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Quantitative CT assessment identifies more heart transplanted patients with progressive coronary wall thickening than standard clinical read

Mihály Károlyi, Márton Kolossváry, Andrea Bartykowszki, Ildikó Kocsmár, Bálint Szilveszter, Júlia Karády, Béla Merkely[1], Pál Maurovich-Horvat[*,1]

MTA-SE Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

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ABSTRACT

Background: We sought to compare quantitative coronary CT angiography (CTA) assessment versus standard clinical reading to identify heart transplanted (HTX) patients with progressive coronary wall thickening.
Methods: 35 patients (23 males, age 58 [IQR: 50;61] years) underwent 256-slice coronary CTA at one year and two years after HTX to rule out cardiac allograft vasculopathy (CAV). In addition to the standard clinical read, we quantified total vessel wall volume in all coronaries up to 2-mm luminal diameter. Fixed threshold settings were used to assess calcified (> 350 HU) and non-calcified vessel wall components with high- (131–350 HU), intermediate- (75–130 HU) and low-attenuation (< 75 HU).
Results: Total lumen volume did not change between baseline and follow-up studies ($p = 0.59$). Total vessel wall volume showed significant increase (464 [IQR: 338; 570] vs. 563 [IQR: 345; 717] mm^3, $p < 0.001$). The volume of high-, intermediate and low-attenuation non-calcified wall components showed progression (332 [IQR: 217;425] vs. 385 [IQR: 238;489], 40 [IQR: 12;48] vs. 59 [IQR: 16;83] and 18 [IQR: 4;21] vs. 46 [IQR: 6;41] mm^3, respectively, $p < 0.05$ all), while calcified volume did not change between baseline and follow-up CTAs (72 [IQR: 16;127] vs. 72 [IQR: 29;102] mm^3, $p = 0.73$). Quantitative analysis identified more patients with progressive coronary wall thickening (≥10% cut-off) than standard clinical read (11 vs. 22, $p = 0.01$).
Conclusion: Quantitative coronary wall assessment is feasible with coronary CTA in HTX patients. Coronary wall thickening within the first two years after HTX is mainly attributable to non-calcified lesion components and might be an early sign of CAV.

1. Introduction

Cardiac allograft vasculopathy (CAV) affects up to 50% of heart transplanted (HTX) patients within 10-years of transplantation.[1] The mortality of patients with 3-vessel CAV can be up to 90% in the first year from diagnosis.[2] The progression of CAV is usually asymptomatic and shows high inter-patient variations. Yearly follow-up with invasive angiography (ICA) and optional intravascular ultrasound (IVUS) is therefore recommended.[3] More than 0.5 mm change in the maximal intimal thickness within the first post-transplantation year is associated with increased mortality.[4] Coronary computed tomography angiography (CTA) has been proposed as an alternative to ICA for routine follow-up of HTX patients.[5] Coronary CTA has sufficient spatial resolution to measure intimal thickening > 0.5 mm, similar to IVUS on clinically relevant coronary arteries.[6] In a recent meta-analysis the sensitivity, specificity, positive and negative predictive value of CT for detection of CAV were 97%, 81%, 78% and 97%, respectively.[7] Up until today, all studies evaluating CAV with coronary CTA have implemented qualitative reading.[8,9] Therefore, the aim of our study was to assess the feasibility of quantitative coronary wall volume change assessment in HTX patients using coronary CTA. Furthermore, we aimed to compare the performance of quantitative coronary CTA assessment versus conventional qualitative clinical reading to rule out progressive coronary vessel wall thickening, indicative for CAV.

2. Methods

2.1. Study population

We included 35 consecutive HTX patients (age 58 [50–61] years, 66% male) who underwent coronary CTA examination at one year and at two years after HTX as part of the routine clinical work-flow at our

* Corresponding author. Heart and Vascular Center, Semmelweis University, Hataror St. 18, 1122, Budapest, Hungary.
E-mail address: p.maurovich.horvat@mail.harvard.edu (P. Maurovich-Horvat).
[1] BM and PMH contributed equally.

