Detection of Lipid-Core Plaques by Intracoronary Near-Infrared Spectroscopy Identifies High Risk of Periprocedural Myocardial Infarction

J. Michael Goldstein, MD; Brijeshwar Maini, MD; Simon R. Dixon, MBChB; Emmanouil S. Brilakis, MD, PhD; Cindy L. Grines, MD; David G. Rizik, MD; Eric R. Powers, MD; Daniel H. Steinberg, MD; Kendrick A. Shunk, MD, PhD; Giora Weiss, MD; Pedro R. Moreno, MD; Annapoorna Kini, MD; Samin K. Sharma, MD; Michael J. Hendricks, BS; Steve T. Sum, PhD; Sean P. Madden, PhD; James E. Muller, MD; Gregg W. Stone, MD; Morton J. Kern, MD

Background—Percutaneous coronary intervention (PCI) is associated with periprocedural myocardial infarction (MI) in 3% to 15% of cases (depending on the definition used). In many cases, these MIs result from distal embolization of lipid-core plaque (LCP) constituents. Prospective identification of LCP with catheter-based near-infrared spectroscopy (NIRS) may predict an increased risk of periprocedural MI and facilitate development of preventive measures.

Methods and Results—The present study analyzed the relationship between the presence of a large LCP (detected by NIRS) and periprocedural MI. Patients with stable preprocedural cardiac biomarkers undergoing stenting were identified from the COLOR Registry, an ongoing prospective observational study of patients undergoing NIRS before PCI. The extent of LCP in the treatment zone was calculated as the maximal lipid-core burden index (LCBI) measured by NIRS for each of the 4-mm longitudinal segments in the treatment zone. A periprocedural MI was defined as new cardiac biomarker elevation above 3× upper limit of normal. A total of 62 patients undergoing stenting met eligibility criteria. A large LCP (defined as a maxLCBI4 mm ≥500) was present in 14 of 62 lesions (22.6%), and periprocedural MI was documented in 9 of 62 (14.5%) of cases. Periprocedural MI occurred in 7 of 14 patients (50%) with a maxLCBI4 mm ≥500, compared with 2 of 48 patients (4.2%) patients with a lower maxLCBI4 mm (P=0.0002).

Conclusions—NIRS provides rapid, automated detection of extensive LCPs that are associated with a high risk of periprocedural MI, presumably due to embolization of plaque contents during coronary intervention. (Circ Cardiovasc Interv. 2011;4:429-437)

Key Words: Distal embolization ■ lipid-core plaque ■ plaque characterization ■ near-infrared spectroscopy ■ periprocedural myocardial infarction ■ percutaneous coronary intervention

Although percutaneous coronary intervention (PCI) routinely achieves excellent angiographic success, 3% to 15% of cases (depending on the definition) are complicated by periprocedural myocardial infarction (MI), thought to be attributable to distal embolization of intraluminal thrombus and/or lipid-core plaque (LCP) contents.1-7 Such infarctions are associated with adverse long-term outcomes and in some cases cause immediate adverse events.1-15 Recent observations indicate that periprocedural MIs are associated with increased atherosclerotic burden and large LCPs.15-26 Embolization of the lipid core of stenotic plaques after PCI has been implicated as an important cause of periprocedural no-reflow and MI in both the presence and absence of intracoronary thrombus.21-26 The efficacy of embolic protection devices (EPDs) in preventing embolic complications after PCI of saphenous vein grafts and carotid arteries suggests that embolic periprocedural MIs occurring during dilations of stenoses in native
coronary arteries may be prevented if LCPs prone to periprocedural MI could be accurately identified. Thus, the present study was conducted to determine whether intracoronary near-infrared spectroscopy (NIRS), a method validated to rapidly identify coronary LCP, can identify plaques that are likely to cause periprocedural MI in patients undergoing elective PCI.

WHAT IS KNOWN

- Percutaneous coronary intervention is associated with periprocedural no-reflow and myocardial infarction in 3% to 15% of cases, complications associated with adverse prognosis.
- Embolization of the lipid core of stenotic plaques after percutaneous coronary intervention has been implicated as an important cause of these events.

