortic ridge level) at the distal rim of the sinuses of Valsalva. The z values of autograft dimensions were calculated according to the regression equations published by Daubeney et al[17] based on the body surface area and echocardiographic measurements. Aortic regurgitation (AR) was assessed by multiple techniques with the parasternal long axis and apical five-chamber view. Pulsed wave Doppler and color flow Doppler imaging were used for mapping the left ventricular outflow tract, including determination of the ratio of jet height to left ventricular outflow tract height. Continuous Doppler imaging was applied to measure the deceleration slope and pressure half-time of the autograft regurgitation jet. The AR was graded using standard criteria in a majority of the examinations.[18] Since it is a multicenter study, the final decision of AR grading was left to the decision of the responsible echocardiographer's preference and experience, and regurgitation severity was reported on a scale of grade 0 to 4. Trace (trivial) aortic insufficiency defined as a very tiny regurgitation jet in early diastole near the detection limit was included in the analysis as grade 0.5. We analyzed a total number of 129 measurements of the neoaortic root dimensions from 48 patients and a total number of 403 measurements of the neo-AR from 135 patients. Mean duration of the echocardiographic follow-up was 5.1 $\pm$ 3.3 years (range 0.2-15 years) for the measurements of the dimensions, and 4.4 $\pm$ 2.4 years (range 0.2-15 years) for the measurements of the neoaortic regurgitation.

Statistical Analysis

Frequencies are given as absolute numbers and percentages. Continuous data are expressed in terms of the mean and standard deviation. Statistical analysis of clinical variables and initial fitting was performed using SPSS 16.0. The echocardiographic data of two or more echocardiographic observations per patient were analyzed by using a hierarchical multilevel linear model (MLWin 2.0, Centre for Multilevel Modeling, London, United Kingdom). This model provides a linear regression line with an intercept and slope for each individual patient. The intercept ($\pm$ standard error) corresponds to the notional value at the time of surgery; the slope ($\pm$ standard error) represents the annual progression of these measurements.[19] The probability of freedom from events was estimated according to the Kaplan-Meier method. The time of the Ross operation was designated as time zero. Freedom-from-event curves were compared using the log-rank test.

Results

Population Characteristics

Demographic data, prior palliative operations, and modifications of the Ross operation are listed in Tables 1, 2, and 3.

Development of the Diameters of the Neoaortic Root With Follow-Up Time

A total 129 measurements of the neoaortic annulus, 96 measurements of the sinus, and 64 measurements of the sinotubular junction of the 48 patients were analyzed. Figure 1 depicts a

Table 1. Population Characteristics.

	n = 48
Median age (range)	10.0 years (54 days - 15 years)
Male	33 (69%)
Median weight	35.5 kg (4.0 - 73 kg)
Complex heart disease versus isolated aortic valve disease	6 (13%)
Patients with procedures prior to Ross	23 (48%)
Primary indication for Ross	
Combined AS and AR	25 (52%)
AR	7 (15%)
AS	16 (33%)
Ethiology of aortic disease	
Congenital	39 (81%)
Myxomatous degeneration	4 (8%)
Endocarditis	5 (10%)

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis.

plot of z values against follow-up time; a smooth curve has been added to indicate the underlying trend. It seems that there is a tendency for the z values to be positive and, possibly, to increase in a fairly linear fashion with follow-up time. Hence, the best fitting regression model to study changes in z values with time was a linear model with the term:

$$\text{Diameter } z \text{ value } (t) = (\text{Initial } z \text{ value} \pm \text{SE}) + (\text{Annual increase of } z \text{ value} \pm \text{SE}) \times \text{time(yr)}.$$

Hence, the terms to estimate changes in z values over time (t) were:

$$\text{Annulus } z\ (t) = (1.5 \pm 0.4) + (0.1 \pm 0.1) \times t,$$
$$\text{Sinus } z\ (t) = (2.5 \pm 0.4) + (0.5 \pm 0.1) \times t,$$
$$\text{Sinotubular junction } z\ (t) = (2.6 \pm 0.9) + (0.7 \pm 0.2) \times t.$$

The z values of the diameters were larger compared to healthy patients ($P < .001$, all). The z values showed a significant increase with follow-up time at the level of the sinus ($P < .001$) and the sinotubular junction ($P < .001$) but not at the annulus ($P = .59$, Figure 2).