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List of abbreviations

CAV	Cardiac allograft vasculopathy
CTA	Computed tomography angiography
LCx	Left circumflex coronary artery
HU	Hounsfield units
HTX	Heart transplantation
ICA	Invasive coronary angiography
IQR	Interquartile range
IVUS	Intravascular ultrasound
LM	Left main coronary artery
RCA	Right coronary artery
SCCT	Society of Cardiovascular Computed Tomography

institution. Patients with impaired renal function (GFR < 30 ml/min/1.73 m^2), poor image quality and with irregular heart rates due to atrial fibrillation, or frequent premature ventricular complex were not included in the study. The first-year and second-year follow-up CTA scans were analyzed retrospectively and no data acquisition was performed in addition to routine examinations. Patients' informed consent was waived by the institutional review board due to the retrospective study design. Patient demographics are summarized in Table 1.

2.2. Coronary CTA scan protocol

All CTA scans were performed on a 256-slice scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) with prospective ECG-triggered acquisition mode. The same coronary CTA scan protocol and settings were used for each patients' baseline and follow-up scans. Images were acquired in cranio-caudal direction during single breath-hold in inspiration. Imaging parameters were used for data acquisition as follows: 100–120 kV tube voltage with 200–300 mAs tube current, 128 × 0.625 mm detector collimation and 270 ms gantry rotation time was used. The same tube voltage settings were used for the follow-up CTA for each patient. A mid-diastolic triggering with 3% padding (75–81% of the R-R interval) was chosen in patients with a heart rate < 80 bpm, whereas in patients with ≥80 bpm systolic triggering (37–43%) was used. Using a dual-syringe system iomeprol contrast media with an iodine concentration of 400 mg/ml (Iomeron 400, Bracco Ltd, Milan, Italy) was delivered into an antecubital vein via an 18-gauge catheter. A four-phasic injection protocol was used with 85–95 ml contrast agent at a flow rate of 4.5–5.5 ml/s.[10] For proper scan timing bolus tracking technique was used with a region of interest (ROI) placed in the left atrium. For heart rate control 7.5–15 mg of ivabradine was used 3 h prior the CTA examination.[11] All patients received 0.8 mg sublingual nitroglycerin prior the CTA acquisition. All CTA datasets were reconstructed with 0.8 mm slice thickness, and 0.4 mm increment with hybrid iterative reconstruction technique (iDOSE,[4] Philips Healthcare, Best, The Netherlands) with a medium iteration level (level 4 of levels 1–7).[12]

2.3. Qualitative image analysis

The Society of Cardiovascular Computed Tomography (SCCT) guidelines were used for conventional data analysis.[13] Coronary CTA reading was performed by a cardiologist with 6 years of experience in coronary CTA imaging. Axial images, multiplanar and curved reformations were used for data analysis. Luminal stenosis was categorized into the following classes: (0) normal – absence of any plaque, no luminal stenosis; (1) minimal – plaque causing < 25% stenosis; (2) mild – 25% to 49% stenosis; (3) moderate – 50% to 69% stenosis; (4) severe −70% to 99% stenosis; (5) occluded. Calcified, non-calcified and partially calcified lesions were distinguished. Baseline and follow-up coronary CTA datasets were loaded side by side for comparison. Progression was defined as the appearance of any novel coronary lesion and/or the classification of a previously described coronary lesion into a higher stenosis category on the follow-up scan. An example for qualitative analysis is shown in Fig. 1.

