Original Article

A novel alignment procedure to assess calcified coronary plaques in histopathology, post-mortem computed tomography angiography and optical coherence tomography

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ABSTRACT

Purpose: Improve mapping and registration of longitudinal view on histopathology vessels in a three-dimensional alignment procedure for postmortem quantitative coronary plaque analyses. This new procedure is applied and results shown using calcified coronary plaque analyses within post-mortem computed tomography angiography (PMCTA), optical coherence tomography (OCT) and the gold standard of histopathology.
Results: In total, 338 annotated histopathology images were included, 166 PMCTA transversal images and 285 OCT images were aligned in the comparison. The results from the comparison using the alignment procedure showed overall that the calcified plaques seem to be overestimated by PMCTA and underestimated by OCT.
Conclusions: The 3D fusion approach, aligning the images of PMCTA, OCT and histopathology as gold standard allowed for a slice-based comparison of the different modalities. The results showed that PMCTA overestimates the calcified plaques while OCT underestimates these, compared to histopathology.

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1. Introduction

Coronary atherosclerosis is a worldwide disease and accounts for millions of deaths every year [1]. Therefore, diagnosing coronary plaques is essential to prevent any cardiac events. An extensive amount of studies have explored different modalities to detect coronary plaques and distinguished plaque types. All modalities have limitations and therefore it is crucial to compare these to a gold standard, if possible.

Post-mortem computed tomographic Angiography (PMCTA) is a relative new modality used to detect coronary atherosclerosis as a non-invasive tool [2,3]. The main limitation in PMCTA is the spatial resolution and the fact that calcified plaque is overestimated [4]. A PMCTA allows for the detection and characterization of both coronary stenosis and plaques with moderate to good correlation to intravascular imaging methods such as Optical Coherence Tomography (OCT) [5,6]. The OCT is a modality given the highest possible spatial resolution but limited in the invasive procedure and constraint in the light penetration depth. OCT has a limited penetration depth and therefore reduced ability to depict the outer vessel wall in the presence of large plaques, limiting its capability for total plaque volume assessment [7]. Additional limitations are seen in coronary angiography, magnetic resonance imaging and intravascular ultrasound. Contrary to these limitations histopathology is acknowledged as gold standard identifying components of the atherosclerotic plaque as it is possible to see all details in the plaque or the imprint of the structure that has been there [8,9]. Such studies are made to explore new technical possibilities and furthermore improve diagnostic interpretation of in-vivo scans.

In comparison studies one of the most challenging parts is an exact procedure aligning the images of each modality with the histopathology data in order to be able to interpret the images of the different modalities. If the alignment is not precise, the results could compare different plaques for the PMCTA and histopathology and not showing correct results. Approaches used to ensure correct alignment of different modalities with histopathology data are rarely described and usually compare corresponding but individual, hand-picked slices [10].

The aim of this study was to develop a three-dimensional alignment procedure for postmortem quantitative coronary plaque analyses and test the procedure using calcified coronary plaque analyses within PMCTA, OCT and the gold standard of histopathology.

2. Material and methods

2.1. 3D Alignment procedure

After PMCTA, OCT and histopathology analyses were made independently to delineate calcified plaque, the 3D fusion procedure was applied in order to be able to compare the three imaging methods for each location within the artery. Instead of finding the approximate correspondence of each slice in the three modalities, this study aims to fuse all histopathology images and OCT images with the PMCTA images in a holistic fusion approach. We matched several landmarks and fuse all the images in 3D to get a complete and highly detailed view of the entire vessel.

For this purpose, the digitally scanned images of all the histopathology slices were cropped to areas of 10x10 mm around the vessel and placed on top of the previous image. Each image was translated and rotated in order to superimpose and align the centers of the lumen of the vessel with the previous image. Finally, a new 3D volume was constructed from the stack of fused histopathology slices in order to create longitudinal cross-sections of the vessel similar to an OCT image stack (Fig. 1C).