The terms to estimate changes in z values over time for a certain patient age at the operation (a) were:

$$\text{Annulus } z\ (t,\ a) = (5.0 \pm 0.8) + (-0.5 \pm 0.3) \times t + (-0.4 \pm 0.1) \times a + (0.1 \pm 0.03) \times t \times a,$$

$$\text{Sinus } z\ (t,\ a) = (3.6 \pm 0.8) + (-0.5 \pm 0.3) \times t + (-0.1 \pm 0.1) \times a + (0.01 \pm 0.03) \times t \times a,$$

$$\text{Sinotubular junction } z\ (t,\ a) = (4.0 \pm 2.6) + (0.7 \pm 0.7) \times t + (-0.1 \pm 0.2) \times a + (0.004 \pm 0.06) \times t \times a.$$

Table 2. Palliative Procedures Prior to Ross Operation.

	36 in 24 patients
Balloon valvulotomy	11
Surgical valvulotomy	13
VSD repair	2
Coarctation repair/dilatation	3
Surgical valvuloplasty/replacement	3
Subaortic membrane resection	4

Abbreviation: VSD, ventricular septal defect.

Table 3. Modifications of the Ross Operation.

	n = 48
Root replacement	44 (92%)
Subcoronary implantation	4 (8%)
Annulus enlargement	5 (10%)
Replacement of ascending aorta	2 (4%)
Aortoplasty	3 (6%)

Accordingly, the initial z value decreased with increasing age at the level of the annulus ($P < .0001$) but not at the level of the sinus ($P = .12$) and the sinotubular junction ($P = .56$). There was a significant annual increase in the z value with increasing age in regard to the annulus ($P = 0.021$) but not in regard to the sinus ($P = .84$) and the sinotubular junction ($P = .95$).

For example, the annulus of a neonate immediately after the Ross operation was larger than the annulus of a 14-year-old adolescent but the dimension normalized with time. In contrast, the annulus of a 14-year-old adolescent immediately after the Ross operation was approximately normal, but it dilated out of proportion with time. The annulus dimensions of a five-year-old child are larger than normal but match somatic growth (Figure 3A). Age at the time of the Ross operation did not impact the initial and the annual increase in the sinus and the sinotubular junction dimensions (Figure 3B and 3C).

Aortic Regurgitation With Time in the Total Study Group

A total number of 403 measurements of the 135 patients were available for analyses. A linear model was chosen to model AR over time:

$$\text{AR grade} = (\text{Initial AR} \pm \text{SE}) + (\text{Annual increase of AR} \pm \text{SE}) \times \text{time (yr)}.$$

Hence, the term to estimate AR over time was:

$$\text{AR grade} = (0.69 \pm 0.05) + (0.06 \pm 0.02) \times \text{time}.$$

There was a slow but significant increase in the grade of AR with follow-up time (0.06 ± 0.02 grade/year, $P < 0.001$, Figure 4A).

