Plaque disruption by coronary computed tomographic angiography in stable patients vs. acute coronary syndrome: a feasibility study

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Received 12 December 2014; accepted after revision 16 September 2015; online publish-ahead-of-print 9 November 2015

**Aims**
This study was designed to determine whether coronary CT angiography (CTA) can detect features of plaque disruption in clinically stable patients and to compare lesion prevalence and features between stable patients and those with acute coronary syndrome (ACS).

**Methods**
We retrospectively identified patients undergoing CTA, followed by invasive coronary angiography (ICA) within 60 days. Quantitative 3-vessel CTA lesion analysis was performed on all plaques ≥25% stenosis to assess total plaque volume, low attenuation plaque (LAP, <50 HU) volume, and remodelling index. Plaques were qualitatively assessed for CTA features of disruption, including ulceration and intra-plaque dye penetration (IDP). ICA was employed as a reference standard for disruption. A total of 145 (94 ACS and 51 stable) patients were identified. By CTA, plaque disruption was evident in 77.7% of ACS cases. Although more common among those with ACS, CTA also detected plaque disruption in 37.3% of clinically stable patients (P < 0.0001).

**Conclusions**
Clinically stable patients commonly manifest plaques with features of disruption as determined by CTA. Though the prevalence of plaque disruption is less than patients with ACS, these findings support the concept that some clinically stable patients may harbour ‘silent’ disrupted plaques. These findings may have implications for detection of ‘at risk’ plaques and patients.

**Keywords**
Acute coronary syndrome • Vulnerable plaque • Coronary computed tomographic angiography • Stable angina • Plaque characterization

**Introduction**
Plaque rupture triggering thrombosis is the proximate cause of most acute coronary syndromes (ACS).¹⁻⁰ Although plaque disruption may precipitate ACS, observations from autopsy and direct coronary imaging studies indicate that plaque disruption may also be clinically ‘silent’.²⁻⁹ Chronic lesion progression has traditionally been viewed as the result of steady, chronic accretion of atherosclerotic plaque. However, prior observations document that clinically stable or even asymptomatic patients may suffer repetitive episodes of silent plaque rupture and intra-plaque haemorrhage.⁴⁻⁷,¹⁰⁻¹⁶ Such lesion events may contribute to a staccato pattern of plaque growth, wherein intra-plaque haemorrhage induces sudden lesion expansion underlying rapid transition from a non-flow-limiting plaque to a flow-limiting stenosis. Though the resulting exertional angina is considered clinically stable once present for several months, it may in fact represent the effects of chronic unstable plaque events.³⁻⁷,¹¹⁻¹⁷

Recent studies demonstrate that coronary computed tomographic angiography (CTA) can detect features of plaque disruption in patients with ACS, indicated by ulceration and intra-plaque dye penetration (IDP); findings validated against invasive coronary angiography (ICA).¹⁸,¹⁹ We postulated that plaque disruption might also be detected by CTA in patients with clinically stable coronary artery
disease. This study was designed to determine whether CTA detects features of plaque disruption in clinically stable patients compared with a control group of ACS patients, in whom plaque disruption would be expected to be more common.

**Methods**

**Study population**

We retrospectively identified patients who underwent CTA and subsequent ICA within 60 days which was used as a reference for plaque disruption. Patients were included if: (i) CTA was performed for clinically suspected coronary artery disease; (ii) CTA identified the presence of coronary artery disease; (iii) and ICA was performed ≤60 days after the index CTA. There was no clinical change in the patients between index CTA and ICA. Patients having inadequate CTA image quality including those with ≥1 uninterpretable segment in a major epicardial coronary artery or subjectively difficult to visualize coronary arteries and plaques, a history of prior coronary revascularization via coronary artery bypass, percutaneous coronary intervention, or chronic total coronary occlusion(s) were excluded from analysis (Figure 1). This study was approved by the Human Investigations Committee at William Beaumont Hospital.

All patients meeting inclusion criteria were categorized as having either presented with clinically stable coronary artery disease or ACS. For the purposes of this study, ACS was defined according to American College of Cardiology/American Heart Association guidelines as either rest angina, new-onset angina, or increasing angina.20 No patients with ACS had acute myocardial infarction, as patients with elevated cardiac enzymes are not permitted to undergo CTA at this institution. All patients having a clinical presentation not meeting this definition of ACS were deemed to have clinically stable coronary artery disease.