2.4. Quantitative image analysis

A dedicated offline workstation (QAngioCT, version 2.1; Medis Medical Imaging Systems, Leiden, The Netherlands) was used for semi-automated lesion quantification. Two experienced observers evaluated the images in a random order, blinded to acquisition date and the results of the clinical read. Datasets were loaded separately into the workstation. First, coronary tree centerline extraction was performed. Second, the proximal and distal endpoints of the coronary tree were set manually for further vessel analysis. A screen shot from the proximal measurement point was taken, while the distal point was set to the same distance on baseline and follow-up CTs, to ensure measurement consistency. The left main (LM) and left anterior descending artery (LAD), left circumflex artery (LCx) and right coronary artery (RCA) were assessed up to 2-mm luminal diameter. A delineation of the inner and outer vessel-wall boundaries was performed along the vessel path and corrected on cross-sectional images, if necessary. Fix window settings of 1400/500 HU were used for segmentations. We used fixed threshold parameters to distinguish lesions components on different HU strata: calcified lesion volumes (> 350 HU), non-calcified lesion volumes with high attenuation (131–350 HU), non-calcified lesion volumes with intermediate attenuation (75–130 HU) and non-calficied lesion volumes with low attenuation (< 75 HU).[14] Lumen volume, overall lesion volume and overall lesion burden (total vessel volume minus the lumen volume, divided by the total vessel volume) were assessed on a per vessel basis. Progression was defined as more than 10% increase in overall lesion volume on the follow-up CTA, as compared to the baseline scan.[15] Fig. 2 shows the quantitative results of a patient with diffuse progressive coronary vessel wall thickening.

2.5. Statistical analysis

We used the Shapiro-Wilk-test to assess the normality of continuous variables. All continuous variables showed non-normal distribution,

Table 1
Patients' characteristics.

Patient data	Study population (n = 35)
Recipient age (years)	58 [IQR: 50;61]
Recipient BMI (kg/m^2)	25 [IQR: 23;27]
Male transplant recipient, n (%)	23 (66)
Recipient eGFR (mL/min/1.73 m^2)	59 [IQR: 50;81]
Recipient cardiovascular risk factors	
Hypertension, n (%)	23 (66)
Diabetes mellitus, n (%)	18 (51)
Dyslipidemia, n (%)	13 (37)
Former smoker, n (%)	3 (9)
Cerebrovascular disease, n (%)	5 (14)
Peripheral arterial disease, n (%)	1 (3)
Family history of CAD, n (%)	2 (6)
Donor age (years)	45 [IQR: 38;50]
Male donor, n (%)	25 (71)
CT Dose Length Product (mGy x cm)	342 [IQR: 218;362]
CT Contrast agent (ml)	90 [IQR: 85;95]
Heart rate during coronary CTA (beats/min)	74 [IQR: 68;79]

Recipient demographic data is given at the time of the first coronary CTA examination.
BMI = Body mass index, eGFR = Estimated glomerular filtration rate.

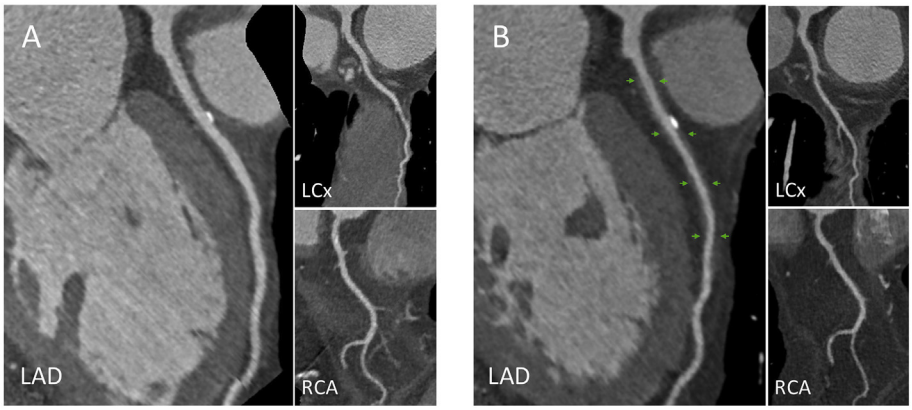

Fig. 1. Progressive coronary wall thickening on coronary CTA.
Curved reformatted CT images at baseline (A) showed only mild atherosclerotic disease with a focal calcified lesion, while follow-up images (B) revealed diffuse coronary wall thickening on the LAD, and LCx, while the RCA is apparently unchanged. LAD = left coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery, CAV = cardiac allograft vasculopathy.

