Congenital Heart Disease

Intracoronary Ultrasound Assessment Late After the Arterial Switch Operation for Transposition of the Great Arteries

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OBJECTIVES This research was undertaken to assess the status of the coronary wall morphology late after the arterial switch operation (ASO) for transposition of the great arteries employing intravascular ultrasound (IVUS).

BACKGROUND Long-term patency of the reimplanted coronary arteries is a key issue after ASO. Follow-up studies have demonstrated coronary obstruction in up to 8% of patients that may be related to progressive fibrocellular intimal thickening.

METHODS Twenty-two asymptomatic children were enrolled at a median age of 9.5 years (range 5 to 22 years); IVUS images were obtained in 20 children at cardiac catheterization 5.0 to 21.6 years after the operation (in two cases IVUS study was not feasible due to technical constraints). Quantitative analysis was performed in 37 coronary arteries involving segments with a mean length of 28.4 ± 1.8 mm.

RESULTS Thirty-three arteries (89%) displayed variable degrees of proximal eccentric intimal proliferation, with the maximal intimal thickening being 0.26 ± 0.14 mm (range 0.06 to 0.71 mm) at the most thickened site. According to the Stanford classification, all children had coronary artery involvement with 50% having moderate-to-severe lesions (>0.3 mm). No risk factors for such abnormalities were encountered, including age, origin of the coronary arteries, hemodynamics, and follow-up duration after surgery.

CONCLUSIONS Intravascular ultrasound assessment late after the ASO revealed proximal eccentric intimal thickening in most of the studied vessels. This observation suggests the development of early atherosclerosis in the reimplanted coronary arteries, which may have a role in the genesis of late coronary events. (J Am Coll Cardiol 2005;45:2061–8) © 2005 by the American College of Cardiology Foundation

The arterial switch operation (ASO) has become the treatment of choice in selected infants with complete transposition of the great arteries (TGA). Long-term success of this operation depends on the continued patency of the reimplanted coronary arteries (1). Follow-up studies have demonstrated coronary obstructions in up to 8% of patients, with the vast majority being symptom-free (2–4). The causes of these abnormalities have not been completely elucidated. A fibrocellular intimal thickening has been observed on postmortem examination in patients who died of subendocardial infarction within months after surgery (5). The paucity of deaths after one year of age has been attributed to the hypothesis that the process of intimal proliferation has subsided or overcome by the growth of the coronary vessels (4). In this regard, it has been shown that the hazard function of coronary events after the ASO shows a bi-modal pattern with a rapidly declining early phase and a slowly increasing phase after six years (2). Sudden and unexpected deaths may occur from myocardial ischemia many years after the ASO. However, late coronary events most often result from silent coronary obstructions and would benefit from reoperation to prevent myocardial infarction (2). As such, additional information is required to clarify the mechanisms responsible for these late events after the ASO.

Intracoronary ultrasound has emerged as an important imaging method to provide cross-sectional, transmural tomographic images of the coronary arteries in vivo, which accurately reflect vessel wall histology (6). This technique has been shown to be superior to selective angiography to evaluate early atherosclerotic coronary artery disease (CAD) in adults (7), coronary vasculopathy in children with Kawasaki disease (8,9), and after cardiac transplantation (10). In the present study, intravascular ultrasound (IVUS) was employed to assess coronary artery wall morphology in children who underwent the ASO for TGA a minimum of five years after surgery.

METHODS

Subjects and study protocol. Twenty-two children were enrolled at a median of 8.6 years (range 5.0 to 21.6 years)

Abbreviations and Acronyms	
ASO	= arterial switch operation
CAD	= coronary artery disease
DSE	= dobutamine stress echocardiography
IVUS	= intravascular ultrasound
LAD	= left anterior descending
PIG	= peak instantaneous gradient
RCA	= right coronary artery
RVOTO	= right ventricular outflow tract obstruction
TGA	= transposition of the great arteries

after the ASO. They were operated on between January 1982 and June 1998 at a median age of 47 days (range 5 to 267 days) with 10 having simple TGA and 12 an associated ventricular septal defect. A total of 17 had the usual origin of the coronary arteries, 3 had a single right coronary artery (RCA), 1 had a single left coronary artery, and 1 had the circumflex artery arising from the RCA. Surgical repair was performed by different surgeons under hypothermic cardio-circulatory bypass using the technique initially described by Jatene (11), incorporating from 1990 on the modifications proposed by LeCompte (12). Mean extracorporeal bypass time and aortic cross-clamp time were 150 ± 30 min and 98 ± 24 min, respectively. Mean intensive care stay was 58 ± 69 h. No infant had signs or symptoms of myocardial ischemia during the hospital stay.

