Non-invasive quantification and characterization of coronary plaque: the role of multidetector CT

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Skejby Sygehus

Skejby Sygehus (Figure 1) is a state-of-the-art university hospital where extensive research and education is carried out, and it is one of the most modern and well-equipped hospitals in Europe. It serves as a basic hospital for Aarhus City, a regional hospital for Aarhus County and the West-Danish regions, and as a national hospital for specific diseases, including coronary artery disease.

This article presents early experience obtained at the hospital with CT plaque imaging using the Philips Brilliance 64-channel scanner and the Brilliance Workspace workstation with Comprehensive Cardiac Analysis (CCA) Version 4.0. All images were analyzed using CT Plaque Analysis, part of the CCA package.

Coronary artery disease

Coronary artery disease (CAD) remains the leading cause of death in the United States and most developed countries, and is an increasing cause of worldwide mortality [1, 2, 3]. Tragically, 50 - 60% of the deaths attributed to CAD occur in individuals who were asymptomatic prior to an acute coronary event [2]. Considering that the prevalence of CAD exceeds 13 million individuals in the United States alone [2], the need for earlier detection of atherosclerotic lesions and concomitant treatment is paramount.

Coronary atherosclerosis, the cause of most CAD, was once believed to be a disease of the lumen whereby plaque was thought to first appear within the lumen and then to develop inward to eventually cause clinically significant, flow-limiting stenoses. However, through autopsy research, it was found that arteries outwardly remodel as plaque accumulates within the vessel wall to a point where the plaque area reaches 40% of the total vessel cross sectional area [4]. At this point, the wall can no longer outwardly remodel and the lumen begins to shrink.

Invasive coronary angiography (CAG) is able to show such luminal narrowing; however, CAG is not able to visualize the atherosclerotic lesion itself, and a stenosis is visible only after a period of substantial disease progression [5]. Consequently, patients may have plaque development for many decades before it is visible on CAG [6], reflecting the fact that a stenosis actually represents only the “tip of the iceberg” of CAD.

Intravascular ultrasound (IVUS) has emerged as the gold standard for imaging atherosclerosis in vivo [7]. IVUS is a catheter-based technique that provides a series of cross-sectional images of the vessel, enabling simultaneous visualization and assessment of the lumen, vessel wall, and atherosclerotic plaque.
Despite these advantages, IVUS is an invasive procedure limited to the presence of favorable anatomy, and provides a limited arterial assessment since not all vessels are catheterized. Like CAG, the invasive nature of IVUS limits its application to symptomatic individuals, thus precluding early disease detection. In addition, IVUS has difficulty in imaging heavily calcified lesions due to their high acoustic impedance, and is limited to larger caliber vessels with low tortuosity.

Technological advances in cardiac multidetector computed tomography (MDCT) throughout the past decade have provided clinicians with a non-invasive way to comprehensively evaluate the coronary arteries. Coronary CT angiography (CCTA) has been shown to have a very high negative predictive value in ruling out clinically significant stenoses [8-12]. In addition, CCTA allows the morphologic assessment and characterization of atherosclerotic lesions, and vascular remodeling. This additional information may provide knowledge regarding the presence of so-called vulnerable plaques [13-16] and the likelihood of future coronary events, which cannot be obtained from the luminal narrowing and potential reduction of flow as demonstrated by CAG [17-19].

**CT acquisition**

Contrast-enhanced, ECG-gated spiral retrospective cardiac CT scans are performed at our institution using a 64-channel scanner (Brilliance 64, Philips Healthcare, Cleveland, Ohio, USA). A dedicated cardiac gating algorithm was used that identified the same physiological phases of the cardiac cycle while taking into account the non-linear changes in the individual cardiac states with the heart rate variations during the CT acquisition [20, 21].

A cardiac adaptive multi-cycle (or multi-segment) reconstruction technique was used that combined data from consecutive cardiac cycles, significantly improving temporal resolution [22]. MDCT images are reconstructed at multiple phases using axial planes, multiplanar reconstructions, and maximum intensity projections at 0.67 – 1.0 mm slice thickness and 0.33 – 0.45 increment.

**CT image analysis**

All image analyses were performed using an advanced cardiac CT application (Comprehensive Cardiac Analysis (CCA), Version 4.0, Philips Healthcare, Cleveland, Ohio, USA) on a dedicated CT workstation (Brilliance Workspace, Philips Healthcare). CCA provides no-click coronary segmentation which enables automatic extraction and visualization of the entire coronary tree. Each artery and subsequent side branches can be selected for analysis. A quick measurement of the luminal stenosis in both diameter and area is available using Coronary Analysis where the vessel and lumen contours are calculated and displayed.