WHAT THE STUDY ADDS

- Catheter-based intracoronary near-infrared spectroscopy has been validated to accurately identify lipid-core plaque.
- Results from this study demonstrate that extensive lipid-core plaques detected by near-infrared spectroscopy are associated with a high risk of periprocedural myocardial infarction, presumably due to distal embolization of plaque contents during coronary intervention.
- Prospective identification of lipid-core plaque with near-infrared spectroscopy may predict lesions at increased risk of periprocedural myocardial infarction and facilitate development of preventive measures, such as distal protection filter devices.

Methods

The present study was conducted in a subset of cases enrolled in the COLOR Registry, a prospective multicenter observational study of patients undergoing NIRS (LipiScan, InfraReDx, Inc, Burlington, MA) before PCI. The COLOR Registry was approved by the appropriate institutional review board of each institution, with informed consent for data collection obtained from each patient. All catheterization procedures used in the COLOR Registry were performed based on clinical indications as determined by the treating physician. All information requested as part of the registry was obtained from clinical data gathered as part of each subject’s standard medical care. Data were collected by coordinators in each center and recorded by InfraReDx, Inc in a database (ClinicalTrials.gov registered NCT00831116).

The subset of COLOR Registry patients selected for the present study met the following criteria: PCI was performed; NIRS measurements were obtained in the culprit vessel before any intervention; at least 1 appropriately timed (between 4 and 24 hours after PCI) postprocedural cardiac biomarker measurement (creatinine kinase-MB [CK-MB] or cardiac troponin I [cTnI]) was available to determine the occurrence of periprocedural MI; there was no angiographic evidence of intracoronary thrombus; and an acute MI was not in progress at the time of the NIRS measurement. Indications for catheterization in the 62 patient set included non–ST-elevation–MI (9.7%), unstable angina (17.7%), stable angina (51.6%), atypical chest pain (6.5%), silent ischemia (3.2%), monitoring of heart failure (1.6%), and other documented purposes (9.7%), such as syncope, cardiomyopathies, or arrhythmias. No cases of STEMI, transplant evaluation, or presurgical evaluation were included.

Periprocedural MI was defined as a postprocedural biomarker elevation above 3× upper limit of normal (ULN) for either CK-MB or cTnI measured 4 to 24 hours after PCI. ULN was defined as 5 ng/mL for CK-MB and 0.4 ng/mL for cTnI.

Coronary Angiographic Data

Invasive angiograms were performed according to standard methods, and images were stored digitally. Patients with angiographic evidence of thrombus were excluded per the study protocol. For the remaining patients, the target lesion undergoing PCI was identified and quantitative analyses performed to determine the percent diameter stenosis and lesion length, according to standard methods. Target lesions were further analyzed qualitatively for “complex” features indicative of unstable ruptured plaque, defined as (1) irregular margins; (2) fissuring, defined as overhanging edges; (3) haziness; and (4) ulceration, defined as the presence of contrast exterior to the vessel lumen. Lesions were considered “complex” if there was frank ulceration or an intraluminal filling defect or if they demonstrated two or more of the following 3 features: irregular margins, fissuring, or haziness. Lesions not fulfilling these criteria were considered “noncomplex.”

NIRS System

NIRS is distinct and complementary to other intravascular techniques in its fundamental basis, figure of merit, and nature of information provided. A recent review describes the differences and similarities with various intravascular imaging techniques and their relevance to coronary plaque characterization. The NIRS LipiScan Coronary Imaging System has been previously described. The system comprises a scanning near-infrared laser, a fiberoptic coronary catheter similar in size (3.2F monorail) and use to an intravascular ultrasound (IVUS) catheter, and an automated pullback and rotation device. The instrument performs approximately 8000 chemical measurements per 100 mm of artery scanned. A predictive algorithm calculates the probability that a LCP is present at each interrogated location in the artery. Immediately after a pullback, the data are automatically displayed in a 2-dimensional map of the vessel called a “chemogram.” The x-axis of the chemogram represents millimeters of pullback in the artery and the y-axis represents degrees of rotation (0° to 360°); a color scale from red to yellow indicates increasing algorithm probability that an LCP is present. The “block chemogram” provides a summary of the results for each 2-mm section of artery. The numeric value of each block in the block chemogram is the 90th percentile of all pixel values in the corresponding 2-mm chemogram segment. The block chemogram is mapped to the same color scale as the chemogram, but the display is binned to 4 discreet colors to aid in visual interpretation (red: P<0.57, orange: 0.57≤P≤0.84, tan: 0.84≤P≤0.98, yellow: P>0.98; algorithm probability that a LCP is present in that 2-mm block). The lipid core burden index (LCBI) is provided as a quantitative summary metric of the LCP presence in the entire scanned region. LCBI is computed as the fraction of valid pixels within the scanned region that exceed an LCP probability of 0.6, multiplied by 1000. Because the chemogram color scale transitions from red to yellow near an LCP algorithm probability of 0.6, the LCBI can be viewed as a quantitative measure of the amount of yellow present on the chemogram. A rigorous, double-blind, prospective validation study of the NIRS catheter system versus histology truth using intact, perfused human coronary artery autopsy specimens achieved an area under the receiver operating characteristic (ROC) curve (AUC) for detection of LCP of 0.80. A concurrent clinical study demonstrated equivalence of data obtained ex vivo with data obtained in vivo.