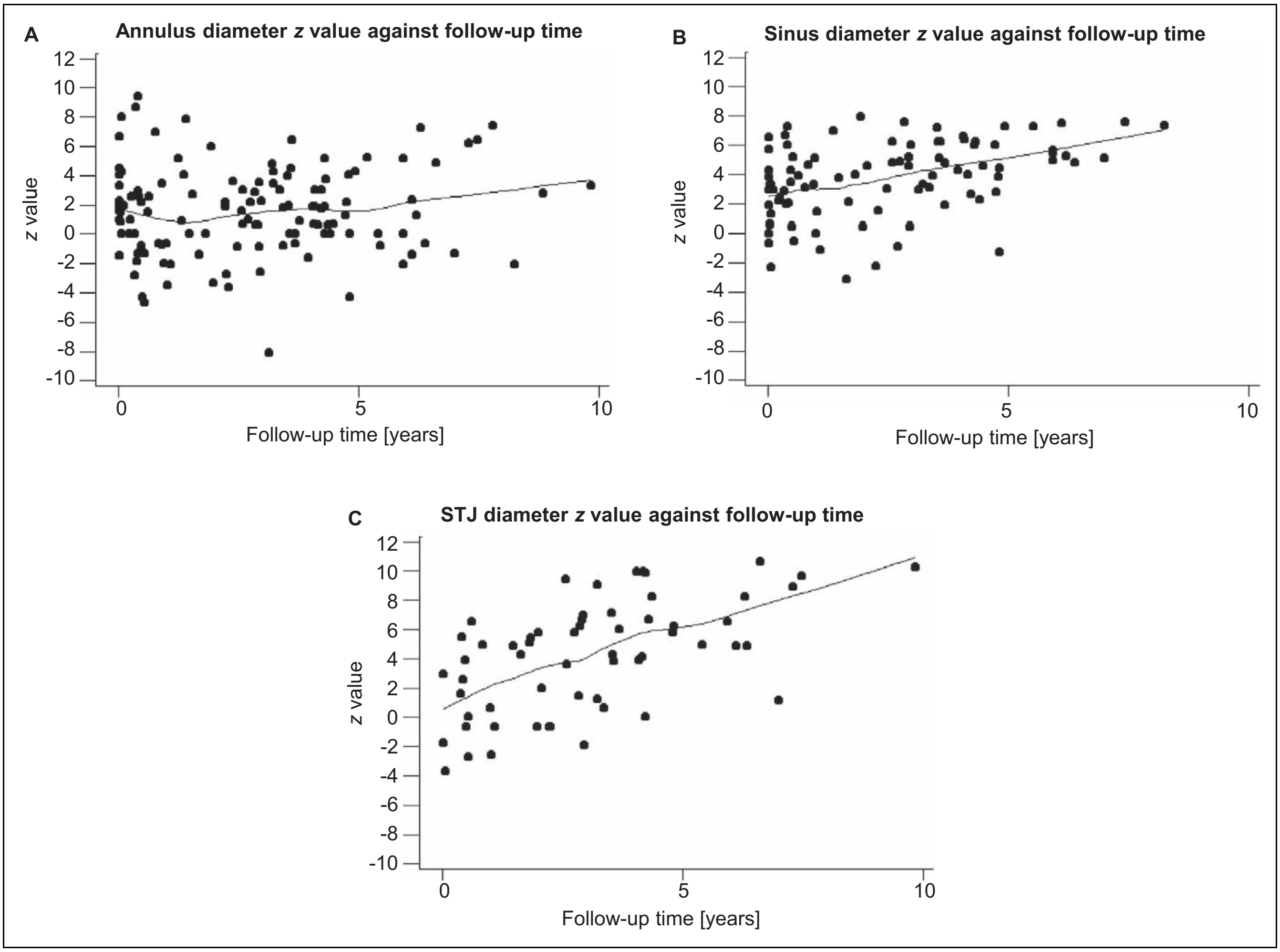

Figure 1. Scatter plot of z values of the aortic annulus (A), sinus (B), and sinotubular junction (STJ) (C) against follow-up time. The smooth curve indicates the underlying trend.

The term to estimate changes in AR grade over time for a certain patient age at the operation (a) was:

$$\text{AR grade} = (0.73 \pm 0.10) + (-0.001 \pm 0.03) \times t + (-0.006 \pm 0.01) \times a + (0.007 \pm 0.003) \times t \times a.$$

There is no significant evidence that age at operation is affecting the initial AR grade ($P = .60$). There is a marginally significant evidence that AR grade tends to increase more quickly after operation for older patients ($P = .040$, Figure 4B).

During follow-up, five patients required autograft explantation for aortic regurgitation. According to the regression equation, the annulus dimensions of a five-year-old child matches somatic growth during follow-up. Therefore, the freedom from autograft explantation curves is stratified for children less than and more than five years of age at the time of the Ross operation (Figure 5). There is no significant difference in freedom from autograft explantation between both the groups ($P = .291$). However, all reoperations were performed in children more than five years of age at the time of the Ross operation.

Discussion

Dilatation and regurgitation of the autograft valve is a major concern following the Ross operation in children[5-7] and in adults.[20,21] Stabilizing techniques to prevent failing of the autograft are efficacious in adolescents and adults.[10-12] In small children, stabilizing the autograft is disadvantageous, since it prevents the growth of the valve. Our data show that stabilizing the annulus is not required in small children and that it is warranted in adolescents.