A new feature of CCA in v 4.0 is CT Plaque Analysis, which provides the ability to quantify and characterize coronary arterial plaque composition from the CT exam. Once the coronary arteries have been identified and centerlines automatically detected, the application then performs a complete coronary plaque assessment using a simplified workflow with detection of findings along the vessel wall performed via a single-click algorithm. It provides measurements for the lumen, vessel, wall and plaque that comply with the standard IVUS measurements while also providing a remodeling index for each finding. The total plaque volumes are calculated both on a per-segment and per-vessel basis.

CT Plaque Analysis provides two methods to interrogate the plaque findings: either via Threshold, where plaque content is based on simple thresholding, or by a novel Gaussian mixture model technique [23]. The latter technique assumes that the detected plaque volume contains one or more different components, each of which could be represented by a Gaussian distribution with a certain mean and standard deviation. Each of these distributions is then combined linearly to model the whole plaque. The relative compositions are determined by the ratio of their distributions within the plaque. Measurements for each finding, vessel and entire coronary tree are available and can be saved and exported in various formats.

**Case Studies**

**Case 1**

A 56-year-old male presented at the emergency room with chest pain and no prior medical history besides hypertension.

The electrocardiogram (ECG) showed ST-depression in leads II, III, aVF, V4-V5 with no ST elevation. The blood samples showed elevated cardiac biomarkers. A non-ST-elevation myocardial infarction (NSTEMI) was diagnosed, and the patient was scheduled for invasive coronary angiography (CAG).
Prior to the CAG, the patient underwent a contrast-enhanced (Iomerone, 80 cc at 6 cc/sec) cardiac CT scan as part of a research project. The ECG-gated spiral retrospective scan parameters were a collimation of 64 x 0.625 mm, pitch of 0.2, gantry rotation time of 0.42 sec, tube voltage 120 kV, and tube current of 1000 mAs. The scan, completed in 7 sec and covering a length of 80.9 mm, was only intended to image the proximal part of the heart as part of a research protocol. Using a k value of 0.014 for a chest CT, the effective radiation dose was 6.6 mSv.

The CT scan showed abnormal coronary anatomy with the left circumflex (Cx) originating from the right coronary artery (RCA) (Figure 2). It also showed several minor calcifications and diffuse atherosclerosis but no segmental stenosis. These findings were confirmed by both CAG and intravascular ultrasound (IVUS).

The curved multiplanar reconstruction (cMPR) showed a plaque in the most proximal part of the RCA with a minor calcification and a large non-calcified area (Figure 3). This was confirmed by CT Plaque Analysis, which revealed a 3.8 mm long, mainly non-calcified plaque. The threshold between calcified and non-calcified tissue was set at 120 HU [24]. The mean HU in the plaque was 50.2; the total plaque volume was 42.7 mm³, and the maximum plaque burden on the cross-sectional images was 54% (Figure 4).

CT and IVUS findings along with percent difference are shown in Table 1. In the proximal part of the RCA, the plaque was identified and virtual histology (VH) confirmed the presence of a mainly non-calcified plaque. By means of IVUS-VH (Volcano Corporation, San Diego, CA, USA), the plaque was classified as a fibroatheroma [25] with necrotic core and fibrous tissue accounting for more than 90% of the plaque volume. Total plaque volume reviewed by IVUS was 48.6 mm³, and the maximum plaque burden on the cross-sectional frames was 66.9% (Figure 5a and b).

Plaque findings by means of CT Plaque Analysis were in agreement with the content findings with a difference of 4 %, which is within the 93 – 97 % accuracy of IVUS-VH and ex vivo histology validation [26]. The differences in maximum burden, volume and length are attributed to the small size of the plaque.

<table>
<thead>
<tr>
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<th>CT plaque analysis</th>
<th>IVUS-VH</th>
<th>Difference (%)</th>
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<tbody>
<tr>
<td>Max burden</td>
<td>54%</td>
<td>66.9%</td>
<td>12.9</td>
</tr>
<tr>
<td>Volume</td>
<td>42.7 mm³</td>
<td>48.6 mm³</td>
<td>12.1</td>
</tr>
<tr>
<td>Content</td>
<td>14% Calcified, 86% Non-calcified</td>
<td>10% Calcified, 90% Non-calcified</td>
<td>4.0</td>
</tr>
<tr>
<td>Length</td>
<td>3.8 mm</td>
<td>3.3 mm</td>
<td>15.2</td>
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Percutaneous coronary intervention (PCI) was not performed since no significant stenosis was present. Instead, standard medical treatment was initiated (aspirin, clopidogrel, ACE-inhibitors, oral beta-blockers and statins). When the patient was re-examined after one month, he was asymptomatic.

**Case 2**

A 59-year-old man was hospitalized due to several attacks of severe chest pain over a three-week period. He had no prior medical history besides hypercholesterolemia.