**CTA scanning techniques**

In patients undergoing CTA before 1 July 2006, imaging was performed on a 64-slice scanner (Sensation 64, Siemens Medical Systems, Forchheim, Germany), and thereafter on a dual-source system (Somatom Definition, Siemens Healthcare, Forchheim, Germany). Beta-blockers and sublingual nitroglycerin (0.4 mg) were administered according to standard institutional protocols. Typical scan parameters included a tube voltage of 100–120 kV, tube current of 425 mAs, gantry rotation time 0.330 s, pitch 0.2–0.43 (adapted to heart rate), and electrocardiographic current modulation with full current between 40 and 70% of the cardiac cycle. Using a medium soft convolution kernel (B36), 0.75 mm multi-phasic axial reconstructions were performed at 0–90% of the R–R interval. Additional reconstruction windows were employed as necessary to minimize motion artefacts.

**CTA analysis**

CTA interpretation was performed by two independent observers, blinded to the clinical presentation and ICA results. The CTA readers (J.G. and K.C.) have a combined >20 years of experience in interpreting CT images and have published prior peer reviewed papers on plaque characterization by CTA. Images were analyzed for degree stenosis and both qualitatively and quantitatively for features of disruption and IDP analysis on a three-dimensional workstation (Aquarius, TeraRecon, San Mateo, CA, USA). The remaining quantitative lesion analysis was performed according to established methods18,21–26 and utilizing software that facilitates calculation of lesion geometry and density (SURE-Plaque, Vital Images, Minnetonka, MN, USA) Plaques were analyzed

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**Figure 1** Patient selection for study inclusion. From our existing database, 186 patients were identified as having undergone a CTA followed by an ICA within 60 days. In addition to exclusion criteria as seen, clinical reasoning for patients undergoing CTA among those that were clinically stable are listed.
from a centerline enhanced cross-sectional image of a curved planar reconstruction of the coronary lumen with adjustable plaque visualization window widths and levels. The inter-observer agreement for designation of a plaque as disrupted by CTA was 95%. The agreement rate for the presence of ulceration was 96% (κ = 0.88; 95% CI 0.80–0.96) and for IDP was 96% (κ = 0.91; 95% CI 0.85–0.97). In cases of disagreement, a decision was reached by consensus.

All plaques having ≥25% diameter stenosis by quantitative CTA analysis were analyzed in detail for morphologic features according to prior methods. Parameters analyzed included: (i) plaque volume; (ii) remodeling index; (iii) plaque attenuation; and (iv) features of plaque disruption. Plaques with a remodeling index ≥1.10 were considered positively remodelled. As has been previously described, 'low attenuation plaque' (LAP) is any plaque having an attenuation of <50 Hounsfield units (HU), and we reported plaque density as both the total volume and proportionate volume of LAP within the lesion. All plaques were analyzed for the presence or absence of calcification. Features indicative of plaque disruption included ulceration, defined as a disruption in the interface between the plaque and lumen with contrast penetration directly from the lumen into the plaque but contiguous with the lumen, and IDP, defined as the presence of discrete zones of density within a plaque, similar to the density of the contrast-filled lumen but not contiguous with the vessel lumen. A plaque was considered to be disrupted by CTA if either or both of these features were present. General image quality was assessed on a qualitative basis, as signal-to-noise ratios were not calculated for this study. Image quality for assessing plaque disruption was a high priority, and any studies as well as individual vessels and/or plaques which were qualitatively un-interpretable were immediately dismissed from analysis. Further, specifically with regard to assessment of IDP and ulceration, a careful 360° review of the imaged vessel and plaque, as well as cross-sectional analysis was completed to ensure areas of IDP were not small branch vessels or artefactual in nature.