The median age and weight of children at the time of the last follow-up study was 9.5 years (range 5 to 22 years) and 32 kg (range 15 to 81 kg), respectively. All children were asymptomatic and not receiving any cardiac medications. No child had risk factors for CAD. After a routine clinical examination, a 12-lead electrocardiogram (ECG) was obtained and standard two-dimensional color Doppler followed by dobutamine stress echocardiography (DSE) performed 1 to 90 days (median 1 day) before cardiac catheterization. Echocardiography was performed at rest and after dobutamine infusion using an ATL HDI 5000 ultrasound machine (Phillips, Bothell, Washington). Dobutamine was incrementally increased every 5 min in doses of 5, 10, 20, 30, 40, and 50 μg/kg/min. Atropine (0.01 mg/kg, maximum cumulative dose 1 mg) was given if needed to reach target heart rate. Left ventricular contractility was assessed using classical views and classified as normal, hypokinetic, akinetic, or dyskinetic. Stress-induced ischemia was defined as a new or worsening wall motion abnormalities or ST-segment depression >2 mm at ECG.

This study was conducted in compliance with the regulations of the Human Investigation Committee of the Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil. Informed consent was obtained from patients or guardians as appropriate.

Cardiac catheterization and angiography. General anesthesia was employed for children younger than 18 years of age. Standard heart catheterization was performed and heparin sulfate (150 IU/kg; max: 10,000 IU) and cephazolin (20 mg/kg; max: 2 g) were administered after vascular accesses were established. An aortic root angiogram was obtained followed by selective coronary artery angiography, which was performed using 6-F large-lumen guiding catheters. Both coronary arteries and ventricles were imaged in multiple axial views. Angiographic evidence of CAD was defined as the presence of any luminal irregularity, loss of branching, and discrete or diffuse stenosis at the ostia or at the distal vessel. Quantitative angiography was not performed.

IVUS examination. Intracoronary nitroglycerine (5 μg/kg; max: 200 μg) was administered to prevent vasospasm, and a 0.014-inch angioplasty guidewire was advanced into the distal right and left coronary arteries. The IVUS images were obtained using a Clear View IVUS unit (Boston Scientific Corporation, Fremont, California). Under fluoroscopic guidance, the ultrasound catheter (Ultra-cross, 3.5-F, 140 cm long, 30 MHz, with an axial resolution of 150 μm) was advanced over the guidewire to the midportion of one of the major coronary arteries, avoiding segments <2 mm in diameter. Image acquisition was obtained at 30 frames/s and continuously recorded on S-VHS videotape during a controlled pullback (0.5 mm/s) and were computer digitized for off-line analysis. Voice annotation and repeated contrast angiography were used to document the imaging location. At the ostium, special care was taken to keep the transducer parallel to the axis of the coronary artery, avoiding off-plane images. This required some proximal slack in the guidewire in some cases. Doppler flow studies were not performed. After the IVUS, coronary angiography was repeated to determine the occurrence of vasospasm. Heparin sulfate was partially neutralized and hemostasis achieved with manual compression. The children were awakened in the catheterization laboratory and discharged home 8 h after the examination.

Off-line IVUS analysis. All images were analyzed using the Echo Plaque 2.5 software (Indec System Inc., Mountain View, California). Luminal and vessel volumes and areas were traced by planimetry. An intimal index was calculated according to previously published protocols (total vessel area minus luminal area divided by total vessel area) (10). Measurements were also obtained at each coronary ostia. The distance between the point of maximal intimal thickness and the ostium was recorded. The degree of intimal thickening at the most diseased segment was assessed using the Stanford classification (13). An intimal thickening <0.1 mm was considered normal and classified as grade 0, whereas >0.3 mm (grades 3 and or 4) was considered significant. Eccentric lesions were defined as those involving <180° of the vessel circumference.