Acquisition of NIRS Data

The NIRS catheter was advanced over an angioplasty guide wire to a reference point distal to the target lesion before PCI. Scanning with automated rotational pullback was then performed at a speed of 0.5 mm/s and 240 rpm with the pullback terminated after the imaging

WHAT THE STUDY ADDS

- Catheter-based intracoronary near-infrared spectroscopy has been validated to accurately identify lipid-core plaque.
- Results from this study demonstrate that extensive lipid-core plaques detected by near-infrared spectroscopy are associated with a high risk of periprocedural myocardial infarction, presumably due to distal embolization of plaque contents during coronary intervention.
- Prospective identification of lipid-core plaque with near-infrared spectroscopy may predict lesions at increased risk of periprocedural myocardial infarction and facilitate development of preventive measures, such as distal protection filter devices.
element entered the guiding catheter. PCI was then performed as planned. In all cases, the NIRS signal was measured before balloon dilatation of any type. In several cases at the discretion of the clinical operator, the NIR measurement was repeated after full balloon dilation and/or after stent placement. NIRS data were stored digitally for subsequent analysis.

Coregistration of NIRS Chemograms With Invasive Angiographic Data

A method was established to ensure accurate coregistration between the intravascular chemogram and the coronary angiogram. The radio-opacity of the imaging element and radio-opaque marker on the NIRS catheter permit the physician to identify the location of the catheter and imaging element in relationship to target vessel fiduciary landmarks as detected by coronary angiography (eg, stenoses of interest, branches, guide catheter, etc). With the use of the NIRS software and the pullback and rotation device (PBR), the physician placed a marker line on the chemogram corresponding to the angiographic landmarks and the locations of acquisition of the NIRS spectra. The target lesion was defined as the lesion undergoing PCI. The treatment zone was defined as the length of vessel in which any balloon inflation was performed. The corresponding treatment zone on the chemogram was identified by colocalized registration marks placed on the chemogram by the treating physician.

Assessment of Presence and Extent of LCP in the Treatment Zone

Early cases of LCP-associated periprocedural MI indicated a possible relationship between embolic risk and LCP.26,32,33 Visual analysis of chemograms associated with periprocedural MI suggested that a large area of LCP and a large circumferential extent of the LCP carried higher risk. Therefore, an objective, easily automated measure of the area and circumferential extent of LCPs in the treatment zone was developed. The maximum value of LCBI for any of the 4-mm segments in the treated segment (maxLCBI_{4mm}) is calculated and used as the index of the presence or absence of a large LCP in the treated area (Figure 1).

Primary End Point

The primary end point of the study was the rate of periprocedural MI in the groups with and without a large LCP in the treatment zone as assessed by NIRS and expressed as maxLCBI_{4mm}.