Next, an independent observer annotated anatomical landmarks (bifurcations, calcified plaques or structures like myocardial tissue) in this stack of images to match these with the corresponding landmarks in the other modalities. This way, each transversal PMCTA image and OCT image was matched with a one (or more) histopathology slices. Fig. 1C shows the program to manually locate corresponding landmarks within the three modalities with on the left-hand side the transversal images of the different modalities (PMCTA, OCT and histopathology from top to bottom) and on the left-hand side the corresponding longitudinal images to place the landmarks.

2.2. Postmortem heart

Data from two coronary arteries (LAD, RCA) were included from one heart to test the alignment procedure. Patients characteristics are included in Table 1 and details on specimen preparation have been described elsewhere [11]. The study was approved by the ethical committee of the Region of Southern Denmark.

2.3. CT acquisition

The PMCTA was performed using a CT750 HD scanner from GE Healthcare with Cardiac snap shot pulse cine protocol. The technical PMCTA and reconstruction details have been described in Table 1 and a former publication [11].

2.4. OCT acquisition

The OCT examination was performed with the Ilumien™ PCI optimization system (LightLab Imaging, St. Jude Medical, Minnesota, USA). The proximal 5 cm of the right and left coronary arteries were measured with the OCT catheter. The technical OCT details have been described in Table 1 and a former publication [11].
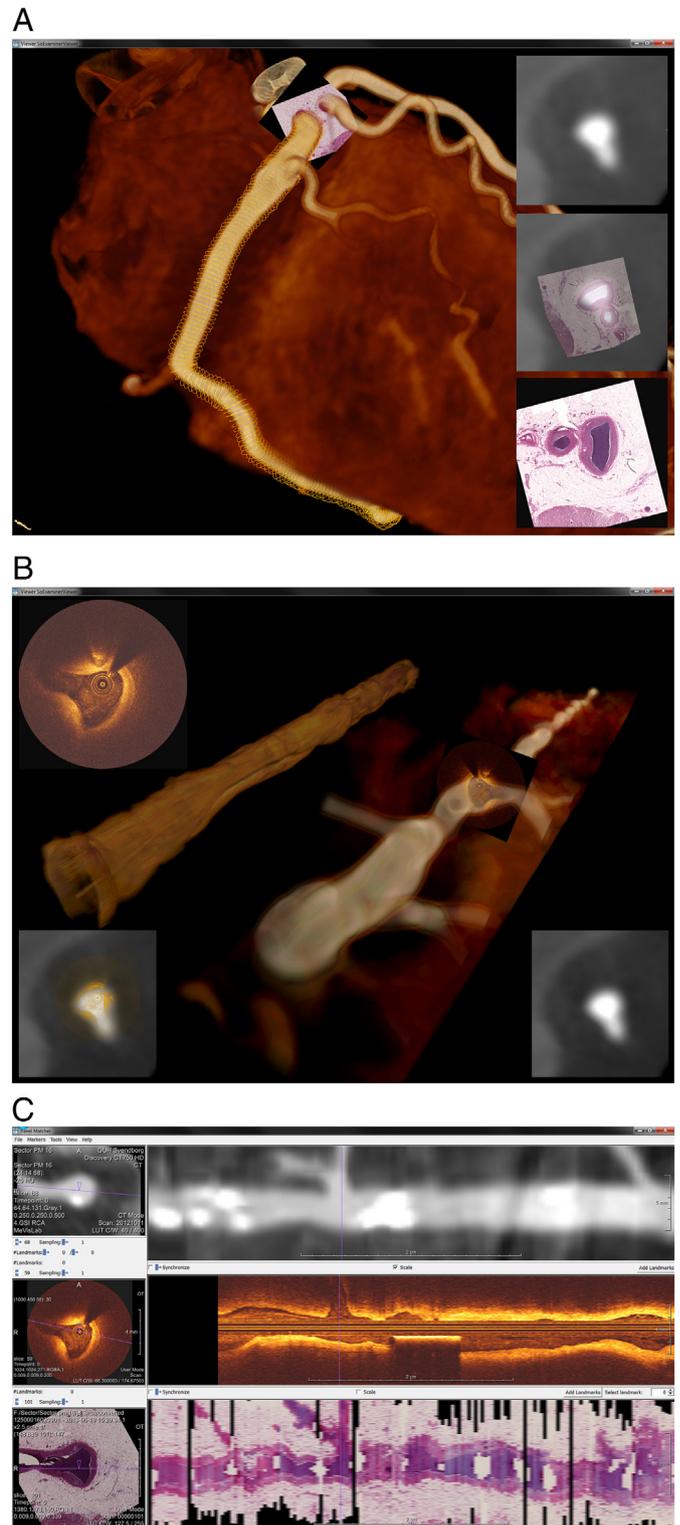