Statistical analysis. Quantitative data are presented as means ± SD or median and ranges. Categorical variables are presented as numbers and frequencies, and were compared using a chi-square or Fisher exact test (when expected values of any cell of the contingency table were <5). Quantitative variables were compared using a two-tailed

unpaired *t* test. Analysis of variance was used to assess the influence of time after surgery in the severity of intimal thickening. The statistical analysis was performed using the SPSS 10.0 (SPSS Institute, Chicago, Illinois) software. The level of significance was set at 0.05.

RESULTS

ECG and echocardiographic findings. All children were in sinus rhythm and had no evidence of ischemia on standard resting electrocardiography. Echocardiography at rest revealed normal left ventricular systolic function with mean ejection fraction of 67.3 ± 8.5%, and no wall motion abnormalities. Seven children had significant right ventricular outflow tract obstruction (RVOTO) defined by right ventricular to pulmonary artery peak instantaneous gradient (PIG) >50 mm Hg. Because two of them had rest PIG >100 mm Hg, DSE was not performed. The remaining 20 had satisfactory images for wall motion assessment. The tests were interrupted in 9 children (45%) before the target heart rate was achieved due to sustained ventricular ectopy, bigeminy, or tachycardia, which was associated with the presence of RVOTO (5 of 6 [83%] vs. 4 of 14 [28%]; p = 0.05). No induced ischemia was observed during the tests. All patients showed left ventricular ejection fraction elevation (58.4 ± 7.9% rest vs. 74.8 ± 8.0% stress; p < 0.001) and end-systolic volume reduction (29.0 ± 14.4 ml rest vs. 19.5 ± 7.7 ml stress; p < 0.001) as assessed by the Simpson's rule.

Cardiac catheterization findings. Hemodynamic data are shown in Table 1. Seven children had high right ventricular systolic pressures ≥0.5 of systemic levels, and 13 had increased left ventricular end-diastolic pressures ≥12 mm Hg.

Bilateral selective coronary angiography was performed in all children. One child was found to have ostial stenosis of the RCA with a normal distal vessel (Fig. 1). There was no angiographic evidence of CAD in the remaining. Stenosis in the main pulmonary artery at the suture line was found in four children and at the origin of one or both pulmonary arteries in three. No complications occurred after catheterization and selective coronary angiography.

Technical aspects of IVUS. Of the 22 children enrolled, IVUS could not be performed in two due to technical constraints. In one child it was not possible to engage the coronary ostia due to a high take-off of the orifices, whereas, in the other, the coronary arteries were too small to accommodate the ultrasound catheter. Among the 20 children who completed the IVUS study, two developed coro-
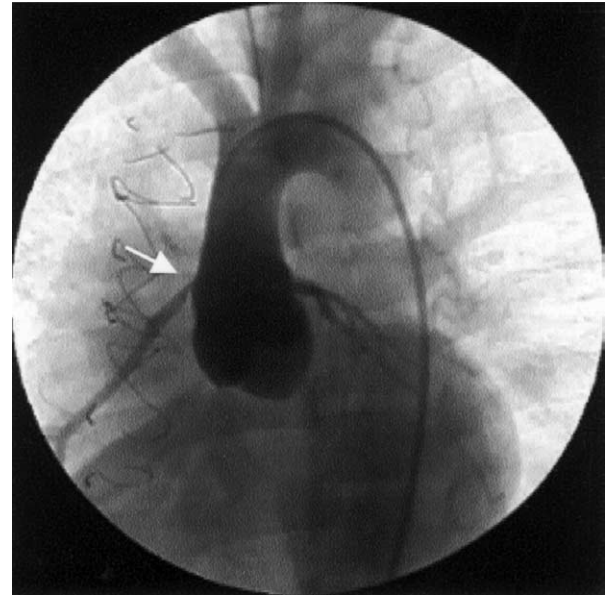

Figure 1. Coronary angiogram showing lumen reduction at the origin of the right coronary artery.

nary vasospasm with no associated ECG changes during the study, which was promptly reversed by an additional dose of nitroglycerin. No other complications were encountered.