Statistical Analysis

For analysis of the predictive risk of periprocedural MI, contingency tables were constructed with risk factor or diagnostic test result (continuous with threshold or categorical) versus the outcome of periprocedural MI. For analysis of categorical factors associated with maxLCBI_{4mm} (dichotomized by threshold selection), contingency tables were constructed with risk factor or diagnostic test result versus maxLCBI_{4mm} above or below the selected threshold. The Fisher exact test was used for categorical variables, the unpaired t test for continuous variables, or the Wilcoxon rank-sum test for interval variables (such as number of stents). A probability value of <0.05 was considered significant. Relative risk was defined as the quotient of the periprocedural MI rate for patients with a certain risk factor and the periprocedural MI rate for those without the risk factor. For ROC analyses using sensitivity and specificity, true positives were defined as cases with a diagnostic value exceeding a threshold and periprocedural MI occurring (with false-positives and true and false-negatives following accordingly). When thresholds were selected by ROC analysis, round values near the equal error rate (intersection of sensitivity and specificity) were selected. All statistical analyses were done using Matlab software R2006b (The MathWorks, Natick, MA) and JavaStat (http://statpages.org/ctab2x2.html, John C. Pezzullo referencing Bernard Rosner, Fundamentals of Biostatistics, 6th edition, 2006, online tools revised January 7, 2010).

Results

Patient Selection

At the time of initiation of this study, 326 patients had complete data available in the COLOR Registry database. Figure 2 shows the process of patient selection, based on the
Only significant clinical association of the presence of maxLCBI4mm$\geq$500 in the treatment zone was an elevated plasma LDL level ($P=0.002$). Clinical and demographic parameters of the 264 excluded patients (see Figure 2) versus the 62 patients included in this study were not significantly different with the exceptions of body mass index, race, and non-insulin-dependent diabetes mellitus. In the 264 excluded patients, body mass index was lower (29.7 $\pm$ 5.6, $P=0.005$), the proportion of whites was lower (218 [74.4%], $P=0.03$), and the incidence of non-insulin-dependent diabetes mellitus was lower (87 [32.9%], $P=0.05$).

**Coronary Angiographic Findings**

The culprit vessel was the left anterior descending in 34 cases (54.8%), circumflex in 16 cases (25.8%), and right coronary artery in 12 (19.4%). At baseline, before intervention, the mean target lesion stenosis was 71% and mean lesion length 9.6 mm. The target lesion manifested complex morphology by angiographic criteria in 31 (50.0%) of plaques. Of those lesions deemed complex, 9 (29.0%) had maxLCBI4mm$\geq$500 and maxLCBI4mm$\leq$500 groups, where applicable.

### Table 1. Baseline Characteristics of Study Participants With and Without a Large Lipid-Core Plaque

<table>
<thead>
<tr>
<th></th>
<th>Total (n=62)</th>
<th>$&lt;$500 (n=48)</th>
<th>$\geq$500 (n=14)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>65.1±8.8</td>
<td>64.2±8.4</td>
<td>67.9±9.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex, n (%), female</td>
<td>11 (17.7)</td>
<td>9 (18.8)</td>
<td>2 (14.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI, kg/m², mean±SD</td>
<td>32.0±6.5</td>
<td>32.7±6.5</td>
<td>29.6±5.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Race, n (%), white</td>
<td>58 (93.5)</td>
<td>44 (91.7)</td>
<td>14 (100.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Prior CAD, n (%), yes</td>
<td>52 (83.9)</td>
<td>40 (83.3)</td>
<td>12 (85.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior MI, n (%), yes</td>
<td>23 (37.1)</td>
<td>17 (35.4)</td>
<td>6 (42.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMI</td>
<td>1 (1.6)</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>DMII</td>
<td>29 (46.8)</td>
<td>23 (47.9)</td>
<td>6 (42.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Smoking, n (%), yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>11 (17.7)</td>
<td>7 (14.6)</td>
<td>4 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Quit</td>
<td>36 (58.1)</td>
<td>30 (62.5)</td>
<td>6 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>14 (22.6)</td>
<td>11 (22.9)</td>
<td>3 (21.4)</td>
<td>1.0†</td>
</tr>
<tr>
<td>HTN, n (%), yes</td>
<td>57 (89.1)</td>
<td>45 (93.8)</td>
<td>12 (85.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL, mg/dL, mean±SD</td>
<td>83.8±36.1</td>
<td>73.8±32.9</td>
<td>110.4±31.4</td>
<td>0.002‡</td>
</tr>
<tr>
<td>HDL, mg/dL, mean±SD</td>
<td>36.1±9.9</td>
<td>36.1±10.7</td>
<td>36.2±7.8</td>
<td>0.96§</td>
</tr>
<tr>
<td>HLD Rn, n (%), yes</td>
<td>53 (85.5)</td>
<td>41 (85.4)</td>
<td>12 (85.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

LCBI indicates lipid-core burden index; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; DM, diabetes mellitus; HTN, hypertension; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and HLD Rn, currently taking hypolipidemia medication. *Two-sided t test or Fisher exact test or Wilcoxon rank sum test between maxLCBI4mm$<$500 and maxLCBI4mm$\geq$500 groups, where applicable. †$n=47$ and 14, due to missing data. ‡$n=47$ and 14, due to missing data. §Defined according to Goldstein, et al. **N Engl J Med.** 2000;343:915–922.

