Composition of Target Lesions by Near-Infrared Spectroscopy in Patients With Acute Coronary Syndrome Versus Stable Angina

Ryan D. Madder, MD; James L. Smith, MD; Simon R. Dixon, MBChB; James A. Goldstein, MD

Background—Whereas acute coronary syndromes (ACS) typically develop from the rupture of lipid core plaque (LCP), lesions causing stable angina are believed to be composed of fibrocalcific plaque. In this study, intracoronary near-infrared spectroscopy (NIRS) was used to determine the frequency of LCP at target and remote sites in patients with ACS versus those with stable angina.

Methods and Results—The study was performed in patients having ≥1 target lesion identified by invasive angiography who also underwent NIRS before intervention. LCP was defined as a 2-mm segment on the NIRS block chemogram having a strong positive reading indicated by a bright-yellow color. Patients with ACS and those with stable angina were compared for the frequency of LCP at target and remote sites. Among 60 patients (46.7% with ACS) undergoing invasive angiography and NIRS, 68 target lesions were identified. Although target lesions in patients with ACS were more frequently composed of LCP than targets in patients with stable angina (84.4% versus 52.8%, \(P=0.004\)), approximately one half of target lesions in patients with ACS were LCP and less common in patients with stable angina (73.3% versus 17.6%, \(P=0.002\)).

Conclusions—Target lesions responsible for ACS were frequently composed of LCP; in addition, LCPs often were found in remote, nontarget areas. Both target and remote LCPs were more common in patients with ACS than in those with stable angina. Approximately one half of target lesions in stable patients were also composed of LCP. (Circ Cardiovasc Interv. 2012;5:55-61.)

Key Words: plaque ■ acute coronary syndrome ■ spectroscopy near-infrared

Plaque composition has important clinical implications.\(^1\)\(^-\)\(^3\) Whereas acute coronary syndromes (ACS) typically develop from rupture and thrombosis of an underlying lipid core plaque (LCP),\(^1\)\(^-\)\(^4\) the target flow-limiting lesion in patients with chronic angina is believed to be stable, typically fibrocalcific, and less lipid laden.\(^5\)\(^-\)\(^6\) However, the term \textit{chronic stable angina} is a clinical designation based on symptom patterns and does not necessarily reflect plaque pathophysiology. In fact, pathological and in vivo studies document that many patients with stable angina have undergone clinically silent plaque disruptions.\(^7\)\(^-\)\(^8\) Such events could underlie the transition from an asymptomatic state to the onset of exertional angina because a plaque rupture may precipitate progression of a hemodynamically insignificant lesion to a flow-limiting stenosis.\(^3\)\(^,\)\(^7\)\(^,\)\(^8\)

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Although a patient presenting with several months of exertional symptoms may fit the traditional definition of stable angina, the original symptom onset may in fact represent an unstable plaque event. Because LCP appears to be the common thread linking plaque vulnerability and frank instability and given that plaque instability is, in many cases, a multifocal pancoronary process,\(^8\)\(^,\)\(^9\) delineation of plaque composition in culprit and nonculprit lesions may be important regardless of clinical presentation. Catheter-based near-infrared spectroscopy (NIRS) has been rigorously validated against autopsy specimens and is now established as a method to accurately identify LCP in patients.\(^10\)\(^,\)\(^11\) The present study used NIRS to determine the frequency of LCP at target and remote nontarget sites within the target vessel in patients with ACS and in patients with stable angina.

Methods

Study Population

The study was conducted in consecutive patients undergoing invasive coronary angiography and NIRS at a single institution. Patients...
were included in the study if (1) invasive angiography demonstrated at least 1 target lesion (defined later in this section) and (2) NIRS was performed within the target vessel before percutaneous coronary intervention (PCI) or stent placement. The decision to use NIRS was made solely by the operator at the time of angiography. Patients were excluded for a history of coronary artery bypass surgery, prior stent placement within the portion of the vessel scanned by NIRS, uninterruptable NIRS spectral images, performance of NIRS only after angioplasty or stent placement, the lack of fiduciary angiographic landmarks on the NIRS recording, or absence of a culprit lesion identified by angiography.