IVUS findings. Thirty-seven major coronary arteries were studied, including the RCA in 19 children, left anterior descending (LAD) in 15, and the circumflex in 3. The mean length of the studied segments was 28.4 ± 1.8 mm. Quantitative analysis of the 37 vessels is summarized in Table 2. The overall mean intimal thickening index was 11.1 ± 7.4% at the most thickened site and 5.7 ± 6.7% at the coronary ostia (p < 0.001). At the most thickened segment, there was no difference in the intimal index between the RCA and the left coronary artery (LAD + circumflex) (10.3 ± 6.8% vs. 11.7 ± 8.3%, respectively; p = 0.95). Likewise, there was no difference in the intimal thickening of the RCA between children with high and normal right ventricular systolic pressure (0.29 ± 0.13 mm vs. 0.22 ± 0.09 mm, respectively; p = 0.23), or in the LAD between children with high and normal left ventricular end-diastolic pressure (0.21 ± 0.13 mm vs. 0.3 ± 0.2 mm, respectively; p = 0.31). Additionally, there was no difference in the intimal index and intimal thickening between children with usual and unusual coronary artery patterns

Table 1. Hemodynamics of the Studied Subjects

Variable (mm Hg)	Mean
RVSP/LVSP (n = 21)	0.4 ± 0.17
LVEDP (n = 22)	11 ± 3.3
RV/MPA gradient (n = 21)	25.8 ± 5.6

LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MPA = main pulmonary artery; RV = right ventricle; RVSP = right ventricular systolic pressure.
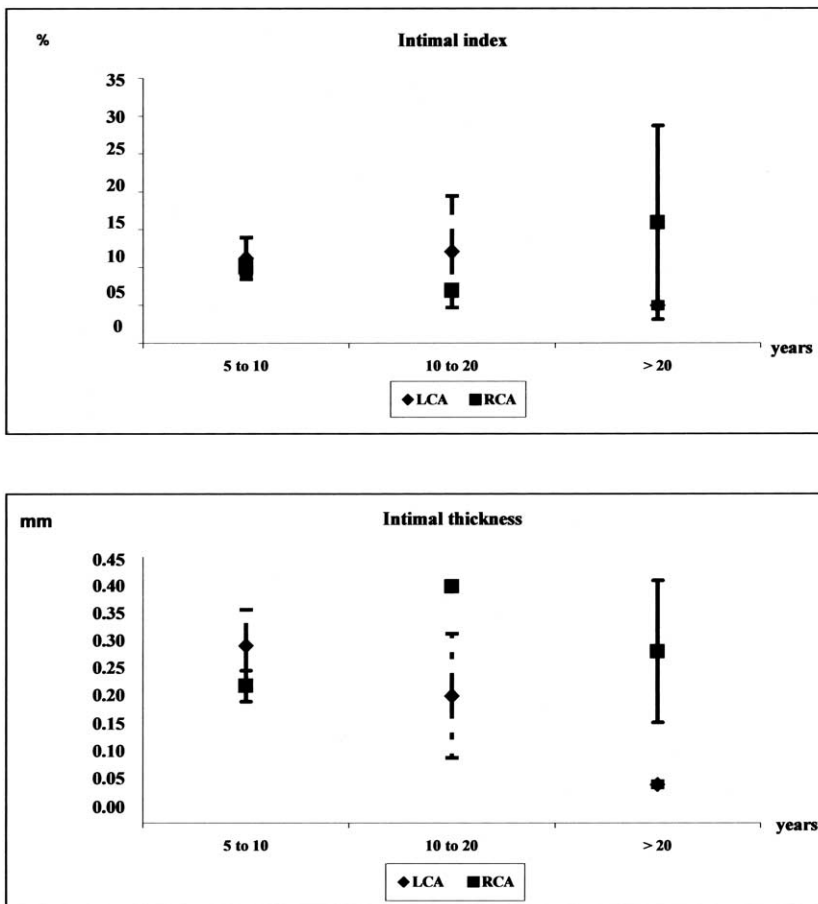
Table 2. Quantitative Intracoronary Ultrasound Analysis of the 37 Studied Coronary Arteries

Variable	Mean
Volume (mm³)	
Vessel	172 ± 103
Lumen	163 ± 101
% of obstruction	6.4 ± 5.7
Area (mm²)	
Lumen	4.0 ± 2.5
Mean intimal thickness	0.78 ± 0.7
Ostial intimal thickness	0.51 ± 0.6

Figure 2. Distribution of the intimal indexes **(top)** and maximal intimal thickness **(bottom)** for right and left coronary arteries according to the duration of follow-up. LCA = left coronary artery; RCA = right coronary artery.