Fig. 1. PMCTA, OCT and histopathology alignment for RCA, A: the entire PMCTA heart with the corresponding histopathology and OCT images, B: Straightened PMCTA and OCT with correlation to axial PMCTA and OCT slices and C: The PMCTA, OCT and histopathology alignment side by side.

2.5. Calcium quantification

All analyses were made blinded to the results of the other imaging methods. Quantitative PMCTA plaque analyses were performed using semi-automatic plaque analysis software called QAngio CT (Research Edition version 2.1.11.1, Medis medical imaging systems bv, Leiden,

Netherlands). The arteries were extracted and segmented after which calcified plaque was automatically identified.

The OCT images were processed and analyzed using QCU-CMS-Research v4, Leiden University Medical Center. Calcium was annotated and delineated on each OCT image.

The histopathology analyses were made by an experienced pathologist (MHM). The hematoxylin and eosin staining shows aggregation of blue-purple densities mixed with fibrosis suggestive of calcification. Hereby, the area of the calcification was annotated in every second transversal image using a newly developed histopathology annotation program. This program makes it possible to mark and annotate structures by drawing freehand shapes (Fig. 2). The shapes can be copied to the sequential images after which they can be moved and adjusted to the new tissue shapes. The program retains a link to the original images to be able to open these corresponding high-resolution images in the NPD view2 program (version 2.3.1 Hamamatsu Photonics, Hamamatsu City, Japan) if a closer examination is needed. All annotated structures of the complete stack of histopathology images with their area measurements can be exported to a Microsoft Excel sheet.

3. Results

In total, 338 (197 RCA, 141 LAD) annotated histopathology images were included, 166 (105 RCA, 61 LAD) PMCTA transversal images and 285 (269 RCA, 16 LAD) OCT images were included in the comparison. The results from the calcium comparison using the alignment procedure are shown in Fig. 3.

Overall, the calcified plaques seem to be overestimated by CTA and the OCT seemed to underestimate the calcified plaques in the RCA. The results for the OCT for LAD are unreliable due to the severe calcifications in this vessel.

4. Discussion

Analyzing PMCTA, OCT and histopathology images for calcified plaques determined the need for an accurate procedure to ensure the same calcified plaque was compared in every modality. The longitudinal view of both PMCTA, OCT and histopathology show advantage in case of slice exceeding structures like calcified plaques as it allows for volumetric measurements and show the extent. This procedure did show many difficulties in aligning and combining these amounts of histopathology data and annotations into one dataset. The annotations on the different modalities were automatically processed, so errors in the annotations were not corrected.

Our comparison study suggested that PMCTA overestimated the calcified plaques, while OCT seemed to underestimate these when compared to histopathology. PMCTA might overestimate calcified plaque due to the blooming artifact while OCT cannot measure bigger calcified areas accurately as the end of the calcified plaque will not be visible due to limited penetration depth. To our knowledge, no former studies evaluated a 3D alignment procedure comparing this big amount on digital data on postmortem data as close as possible to an in vivo situation including the entire heart in a chest phantom. Although, former studies have shown correlations between PMCTA, OCT or other imaging modalities with histopathology on calcified plaques, although mostly only on extracted arteries or only visual measured alignment used. Leschka et al. [12] found that PMCTA had a detection rate of 76% for calcified plaques in 25 postmortem hearts placed directly on the scanner bed, PMCTA evaluation made with manually placed ROI and histopathology inspection made with manual measured alignment. Barreto et al. [13] used seven human coronary arteries to compare PMCTA using dual energy technique with histology on only arteries exacted from the postmortem hearts and no description of the alignment procedure. They found a slightly overestimation of calcified plaque using high kV setting in PMCTA compared to histology data. These results are in agreement with our findings.