Focal areas of intra-lesion high attenuation, qualitatively distinct from adjacent LAP but similar to the attenuation of luminal contrast, were deemed IDP. To establish that these focal densities noted as IDP were likely accumulations of intra-plaque contrast dye, each zone of IDP was analyzed for HU attenuation, and then compared with the HU in the adjacent contrast-filled lumen, and compared as well to areas deemed calcific if present in a given vessel (Figure 2). The IDP HU

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**Figure 2** Example CTA with plaques for analysis. The CTA image is shown with a cross-sectional slice top left (demarcated on the larger image by a green line). The representative non-calcified and calcified plaques are shown with average Hounsfield units (HU). The yellow dashed area demarcates the representative plaque, with LAP (white arrow) seen within, as well as focal areas of calcification (black arrow) and intra-plaque dye penetration (IDP) which is characterized by contrast seen within a LAP, without being contiguous with the vessel lumen (yellow arrows, short and long axis views). Yellow dashed lines represent plaque extent.
samples were taken from a multi-planar reformat imaged of the plaque and the adjacent lumen. Five regions of interest were sampled, and averaged from within the IDP as well as the adjacent lumen and were used for statistical comparisons. In segments where a calcified plaque was also present, a similar five point mean HU attenuation was obtained for each such plaque.

Invasive coronary angiography
ICA was performed according to standard methods and images were stored digitally. Angiograms were evaluated by two independent observers blinded to each other as well as to clinical findings and CTA results. These observers (J.G. and R.M.) have a combined 30 years of experience in interpreting and performing ICA and have published peer reviewed articles on plaque disruption by ICA. Angiographic plaque morphology was analyzed according to established invasive criteria.\(^{28-30}\) Lesions were considered ‘complex’ if they exhibited either: (i) ulceration, defined as the presence of contrast beyond the vessel lumen; (ii) intraluminal filling defect consistent with thrombus; or (iii) a combination of haziness, irregular margins, or fissuring, defined as overhanging edges. All other lesions not fulfilling these criteria were considered ‘non-complex’. The inter-observer agreement on plaque complexity was 97% (k = 0.93 95% CI 0.87–0.98). When disagreement existed between the two observers in regard to designation of a plaque as complex, a final decision was reached through consensus.

Invasive angiograms were also analyzed to determine the ‘culprit’ status of all plaques identified by CTA. Plaques were deemed culprit lesions if they were labeled as >70% stenosis by the physician performing the catheterization, and which subsequently underwent revascularization.

Statistical analysis
A comparison of the morphologic characteristics of plaques with and without features of disruption by CTA was performed using a repeated measures analysis. To perform a repeated measures analysis adjusting for plaques within the same patient, the data needed to be normally distributed. Various transformations were made on non-normally distributed variables and the analysis was completed on the best-fitted transformation. For categorical variables, repeated measures analysis was performed using generalized estimating equations with an exchangeable correlation model. For continuous variables, repeated measures analysis was performed using mixed effects models with plaque type as a fixed effect. For specific comparison of attenuation at differing locations, a Pearson or Spearman correlation coefficient was used for normally and non-normally distributed data, respectively.

Categorical variables are reported as counts and percent frequencies. Continuous variables are shown as means ± standard deviation, and where appropriate median ± standard deviation was used. All analyses used The SAS\textsuperscript{\textregistered} System for Windows version 9.3 (Cary, NC, USA).

### Results

#### Clinical characteristics

Between May 2004 and January 2008, we identified 186 patients who underwent CTA followed by ICA within the following 60 days. A total of 41 patients were excluded from analysis and the present analysis was performed in the remaining cohort of 145 patients, including 51 (35.2%) patients classified as clinically stable and 94 (64.8%) patients who presented with ACS (Figure 1). Reasons for CTA among clinically stable and ACS patients are reviewed in Figure 1. Demographics and risk factors in both groups are summarized in Table 1. Study groups were well matched, although clinically stable patients were older and more likely to have diabetes.