The patient presented with a normal ECG and normal biomarkers, but he was submitted to a sub-acute CAG due to the severe and sustained chest pain. CAG found diffuse atherosclerosis in all main vessels. In particular, a stenosis in the LAD and the first diagonal branch (D1) distal to the bifurcation was observed. Furthermore, significant stenoses were detected at the Cx/first obtuse marginal (OM) bifurcation (Figure 6) and in the RCA just distal to the crux (Figure 7). IVUS was performed in the Cx and RCA.

Prior to the CAG, the patient underwent a contrast-enhanced (Omnipaque 350, 75 cc at 6 cc/sec) cardiac CT scan as part of a research project. The spiral retrospective scan parameters were 64 x 0.625 mm collimation, 0.2 pitch, 0.42 sec gantry rotation time, 120 kV tube voltage, and tube current of 800 mAs. An ECG-triggered dose modulation protocol (DoseRight Cardiac, Philips Healthcare, Cleveland, Ohio, USA) was applied to reduce radiation dose during systole. The scan covered a length of 132.8 mm in just under 10 sec for an effective dose of 8.7 mSv. The CT findings were consistent with the CAG, revealing severe atherosclerosis with multiple non-calcified plaques in all main vessels.

Despite the sub-occlusion in segment two of the LAD, CCA with CT Plaque Analysis was able to segment the artery as demonstrated in the volume rendered and cMPR images (Figures 8, 9). Further analysis by CT Plaque Analysis revealed a primarily non-calcified plaque (11% calcified and 89% non-calcified) with a mean HU of 39.4 and a total plaque volume of 62.8 mm³ (Figure 10).
In the RCA a non-calcified plaque was visible just distal to the bifurcation (Figure 11). The vessel was segmented and CT Plaque Analysis demonstrated a non-calcified plaque. The mean HU was 57.7, the maximum plaque burden 79%, the plaque length 7.3 mm, and the total plaque volume 66.6 mm$^3$. The corresponding IVUS-VH image showed a fibroatheroma consisting of mainly fibrous and fibro-fatty tissue. In this case, the maximum plaque burden was 76.1%, the plaque length 7.4 mm, and the total plaque volume was 58.1 mm$^3$ (Figure 12a and b). The findings for the two different imaging modalities are shown in Table 2. There is good...
agreement in maximum burden and plaque length. The volume difference in plaque is within the range of up to 18% difference in cross sectional area measurements that can be found with different IVUS imaging catheters. [27]. The percentage difference in content findings can be attributed to the inherent underestimation in calcium by IVUS due to inadequate penetration of calcium by the IVUS transducer signal and the overestimation of CT in instances of blooming due to calcification.

The patient was treated with stent implantation in the LAD segment one and two and in the Cx obtuse marginal branch while PCI with balloon angioplasty was performed in D1. When the patient was re-examined after three months, he was asymptomatic and able to play tennis as he did before.

Discussion

The Philips CT Plaque Analysis, with its simplified workflow, provides physicians with plaque information, including the location, morphology, and composition. As the case studies demonstrate, CT-based plaque indices agree with the findings of CAG and IVUS with virtual histology. This type of information could potentially be useful in risk stratifying patients with sub-clinical cardiovascular disease and may guide preventive treatment. However, the clinical value of these new tools will have to be confirmed by randomized trials proving a prognostic value of such early risk stratification. Consequently, they must still be regarded as experimental at this stage.

In addition, these tools may enable the evaluation of different therapeutic strategies to prevent the further development of sub-clinical disease. For research purposes, CT Plaque Analysis provides an excellent way to standardize the evaluation of different plaque types. The expected further technical development of this application will likely allow for an even more precise plaque characterization. With the advent of the next generation of scanners, such as the Brilliance iCT (Philips Healthcare) with improvements in speed, tube power, and coverage along with dose reduction technologies, there are opportunities to further investigate plaque characterization in a wider range of patient cohorts.

Conclusion

Philips CT Plaque Analysis may help in further understanding the morphology and the underlying composition of significant and non-significant atherosclerotic lesions. These lesions can be interrogated to provide additional information on the entire disease state of the patient, and may guide further prevention and treatment options, which will hopefully prevent future adverse cardiovascular events.

<table>
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<tr>
<td>Max burden</td>
<td>79%</td>
<td>76.1%</td>
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<tr>
<td>Volume</td>
<td>66.6 mm³</td>
<td>58.1 mm³</td>
</tr>
<tr>
<td>Content</td>
<td>15% Calcified, 85% Non-calcified</td>
<td>3% Calcified, 97% Non-calcified</td>
</tr>
<tr>
<td>Length</td>
<td>7.3 mm</td>
<td>7.4 mm</td>
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</table>

Table 2. Results of CT Plaque Analysis and IVUS-VH for the RCA plaque.

References