WHAT IS KNOWN

- Whereas acute coronary syndromes typically develop from rupture and thrombosis of an underlying lipid core plaque (LCP), flow-limiting lesions in patients with chronic angina are believed to be stable, typically fibrocalcific, and less lipid laden.
- The term chronic stable angina is a clinical designation based on symptom patterns and does not necessarily reflect underlying plaque pathophysiology.

WHAT THE STUDY ADDS

- Using intracoronary near-infrared spectroscopy to characterize plaque composition, this study found that patients with acute coronary syndromes typically have target lesions composed of LCP and commonly harbor remote, nontarget LCPs.
- Although as expected both target and remote LCPs were more frequent in patients with acute coronary syndromes compared with those with stable angina, intriguingly, the majority of target lesions in stable patients were composed of LCP.
- Overall, the findings of this study support the concept that clinical symptomatic presentation does not necessarily reflect underlying plaque pathophysiology.

Invasive Coronary Angiography

Angiography was performed according to standard methods, and images were stored digitally. A target lesion was defined as a lesion causing >70% stenosis, as assessed visually by the physician performing the angiography, that was believed to be responsible for the clinical presentation and was treated by PCI at the time of the index procedure. All coronary stenoses not meeting this definition were considered nontarget lesions.

Angiographic plaque morphology was analyzed according to established criteria by 2 independent observers blinded to each other, the clinical presentation, and NIRS results. Lesions were considered complex if they exhibited either (1) ulceration, defined as the presence of contrast beyond the vessel lumen; (2) intraluminal filling defect consistent with thrombus; or (3) a combination of haziness, irregular margins, or fissuring, defined as overhanging edges. All lesions not fulfilling these criteria were considered noncomplex.

Near-Infrared Spectroscopy

The NIRS imaging system (LipiScan) has been previously described. After invasive angiography was used to identify the target vessel, NIRS was performed within the target vessel with the use of a motorized pullback device. Coregistration between the intravascular NIRS chemogram and the invasive angiogram was established in the following manner: (1) The target lesion was identified from the invasive angiogram; (2) key angiographic landmarks within the target vessel were identified as reference points (ie, stenoses of interest, branches); (3) the NIRS catheter was advanced to a reference point distal to the target lesion; (4) the radiopaque distal imaging tip of the NIRS catheter was manually pulled back to position it at a predetermined angiographic reference point, using intermittent fluoroscopy and contrast injections to assure precise positioning; (5) motorized pullback was initiated; and (6) bookmarks were embedded within the NIRS chemogram at each angiographic reference point to identify such point’s anatomic position within the artery.

NIRS Image Analysis

NIRS block chemograms were analyzed for the presence of LCP, defined as a 2-mm segment on the block chemogram having a strong positive reading, as indicated by a bright-yellow color (95% specificity that LCP is present). Blocks not strongly positive were deemed negative for LCP at that site. Block chemogram segments containing \( \geq \)2 mm of continuous blocks characterized by strong positive readings were considered a single LCP. Two strongly positive blocks separated by \( \geq \)1 not strongly positive block were considered as separate LCPs. To provide an estimate of the length of LCP at each site, the frequency of finding \( \geq \)4 mm of a continuous strongly positive signal on the block chemogram (LCP \( \geq \)4 mm) was determined within each target vessel. To assess the amount of lipid within each LCP, the lipid core burden index (LCBI) was quantitatively measured for each LCP, as previously described.

The site of LCP on the block chemogram was localized to the corresponding site on the invasive angiogram on the basis of the anatomic fiduciary landmarks identified during the motorized pullback within the target vessel. This coregistration permitted determination of the frequency of LCP at target sites. The frequency of LCP at sites remote from the target lesion was determined with the use of a similar coregistration method.

Statistical Analysis

Patients presenting with ACS were compared with those with stable angina for baseline characteristics, number of target lesions, target lesion LCP, and frequency of remote, nontarget LCPs. Target lesions in patients with ACS were compared to target lesions in patients with stable angina for complex lesion morphology, LCP, LCP \( \geq 4 \) mm, and LCBI. Similarly, remote nontarget LCPs were compared for LCP \( \geq 4 \) mm, and LCBI.

