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Comparison of coronary plaque subtypes in male and female patients using 320-row MDCTA

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Abstract

**Objective**—Determine plaque subtype and volume difference in male and female patients with obstructive and non-obstructive CAD using 320-row MDCTA.

**Materials and methods**—128 patients with suspected CAD underwent MDCTA. All studies were divided into two groups based on disease severity. 0–70% stenosis (non-obstructive CAD) & >70% (obstructive). All were compared for plaque quantity and subtypes by gender. Main arteries, RCA, LM, LAD and LCX were analyzed using Vitrea 5.2 software to quantify fatty, fibrous and calcified plaque. Thresholds for coronary plaque quantification (volume in mm\textsuperscript{3}) were preset at 35 ± 12 HU for fatty, 90 ± 24 HU for fibrous and >130 HU for calcified/mixed plaque and analyzed using STATA software.
Results—Total plaque burden in 118 patients [65M: 53F] was significantly higher in all arteries in males compared to females with non-obstructive disease. Total plaque volume for males vs. females was: RCA: $10.10 \pm 5.02 \, \text{mm}^3$ vs. $6.89 \pm 2.75 \, \text{mm}^3$, respectively, $p = 0.001$; LAD: $7.21 \pm 3.38 \, \text{mm}^3$ vs. $5.89 \pm 1.93 \, \text{mm}^3$, respectively, $p = 0.04$; LCX: $9.13 \pm 3.27 \, \text{mm}^3$ vs. $7.16 \pm 1.73 \, \text{mm}^3$, respectively, $p = 0.002$; LM $15.13 \pm 4.51 \, \text{mm}^3$ vs. $11.85 \pm 4.03 \, \text{mm}^3$, respectively, $p = 0.001$. In sub-analyses, males had significantly more fibrous and fatty plaque in LM, LAD & LCX than females. However in the RCA, only fibrous plaque was significantly greater in males. Calcified plaque volume was not significantly different in both genders. Only 8% of patients had obstructive CAD (>70% stenosis); there was no significant difference in plaque volume or subtypes.

Conclusion—in patients with non-obstructive CAD, males were found to have significantly higher total coronary plaque volume with predominance of fibrous and fatty subtypes compared to females of the same age and BMI. There was no significant difference in plaque subtype or volume in patients with obstructive disease.

Keywords
Coronary plaque subtypes; Coronary artery disease; 320-row MDCTA

1. Introduction

Atherosclerosis is a chronic inflammatory process responsible for a host of disease processes including coronary events, stroke, peripheral vascular disease and hypertension [1,2]. A greater proportion of acute coronary events including acute myocardial infarction and sudden cardiac death occur in patients without prior symptoms as these events are initiated by rupture of mildly stenotic vulnerable plaque [3]. Such plaque is usually non-calcified (lipid-rich) and slowly progresses over many years before the clinical event. Conventional angiography is invasive with its antecedent risks; moreover, evaluation of the lumen may not be sufficient for evaluating mildly stenotic vulnerable plaque. Direct observation and assessment of coronary plaque burden and plaque subtypes with intravascular ultrasound (IVUS), optical coherence tomography, infrared spectroscopy and angioscopy as well as non-invasive imaging techniques like Multi Detector Computed Tomography (MDCT) and Magnetic Resonance Imaging are gaining momentum. Recent advances and the non-invasive nature of MDCT make this imaging modality uniquely suited to further our understanding of the natural history of coronary artery disease (CAD) and therefore has generated a remarkable interest for assessment of CAD [4,5].

Taking into consideration that non-calcified plaque is more often associated with acute coronary syndrome compared to calcified plaque [6–8], the importance of identifying different plaque types and quantifying percent stenosis and plaque volume remains an important concern. Also some reports have suggested that non-calcified plaque may have a higher tendency to regress in the context of medical therapy which targets coronary atherosclerosis [9]; again emphasizing the need for plaque characterization. MDCT permits imaging of calcified atherosclerotic plaque (CAP) using a non-contrast technique. The additional detection of non-calcified arteriosclerotic plaque (NCAP) and mixed calcified...
atherosclerotic plaque (MCAP) and luminal narrowing can be assessed using contrast-enhanced image acquisition.

