Reproducibility of IVUS Measurements in Heart Transplant Recipients: Increased Quality of Data by Using Dedicated Software for Image Analysis

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Abstract

Cardiac allograft vasculopathy (CAV) is the major cause limiting long term graft survival after heart transplantation (HT), and is characterized by changes in coronary artery geometry, such as intimal thickening and vessel remodeling. Given the limited strategies available to reduce its impact on outcome, early diagnosis of CAV – for which intravascular ultrasound (IVUS) is the gold standard – is crucial to appropriately modulate therapy and to reduce contributing risk factors.

However, a highly reproducible image-analysis method is required to capture the complex mechanisms beyond CAV–related changes in coronary geometry.

1. Introduction

Cardiac allograft vasculopathy (CAV) is a major determinant of long-term mortality in cardiac transplant patients. Differently than native atherosclerosis, it is characterized by diffuse intimal thickening with luminal narrowing and pruning of distal branches of graft coronary arteries. Multiple factors are likely to contribute to the development of this pathological process, ultimately resulting in graft failure [1].

Significant structural changes occur in the coronary artery, during the first year after cardiac transplantation [2,3]. Negative remodeling (reduction in vessel size) and progression of intimal thickening, may both contribute to a loss of lumen diameter. Intravascular ultrasound (IVUS) is currently the most sensitive method for detecting these changes [4]. Previous studies using IVUS have demonstrated varying degrees of alteration in vessel size, both negative and positive remodeling, and hetherogeneous amounts of intimal thickening early after transplantation [5-11]. The discrepancies in these studies can be explained by the use of two-dimensional IVUS analysis and the need of sufficient serial data in the same patients.

With automated catheter pullback devices and improved data integration and analysis software, it is now possible to construct three-dimensional IVUS images of the coronary arteries and achieved a highly accurate analysis of volumetric changes [12]. The most rigorous IVUS approach uses serial automated pullback in the same patients to determine the changes in vessel, plaque and lumen volume [13].

Determinig the degree to which lumen loss occurs as a result of negative remodeling as opposed to intimal thickening and identifying the clinical factors associated with these changes is crucial to identify strategies for prevention and treatment of CAV. Therefore, the complex mechanism beyond the variability of coronary geometry observed in CAV development require a highly reproducible method to capture not only changes in intimal thickness (a measurement with validated prognostic relevance), but also in vascular remodeling modality.

2. Methods

Study design

This longitudinal study includes 30 patients who received HT at our institution. After obtaining patients' informed written consent, left heart catherization, including selective angiography, and IVUS of the left-anterior descending artery (LAD), was planned at 1 and 12 months after transplantation. Only patients who completed both phases of the study protocol were included in the final analysis.

Chronic immunosuppressive therapy consisted in a standardized protocol based on the association of cyclosporine, azathioprine and prednisone [14]. Acute graft rejection was monitored by endomyocardial biopsy, according to established protocols. The study was approved by the local ethic committee.

Intravascular Ultrasound

IVUS of LAD was performed using a percutaneous transfemoral approach [16]. IVUS images were obtained using a commercially available IVUS catheter (Eagle Eye

Gold imaging Catheter, Volcano corporation) placed under fluoroscopic guidance to the periphery of LAD. Automatic pullback (1mm/sec motorized device) was performed, and images were stored on a CD-ROM, from which image analysis was performed off-line.

We compared two methods of measurements of IVUS parameters. Manual planimetry was performed following American College of Cardiology recommendations [13]. We considered the area bounded by external elastic membrane to be the external vessel wall area, and the difference between external elastic membrane area and lumen area was calculated to give the intimal area. To minimize bias in the matching of individual sites in artery-wall evaluation, we adopted the volumetric approach described by Pething et al. [7,8]. For volumetric analysis, serial cross-sectional images of the first 30 mm of the LAD were taken every 2 mm. Vascular sites with major side branches or calcifications occupying a vessel circumference of more than 30% were excluded from quantification. Vessel, lumen and intimal volumes were then calculated, multiplying the average cross-sectional areas by 30 mm, approximating the coronary artery as a cylinder [7].

Semi-automatic planimetry was performed by two operators that used a commercial software (QIvus Clinical Edition Medis, Rotterdam, NL). Lumen and vessel borders were automatically detected by the software, and then adjusted manually for possible detection artifacts. The first 30 mm of each LAD were analyzed by 0.5 mm increments, resulting in 60 cross-sectional images from which volumetric reconstruction occurred automatically by interpolating the measurements of the remaining frames. Plaque volume measurements were derived by subtracting lumen volume to vessel volume. After correcting for cardiac motion, lumen volume and plaque (intimal) volume were quantified and the percent change in vessel, lumen and plaque volumes from baseline to year 1 was calculated by using the algorithm, vessel volume. Cross-sectional images were used to create longitudinal view, which provides anatomical reference and guides contour detection.

Analysis

We compared the measurements obtained with the two techniques and assessed interobserver variability of the software-based technique, by repeating the same randomly chosen measures. In addition, we compared reproducibility of maximal intimal thickness (MIT), a linear measure obtained manually and with proven prognostic relevance, with volume measurements obtained with the software based method.

Linear regression analysis was performed to determine the correlation between continuous variables. Continuous variables are expressed as mean ± SD (standard deviation) and categorical data as percentage.

Statistical analysis was performed using JMP Statistical Discovery Software (SAS Institute, Cary, NC).

3.   Results

This report includes 30 patients who underwent IVUS evaluation of their LAD at baseline and 1 year follow up and had acceptable recordings for volumetric analysis.