Comparisons of categorical variables were made using Pearson \( \chi^2 \) or Fisher exact test. Continuous variables were compared using parametric Wilcoxon rank tests. When appropriate, a general linear model with repeated-measures analysis was performed to adjust for dependence resulting from multiple lesions within the same patient. 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 a mixed-effects model. All categorical variables are reported as counts and percent frequencies. Continuous variables are reported as mean \( \pm \)SD.

To assess the ability of the LCBI to differentiate target lesions in ACS from those in stable angina based on lipid burden, a receiver operating characteristic curve analysis was performed. From this
There were no clinical complications attributable to NIRS by angiography. At least 1 target lesion was identified in each patient. Multiple target lesions were identified in 7 (11.7%) patients, including 4 with >1 target lesion in a single vessel and 3 with target lesions in 2 separate vessels. There was no difference in the number of target lesions among those with ACS versus stable angina (1.1 ± 0.4 versus 1.1 ± 0.3, P = 0.86). Complex lesion morphology was noted in 30 (44.1%) target lesions overall and was present in 40.6% and 47.2% of ACS and stable angina target lesions, respectively (P = 0.28). The interobserver agreement for angiographic complex morphology was 91.0%.

Target Lesion Composition by NIRS

Target lesions were composed of LCP in 84.4% of patients with ACS versus 52.8% of those with stable angina (P = 0.004) (Table 2, Figures 2–4). Target lesions in patients with ACS more often contained LCPs ≥4 mm (65.6% versus 30.6%, P = 0.004) and were characterized by a greater LCBI (391 ± 229 versus 226 ± 268, P < 0.001). The excess of LCP at target sites in patients with ACS versus LCP at target sites in those with stable angina persisted in an analysis restricted to patients receiving statin therapy.

There were no significant differences in complex lesion morphology at LCP-positive target lesions in patients with ACS versus those with stable angina (33.3% versus 42.1%, P = 0.54). There was also no difference in the frequency of LCP ≥4 mm (ACS, 77.8%; stable angina, 57.9%; P = 0.15) or of LCBI of target lesions (ACS, 451 ± 181; stable angina, 451 ± 181).

### Table 1. Baseline Characteristics According to Clinical Presentation

<table>
<thead>
<tr>
<th></th>
<th>ACS (n=28)</th>
<th>Stable Angina (n=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±10</td>
<td>66±12</td>
<td>0.004</td>
</tr>
<tr>
<td>Male sex</td>
<td>21 (71.4)</td>
<td>22 (68.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (35.7)</td>
<td>11 (34.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (78.6)</td>
<td>25 (78.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>22 (78.6)</td>
<td>27 (84.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Smoker</td>
<td>12 (42.9)</td>
<td>4 (12.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Aspirin</td>
<td>15 (53.6)</td>
<td>27 (84.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14 (50.0)</td>
<td>19 (59.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>13 (46.4)</td>
<td>16 (50.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Statin</td>
<td>15 (53.6)</td>
<td>25 (78.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of Target Lesions in Patients With ACS Versus Stable Angina

<table>
<thead>
<tr>
<th></th>
<th>ACS Targets (n=32)</th>
<th>Stable Angina Targets (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex by ICA</td>
<td>13 (40.6)</td>
<td>17 (47.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>LCP</td>
<td>27 (84.4)</td>
<td>19 (52.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>LCP ≥4 mm in length</td>
<td>21 (65.6)</td>
<td>11 (30.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>LCBI</td>
<td>391 ± 229</td>
<td>226 ± 268</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD. ACS indicates acute coronary syndromes; CA, invasive coronary angiography; LCP, lipid core plaque; LCBI, lipid core burden index.
Similarly, the receiver operating characteristic curve analysis demonstrated that target-lesion LCPs in ACS versus stable angina could not be reliably differentiated based on the LCBI because the area under the curve was only 0.51 (95% CI, 0.33–0.69).

