Comparison of Segmental Versus Longitudinal Intravascular Ultrasound Analysis for Pediatric Cardiac Allograft Vasculopathy

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ABSTRACT

Intravascular ultrasound (IVUS) has been routinely used in some centers to investigate cardiac allograft vasculopathy in pediatric heart transplant recipients. We present an alternative method using more sophisticated imaging software. This study presents a comparison of this method with an established standard method. All patients who had IVUS performed in 2014 were retrospectively evaluated. The standard technique consisted of analysis of 10 operator-selected segments along the vessel. Each study was re-evaluated using a longitudinal technique, taken at every third cardiac cycle, along the entire vessel. Semiautomatic edge detection software was used to detect vessel imaging planes. Measurements included outer and inner diameter, total and luminal area, maximal intimal thickness (MIT), and intimal index. Each IVUS was graded for severity using the Stanford classification. All results were given as mean ± standard deviation (SD). Groups were compared using Student t test. A P value $<.05$ was considered significant. There were 59 IVUS studies performed on 58 patients. There was no statistically significant difference between outer diameter, inner diameter, or total area. In the longitudinal group, there was a significantly smaller luminal area, higher MIT, and higher intimal index. Using the longitudinal technique, there was an increase in Stanford classification in 20 patients. The longitudinal technique appeared more sensitive in assessing the degree of cardiac allograft vasculopathy and may play a role in the increase in the degree of thickening seen. It may offer an alternative way of grading severity of cardiac allograft vasculopathy in pediatric heart transplant recipients.

CARDIAC allograft vasculopathy plays a prominent role in the long-term morbidity and mortality of pediatric heart transplant recipients [1]. Angiography has been shown to underestimate the degree of intimal thickening with positive findings only late in the disease process [2]. Intravascular ultrasound (IVUS) detects the intimal thickening much earlier than angiography and can help improve the management of the disease process and provide a valuable tool for future follow-up. Grading the degree of intimal thickening is currently limited to the Stanford classification system designed from IVUS analysis from adult heart transplant recipients [3]. The Stanford classification is based on measurement of the thickest part of the intima, maximal intimal thickness (MIT), and the amount of thickening observed around the circumference of the vessel, defined as more or less than 180 degrees. IVUS images allow other data points to be measured, such as outer and inner diameters, and total and luminal areas. These do not contribute to grading the severity of cardiac allograft vasculopathy using the Stanford classification. The original description of the grading system identified only the part of the vessel most severely affected, limiting the assessment to specific data points along the vessel. It did not consider the disease process along the length of the vessel studied. Our methodology previously extended this technique to incorporate more segments by using a "random" selection of acquired images throughout the coronary vessel. However, this extended technique incorporates a selection bias and

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0041-1345/17
http://dx.doi.org/10.1016/j.transproceed.2017.04.026

makes chronological comparison of identical segments impossible through the lack of a systemic approach.

Recently, in conjunction with colleagues at the Great Ormond Street Hospital (London, UK), we have started using a more systematic method of analysis that longitudinally evaluates the entire vessel studied. This study examines the IVUS findings of pediatric heart transplant patients over the course of a calendar year and compares the results achieved using the different methods of analysis.

METHODS

This retrospective study was approved by the Institutional Review Board. At the time of transplantation a research consent form was signed allowing for retrospective analysis of clinical data. All pediatric transplant recipients at our institution undergo coronary angiography and IVUS as part of their annual catheterization beginning at 7 years of age. All IVUS studies were performed at Loma Linda University Children's Hospital. In all patients, the left anterior descending artery was assessed using a Volcano Revolution 45 mHz rotational IVUS imaging catheter (Volcano Corp, San Diego, Calif, United States). The IVUS catheter was mounted on an automatic pullback sled at a rate of 1 mm/sec. Each IVUS study was retrospectively analyzed using our standard protocol for morphometric analysis, originally based on studies in adult heart transplant recipients [4–6]. Ten randomly selected segments were chosen by the operator and analyzed along the course of the vessel, paying attention to even distribution along the vessel length.