This study has several limitations: only two arteries from one heart were included. Only 16 images of sufficient quality could be obtained from the LAD. Furthermore, all well-known factors when working in a postmortem setting as no dynamic movement, deviant pressure in the coronary arteries, fluctuating hemodynamic influence on the vessel wall, etc. [13]. The limitations of the postmortem settings will affect the results, but the alignment method enables the comparison of PMCTA and OCT with the gold standard of histopathology, which is the closest to the ground truth we come. This brief communication shows new possibilities with the procedure for aligning different modalities. More analyses and comparisons of coronary plaques (including non-calcified) will be carried out on the full population of 20 hearts in future research. Future patients might benefit from this study as the automatic assessment of PMCTA plaque constitution can be improved with these results.

5. Conclusions

The 3D fusion approach, aligning the images of PMCTA, OCT and histopathology as gold standard allowed for a slice-based comparison of the different modalities. The results showed that PMCTA overestimates the calcified plaques while OCT underestimates these, compared to histopathology.

Table 1
Background information of the patient, technical parameters of the PMCTA and PMOCT scanning as OCT catheter and guidewire specifications

| Patient			
Physical characteristic	73-year-old male	BMI: 21.9	Heart weight: 390 g
Anamnesis	Hypertension	High cholesterol	Died presumably of a ruptured aorta aneurism
Heart scanned in	Chest phantom with extra fat	Kyoto Kagaku, Lungman, Kyoto, Japan	
PMCTA			
Technical parameters	100 kV	650 mA	Tube rotation time: 0.35 s	Detector collimation: 40 mm
	Slice thickness 0.625 mm	Standard kernel	Bowtie filter/SFOV: Cardiac Small
OCT			
Technical parameters	Automatic pullback devise with speed 20 mm/s	sphygmomanometer controlled the pressure inside the coronary artery at a physiologic level (60–80 mmHg)	Saline flush (0.9%, 37 °C)
Equipment	OCT catheter: C7 Dragonfly™ model 100–100-00 from St Jude Medical	OCT guidewire: PressureWire™ Certus™, model C12008, St. Jude Medical at 0.014 In	