Remote, Nontarget LCP
Twenty-nine remote nontarget LCPs were identified by NIRS, located at a distance of 15.7 ±10.3 mm from the target lesion. In 18 (62.1%) instances, the remote LCP was located proximal to the target lesion, and in 11 (37.9%) instances, the remote LCP was located distal to the target lesion. Remote LCPs were identified in 73.3% of ACS cases (Figures 2 and 3) versus only 17.6% of stable angina cases (P=0.002) (Figures 2 and 4). The excess of LCP at remote, nontarget sites in patients with ACS versus those with stable angina persisted in an analysis restricted to patients receiving statin therapy. The frequency of LCP ≥4 mm in a remote location was not significantly different in ACS versus stable angina (36.7% versus 14.7%, P=0.07), nor did the remote-area LCBI differ for ACS versus stable angina (408 ±132 versus 618 ±515, P=0.10). Remote, nontarget LCPs were characterized as angiographically complex in 17.9% of instances.

Discussion
The primary findings of this study of the frequency of coronary LCP as detected by intracoronary NIRS are as follows: (1) The target lesions responsible for ACS are, in most cases, composed of LCP; (2) patients with ACS also commonly harbor remote, nontarget LCP; and (3) although as expected LCPs, both target and remote, were more frequent in patients with ACS than in patients with stable angina, approximately one half of target lesions in stable patients were composed of LCP. The present findings are in accord with those obtained with the use of other methods to assess plaque composition. Results obtained with the use of angioscopy, intravascular ultrasound, and optical coherence tomography all indicate that target lesions in patients with ACS are typically composed of LCP.8,16–19 The present findings that target lesions in patients with ACS are commonly found to be composed of LCP and that such lesions appeared complex by angiography are consistent with the concept that occurrence of an ACS is, in most cases, attributable to destabilization of an LCP.1,2 In addition to their contribution to enhanced understanding of the pathophysiology of ACS, the present findings have implications for complications that might be expected during PCI. Although no patients in this study experienced angiographic no-reflow or acute stent thrombosis after intervention, the stenting of stenotic LCPs as detected by NIRS, is associated with an increased risk of periprocedural infarction during PCI and acute stent thrombosis.20–23

In the present study, target lesions in patients with stable angina were less likely to be composed of LCP than were lesions in patients with an ACS, an observation consistent with the concept that target lesions in patients with stable angina are clinically stable with a more fibrocalcific and less lipid-laden composition.3,6 However, NIRS demonstrated that approximately one half of the target lesions in these clinically stable patients were composed of LCP. This observation is in
ever, pathological and angiographic studies now document that some patients with clinically stable angina have pathological or direct coronary imaging evidence of plaque disruptions.\textsuperscript{3,7,8} Such events could underlie the initial transition from an asymptomatic state to the onset of exertional angina because the plaque disruption facilitates rapid lesion progression from a hemodynamically insignificant lesion to a flow-limiting stenosis.\textsuperscript{3,7,8} The present observations that (1) target lesions in these patients with stable angina were frequently composed of LCP and (2) these target lesions composed of LCP in stable angina were indistinguishable from target lesions composed of LCP in ACS with regard to complex lesion morphology, length of lesion, or lipid content by LCBI support the concept that the type of clinical presentation (ACS or stable angina) does not necessarily reflect underlying plaque pathophysiology. In addition, these observations emphasize the limited value of angiography alone in identifying rupture-prone lesions.

The present study also demonstrates that patients with ACS frequently harbor remote, nontarget LCP, a finding consistent with the concept that plaque instability is a multifocal process as documented by other direct coronary imaging studies and pathological studies.\textsuperscript{9–24} The higher frequency of remote nontarget LCP within the target vessels of patients with ACS than in patients with stable angina may partly account for the relatively higher recurrent cardiovascular event rates observed after PCI in patients with ACS versus those with stable angina.\textsuperscript{25–27} Although more common within the target vessel of patients with ACS, the remote, nontarget LCPs were not different among patients with ACS and stable angina with regard to lipid content. The clinical implications of this finding are unclear. Future studies in larger numbers of patients will be required to compare further the relationships between both composition and architectural characteristics of nontarget plaques in patients with ACS and stable angina. These patients, especially those with ACS, may harbor unstable and vulnerable lesions in nontarget vessels.\textsuperscript{26} It is therefore important to emphasize that in the present study, only coronary vessels containing target lesions were interrogated; further studies with multivessel imaging will be necessary to draw firm conclusions regarding the true prevalence of remote LCP in stable versus unstable patients.