**Table 1** Baseline patient characteristics by presentation

<table>
<thead>
<tr>
<th></th>
<th>Acute coronary syndrome (n = 94)</th>
<th>Clinically stable (n = 51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 13</td>
<td>64 ± 9</td>
<td>0.026</td>
</tr>
<tr>
<td>Male (%)</td>
<td>56.7</td>
<td>62.7</td>
<td>0.487</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>65.9</td>
<td>70.5</td>
<td>0.459</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>64.8</td>
<td>61.1</td>
<td>0.982</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12.7</td>
<td>29.4</td>
<td>0.012</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>72.3</td>
<td>76.9</td>
<td>0.694</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>45.1</td>
<td>35.4</td>
<td>0.273</td>
</tr>
<tr>
<td>Total plaques ≥25% stenosis (plaque per patient)</td>
<td>439 (4.7 ± 2.1)</td>
<td>240 (4.7 ± 2.5)</td>
<td>0.880</td>
</tr>
<tr>
<td>Mean patient age with a disrupted plaque by CTA</td>
<td>60.3 ± 12.1</td>
<td>64 ± 10.6</td>
<td>0.223</td>
</tr>
<tr>
<td>Diabetes status of patients with a disrupted plaque by CTA</td>
<td>9 (12.3)</td>
<td>6 (31.2)</td>
<td>0.071</td>
</tr>
<tr>
<td>Days from index CTA to ICA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 days</td>
<td>51 (54.3)</td>
<td>2 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;3 days</td>
<td>64 (68.1)</td>
<td>3 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;7 days</td>
<td>72 (76.6)</td>
<td>7 (13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;14 days</td>
<td>78 (83.0)</td>
<td>15 (29.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;30 days</td>
<td>93 (98.9)</td>
<td>35 (68.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;60 days</td>
<td>94 (100.0)</td>
<td>51 (100.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, percentage, or count (%) where appropriate. CTA, coronary computed tomographic angiography; ICA, invasive coronary angiography.
Prevalence and patterns of plaque disruption by CTA in clinically stable patients

Among clinically stable patients, CTA detected 240 plaques causing ≥25% luminal stenosis. (4.7 ± 2.5 lesions per patient, Table 1). At least 1 disrupted lesion was detected by CTA in 19 patients (37.3%) and multiple disrupted lesions were detected in 9 patients (17.6%) (Figures 3 and 4). Of the total 31 disrupted lesions found by CTA, IDP was evident in 23 (74.2%), ulceration in 14 (45.2%) and both features of disruption identified in 6 (19.4%) plaques (Table 2).

Prevalence and patterns of plaque disruption by CTA in ACS patients

Among patients presenting with ACS, CTA detected 439 plaques causing ≥25% luminal stenosis. (4.7 ± 2.1 lesions per patient, Table 1). At least 1 disrupted lesion was detected by CTA in 72 patients (77.7%), and multiple disrupted lesions were detected in 45 patients (47.5%) (Figure 3). Of the total 146 disrupted lesions found by CTA, IDP was evident in 101 (69.2%), ulceration in 72 (49.3%) and both features of disruption identified in 31 (21.3%) plaques (Table 2).

Prevalence of CTA features of plaque disruption in stable vs. ACS patients

Compared with clinically stable patients, those with ACS more commonly manifested at least one plaque as well as multiple disrupted plaques with CTA features of disruption (Table 1, Figure 3). Although no difference was identified in the total number of plaques in patients with clinically stable coronary artery disease compared with those with ACS, plaques having CTA features of disruption accounted for a smaller percentage of the total lesion burden in those with clinically stable coronary artery disease.

CTA features of disruption vs. ICA as the reference standard

Among all clinically stable patients, of the 240 plaques analyzed by CTA, 31 (12.9%) lesions were deemed angiographically complex at the time of ICA (Tables 1 and 2), with such examples seen in Figures 5 and 6. Among the 31 disrupted plaques by CTA, ICA documented angiographic complexity in 19 (61.3%) (Table 2). By comparison, only 11 of 209 (5.3%) non-disrupted lesions by CTA were angiographically complex (61.3 vs. 5.3%, P ≤ 0.0001, Table 3). Similarly for ACS patients, among the 146 plaques analyzed showing CTA features of disruption, 85 (58.2%) were deemed concordantly angiographically complex (Table 2), with such examples seen in Figures 7 and 8. Conversely, among the 293 non-disrupted plaques by CTA, a mere 14 (4.7%) were deemed angiographically complex by ICA (55.1 vs. 4.7%, P < 0.0001, Table 3). These data show among both clinically stable and ACS patients that disrupted plaques by CTA are 12 times more likely to be complex by ICA than their non-disrupted counterparts.

Comparative CTA morphology of all disrupted vs. non-disrupted plaques

Comparing the morphologic features of disrupted and non-disrupted plaques independent of clinical presentation, disrupted plaques showed a statistically significant higher plaque volume, higher volume of LAP, greater proportionate volume of LAP and cause a greater severity of stenosis (Table 3). Similarly, disrupted plaques were more often positively remodelled, and had a higher overall remodelling index.

