An Automated Approach to Quantify Volumetric Coronary Plaque Composition by Multi-Slice Computed Tomography: An Ex-Vivo Feasibility Study

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Abstract

This study explores the possibility to use the Hounsfield unit (HU) distribution of a coronary plaque to quantify its composition when imaged with multi-slice computed tomography (MSCT). Explanted left anterior descending specimens were imaged with different contrast strengths. In one specimen, 5 sections of 0.9 to 1.4 mm long were 3D-quantitatively evaluated against quantitative volumetric histopathology. There were no substantial differences found between the two quantitative methodologies. Both quantitative methodologies showed a remarkable positive correlation.

This ex-vivo multi-modality imaging study shows encouraging results for quantitative MSCT-CA based plaque composition measurements compared against quantitative histopathology.

1. Introduction

Multi-slice computed tomography coronary angiography (MSCT-CA) is making rapid progress into clinical practice. Although only recently introduced, it may become a standard diagnostic imaging tool for patients suspected of coronary artery disease (CAD) in the near future [1]. However, plaque compositional imaging by MSCT-CA has been limited to measurements of the total amount of calcium present in the complete coronary artery tree (e.g. Agatston score) and/or small regions at individual cross-sectional locations within coronary plaques only [2,3]. Furthermore, in most of the reported studies only qualitative and/or semi-quantitative measurement methods for MSCT-CA plaque composition were applied. An automated approach for quantification of volumetric coronary plaque tissue composition by MSCT-CA has not been reported yet.

This paper proposes a method for automated volumetric quantitative MSCT-CA (QMSCT-CA) plaque compositional measurements and reports an ex-vivo feasibility study with as reference method automated quantitative 3D histopathology.

2. Methods

2.1. Human coronary specimen data

A left anterior descending coronary artery (LAD) was excised within 24h post-mortem 1cm proximal to the bifurcation with the left circumflex (LCX) and covered a length of 40 mm. The specimen was prepared with only the adventitia left surrounding it in a 4% formaldehyde fixation bath with two 6 French sheats stitches at the distal- and proximal end. The Medical Ethical Committee of the Middelheim Hospital Antwerp, Belgium approved the study.

2.2. MSCT-CA imaging

Before MSCT-CA imaging, the specimen was immersed into an olive oil bath, to simulate epicardial fat, at room temperature. To investigate the enhancement effects of contrast on the quantification of the plaque composition, the specimens were imaged and analyzed enhanced and non-enhanced.

The MSCT-CA scan (Sensation 16, Siemens, Germany) was performed with the following parameters: slices/collimation 16/0.75mm, rotation time 375ms, feed/rotation 3.0mm (pitch 0.25), kV 120,mAs 400, effective slice thickness 1 mm, reconstruction increment 0.5mm, Field of View 100mm, convolution filter B60f.

The imaging data were stored in DICOM format on DVD. From the MSCT-CA scanned volume, the coronary specimen data was semi-automatically extracted by vessel extraction software (MSCT Extractor, CURAD BV, Wijk bij Duurstede, Netherlands), allowing presentation of the data in a similar fashion as if one performs a pullback of a coronary catheter such as ICUS or OCT in reconstructed L-views.

To be able to identify the lumen/intima border in the non-enhanced MSCT-CA scan, at first the plaque was identified in the enhanced scan and then copied. After the plaque segmentation, the HU value distribution of the voxels within the plaque were calculated for each sub-segment and plotted as a histogram. The HU distribution curve was subdivided into half, with the two parts comprising the same HU range. "Soft tissue" was determined as belonging to the lower HU values and "hard tissue" to the higher HU values. Voxels belonging to an elevated tail at the high HU-side were labeled calcified, resulting in 3 defined tissue component categories for MSCT-CA: 1) CT-Soft, 2) CT-Hard and 3) CT-Calcium).

2.3. Histology

After imaging, histology was performed following a systematic sectioning methodology as proposed by Gundersen and Jensen [4] (Fig. 1).

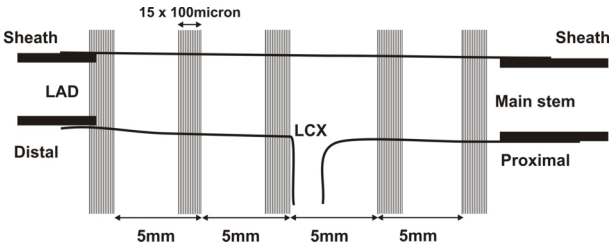

Figure 1. This figure presents the schematic sampling diagram of the histology sectioning. At 5 locations within the coronary specimen 15 histology sections were taken 100µm apart. At the distal and proximal end of the specimen, sheaths were inserted indicated by the thick black lines.

This study demonstrated that in adjacent 5mm sections there was a large variation in plaque composition as a result of the heterogeneity of coronary atherosclerosis at close distances. Histology analysis was performed by using Trichrome Masson staining resulting in 3 defined histology tissue components: 1) Smooth Muscle Cells (HIST-SMC), 2) Collagen (HIST-Coll) and 3) Calcium (HIST-Calcium). Computer-assisted quantitative histology software (CURAD) was used to calculate the relative contribution of the different tissue components and an experienced pathologist (MK) evaluated and approved these results (Fig. 2).