In the present study, the mean initial diameters of the aortic annulus immediately after implantation are already larger than that in healthy children. This is not surprising, since the pulmonary autograft is usually larger than the aortic valve. Tantengco and colleagues observed a mean z value of the annulus of 1.4 after autograft implantation.[22] Our data support this observation, the mean z value of the annulus in the present study being 1.5. Our data reveal that age at the time of the Ross operation has a major impact on the initial annulus size. According to the present regression equations, a neonate presents with an annulus z value of 5. A 14-year-old adolescent

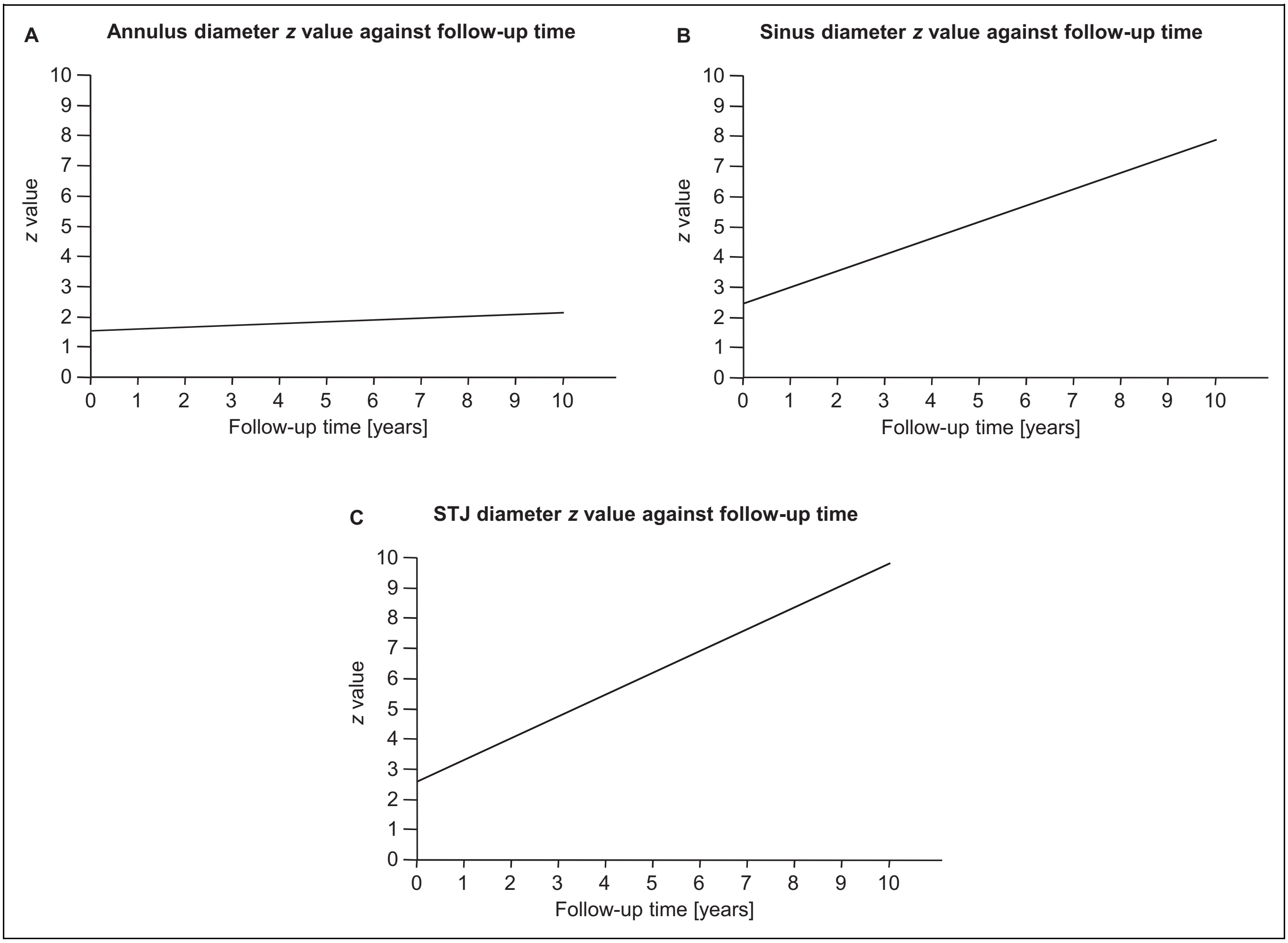

Figure 2. Diagram of z values of the aortic annulus (A), sinus (B), and sinotubular junction (STJ) (C) against follow-up time.

in contrast shows almost normal dimensions immediately after autograft implantation.