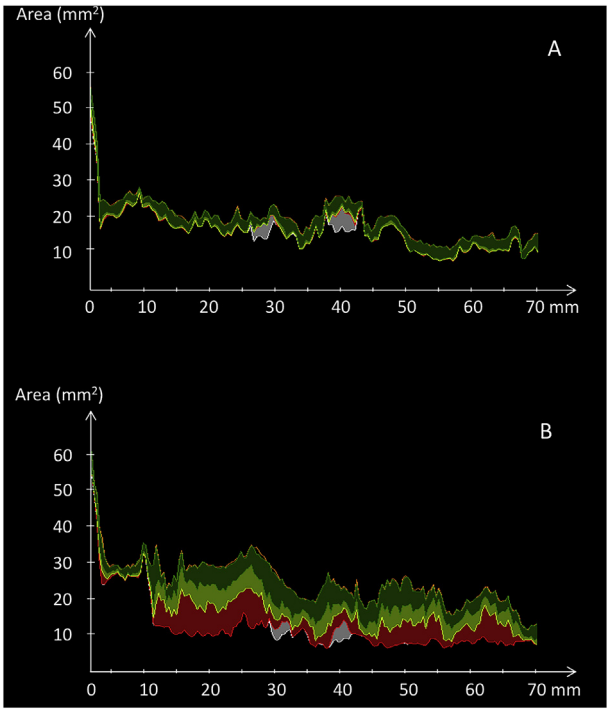

Fig. 2. Quantitative coronary wall analysis.
Coronary lesion tissue volumes at baseline (A) and at follow-up (B) of the same HTX patient as seen on Fig. 2, quantified with dedicated software. The excessive lesion volume progression was mainly attributable to the increase of non-calcified lesions (from 222 mm^3 to 882 mm^3), while calcified components remained practically unchanged (15 mm^3 and 20 mm^3). Red: low-attenuation non-calcified tissue (necrotic core), yellow: intermediate-attenuation non-calcified (fibro-fatty) tissue, green: high-attenuation non-calcified (fibrous tissue), white: calcified tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

therefore non-parametric tests were used and median and interquartile range [IQR] is reported. Categorical variables are expressed as numbers and percentages. Wilcoxon signed-rank test was used to compare the plaque volumes of the baseline and follow-up CTA. Categorical data was compared using the McNemar test. The inter-reader reproducibility between quantitative plaque measurements was calculated using the intra-class correlation coefficient (ICC). The following descriptive scale was used for values of the ICC: < 0.40 poor, 0.40–0.59 fair, 0.60–0.74 good and 0.75–1.00 excellent.[16] All statistical calculations were performed using SPSS software (SPSS version 23; SPSS, Armonk, NY). A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Qualitative image analysis

Coronary lesions were detectable in 74% (26/35) of the patients at baseline standard CT read, while on the follow-up CTs 80% (28/35) of the patients had at least one lesion present (p = 0.48). At baseline 19% (82/427), whereas at the follow-up 27% (116/427) of the coronary segments showed any lesion (p < 0.001). The distribution of the segments containing non-calcified, calcified and partially calcified lesions were 61% (50/82), 22% (18/82) and 17% (14/82) at the first CT, and 64% (74/116), 20% (23/116) and 16% (19/116) at the follow-up CT (p < 0.001, p = 1.00 and p = 0.26, respectively). At the baseline CT scan 55% (45/82) of the lesions caused minimal stenosis, 39% (32/82) mild and 6% (5/82) moderate luminal narrowing. No severe coronary stenosis was revealed. At the follow-up CT scan, 50% (58/116) of the coronary lesions caused minimal, 36% (42/116) mild, 10% (12/116) moderate luminal narrowing and in 4% (4/116) of the segments severe stenosis was detected (p < 0.001, p = 0.14, p = 0.08, p = 0.25, respectively). Patients with severe stenosis were referred for ICA, which confirmed the severe luminal stenosis in all cases.