(median 7.8% [5.7% to 10.8%] vs. 7.2% [6.2% to 23.4%], respectively; p = 0.497, and 0.26 ± 0.14 mm vs. 0.25 ± 0.15 mm, respectively; p = 0.96]). Finally, there was no association between the degree of the intimal thickening or the intimal index and the duration of follow-up (Fig. 2). At the most thickened site, the maximal intimal thickness varied from 0.06 to 0.71 mm (mean 0.26 ± 0.14 mm). The

mean distance between this point and the coronary ostia was 11.4 ± 8.6 mm. The pattern of intimal thickening was eccentric in all children. Figure 3 shows the distribution of involvement of the major coronary arteries according to the severity of the coronary artery wall abnormalities. Thirty-three of the 37 studied vessels (89%) had some degree of intimal thickening (≥0.1 mm) with 11 (30%) having
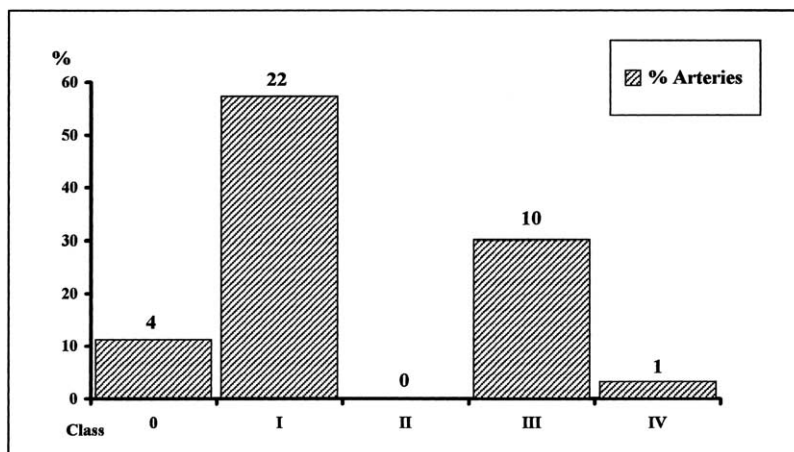

Figure 3. Distribution of the percentage of arteries in the different classes according to the Stanford classification. The absolute number of arteries at each class is represented **above each bar**.
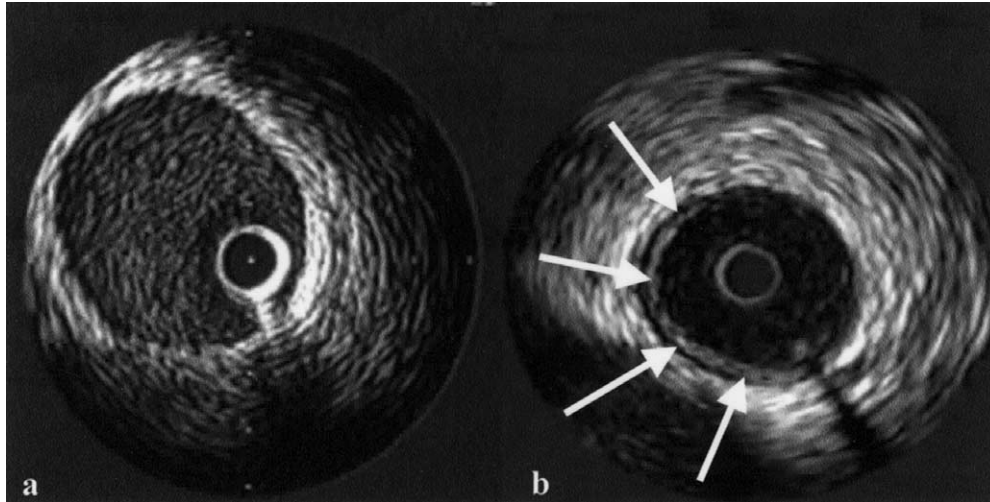
Figure 4. Intracoronary ultrasound image of a normal coronary artery segment (a) and anterior descending segment (b) with intimal proliferation comprising 180° of the vessel circumference (**arrows** indicate intimal thickening).

moderate-to-severe vessel wall involvement. All children had at least 1 coronary artery showing intimal proliferation, with 10 (50%) having moderate-to-severe degrees (>0.3 mm). Intimal thickening was responsible for approximately 6.4% reduction in the total volume of the artery and corresponded to 16% of the vascular area and 5% of the ostial area. Figure 4 shows examples of normal and abnormal IVUS findings.