Measurements at each segment included outer and inner diameter (mm) and total and luminal area (mm^3). The 10 results were averaged to give mean diameters and areas. Intimal index was calculated using the following formula: (mean total area−mean intimal area)/mean total area. The intimal circumference (greater or less than 180 degrees) and the MIT were noted. These two findings were used to grade the degree of intimal thickening using the Stanford classification system (class 1, trivial; class 2, mild; class 3, moderate; class 4, severe) [4].

Each study subsequently underwent analysis using the new technique, which involved longitudinal analysis of the IVUS study. Each study was loaded into the software analysis program, QIVUS (Medis Medical Imaging Systems, Leiden, Netherlands). QIVUS was originally designed for stent analysis in adult coronary disease and has had limited application in adult transplant recipients [7]. The software used a single slice and a semiautomated three-dimensional (3D) contour detection for vessel analysis [8]. Each IVUS segment was established from a distal branch vessel to the circumflex/left anterior descending artery junction. Starting distally, single slices were analyzed every third cardiac cycle. The outer edge and the luminal edge of the vessel were outlined at each slice. The data was analyzed by the software and exported to an Excel file. At each slice, the software analyzed outer and inner diameter and total and luminal area. The MIT and minimal intimal thickness at each segment were manually measured and copied to the Excel file. The results for both analyses were averaged for mean outer and inner diameter, mean total and luminal area, and MIT. Mean intima-medial thickness was averaged in the longitudinal analysis. At the onset of using the longitudinal method, 10 studies from each institution were analyzed for observer variability. The 10 studies from Great Ormond Street were not included in the analysis here and served only to assess observer variability.

All results were given as mean ± standard deviation. The two methods were compared using a paired Student t test. A P value $<.05$ was considered significant.

RESULTS

In 2014, 58 patients underwent IVUS with 1 patient having 2 annual studies in the calendar year for a total of 59 studies. Patient demographic data are shown in Table 1. There were no procedural complications. There were no changes noted on coronary angiography. No patient was excluded from the analysis. Each study was analyzed using the standard analysis and the longitudinal analysis. Standard analysis took approximately 15 minutes to perform. Initially, the longitudinal analysis took approximately 40 minutes to perform. However, analysis did improve to 20 to 30 minutes over time. No observer variability was noted.

Table 2 compared the standard and longitudinal IVUS analysis methods. There was no difference in mean outer diameter, mean inner diameter, or mean total area between the 2 methods. The mean luminal area was significantly lower using the longitudinal method (6.91 ± 1.81 mm^3, standard, vs 6.60 ± 1.78 mm^3, longitudinal, $P = .029$), resulting in a significantly higher mean intimal index using the longitudinal method (0.08 ± 0.07, standard, vs 0.15 ± 0.07, longitudinal; $P < .001$). MIT was significantly higher using the longitudinal method compared with the standard method (0.22 ± 0.16 mm, standard vs 0.32 ± 0.19 mm, longitudinal; $P < .001$). Mean intima-medial thickness was 0.19 ± 0.09 mm using the longitudinal method. When compared with the measured MIT using the standard

Table 1. Patient Demographic Data

Total number of patients	57
Mean age at time of IVUS	15.3 ± 3.3 y
Male	27
Female	30
Mean age at transplantation	2.7 y ± 4.5 y
Transplanted <1 y of age	38
Transplanted >1 y of age	20
Pretransplantation diagnosis	
Congenital	34
HLHS	25
Single ventricle	4
Ebstein anomaly	1
Shone's	1
TGA	1
AS/AI	1
PA/IVS	1
Noncongenital	22
Dilated CM	17
CAV	3
Restrictive CM	1
Cardiac tumor	1
Mean transplant age at time of IVUS	12.5 ± 5 y

Abbreviations: HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; AS/AI, aortic stenosis/aortic insufficiency; PA/IVS, pulmonary atresia with intact septum; CM, cardiomyopathy; CAV, cardiac allograft vasculopathy.