MDCTA is emerging as an effective imaging modality for differentiating plaque subtypes i.e. NCAP, CAP, MCAP as well as to determine percent stenosis [10]. The advent of newer scanners, i.e. 256 and 320 row-MDCT, may further refine image quality for evaluating sub-millimeter plaque subtypes; moreover, the ability to reduce data acquisition time [10] and dose by reducing volume scan length is possible [11,12]. In this study, we sought to compare plaque subtypes in patients with known CAD (Obstructive vs. non-obstructive) with reference to gender using 320-row MDCT.

2. Methods
This HIPAA-compliant study was approved by our institution’s Committee on Clinical Investigations. Informed consent was waived as this was a retrospective study. A retrospective review of consecutive MDCT examinations in our database performed between June 2008 and December 2008 yielded 128 patients who had undergone MDCTA (Table 1). The indication for MDCTA comprised the assessment of the coronary arteries for atypical chest pain and visualization of cardiac anatomy before or after surgical procedures. Exclusion criteria for MDCTA were contraindication to iodinated contrast agents, renal insufficiency (serum creatinine > 1.5 mg/dl) and atrial fibrillation. Two independent radiologists with level 3 certification of SCCT and who were blinded to the patient details or the results of the examinations performed the analysis using axial maximum intensity (MIP) and multiplanar (MPR) images using the 16-segment model proposed by the American Heart Association. All patients with <70% stenosis were classified as having non-obstructive disease. Those patients with ≥70% stenosis were classified as having obstructive disease based on radiologist readings. Patients were then stratified by gender for sub-analyses of plaque quantification. Plaque quantification was performed in the main coronary vessels including RCA (Segment I, II & III), LM (Segment V), LAD (Segment VI, VII, VIII) and LCX (Segment XI, XIII & XV) for a total of 10 segments based on the AHA 16-segment coronary artery model [13]. Branches were not included in plaque quantification because of a high incidence of anatomic variability.

3. CT imaging protocol
All patients were scanned on a 320-row MDCT scanner (Toshiba Aquilion One) using a prospective gating technique. Patients were connected to EKG leads and placed in a standard position to enable CT synchronization with the EKG. Oral or intravenous beta blockade with Metoprolol was administered in patients with a heart rate (HR) greater than 65 beats per minute (bpm) to avoid cardiac motion artifacts and assure accurate gated imaging. Sublingual nitroglycerine 0.4 mg was given to all patients just prior to the scan unless contraindicated (there were no patients with contraindication in our study). The starting point of the volume scan and coverage area was craniocaudally from one centimeter below the tracheal bifurcation to the diaphragm. Prior to the examination, all patients were instructed on quiet breathing and breath holding in order to minimize artifacts during scanning. An intravenous bolus of non-ionic iodinated contrast agent Optiray-350 (70–90
ml) was given at the rate of 4–5 ml per second followed by a bolus of saline. The region of
interest was placed over the descending aorta and exposure triggered at 300 Hounsfield units
(HU). All patients were imaged at 60–80% of R–R interval using a prospective gating
 technique. Scanning parameters were determined based upon patient’s weight, height and
BMI values (Table 2). Transaxial images were reconstructed with 0.5 mm slice thickness.

4. Coronary plaque identification and quantification

Analysis was performed for all patients by using standard axial, MIP and MPR reformats.
All reconstruction and plaque analyses were performed using Vitrea workstation (Vital
images; version 5.2) [5,14–16]. The readers had access to scroll through axial images, to
interactively perform multiplanar reconstructions, maximum intensity projections, as well as
curved multiplanar reformats for both data sets. Using sculpt tool and various window
levels, the main coronary vessels were exposed. The probe feature was then used to quantify
plaque in the four major coronary vessels; Right coronary artery (RCA), Left main artery
(LMA), Left anterior descending artery (LAD) and Left circumflex artery (LCX). Stents and
distal segments with diameter less than 2 mm were not included in analysis, the latter due to
limited spatial resolution [17]. Coronary plaque characteristics (fibrous, fatty, and calcified)
were analyzed in all patients. Coronary plaques with densities of 35 ±12 HU, 90 ± 24 HU,
and >150 HU were defined as fatty, fibrous and fully calcified plaque, respectively. These
coronary plaque thresholds were based on HU density ranges as reported and validated by
others comparing MDCTA to IVUS [5,16–22] and histo-pathological comparisons with CT
[23,24].