CTA features of disrupted plaques: comparison of stable vs. ACS patients

Comparing CTA features of disrupted plaques only according to clinical presentation, lesions in those with ACS showed a statistically significant higher plaque volume, higher volume of LAP, and more severe stenosis compared with clinically stable cases (Table 2). No
Figure 4 Patient with ACS manifesting multiple unstable plaques. ICA of the left circumflex (top left), illustrating ostial hazy lesion (red arrows); corresponding CTA image (bottom left) reveals zone of focal IDP (yellow arrow) within larger LAP (white arrow). Cross-sectional CTA view through the plaque reveals IDP as punctate area of dye penetration (yellow arrow). ICA of the RCA (middle top) shows hazy ulcerated plaque (red arrows, black border); corresponding CTA image (top right) documents mixed composition elements with calcific plaque (black arrow, white border), LAP (white arrow) and an area of plaque ulceration (yellow arrow). CTA cross-sectional images from the plaque zone demarcated by the green line (middle and right bottom panes), compare plaque densities at different CTA window widths and levels: These images delineate the full extent of LAP (yellow dashed area) and the focal areas of IDP and ulceration (yellow arrow).

Table 2 CTA morphologic characteristics of disrupted plaques in ACS patients vs. those with a clinically stable presentation

<table>
<thead>
<tr>
<th></th>
<th>ACS (n = 146)</th>
<th>Clinically stable (n = 31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis (%)</td>
<td>64 ± 16</td>
<td>50 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcification</td>
<td>79 (54.1)</td>
<td>22 (71.0)</td>
<td>0.114</td>
</tr>
<tr>
<td>Plaque volume (mm³)</td>
<td>269 ± 322</td>
<td>118 ± 91</td>
<td>0.014</td>
</tr>
<tr>
<td>Volume LAP (mm³)</td>
<td>84 ± 147</td>
<td>24 ± 17</td>
<td>0.025</td>
</tr>
<tr>
<td>Proportionate volume LAP (%)</td>
<td>30 ± 32</td>
<td>22 ± 8</td>
<td>0.169</td>
</tr>
<tr>
<td>Proportionate volume LAP ≥ 25%</td>
<td>68 (46.6)</td>
<td>10 (32.3)</td>
<td>0.167</td>
</tr>
<tr>
<td>Remodelling index</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1</td>
</tr>
<tr>
<td>Positively remodelled</td>
<td>134 (91.8)</td>
<td>29 (93.5)</td>
<td>1</td>
</tr>
<tr>
<td>Plaque burden (mm²)</td>
<td>21 ± 14</td>
<td>16 ± 6</td>
<td>0.053</td>
</tr>
<tr>
<td>Ulceration by CTA</td>
<td>72 (49.3)</td>
<td>14 (45.2)</td>
<td>0.693</td>
</tr>
<tr>
<td>IDP by CTA</td>
<td>101 (69.2)</td>
<td>23 (74.2)</td>
<td>0.675</td>
</tr>
<tr>
<td>Concordantly complex by ICA</td>
<td>85 (58.2)</td>
<td>19 (61.3)</td>
<td>0.849</td>
</tr>
<tr>
<td>Deemed culprit by ICA</td>
<td>58 (39.7)</td>
<td>10 (32.2)</td>
<td>0.543</td>
</tr>
</tbody>
</table>

Values shown are mean ± standard deviation or count (%) where appropriate. CTA, coronary computed tomographic angiography; IDP, intra-plaque dye penetration; LAP, low attenuation plaque; ICA, invasive coronary angiography.
differences were seen between groups with regard to remodelling index, proportionate volume of LAP, type of disruption seen on CTA (ulceration or IDP), nor concordant complexity on ICA.

**CTA disrupted plaques: relation to ICA culprit plaques**

A total of 108 plaques were identified by ICA as ‘culprit’ lesions which underwent revascularization. Among these, 68 were concordantly disrupted by CTA (63%) and 72 (67%) were deemed angiographically complex upon blinded review. Table 2 reviews the relationship between ACS and clinically stable patients with regard to plaque disruption, and there was no difference seen between groups regarding culprit status and plaque disruption ($P = 0.54$). Interestingly, of the 68 ICA culprit plaques which were disrupted by CTA, 60 (88%) were concordantly angiographically complex.