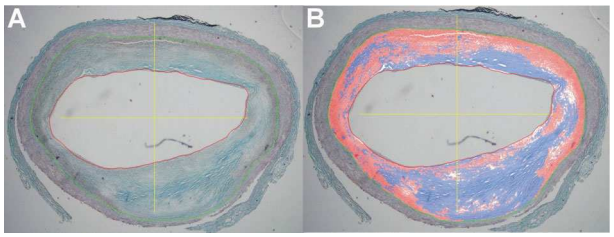

Figure 2. This figure shows a Tri-chrome Masson stained histology section (panel A) and its result of the computer-assisted quantitative measurement by a color-coded overlay. Pixels containing collagen are colored blue, calcium pixels are colored white and smooth muscle cells pixels are colored red.

2.4. OCT imaging

A complex and crucial element is the matching of the histology sections with respect to the MSCT-CA images. A direct visual 1-to-1 comparison of the reconstructed cross-sectional images from the MSCT-CA data to the histology sections is difficult, if not impossible, due to the aforementioned large differences in image resolution. Since OCT has an almost similar lateral image resolution (7µm) as histology, it was applied to establish the link (e.g. synchronization) between MSCT-CA and histology.

OCT imaging was performed using a commercially available 0.019-inch imaging catheter and a 1300nm light source (Lightlab Imaging, Boston, MA, USA).

2.5. MSCT-CA vs. histology

In the vessel analysis software, both the OCT and MSCT-CA image data were loaded and longitudinally reconstructed [5]. Using the identification of the sheath boundaries in both modalities as distance calibration, the cross sectional image data could be automatically synchronized between OCT and MSCT. Then, a visual matching was performed between the histology sections and the OCT images based on the lumen morphology (Fig. 3).

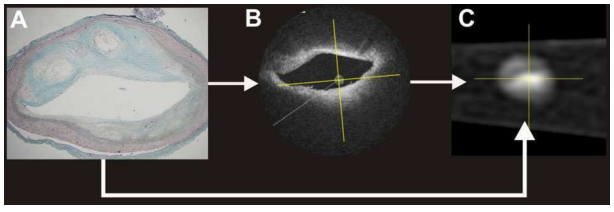

Figure 3. This figure presents the identification process to trace the position where the histology section is taken

with respect to the MSCT-CA image data. On basis of similarity of the lumen morphology, the histology section was first identified in the OCT image data set (panel B), which indirectly leaded to identification of the position of this particular histology section within the MSCT-CA image data, since the OCT and the MSCT-CA data sets are synchronized.Aided by the synchronization, each visually matched OCT image was mapped to the location of the particular histology section within the MSCT-CA image data. In this way, the sub-segments from the histology data could be matched with the corresponding sub-segments in the MSCT dataset.

3. Results

3.1. OCT imaging and histology matching

From the 5 sub-segments 75 histology sections were derived and analyzed. Seventy histology sections could be matched to the OCT images. In the distal sub-segment the sheath blocked partially the view due to which 5 histology sections could not be matched. The results of the 15 consecutive individual histology sections for each of the sub-segments were summed for volumetric calculations and the relative contribution for each tissue component to the total plaque volume was calculated (Fig. 4).

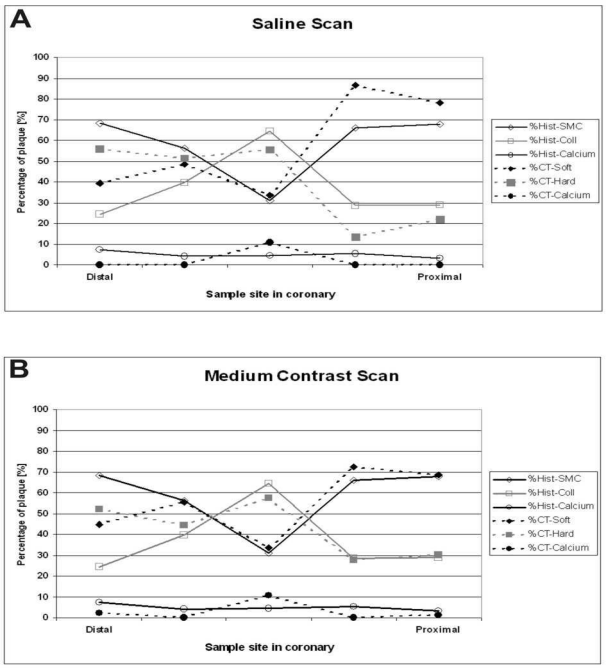

Figure 4. Panel A, shows the MSCT-CA results for the saline scan expressed in percentages of plaque volume (thick dashed lines) together with the quantitative histology results (thick solid lines). Panel B shows the results of the medium contrast scan.