Thresholds for coronary plaque quantification were preset in the Vitrea analysis tool before
performing the analysis. To standardize plaque analysis and compensate for variable
coronary arterial lengths in patients and between genders, plaque volume (mm$^3$) per artery
length was used. The software analysis tool provides color coding for lumen and the
different plaque components and automatically generates total volume and percentage of
different plaque components (Fig. 1 A & B). Calcified plaque usually causes partial volume
artifact in quantifying fibrous and fatty plaque. To avoid calcium blooming artifact, manual
adjustments were done by redrawing contours in those particular segments. All analyses
were performed by two independent readers to assess the inter-observer and tool
reproducibility. The average of both readings was used for final analysis.

5. Statistical analysis

Patient characteristics were expressed as mean ± SD for continuous and percentages for
categorical variables. The two tailed student’s t test and chi-square test, respectively, were
performed to assess clinical variables between groups. Kruskal–Wallis test (a non paranetric test to compare three or more groups) was used to compare plaque burden in
different vessels in both genders. $p$ value <0.05 was considered as significant. The Intra-
observer and Inter-observer variability were calculated according to Bland and Altman’s
statistical method [25,26]. A value of 1 indicates perfect correlation and any value above 0.7
shows excellent correlation [27].
6. Results

128 consecutive patients underwent MDCTA for suspected CAD; their baseline characteristics and risk factors are shown in Table 1. 118 patients had non-obstructive CAD with a mean age of 61 ± 14 years and BMI of 28 ± 6. In this non-obstructive CAD group, 63 subjects were men and 55 were women. There was no statistical difference between men and women in age, 60 ± 15 vs. 63 ± 13 years, respectively (p = 0.377), or BMI, 28 ± 5 vs. 28 ± 7, respectively (p = 0.871). The average vessel lengths (mm) used for plaque quantification were RCA: 139.74 ± 39.50; LM: 11.83 ± 5.11; LAD: 127.92 ± 33.38 and LCX: 106.41 ± 33.03. The total plaque volume was significantly higher in each of the 4 vessels in males compared to females. Total plaque volume (mm³) for males vs. females was: RCA: 10.10 ± 5.02 vs. 6.89 ± 2.75, respectively, p = 0.001; LAD: 7.21 ± 3.38 vs. 5.89 ± 1.93, respectively, p = 0.04; LCX: 9.13 ± 3.27 vs. 7.16 ± 1.73, respectively, p = 0.002; and LM: 15.13 ± 4.51 vs. 11.85 ± 4.03, respectively, p = 0.001 (Table 3). The Intra-observer and Inter-observer agreement indexes were 0.99 and 0.98, respectively, showing excellent correlation between readings. In sub-analyses for plaque subtypes, males had more fibrous and fatty plaque in LM, LAD & LCX than females. In the RCA, only fibrous plaque was significantly greater in males than females (3.05 ± 1.08 vs. 2.11 ± 0.73, respectively, p ≤ 0.0001). The calcified plaque volume was similar in all vessels in both genders. Only 8% of patients had obstructive CAD (≥70% stenosis); however, there was no difference in plaque volume or subtype by gender (Table 3).

7. Discussion

The current study adds to the literature and provides an important insight into our understanding of the impact of gender on the natural history of atherosclerosis. The results of our study show that, in patients with non-obstructive CAD, males were found to have higher total coronary plaque burden with a predominance of fibrous and fatty subtypes of plaque when compared to females of the same age and BMI, findings which are concordant with prior gender specific studies using MDCTA [28,29]. Similarly, two gender specific studies using IVUS have demonstrated that the coronary plaque burden was significantly lower in women compared to men [30,31]. Female patients in our study had a mean age of 63 ± 13 years, which was similar to that of men, 60 ±15. In the Framingham Heart Study, the incidence of clinically-evident CAD in women increased after menopause and reached that of men around age 75 years [32]. Therefore, the lower total plaque burden and lower prevalence of fatty plaques in women, who are of similar age as men in the current study, provide support for the traditional view that clinical events typically begin later in life in women compared to men, a finding which is attributed to the protective influence of endogenous estrogen and supports the use of aggressive medical therapy in both women and men with non-obstructive disease.