Limitations

Although the accuracy of NIRS to detect the presence and assess the lipid core burden of a given lesion has been rigorously validated versus histopathologic specimens,\textsuperscript{10} there are several potential limitations to consider that may influence the interpretation of the present results. First, this article reports a small study undertaken to analyze the composition of target lesions in a highly selected patient population with ACS and stable angina. Appropriate caution is necessary when extrapolating these results to a more generalized population. Second, patients in this study underwent NIRS of the target vessel only; it remains unclear whether multivessel scanning would affect the reported frequency of remote nontarget LCP in patients ACS versus patients with stable angina. Third, NIRS lacks the ability of other imaging modalities to identify additional features of

Figure 4. Target lesion composition by near-infrared spectroscopy (NIRS) in patients with stable angina. A, Angiography in a 77-year-old male patient with stable angina and an abnormal stress test demonstrated a target lesion (short black arrow) within the left anterior descending coronary artery near the origin of the first diagonal branch (long black arrow). NIRS revealed a large lipid core plaque at the site of the target lesion (*) extending to the origin of the first septal perforator (solid white arrow). Green bookmarks on the NIRS chemogram represent (top to bottom) the first diagonal branch, the first septal perforator, and the second diagonal branch (dashed white arrow). B, Angiography in a 45-year-old patient with stable angina shows a target lesion in the mid-left anterior descending coronary artery (short white arrow) and a mild stenosis in the distal vessel (short black arrow). NIRS interrogation revealed no evidence of lipid core plaque at the target site (long white arrow) or at the remote, nontarget lesion (long black arrow).

accord with prior angioscopic findings in which nearly two thirds of ischemia-related lesions in patients with stable angina were observed to have a yellow color, indicating the presence of a lipid core.\textsuperscript{16}

We can only speculate with regard to the mechanisms accounting for this mismatch between clinical presentation and lesion phenotype in patients with stable angina. The term stable angina is a clinical designation based on symptom pattern and does not necessarily reflect underlying plaque pathophysiology. Chronic stable angina classically is believed to result from slow, steady accretion of plaque, the composition of which is predominantly fibrocalcific.\textsuperscript{5,6} How-
vulnerability, including remodeling index, plaque volume, and fibrous cap thickness. The clinical implication of finding an isolated LCP that neither is positively remodeled nor has a thin fibrous cap is uncertain. This limitation may be partially overcome with novel imaging devices that provide simultaneous intravascular ultrasound for lesion architecture and NIRS for plaque composition.28 Fourth, we cannot exclude the possibility that aspiration thrombectomy before NIRS-intravascular ultrasound in the 2 patients with STEMI may have influenced imaging results. In addition, the absence of quantitative assessment of target lesion stenosis severity is noted. Fifth, the present results were derived from a selected patient population. Finally, patients with ACS and those with stable angina differed with respect to age, smoking status, and statin therapy. Although more patients in the ACS group were taking statins at baseline, the excess of LCP at target and remote sites in patients with ACS versus those with stable angina persisted in an analysis restricted to patients receiving statin therapy. Nevertheless, future studies based on a larger cohort of patients will be necessary to characterize the confounding that may occur because of these variables.

Conclusions
Target lesions responsible for ACS are frequently composed of LCP and patients with ACS commonly harbor remote, nontarget LCPs. LCPs, both target and remote, are more common in patients with ACS than in those with stable angina; however, approximately one half of all target lesions in stable patients are also composed of LCP.

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Disclosures
Dr Dixon has received research grant support from InfraRedx. Dr Goldstein is a consultant for and an owner of equity in InfraRedx.

References


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