**Age and diabetes as independent risk factors for plaque disruption**

In our study, the clinically stable population was older and had a higher percentage of diabetic patients. When looking at only those patients who had evidence of plaque disruption by CTA, the average age of clinically stable patients was 64.0 ± 10.6, while the average age of a similar ACS patient was 60.3 ± 12.1 ($P = 0.22$, Table 1). Of the total 51 clinically stable patients, a disrupted plaque by CTA was found in 19 patients (37.2%). Of these, 6 (31.6%) were diabetic and 13 (68.4%) were non-diabetic. Of the 94 ACS patients, a disrupted plaque was found by CTA in 73 patients (77.7%). Of these, 9 were diabetic (12.3%) and 64 were non-diabetic (87.6%). There was no statistical difference among clinically stable and ACS patients with regard to diabetes and plaque instability by CTA ($P = 0.07$, Table 1).

**Validation of IDP: comparison to lumen contrast**

To confirm the likelihood that IDP reflects contrast dye within the plaque, we performed a detailed analysis of these regions compared with the adjacent contrast-filled lumen (Figure 2); in those lesions which also contained calcification, we compared density of IDP vs. the calcific zone. Of the total 73 patients with at least one plaque manifesting IDP, HU within the IDP zone was nearly identical to
that in the lumen (Figure 9). In addition, in the 14-vessel segments containing both zones of IDP and segments of calcification, there was no significant correlation between the IDP HU and the calcified plaque HU, denoting the IDP less likely to be calcification. A summary of the median HU for the lumen, IDP, and calcific plaque are shown in Figure 10.

Table 3  Plaque characterization among all disrupted vs. all non-disrupted plaques

<table>
<thead>
<tr>
<th></th>
<th>CTA disrupted (n = 177)</th>
<th>CTA non-disrupted (n = 502)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis (%)</td>
<td>61 ± 17</td>
<td>52 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcification</td>
<td>101 (57.1%)</td>
<td>406 (80.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque volume (mm³)</td>
<td>242 ± 300</td>
<td>125 ± 101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume LAP (mm³)</td>
<td>74 ± 136</td>
<td>20 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportionate volume LAP (%)</td>
<td>28 ± 30</td>
<td>18 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportionate volume LAP ≥25%</td>
<td>78 (44.1%)</td>
<td>79 (15.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remodelling index</td>
<td>1.44 ± 0.34</td>
<td>1.26 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positively remodelled</td>
<td>163 (92.1%)</td>
<td>338 (67.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque burden (mm²)</td>
<td>21 ± 13</td>
<td>16 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concordantly complex by ICA</td>
<td>100 (56.5%)</td>
<td>25 (5.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically stable</td>
<td>19 (61.3%)</td>
<td>11 (5.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACS</td>
<td>81 (55.1%)</td>
<td>14 (4.7%)</td>
<td>&lt;0.001</td>
</tr>
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</table>

Values shown are mean ± standard deviation or count (%) where appropriate.
CTA, coronary computed tomographic angiography; LAP, low attenuation plaque.
Discussion

This study is the first to document that CTA detects features of plaque disruption in clinically stable patients. In support of this novel concept, our data suggest lesions in which CTA detected evidence of disruption had a nearly 12-fold greater frequency of concurrent complexity by ICA compared with non-disrupted lesion. Furthermore, lesions having CTA features of plaque disruption were significantly more likely to have additional morphologic features characteristic of high-risk plaques, including a greater plaque volume and a greater volume of LAP. Finally, this study observed that plaques having CTA features of disruption were more common in patients with ACS, in whom plaque disruption has been previously demonstrated by invasive coronary imaging techniques to be more common.12–19 These results support those of prior studies documenting that CTA can delineate features of plaque disruption in ACS patients with invasively proven plaque rupture.18,19

The present observations demonstrating evidence of plaque disruption in greater than one-third of clinically stable patients by CTA are novel, yet consistent with the concept that plaque disruption may be clinically silent. Traditionally, stable angina is thought to result from a stable flow-limiting stenosis. However, the term ‘stable’ is a clinical designation-based upon symptom patterns and does not necessarily reflect underlying plaque pathophysiology.3–7,11–17 Histopathological studies clearly document that lesion progression is not necessarily a process of slow, steady, indolent accretion of plaque; rather, many lesions may undergo plaque disruption events which are clinically unapparent.5–11 Observations from pathological and direct coronary imaging studies now document that some patients with clinically stable angina manifest evidence of plaque disruption.5–17 Presumably, such disruptions may induce rapid plaque progression from a haemodynamically insignificant lesion, to a flow-limiting stenosis manifest clinically as the transition from an asymptomatic state to the onset of stable exertional angina.5–19