3.2. MSCT-CA vs. histology

Both the saline (Fig. 4A) and the contrast scan (Fig. 4B) show a close relationship between the 3 defined tissue components of both modalities, (e.g. Hist-SMC vs. CT-Soft; Hist-Coll vs. CT-Hard and Hist-Calcium vs. CT-Calcium, respectively) with the enhanced scan showing the closest relationship. The relative mean plaque area results of the three defined tissue components between the modalities in the saline scan: Hist-SMC 58±16% vs. CT-Soft 48±24%, Hist-Coll 37±16% vs. CT-Hard 33±20% and Hist-Calcium 5±2% vs. CT-Calcium 3±5%; respectively, did not show statistically significant differences. Neither the contrast enhanced scan results: Hist-SMC 58±16% vs. CT-Soft 46±16%, Hist-Coll 37±16% vs. CT-Hard 35±13% and Hist-Calcium 5±2% vs. CT-Calcium vs. 3±5%, respectively, showed statistically significant differences applying a student's t-test. Although in total a low number of samples for statistical analysis are available, the results are showing a clear trend.

The HU distribution of the contrast-enhanced scan appears to be broader and shows more structure than the HU distribution from the saline scan (Fig. 5). The relatively large deviation in the result of the distal segment was caused by the fact that at this site of the vessel there was only a small intimal thickening present, which was below the scanning capabilities of the CT.

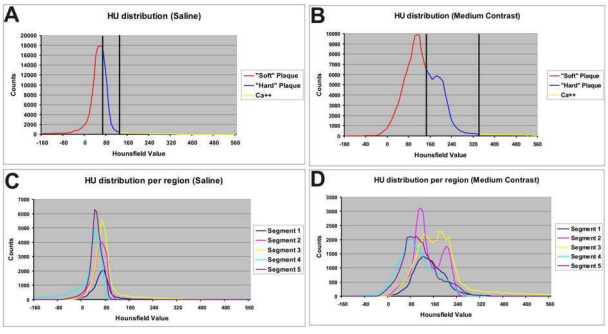

Figure 5. Panels A and B show the Hounsfield unit (HU) distributions as determined for the total plaque volume in the saline (A) and medium contrast (B) scan, together with the discrimination values (vertical lines). Panels C and D show the HU distributions for each of the 5 plaque sub-segments imaged with the saline (C) and medium contrast (D) solution. It can be appreciated that due the influence of the contrast medium, the HU distributions

are broadened.

4. Discussion and conclusions

This ex-vivo study shows the feasibility of quantitative volumetric plaque tissue composition analysis by MSCT-CA. The influence of the use of contrast agents has been evaluated. These are needed to visualize the coronary arteries *in-vivo* and have an effect onto the plaque HU distribution. The HU distribution depends strongly on the administered contrast concentration. This complies with the results of Cademartiri et al. who found a nearly linear relation of the measured HU values in a plaque as a function of luminal contrast. Consequently, the plaque HU distribution broadens with increasing luminal contrast and shows more structure. Although absolute HU values should therefore be used with caution, the discriminating power of the HU distribution seems to improve by the luminal contrast. This is supported by our result that the contrast-enhanced scan shows a closer correlation to histology than the saline scan (Fig. 6). The mechanistic details of this contrast influence, taking into account scanner resolution, applied CT reconstruction algorithms and convolution kernels needs to be explored further.

In contrast to this study, other MSCT-CA plaque compositional studies reported mostly disappointing results. The deviation in outcome between this study and the others could have been caused by application of different methods. MSCT-CA imaging of a rapidly moving coronary artery *in-vivo* causes much more possible artifacts than *ex-vivo* imaging of a coronary specimen. Furthermore, most other studies used ICUS as reference method, which presents plaque compositional results differently than histology, making comparison of the studies difficult. Also, and maybe even more importantly, most of these studies applied a limited MSCT-CA plaque compositional measurement method, by measuring manually HU values at a very limited number of positions within a coronary plaque at a given individual cross-sectional location in the coronary vessel. Furthermore, the influence of the administered contrast medium had not been taken into account.

With our approach we can derive the plaque composition from the HU distribution. The choice of the 3 sub-classes definition of tissue components (e.g. soft, hard and calcium) is rather crude and has limitations. However, the commonly used ICUS derived compositional techniques also result in a limited number of different tissue components. *In-vivo* validation of our approach most likely will be performed by using ICUS as reference method and derived compositional techniques such as virtual histology and/or echogenicity.

The specimen was imaged after fixation with formaldehyde (4%). The advantage is that the circular shape of the vessel is preserved, however, the fixation could have altered the morphology and drains water content from the plaque. There is little known about the fixation effects with respect to MSCT imaging in particular, but previous reports comparing fixed versus freshly harvested coronary arteries applying ICUS as imaging modality, showed only minor changes in measured plaque morphology.

The use of a 16-slice scanner is a limitation. However, without motion the spatial resolution of the scanner types is almost identical. The advantage of the 64-slice scanners (and beyond) is the speed of acquisition. This results in reduced motion artefacts, which could provide the ability to perform tissue characterization with MSCT-CA.

This *ex-vivo* study shows the feasibility and encouraging results of compositional coronary plaque measurements by MSCT-CA.

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