Hence, neonates seem to have larger autografts than older children. In some small children, the autograft may already be relatively large preoperatively due to increased pulmonary blood flow in the presence of a left-to-right shunt. In the present study, older children did not exhibit shunt lesions. Another potential explanation for large annulus sizes in neonates may be the immediate dilatation of the pulmonary autograft when transferred into the systemic circuit.[22] This effect may be more distinctive in small children due to the delicate tissue. An excess of immediate dilatation may result in regurgitation. However, in the present study, neonates did not exhibit higher grades of AR than older children initially after the operation.

Despite these large annulus dimensions in neonates, we dissuade from stabilizing the annulus in small children. It is potentially disadvantageous since it prevents growth, and, according to the present data, it is not necessary. We observed a significant decrease in annulus *z* values with time, in small children. According to the regression equations, the annulus of a neonate is normal ten years after the Ross operation. In addition, there is evidence that AR does not develop in small children. In contrast, in adolescents we observed an increase in annulus *z* values with time and an increase in AR with time. All reoperations for AR in the present study were required in children of more than 5 years of age at the time of the Ross operation.

Lower systemic pressure in smaller children may be protective for annulus dilatation. This may be a potential explanation for the decrease in annulus *z* values with time, in small children. Hence, aggressive postoperative control of blood pressure seems reasonable to avoid any arterial hypertension after the Ross operation.[23]

The literature provides coherent data with regard to the development of sinus and sinotubular junction dimensions with time. Pasquali and colleagues,[7] Kouchoukos and colleagues,[9] and Solowiejczyk and colleagues[6] observed dilatation of the sinus and the sinotubular junction. This is in line with our observations. In the present study, we observed dilatation of the sinus and the sinotubular junction irrespective of the age at the time of surgery.

The literature provides incoherent data with regard to the development of annulus dimensions with time. According to our data, the development of annulus dimensions is age dependent in children. However, this does not explain the different