The clinical characteristics of these patients are outlined in Table 1. The average time after transplantation for the first IVUS study was 40 ± 13 days, and for the second study was 369 ± 21 days.

Table 1.   Patient characteristics

Recipient age (yr)	52.4 ± 11.6
Recipient gender (male/female)	26/4
Donor age (yr)	31.1 ± 9.2
Donor gender (male/female)	22/8

Two-dimensional and volumetric analysis indicated significant changes in coronary anatomy during the first year after transplantation. We correlated the measurements obtained manually with those obtained by the software (Table 2).

Table 2.   Serial IVUS analysis of correlation

IVUS parameter	R at Baseline	R at Year 1
Vessel volume (mm^3)	0.57	0.67
Lumen volume (mm^3)	0.67	0.85
Plaque volume (mm^3)	0.79	0.87
MIT (mm)	0.62	0.79

Changes in plaque, vessel and lumen volumes detected manually poorly correlated with the software measure. Analyzing the overall changes (Δ) in vessel volume, lumen volume and plaque volume between baseline and follow-up IVUS, we found that and the variation between the manual and semi-automatics planimetry is over the 10% (i.e. R=0.54 for Δ lumen volume after 1 year).

Vessel volume baseline
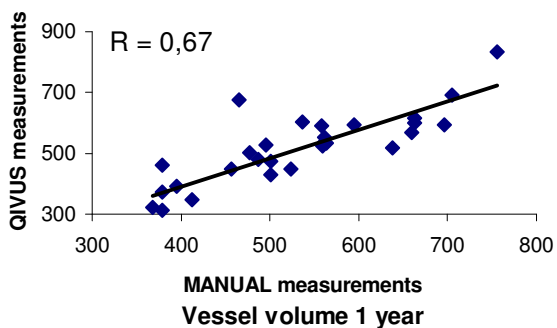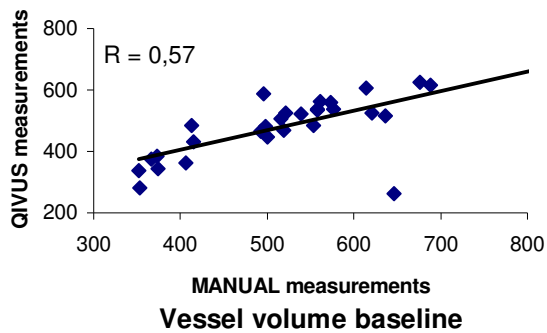
R = 0,57

Vessel volume 1 year

R = 0,67

Figure 1. Correlation between the two different planimetry method.

By contrast, interobserver variability of software-based measurements was lower than 5%, both for volumetric measurement and for MIT change.

Table 3. Correlations between measurements taken by 2 independent observer using the software

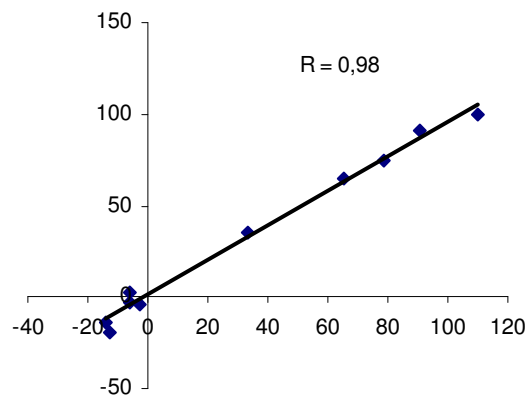| IVUS parameter	R at Baseline	R at Year 1
Vessel volume (mm^3)	0.97	0.98
Lumen volume (mm^3)	0.96	0.99
Plaque volume (mm^3)	0.97	0.98
MIT (mm)	0.98	0.98

R = 0,98

Figure 2. Correlation between Δmean lumen volume (mm^3), calculated semi-automatics planimetry method. Δ indicates the annual change.

Vessel volume baseline
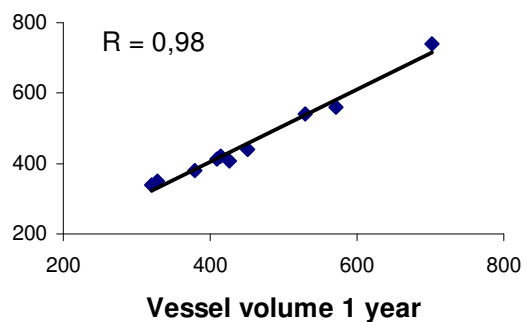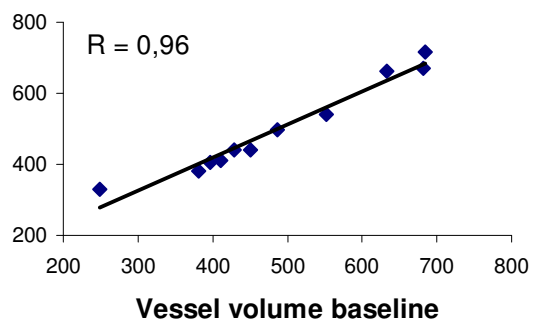
R = 0,96

Vessel volume 1 year

R = 0,98

Figure 3. Correlation between the semi-automatics planimetry method.

4.   Conclusions

Measures of coronary volume, obtained with the same instrument, significantly varied depending on the analysis method. A software analysis based on semi-automated border detection provided a better accuracy and measurements repeatability than manual analysis.

Volumetric measures obtained by the software-based technique resulted as reproducible as MIT measures. These findings allow wide use of volumetric parameters for prognostic validation and for a comprehensive description of CAV development.

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