3.2. Quantitative image analysis

The total length of analyzed coronary arteries did not differ between the baseline and follow-up CTAs, 248 [IQR: 213;295] mm versus 250

Table 2
Coronary wall thickness progression between baseline and follow-up coronary CTA as quantified with semi-automated software.

	Baseline CTA	Follow-up CTA	p
Lesion burden (%)	17 [IQR: 14; 19]	20 [IQR: 15; 24]	< 0.001
Total lesion volume (mm^3)	464 [IQR: 338; 571]	563 [IQR: 345; 718]	< 0.001
Total lumen volume (mm^3)	2227 [IQR: 1611; 2783]	2197 [IQR: 1677; 2528]	0.59
Low att. lesion vol. (mm^3)	332 [IQR:217;425]	385 [IQR: 238;489]	0.01
Inter. att. lesion vol. (mm^3)	40 [IQR: 12;48]	59 [IQR: 16;83]	0.01
High att. lesion vol. (mm^3)	18 [IQR: 4;21]	46 [IQR: 6;41]	< 0.001
Dense calcium vol. (mm^3)	72 [IQR: 16;127]	72 [IQR: 29;102]	0.73

[IQR: 213;296] mm, (p = 0.18). Total lumen volume did not change between baseline and follow-up studies (2237 [IQR: 1610;2783] vs. 2197 [IQR: 1677;2527] mm^3, p = 0.59). Total vessel wall volume showed significant increase during the follow-up period (464 [IQR: 338; 571] vs. 563 [IQR: 345; 718] mm^3, p < 0.001). Accordingly, overall lesion burden increased from 17% [IQR: 14; 19] to 20% [IQR: 15; 24], p < 0.001.

The volume of high-, intermediate and low-attenuation non-calcified coronary vessel wall components showed significant increase (332 [IQR:217;425] vs. 385 [IQR: 238;489], 40 [IQR: 12;48] vs. 59 [IQR: 16;83] and 18 [IQR: 4;21] vs. 46 [IQR: 6;41] mm^3, respectively, p < 0.05 all), while calcified volume did not change between baseline and follow-up CTAs (72 [IQR: 16;127] vs. 72 [IQR: 29;102] mm^3, p = 0.73). Lesion volumes are summarized in Table 2.

3.3. Progressive vessel wall thickening

Based on conventional coronary CTA reading, progression was present in 11 of 35 (31%) patients, whereas quantitative analysis revealed progression in twice as many patients, 22 of 35 (63%), p = 0.01. Individual lesion volumes showed very good inter-observer agreement for calcified, high-, intermediate-, and low-attenuation non-calcified volumes (ICC: 0.93 [95%CI 0.65; 0.98], 0.92 [95%CI 0.66; 0.98], 0.92 [95%CI 0.66; 0.98] and 0.88 [95%CI 0.53; 0.97], respectively). These resulted in an excellent reproducibility for overall lesion volume and overall lesion burden (ICC: 0.87 [95%CI 0.48; 0.97] and 0.85 [95%CI 0.43; 0.96], respectively.)

4. Discussion

In the present study, we focused on the role of quantitative coronary wall assessment in HTX patients using coronary CTA. We compared our results with standard clinical CT read. Majority of the patients showed slight increase of coronary vessel wall volume during the follow-up period, which might indicate CAV progression. This progression was mainly attributable to non-calcified lesions, while calcified volumes remained unchanged. We demonstrated that quantitative analysis of coronary CTA images identifies more patients with progressive coronary vessel wall thickening, than qualitative assessment.