Given that total plaque burden is considered the most important predictor of coronary events and that rupture of non-calcified vulnerable plaque has been implicated as the cause of ACS, the importance of plaque quantification cannot be underestimated [33–35]. There is intense interest in using MDCTA to identify and quantify plaque volume because of its non-invasive nature and its ability to differentiate plaque density [10,18]. In a study using myocardial...
perfusion with SPECT, mixed plaque was more likely associated with an increased likelihood of myocardial perfusion abnormalities [36]. There has also been a suggestion that MDCTA may be useful in differentiating stable vs. unstable plaque [37] and another study has suggested that coronary MDCTA can provide additional prognostic information to baseline risk stratification [29]. Coronary angiography, an invasive method and the gold standard with respect to treatment, images the lumen but the vessel can increase in size due to remodeling, thus allowing the vessel to appear normal until late in the process and then it reveals only 1–5% of disease [38]. In contrast, MDCTA accurately measures the components of the arterial wall and shows excellent inter- and intraclass correlation coefficients for measuring plaque volume and percentage of fatty, fibrous and calcified components which varied from 0.99 to 0.93 compared to plaque volumes measured by IVUS-virtual histology (IVUS-VH) [16]. Thus, an advantage of MDCTA is that it can provide information beyond that provided by conventional coronary angiography.

IVUS-VH has been a major advance and has become the gold standard to assess plaque components directly, quantify plaque volume and identify vulnerable plaque [39]. IVUS-VH also measures intraluminal plaque plus media which is important but does not define the outer boundary of the adventitia which may play an important role in the atherosclerotic process as suggested by proliferation of adventitial vasa vasorum and plaque neovascularity [33,40]. However, as with coronary arteriography, IVUS is invasive and associated with a small but significant risk. The spatial resolution is excellent, 100–150 μm but still not in the realm of resolving the thin-cap fibroatheroma of <65 μm (the pathological measurement and definition) of the thin fibrous cap [41]. Optical coherence tomography (OCT), which has a resolution of 10–20 μm, has the ability to evaluate plaque with complex heterogeneous morphology, such as previous plaque rupture with healing, to measure thin fibrous caps and to identify plaque that may be prone to rupture [42,43]. Although MDCTA is an important imaging method for differentiating the components of plaque and imaging the entire arterial wall, its resolution of 400 μm prevents it from differentiating thin or thick fibrous caps [44–47]. Therefore, the findings at OCT will be invaluable to correlate with non-calcified plaque as demonstrated by MDCTA [42,43].

Our results demonstrate that 320-row MDCT imaging can further differentiate non-calcified plaque into fibrous and fatty components; this is important information since plaque composition is a predictor of plaque stability with non-calcified plaques, which are fatty, more likely to rupture and result in acute coronary syndromes than fibrous or calcified plaques. The observations in our study of higher plaque burden and more fatty plaque in men compared to women when non-obstructive disease is considered, support the suggestion that non-calcified plaque is associated with higher risk of cardiovascular events. This also supports the need for lifestyle modification and or aggressive medical therapy to arrest or reverse an otherwise progressive disease in both women and men. Moreover, the finding of no significant differences in plaque subtypes between males and females with stenosis ≥70% (obstructive disease) supports the need for angiography and/or revascularization in both men and women if symptoms persist with maximal medical therapy. Therefore, MDCTA may be uniquely suited to study the natural history of CAD and by identifying plaque composition, may provide additional prognostic information to the baseline risk stratification.
8. Limitation

Limitations of our study include its retrospective, observational analysis from a single institution using only MDCTA. Our study population comprised symptomatic individuals; therefore, the results are not generalizable to asymptomatic populations. Finally, comparison with IVUS or OCT was not performed in these patients. A follow-up study examining plaque composition in relation to clinical events could potentially determine which particular plaque subtype may be predictive of acute coronary syndromes in men and women.

References


Atherosclerosis. Author manuscript; available in PMC 2016 February 18.
Fig. 1.
(A & B): Coronary artery cross-sections: demonstrate outer wall, luminal wall and three different types of non-calcified plaque (represented by different colors).
Table 1
Clinical characteristics in those with (non-obstructive); mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Male N = 65</th>
<th>Female N = 53</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 15</td>
<td>63 ± 13</td>
<td>0.377</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 5</td>
<td>28 ± 7</td>
<td>0.871</td>
</tr>
<tr>
<td>Smoking status (n/%)</td>
<td>30/46</td>
<td>25/47</td>
<td>0.873</td>
</tr>
<tr>
<td>H/O hypertension (n/%)</td>
<td>33/50</td>
<td>28/52</td>
<td>0.822</td>
</tr>
<tr>
<td>H/O diabetes (n%)</td>
<td>9/13</td>
<td>8/15</td>
<td>0.849</td>
</tr>
<tr>
<td>H/O myocardial infarction (n%)</td>
<td>7/10</td>
<td>2/03</td>
<td>0.138</td>
</tr>
<tr>
<td>Family H/O CAD (n%)</td>
<td>34/52</td>
<td>29/54</td>
<td>0.796</td>
</tr>
</tbody>
</table>
Table 2