A

B

C
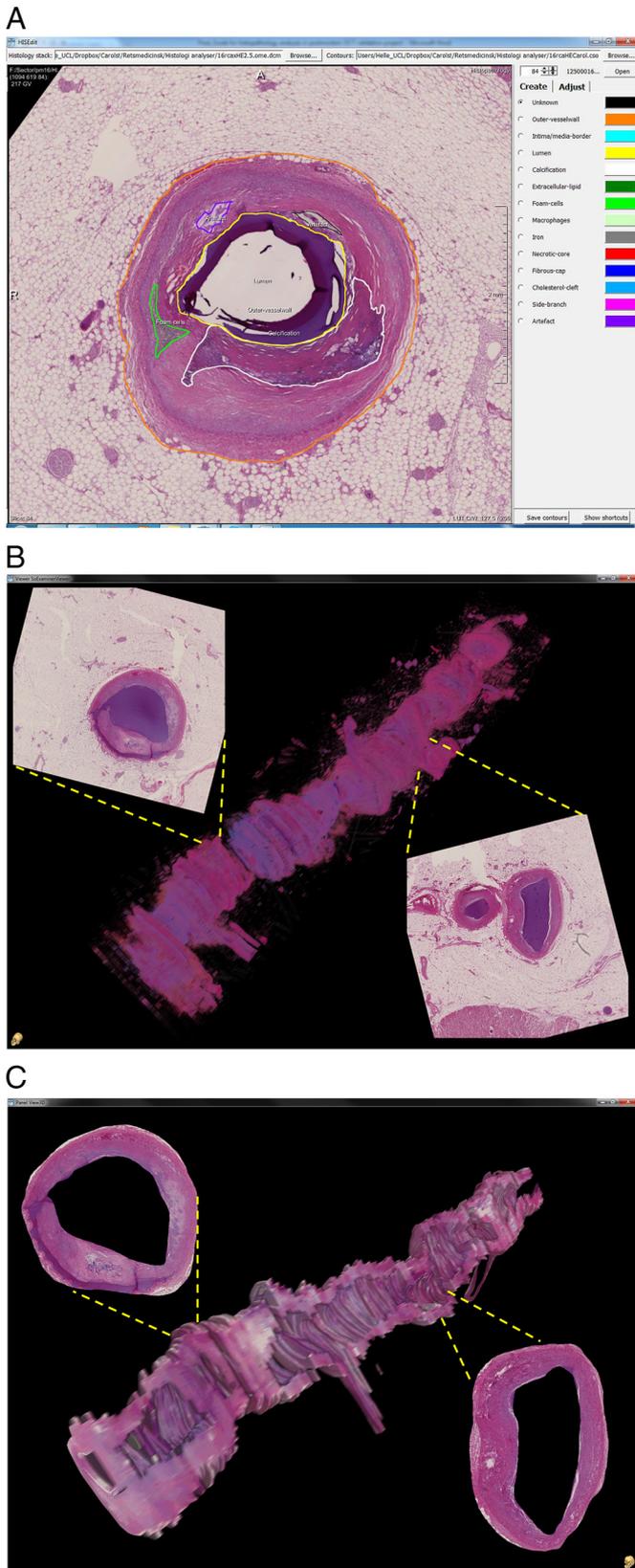
Fig. 2. Histopathology showed on the analyzed vessel. A: annotations on a histopathology image in the new developed program B: longitudinal 3D reconstruction of the postmortem coronary artery vessel showing the outer vessel wall with corresponding histopathology images C: traverse longitudinal 3D reconstruction of the analyzed coronary artery showing the inner vessel wall with corresponding histopathology images.
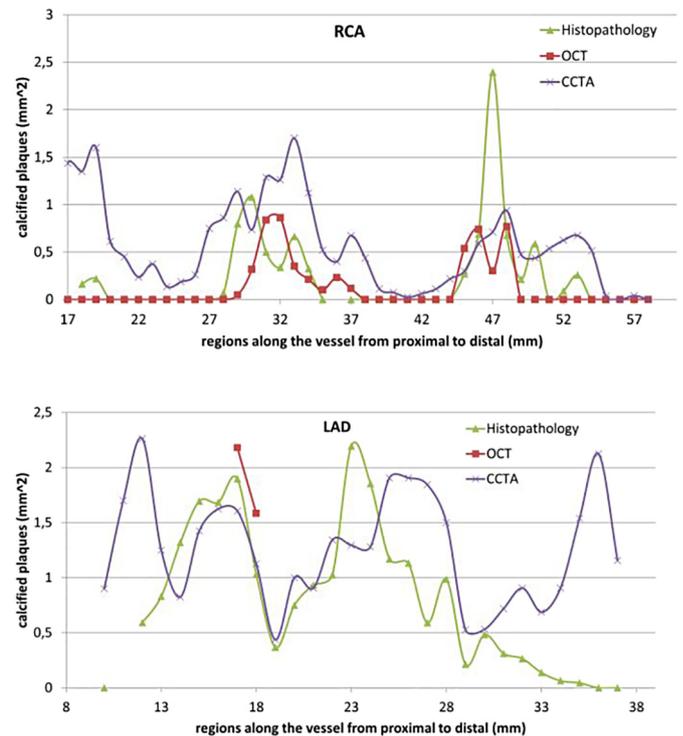

Fig. 3. Results showed as the mean of the calcified plaque areas (mm^2) on every 1 mm region along the vessel for histopathology, OCT and PMCTA in RCA and LAD, respectively.

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