CAV remains the key limiting factor of HTX patients' long-term survival and it is considered as an immune-mediated endothelial injury of the graft organ aggravated by several non-immunologic factors. It manifests as a luminal narrowing of the intramyocardial and epicardial coronary arteries with concomitant myocardial ischemia and graft function failure. In most cases CAV advances silently as ~90% of the transplanted hearts remain denervated.[17] Therefore, regular screening with ICA is recommended on a yearly basis.[5] The anatomical and histopathological characteristics of CAV differ from the atherosclerotic process. Typically, the disease affects small, distal vessels, while luminal narrowing of the larger epicardial coronaries occurs only in the advanced phase of CAV.[18] Unlikely the eccentric and focal lesions characteristic for atherosclerotic disease, CAV often manifests with concentric intimal hyperplasia with no positive wall remodeling, which might mimic normal coronary wall, therefore it might easily be overlooked by an unexperienced angiographer.[19] The addition of IVUS to ICA reveals about 19% more coronary arteries affected with CAV, than ICA alone, which makes this imaging modality the most sensitive test available to monitor CAV progression in the clinical setting.[20] However, it is an invasive technique with a considerable complication rate of 1–2%. In addition, due to its invasive nature and inconvenience for the patients it decreases patient's adherence to the regular invasive follow-up protocol.

Coronary CTA combines the advantages of both ICA and IVUS with its ability to visualize coronary wall and lumen in a non-invasive fashion. Despite of the relatively high heart-rate and suboptimal heart-rate control of HTX patients the image quality of the coronary CTA exam is usually sufficient for CAV assessment, probably due to the low heart rate variability.[21] The excellent sensitivity and negative predictive values of 64-slice CT generations to identify wall irregularities suspicious for CAV (92–100% and 92–100%) and significant luminal narrowing ≥50% (94% and 99%) prompted several groups – inclusive ours – to replace conventional ICA with CT for annual screening of the HTX patients.[7,18] Moreover, current CT scanner generations with high temporal resolution combined with iterative image reconstruction algorithms allow for serial follow-up studies at low radiation dose in this population.[22] Furthermore, it is important to note that the radiation dose of invasive coronary angiography is comparable with coronary CTA acquired by current scanner generations.[23] Currently, there is no standard reading method available for the investigation of CAV on coronary CTA images, and the discrimination of CAV from atherosclerotic lesions might be challenging. Most groups use SCCT guidelines originally developed to grade atherosclerotic plaques by composition and the subsequent luminal narrowing. A 3-point scale derived from ICA studies was suggested to grade CAV, where grade A represents discrete proximal tubular narrowing, grade B diffuse concentric luminal stenosis, and grade C diffuse irregular concentric luminal narrowing, where occluded branches may be present.[19] At the same time visual assessment of coronary lesions is highly dependent on reader's experience, therefore a robust quantitative assessment seems to be essential.[24] Recently, quantitative software tools were introduced for assessment of stenosis severity on coronary CTA. Higher accuracy was reported in comparison with conventional visual analysis (95% vs. 87%; p = 0.08), with an improved positive predictive value (100% vs. 78%; p < 0.05).[25] Furthermore, excellent inter-observer (ICC: 0.90–0.98), and inter-scan reproducibility (r: 0.88–0.96) were reported for plaque volume assessment using dedicated quantification software, which paved the road for conducting serial follow-up studies.[26,27] In line with these findings, we have observed excellent inter-observer reproducibility of quantitative measurements (ICC: 0.85–0.93).