Scanning parameters based on BMI value.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Tube current, mA</th>
<th>BMI</th>
<th>Tube current, mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>450</td>
<td>23</td>
<td>400</td>
</tr>
<tr>
<td>19</td>
<td>500</td>
<td>25</td>
<td>450</td>
</tr>
<tr>
<td>21</td>
<td>520</td>
<td>30</td>
<td>500</td>
</tr>
<tr>
<td>23</td>
<td>550</td>
<td>30–40</td>
<td>580</td>
</tr>
</tbody>
</table>
Table 3

Plaque volume (mm³) in both male and female gender.

<table>
<thead>
<tr>
<th></th>
<th>LM</th>
<th></th>
<th>LAD</th>
<th></th>
<th>LCX</th>
<th></th>
<th>RCA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>p Value</td>
<td>Female</td>
<td>Male</td>
<td>p Value</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Non-obstructive CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty</td>
<td>4.11 ± 1.63</td>
<td>5.95 ± 1.89</td>
<td>&lt;0.0001</td>
<td>2.72 ± 0.68</td>
<td>3.39 ± 1.31</td>
<td>0.007</td>
<td>3.27 ± 0.74</td>
<td>4.48 ± 1.50</td>
</tr>
<tr>
<td>Calcified</td>
<td>5.65 ± 2.31</td>
<td>6.17 ± 3.34</td>
<td>0.43</td>
<td>1.34 ± 1.03</td>
<td>1.89 ± 2.14</td>
<td>0.18</td>
<td>1.98 ± 1.26</td>
<td>2.09 ± 1.76</td>
</tr>
<tr>
<td>Fibrous</td>
<td>2.10 ± 1.0</td>
<td>3.12 ± 1.27</td>
<td>0.0002</td>
<td>1.83 ± 0.66</td>
<td>2.30 ± 0.72</td>
<td>0.004</td>
<td>1.91 ± 0.68</td>
<td>2.75 ± 0.85</td>
</tr>
<tr>
<td>Total</td>
<td>11.85 ± 4.03</td>
<td>15.13 ± 4.51</td>
<td>0.001</td>
<td>5.89 ± 1.93</td>
<td>7.21 ± 3.38</td>
<td>0.04</td>
<td>7.16 ± 1.73</td>
<td>9.13 ± 3.27</td>
</tr>
<tr>
<td>Obstructive CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty</td>
<td>4.93 ± 1.53</td>
<td>6.46 ± 1.53</td>
<td>0.06</td>
<td>3.15 ± 1.15</td>
<td>3.31 ± 0.99</td>
<td>0.72</td>
<td>4.17 ± 1.22</td>
<td>5.49 ± 1.27</td>
</tr>
<tr>
<td>Calcified</td>
<td>5.17 ± 1.78</td>
<td>6.51 ± 3.44</td>
<td>0.17</td>
<td>1.25 ± 0.83</td>
<td>1.34 ± 0.71</td>
<td>0.77</td>
<td>1.70 ± 1.35</td>
<td>2.09 ± 1.30</td>
</tr>
<tr>
<td>Fibrous</td>
<td>2.68 ± 0.88</td>
<td>3.34 ± 1.23</td>
<td>0.11</td>
<td>2.16 ± 0.66</td>
<td>2.31 ± 0.59</td>
<td>0.59</td>
<td>2.47 ± 0.68</td>
<td>3.12 ± 1.00</td>
</tr>
<tr>
<td>Total</td>
<td>12.79 ± 2.70</td>
<td>16.33 ± 5.18</td>
<td>0.02</td>
<td>6.57 ± 2.14</td>
<td>6.97 ± 1.74</td>
<td>0.63</td>
<td>8.38 ± 2.15</td>
<td>10.69 ± 1.71</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SD.