The child with ostial RCA stenosis on angiography was subsequently found to have an elliptical-shaped ostium demonstrated by IVUS. The luminal area at the ostium was similar to the luminal area of the proximal one-third of the RCA (Fig. 5).

DISCUSSION

This study is the first to assess coronary artery wall morphology using IVUS in children who have had an ASO for TGA. Proximal eccentric intimal thickening was observed in most (89%) of the studied coronary arteries, with 30%

(50% of patients) having significant proliferation (>0.3 mm). This observation presents additional insights to possible mechanisms contributing to late coronary events after the ASO.

Clinical assessment. In this study, all children were asymptomatic and not taking any medications. Functional assessment using echocardiography at rest and DSE revealed preserved left ventricular systolic function with satisfactory response to stress. Because this is a small series of patients with none having significant coronary obstruction, it was not surprising that DSE did not demonstrate any wall motion abnormality. Interestingly, DSE triggered ventricular arrhythmias in almost one-half of our patients and was associated with the presence of RVOTO.

Normal IVUS findings in adults and children IVUS. Intravascular ultrasound represents a unique tool to accurately define vessel wall morphology in vivo and quantify wall thickness and lumen dimensions, with close correlation with in vitro histological measurements (6). In the normal
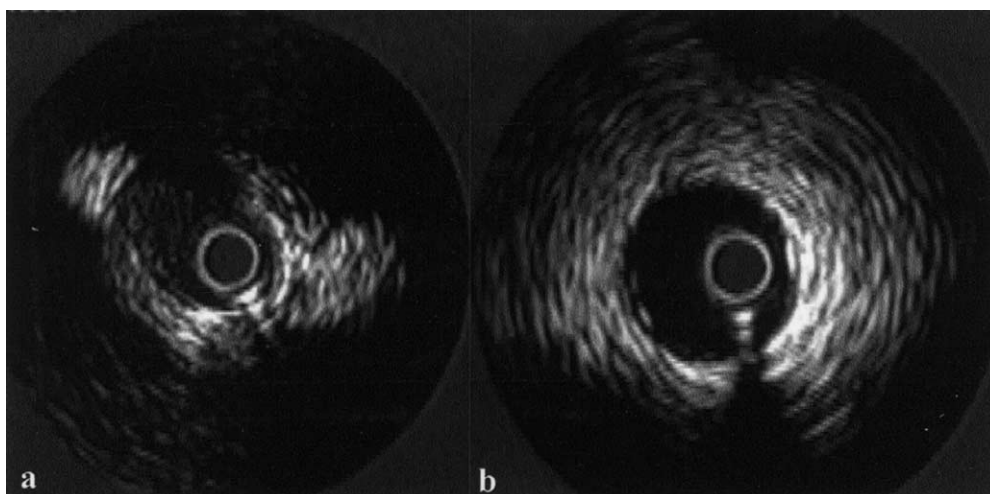

Figure 5. Intracoronary ultrasound image of an elliptical ostia (a) followed by a normal segment (b).

coronary arteries in adults, IVUS studies have demonstrated a three-layered appearance with a bright inner ring, a middle echolucent zone, and an outer bright ring (6,13). In contrast, there is a paucity of information regarding the coronary wall morphology in children. In the study by Sugimura (8), which was conducted to assess the coronary wall in children with Kawasaki disease, IVUS was also performed in a small control group of patients with simple, nonoperated congenital heart defects. In that study, unlike in adults, the normal coronary morphology displayed a smooth homogenous wall appearance without any evidence of the three layers both in the nonaffected segments of the diseased arteries in Kawasaki patients and in the control group. Similar findings have been documented in new cardiac recipients who had received hearts from young donors (14). In their study, St Goar et al. (14) have shown that no donor heart under the age of 25 years had ultrasound evidence of coronary layering. The data from these studies suggest that the three-layer appearance develops gradually with aging, and the presence of intimal thickening in children and adolescents is uncommon, at least with the resolution of a 30-MHz transducer, also employed in these previous investigations (8,14).