Our results demonstrate progression of coronary vessel wall volume already within the first two years after heart transplantation. This progression was mainly attributable to non-calcified lesions causing only mild luminal narrowing. When evaluating lesion characteristics, the main components of non-calcified lesions showed high-attenuation (131–350 HU) corresponding to fibrous tissue, while smaller percentage of the lesions showed intermediate attenuation (75–130 HU) consistent with fibro-fatty tissue, and low-attenuation (< 75 HU) analogous with lipid-rich content.[14] These findings are characteristic for CAV, in which coronary lesions are rather diffuse, and focal significant luminal narrowing develops only in a small number of patients. Most non-HTX studies used semi-quantitative plaque assessment and investigated atherosclerotic plaque regression/progression under lipid lowering therapy in patients with established coronary artery disease. In addition, these studies had longer follow-up periods. Nevertheless, prior studies reported 6–13% increase in plaque burden within 2–3 years' follow-up period, generally due to non-calcified volume changes, where calcified lesions mostly remained unchanged.[15] Only very limited data are available concerning the follow-up of HTX patients using serial coronary CTA. The only study conducted by Rohnean et al. also reported rather slow progression of CAV after a 5-years follow-up period of HTX patients as detected with qualitative coronary CTA assessment.[18] According to their results, the time to significant stenosis was consistently longer than 3 years among the 62 HTX patients evaluated, and therefore they recommended to consider a 2-year interval between follow-up studies among patients with normal baseline CT. Patients were classified as having normal coronaries, any wall thickening or significant stenosis. Importantly, in our study we found twice as many patients with significant coronary vessel wall thickening when using quantitative analysis, as compared with standard clinical read. Our findings draw attention to early CAV progression. Even experienced observes might miss the correct diagnosis when concentrating only on focal luminal lesions. The detection of CAV progression in a

very early phase might create the possibility to alter immunosuppressive therapy effectively in the initial phase of the disease and avoid serious complications, such as heart failure, ventricular arrhythmias or sudden cardiac death. Further studies with longer follow-up periods are warranted to define the prognostic value of subclinical CAV progression as detected with quantitative coronary CTA analysis. We have detected predominantly non-calcified lesions. These findings are in line with serial IVUS and virtual histology studies. Torres et al. reported CAV in 55% of the patients when assessed with IVUS and in only 32% when evaluated with subjective reading of ICA ($p = 0.01$). Although they evaluated only the first segment of the left anterior descending coronary with virtual histology IVUS, they demonstrated that fibrous tissue is the predominant component of CAV.[28] Similarly, a recent study using near-infrared spectroscopy and IVUS showed that calcification was barely present in CAV lesions, while a higher prevalence of lipid-rich lesions was observed in CAV, as compared to atherosclerotic plaques.[29]

Our study results are limited to patients undergoing heart transplantation. Patients with general contraindications to coronary CTA were not included in the study, however among HTX patients the most frequent contraindication is impaired renal function, which is also a contraindication for ICA. Furthermore, we did not use a reference standard measurement, however the accuracy of coronary CTA for the detection of coronary atherosclerotic plaque and luminal narrowing is well established in the literature. Moreover, the software we used for quantitative CT analysis was validated against IVUS,[14] and it would not be ethical to expose a patient population, which is already susceptive for malignancies, to additional invasive studies and ionizing radiation exposure. Also, we have analyzed coronary arteries only up until 2-mm luminal diameter, although CAV might affect smaller branches in the early phase of the disease. At the same time these vessels are not suitable for revascularization. Lastly, as a head-to-head comparison between the commonly accepted segment based qualitative reading and semi-automated vessel based quantitative analysis is not feasible, we compared our findings at a patient-based level. This illustrates the inherent limitations of qualitative coronary CTA interpretation in CAV follow-up.

5. Conclusions

Quantitative vessel wall assessment is feasible with coronary CTA in HTX patients. CAV progression within two years after HTX is mainly attributable to non-calcified lesion components, while calcified lesions remain unchanged. When using quantitative analysis with coronary CTA, CAV is detected in significantly more patients using $\geq 10\%$ cut-off than detected with standard CT read. This may imply that CAV might be detected in an early stage when using quantitative CT analysis.

Conflicts of interest

None.

Disclosures

The authors of this manuscript have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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