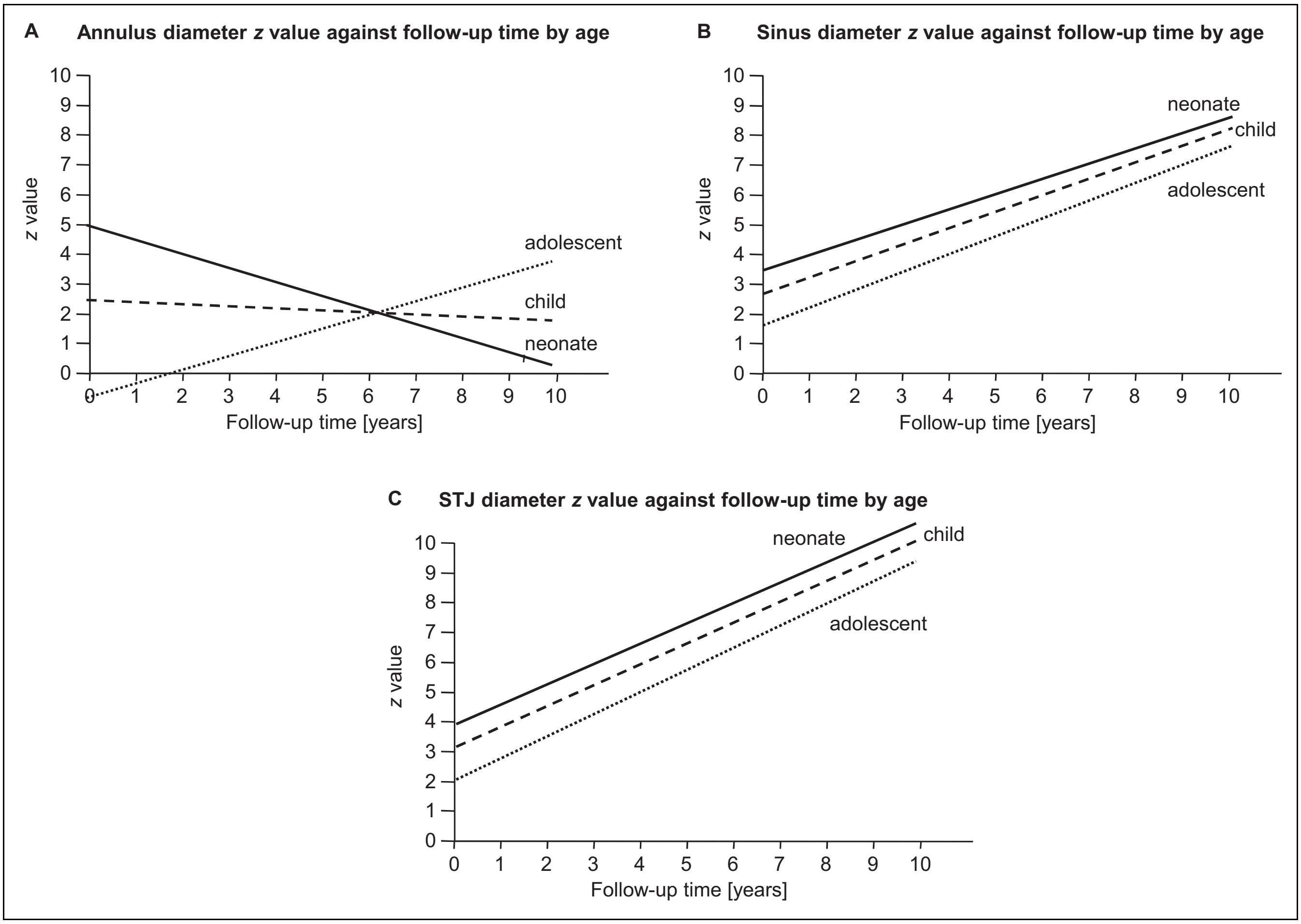

Figure 3. Diagram of z values of the aortic annulus (A), sinus (B), and sinotubular junction (STJ) (C) against follow-up time for a neonate, a 5-year-old child, and a 14-year-old adolescent.

observations of Pasquali, Kouchoukos, and Solowiejczyk and colleagues. Kouchoukos and colleagues observed no increase in the annulus dimensions over time in a relatively old pediatric cohort with a mean age of 31 years at the operation.[9] In contrast, Pasquali and colleagues demonstrated a significant increase in the *z* values of the annulus in patients with a mean age of 9 years at the time of operation.[7] Solowiejczyk and colleagues observed a minimal change in the *z* scores of the annulus in patients with a median age of 8 years at the time of operation.[6] From our data, we would have expected an increase in annulus dimensions in the relatively old cohort of Kouchoukos and colleagues. The mean patient age in the cohorts described by Pasquali and Solowiejczyk and colleagues are similar to the present population. Therefore, we would have expected no significant annular dilatation.

With regard to the literature, it is not possible to judge the impact of age at the time of implantation on autograft dilatation since several autograft implantation techniques (root replacement, root inclusion, subcoronary technique) and root enforcement techniques were applied. These modifications prevent autograft dilatation and regurgitation.[10-12] In the present cohort, a subcoronary implantation was performed only in four adolescents. In the remainder, a root replacement was performed. The regression equations for the development of autograft dimensions and autograft regurgitation with time have been published previously.[8] In this data set, the four patients who underwent subcoronary implantation of the autograft have been included. As the present analyses refers to these models, the four patients were also included in the present analyzes. One of these patients was 13 years old at the time of surgery, and the other three were 15 years old. The subcoronary implantation has been shown to reduce autograft dilatation.[11] Even so, the present analysis is a significant evidence that the annulus dimensions increase in older children. Hence, exclusion of the four patients would most likely confirm the results. The real extent of annular dilatation in adolescents following root replacement may be underestimated. In the present cohort, an annulus enlargement was performed in only five children. This modification may have an impact on the development of autograft dimension. The aim of the present study was to assess the impact of age at the time of the Ross operation. Further studies, with larger number of patients, are warranted to validate the statistic methodology, including other potential risk factors for autograft dilation and neoaortic regurgitation.