Intimal thickness and atherosclerosis in the young. Limited information is available to describe the normal range of coronary intimal thickness in humans. A postmortem study by Velican and Velican (15) showed that intimal thickness progresses with age, from a mean of <0.1 mm in children <10 years to 0.2 mm for ages 20 to 25 years in the LAD. It is of note that their mean values are universally less than the mean value (0.26 ± 0.14 mm) demonstrated by IVUS in the present investigation. Although autopsy studies have demonstrated that atherosclerosis begins at a very early stage in life (16), in most of these investigations, dissection of the coronary arteries was longitudinal, not cross-sectional. In addition, necropsy data probably overestimates vessel wall thickness because the explanted vessels are not distended by physiological pressures (14).

Intimal thickness and atherosclerotic CAD by IVUS in the young. New cardiac transplant recipients have been used as a unique group in which it is possible to image the coronary arteries of young donor hearts to assess possible early atherosclerotic CAD (14,17,18). Intravascular ultrasound studies in these patients have shown some variation in the thickness of the coronary artery intimal layer as well as unequivocal findings of early focal atherosclerotic disease (14,17,18). An atherosclerotic plaque is characterized as an eccentric lesion with a predilection for proximal sites in major coronary arteries usually adjacent to bifurcations (17,18). In adults, an atherosclerotic lesion has been defined as any site with an intimal thickness ≥0.5 mm, which represents at least three standard deviation greater than normal values (17,18). Although a less stringent, but more reasonable, definition may include focal lesions >0.3 mm (18), no data are available for children and adolescents. It is important to acknowledge that intimal thickening is a continuous variable and that defining atherosclerosis as a categorical variable may have some limitations. Additionally, less significant but diffuse intimal thickening may be encountered instead of a localized lesion. On the other hand, the use of the intimal thickening index as a quantitative measurement of intimal proliferation may not be adequate to differentiate between significant focal eccentric intimal proliferation and mild concentric thickening. To help to overcome these limitations, the Stanford classification (13) has been developed. This grading system takes into account not only the thickness of the intima but also the circumferential involvement. Initially used in adult transplant subjects (7,13), it was subsequently applied for the pediatric population, being validated in transplant (10,19) and Kawasaki patients (19). Class 0 is considered to be normal in children (19) and ≥2 defined as significant disease for pediatric heart transplant recipients (10).

IVUS findings in this investigation. This study suggests late abnormal coronary artery wall morphology assessed by IVUS in patients who underwent the ASO for TGA; IVUS revealed some degree of intimal thickening in at least one major coronary artery in all patients, with only 4 of the 37 studied vessels being disease-free. According to the Stanford classification (13), 50% of patients and 30% of arteries in this series had more than moderate lesions (eccentric intimal thickening >0.3 mm). In contrast, Tuzcu et al. (18), studying heart transplant recipients 30.9 ± 13.2 days after transplantation and using the same cutoff point of >0.3 mm at the greatest intimal thickness site, have shown that "only" 21% of their transplant donors 13 to 20 years old had atherosclerosis. In addition, the mean intimal thickening value observed in these patients was significantly lower (<0.13 mm) than the value encountered herein (0.26 ± 0.14 mm). In this regard, St Goar et al. (14) also documented lower values in recipients studied at baseline (<2 months) after transplantation (0.09 ± 0.02 mm). In the present study, the observation that all lesions were eccentric and had a predilection for the proximal vessel is intriguing and may be indicative of an early atherosclerotic process (18). We were unable to find risk factors for such abnormalities, probably due to the limited number of patients enrolled.

Coronary angiography. In a longitudinal study, coronary obstructions have been observed in up to 8% of patients (2). Indeed, some of these lesions appeared late, as demonstrated by repeat angiograms. Due to the relatively low sensitivity of the noninvasive methods to detect coronary insufficiency in symptom-free patients who underwent the ASO (2), we would agree that coronary angiography should be routinely performed as part of a late follow-up protocol. However, this method should be interpreted in the light of its limitations to detect early intimal thickening, which is better assessed using IVUS (2,13,17,18). Because coronary angiography portrays the vessel lumen as a silhouette, the complex eccentric nature of the CAD is neglected. Furthermore, it has been demonstrated that early atherosclerotic

CAD is associated with compensatory vessel remodeling, preserving the coronary lumen from encroachment of the atherosclerotic plaque (20). In this investigation, IVUS also seemed to be useful to demonstrate an elliptical shape of the coronary ostium with no reduction in the cross-sectional area in a single child with suspected RCA ostial stenosis by angiography.