The search for ‘vulnerable plaque’, the morphological precursor to most cases of ACS and sudden death, is the subject of intense investigation.1–8,11–14,16–19,21–27,31–34 The present CTA findings are consistent with and extend those of prior invasive and CTA plaque characterization studies. The landmark PROSPECT study documented that vulnerable lesions are characterized by invasive direct coronary imaging as having a large plaque burden, a necrotic core, and a smaller mean luminal area.13 Recent near infrared spectroscopy studies have documented that target lesions in stable patients are commonly lipid-core plaques.14 Previous non-invasive CTA studies document that culprit lesions in patients with ACS are characterized by positive remodelling and low attenuation,16–19,23,25,26 as well as features of frank plaque disruption18,19; while prior prospective CTA studies in stable patients document patients with ‘2-feature

Figure 7 Patient presenting with ACS manifesting plaque ulceration. ICA of the proximal LAD (top left) showing haziness (red arrows) and calcific plaque (black arrow). Corresponding CTA image (bottom left) detailing the area of LAP (white arrow) and plaque ulceration (yellow arrow). Calcified plaque is seen (black arrow). CTA image (top right) with cross-section detailing plaque ulceration (yellow arrow). CTA image (bottom right) seen at different image window level, highlights the ulceration (yellow arrow).
positive plaques exhibiting positive remodelling and low attenuation, labelled plaques, are at higher risk for future disruption and adverse cardiac events, suggesting such lesions may represent 'vulnerable' lesions. While direct coronary imaging is the 'gold standard' for plaque morphology in general and plaque disruption in particular, ICA is reasonably accurate for delineation of frank plaque ruptures. The present observations show that patients presenting as clinically stable were older and more likely to be diabetic. These findings are consistent with prior data documenting that elderly patients more commonly manifest stable ischaemic heart disease. Approximately 30% of the stable patients had diabetes, which is consistent with the prevalence of this disease in most studies of both stable and unstable coronary disease cohorts. Prior studies have shown that CTA may be of incremental benefit in risk stratification and prediction of events in diabetic patients, even over and above that of coronary calcium scoring. That stable diabetics in this study often manifested plaque disruption may be explained in part by the fact that diabetics may not manifest typical ischaemic symptoms, and that unstable plaque events may in fact be clinically silent. This may explain the lack of an overt, classical clinical presentation among the present diabetic cohort with 'clinically stable' presentations. Although CTA has been proposed to detect

the presence and magnitude of CAD and to identify high-risk plaques in asymptomatic diabetic patients, further prospective studies are necessary to validate whether such a screening strategy imparts clinical value. In the present retrospective study, among ACS and clinically stable patients with evidence of disrupted plaques identified by CTA, mean age, and rates of diabetes did not appear to be different.

Observations from this study raise the provocative question whether non-invasive CTA has potential to detect sub-clinical plaque disruption that may be another high-risk feature and perhaps in some cases may presage subsequent abrupt plaque instability. This concept is illustrated by a patient who underwent CTA for chest pain of uncertain aetiology, revealing what was clinically interpreted as a non-flow limiting stenosis; 3 months later she presented with an inferior STEMI attributable to a mid-RCA culprit occlusion precisely at the site of the prior non-flow limiting stenosis. Closer inspection of the initial CTA performed 3 months earlier reveals that this precursor lesion was a bulky, positively remodelled LAP with evidence of IDP. These observations support the concept that CTA can potentially detect early 'silent' plaque disruption that may be the harbinger of clinical plaque instability. We postulate the existence of a spectrum of lesion stability spanning silent and quiescent, 'vulnerable', disrupted but silent, and frankly unstable. Where a

Figure 8 Patient presenting with ACS with CTA demonstrating plaque ulceration. ICA (top left) showing proximal LAD and first diagonal with long, hazy stenosis (red arrows). Corresponding CTA (bottom left) showing areas of LAP (white arrows) and the irregular plaque border consistent with plaque ulceration (yellow arrow). Zoomed in and rotated CTA image (top left) and cross-section showing area of plaque ulceration (yellow arrow) and LAP (white arrow). CTA image at higher window width and level (bottom right) which highlights the LAP (white arrow) and the ulceration (yellow arrow).
given plaque disruption falls in the spectrum from clinically silent to dramatic ACS is likely the result of the interplay of underlying plaque volume, stenosis severity, lesion and blood thrombogenicity, endothelial shear stress among other factors.\textsuperscript{1 – 10,42 – 44} Taken together, these findings further embolden a non-invasive approach for the detection of patients and plaques that may be at the greatest risk.