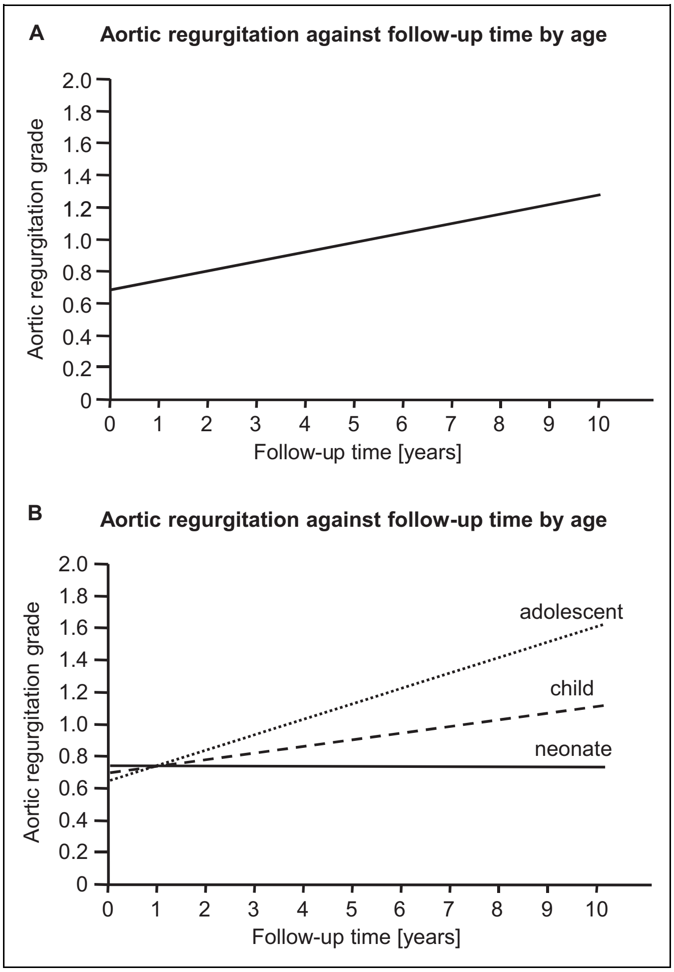

Figure 4. Diagram aortic regurgitation against follow-up time (A), and plot aortic regurgitation against follow-up time for a neonate, a 5-year-old child, and a 14-year-old adolescent (B).

In conclusion, young children show larger initial annulus sizes than older children. However, annulus diameters tend to normalize in young children, whereas they increase in older children. Autograft regurgitation develops slowly, but significantly, and predominantly in older children. Stabilizing measures to prevent autograft root dilatation are warranted in adolescents, but they are not required in young children.

Study Limitations

The study design was a retrospective follow-up study covering a long period of patient inclusion. Changes in preoperative, operative, and postoperative management may have affected the outcome parameters in a way not covered by our analysis. The comparability of the echocardiographic findings at the time of final follow-up is limited, since these data were obtained by various pediatric cardiologists in different outpatient clinics. Four patients with the use of the subcoronary technique, five patients with various techniques of annular enlargement, and two patients who underwent replacement of the ascending aorta were included. These modifications of the Ross operation may have an impact on AR grade and root dimension. However, due to the small number of patients, a meaningful subanalysis was not possible.

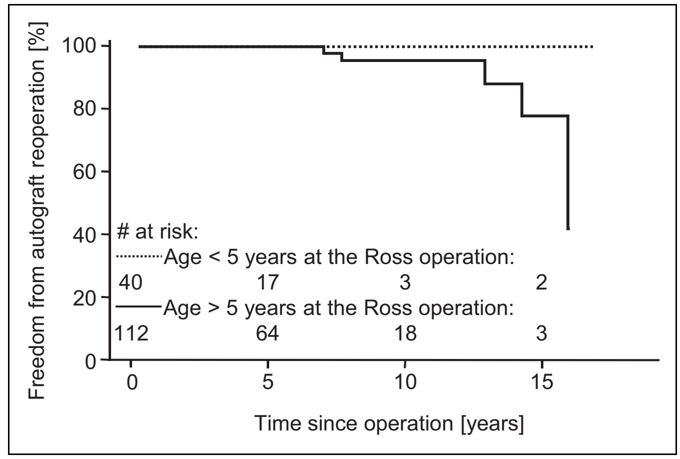

Figure 5. Freedom from reoperations of the autograft in patients less than and more than 5 years of age, at the time of the Ross operation.

There are limitations rising from mixed models that have to do mostly with their use on the underlying data. Some of the limitations may have to do with the assumptions of linear modeling. Especially, for mixed models several levels of errors are assumed. However, there are procedures to check for the validity of these assumptions. As in every model, there can be other unknown sources of explainable variance. Also, increasing number of levels or random effects leads to an increase in assumptions, complexity of the algorithms, and the complexity of interpretation of the coefficients at various levels. This is not a case in the present analysis, since we use only random patient intercepts and slope. The main limitation of mixed models when used in the appropriate setting (appropriate data, validity of assumptions) is the complexity of the computation procedure and the complexity of reporting models with numerous levels.

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Declaration of Conflicting Interests

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