Mechanisms involved in early and late cardiac events after ASO. Fibrocellular intimal thickening has been implicated as the cause of myocardial infarction within months after the ASO (2,4,5). Legendre et al. (2) have demonstrated that coronary anatomy and surgical technical difficulties were correlated with the occurrence of coronary events early in the postoperative period. Late myocardial infarction and death are uncommon after the ASO, albeit representing a devastating issue. In the same study (2), the only late coronary events were reoperations for obstructions not related to intraoperative problems or early ischemia. It has been postulated that reimplantation of the coronary arteries results in proximal flow disturbance, which may alter local shear stress and induce intimal thickening (2,4). Also, it has been suggested that flow patterns in the coronary arteries may be particularly important in the genesis of an early atherosclerotic lesion (18). As such, progressive proliferation likely modulated by atherosclerosis may have a role in the genesis of these late obstructions. It is possible that some of the patients who underwent the ASO later develop overt clinical CAD as a result of a complication, such as a plaque rupture. Although the main focus of this study was coronary wall morphology and not vascular function, this latter aspect may be also important to determine myocardial ischemia and late events, especially acknowledging that denervation occurs after transection of the great arteries for the ASO (21). Additionally, myocardial hypertrophy due to residual lesions has adverse effects on coronary flow reserve (22) and may contribute to myocardial ischemia in scenarios of high metabolic demands.

Implications in clinical practice. In patients who underwent cardiac transplantation, intimal proliferation is progressive, and coronary events will eventually ensue (7,10,13,19). In the patients studied herein, it is difficult to predict how the coronary wall abnormalities will behave with time and what lesions should be treated to prevent coronary events. At this time, it is unclear when and how often IVUS should be employed for late assessment of the coronary arteries after the ASO. It seems reasonable to apply this technique for patients in whom coronary angiography revealed an ostial stenosis, a de novo lesion, or progression of a previous lesion.

The data from this study suggest that we should apply strategies to control risk factors for CAD in the late follow-up of these patients. Whether early intervention to curtail atherosclerosis in an occasional patient with associated risk factors can limit the development of symptomatic disease is speculative.

Study limitations. We acknowledge that a continuous measure of intimal thickening, while making scientific sense, would require a control group for comparison. However, it would be obviously unethical to perform IVUS in a control group of healthy children. Also, due to the absence of coronary events in patients who underwent other surgical procedures to repair defects that do not involve coronary transfer, such as ventricular septal defects, Tetralogy of Fallot, etc., it is hard to justify late invasive coronary investigations. Therefore, we used historical controls to describe normal (albeit limited) IVUS data in children, adolescents, and young adults (7,8,14,17,18). It is of note that a 30-MHz ultrasound transducer was also employed in these previous investigations. In addition, in the study by Sugimura et al. (8), the control group was similar to the population described herein in regards to age (10.2 ± 2.8 years). As such, it is unlikely that the findings presented herein represent a physiological process of atherosclerosis that could also be encountered in a normal population. The common finding of significant coronary wall involvement in 50% of our patients based on the well-accepted Stanford classification further corroborates with this impression. Whether the use of a higher frequency transducer ($\geq$40 MHz), which may be able to detect the three layers even in the absence of pathologic intimal thickening, could alter the significance of our observations is unclear. Serum levels of cholesterol were not routinely assessed herein. However, this probably has a limited impact on our conclusions because the IVUS findings were similar in the entire cohort of patients.

Conclusions. Late IVUS assessment in children who underwent the ASO for TGA revealed proximal eccentric intimal thickening in most (89%) of the studied coronary arteries. A total of 50% of patients and 30% of arteries had significant proliferation (>0.3 mm). These observations suggest the development of early atherosclerosis in the reimplanted coronary arteries, which may have a role in the genesis of late coronary events.

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