**Figure 9** Scatterplots comparing mean IDP and lumen HU (left, Pearson correlation coefficient $r = 0.97$, $P < 0.0001$), and IDP and calcific plaque (right, Spearman correlation coefficient $r = -0.012$, $P = 0.68$). There is a tight, linear relationship with the IDP HU and the nearby lumen HU. There is no correlation of the HU between calcific plaque and that of IDP.

**Figure 10** Box and Whisker plot of median luminal, IDP and calcific plaque HU with inter-quartile ranges (25th, 75th). There is a tight correlation between the HU of IDP and lumen HU across all plaques, while the calcific plaque HU were far higher on average.

**Limitations**

There are several potential limitations to consider that may influence the interpretation of the present results. The most pressing limitation is the lack of direct intracoronary imaging correlates of plaque disruption by optical coherence tomography or intravascular ultrasound which is the true ‘gold standard’ for detection of plaque disruption. CTA spatial resolution limits may preclude detection of more subtle plaque disruptions that might be evident by direct coronary imaging counterparts, undoubtedly rendering it less sensitive and specific to some degree. In some patients with ACS, CTA detected features of disruption not deemed complex by angiography. We can only speculate whether angiography missed more subtle frank ruptures, or whether such findings may reflect erosions or intra-plaque haemorrhage beyond the resolution capabilities of ICA alone. CT scanning techniques (e.g. mAs and kV, rate, volume of contrast injected and luminal contrast), and plaque specific analysis depends on the HU threshold to define LAP, which varies in the literature.\textsuperscript{23,26,27,45,46} To minimize this latter limitation, we utilized a previously established definition of LAP as $<50$ HU\textsuperscript{26} given the inability to control for these issues in this retrospective study. Further prospective study would require meticulous attention to each of these factors and perhaps utilize a lower cut-off of $<30$ HU to improve sensitivity and specificity.\textsuperscript{45,46} IDP may be difficult to discern from spotty, low-density intra-plaque calcification of, and thus our rigorous analysis was undertaken. However, it must be noted that some plaques which we are visualizing may in fact be intra-plaque calcification. Future study with direct coronary imaging would be prudent to adjudicate this. Age and diabetes in our study population differing from our control population was covered at length, however, should certainly be controlled for better in future prospective study. Lastly, there is a variable time gap between the index CTA and the ICA between the groups, which in some patients might influence the correlation of plaque morphology if an
event occurred between the two studies. Though the patients were clinically stable between the two studies, certainly, as our paper suggests, plaque events can be clinically silent and more stringent attention to time gaps in future prospective study would be prudent. These limitations emphasize that caution should be employed in interpretation of our findings and extrapolating these results to a more generalized population.

Conclusions

Clinically stable patients commonly manifest plaques with features of disruption as discovered by CTA. Though the prevalence of plaque disruption is less than patients with ACS, these findings support the concept that clinically stable patients may harbour ‘silent’ disrupted plaques. These findings may have implications for detection of ‘at risk’ plaques and patients.

Acknowledgements

We would like to acknowledge Mark Pica as part of our research staff for his efforts to gather research data for this and other research projects.

Conflict of interest: none declared.

References


Figure 11 Patient with ‘vulnerable’ disrupted plaque seen by CTA within the RCA, followed 3 months later by acute inferior MI in the same location as the ‘vulnerable’ plaque. (A) CTA with evidence of LAP (white arrows) and IDP (yellow arrow). (B) Zoomed in view, cross-section showing zone of IDP (yellow arrows) and LAP (white arrow). (C) ICA 3 months later with acute occlusion at same site of previous plaque instability within the RCA (red arrow) (D) (below) ECG from this presentation showing inferior STE.