### Table 2. Procedural and Angiographic Lesion Characteristics of Study Participants With and Without a Large Lipid-Core Plaque

<table>
<thead>
<tr>
<th></th>
<th>Total (n=62)</th>
<th>$&lt;$500 (n=48)</th>
<th>$\geq$500 (n=14)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree stenosis, %, mean±SD</td>
<td>71±14</td>
<td>70±15</td>
<td>74±12</td>
<td>0.39†</td>
</tr>
<tr>
<td>Length, mm, mean±SD</td>
<td>9.6±4.4</td>
<td>9.5±4.6</td>
<td>10.0±3.7</td>
<td>0.76†</td>
</tr>
<tr>
<td>Complex plaque, n (%)‡</td>
<td>31 (50.0)</td>
<td>22 (45.8)</td>
<td>9 (64.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>No. of stents used, median (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (1–3)</td>
<td></td>
</tr>
<tr>
<td>Length of artery stented, mm, mean±SD</td>
<td>35.0±22.9</td>
<td>30.3±18.6</td>
<td>51.0±29.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

LCBI indicates lipid-core burden index; IQR, interquartile range. *Two-sided t test or Fisher exact test or Wilcoxon rank sum test between maxLCBI4mm$<$500 and maxLCBI4mm$\geq$500 groups, where applicable. †$n=47$ and 14, due to missing data. ‡Defined according to Goldstein, et al. **N Engl J Med.** 2000;343:915–922.

**Coronary Angiographic Findings**

The culprit vessel was the left anterior descending in 34 cases (54.8%), circumflex in 16 cases (25.8%), and right coronary artery in 12 (19.4%). At baseline, before intervention, the mean target lesion stenosis was 71% and mean lesion length 9.6 mm. The target lesion manifested complex morphology by angiographic criteria in 31 (50.0%) of plaques. Of those lesions deemed complex, 9 (29.0%) had maxLCBI4mm$\geq$500 and maxLCBI4mm$\leq$500 groups, where applicable. *Two-sided t test or Fisher exact test or Wilcoxon rank sum test between maxLCBI4mm$<$500 and maxLCBI4mm$\geq$500 groups, where applicable. †$n=47$ and 14, due to missing data. ‡Defined according to Goldstein, et al. **N Engl J Med.** 2000;343:915–922.
There were no major adverse events attributed to the performance of NIRS. Two patients had transient chest pain during the procedure that resolved after PCI. In 1 additional patient there was slow flow at the time of catheter removal from an artery that did not receive an intervention. No MI or other complications occurred in these 3 patients.

**Periprocedural MI**

Periprocedural MI occurred in 9 of 62 (14.5%) cases, with cTnI >3×ULN in all 9 cases and CK-MB >3×ULN in 7 cases. In the 2 cases in which cTnI was >3×ULN but CK-MB was <3×ULN, the values were 2.6× and 2.8×ULN for CK-MB. cTnI was elevated >5×ULN in 6 cases and CK-MB was elevated >5×ULN in 5 of those 6 cases.

**NIRS Results and the Relationship With Periprocedural MI**

Figure 3 shows the chemograms from the areas in which a balloon was inflated for all 62 study subjects. Chemograms from patients with a periprocedural MI are shown on the left; chemograms from those without periprocedural MI are shown on the right. Asterisks indicate chemograms with maxLCBI4mm $\geq$500. Periprocedural MI occurred in 2 of 48 patients (4.2%) with maxLCBI4mm $\geq$500 compared with 7 of 14 patients (50.0%) with maxLCBI4mm $\geq$500 (P=0.0002). The relative risk of periprocedural MI for patients with maxLCBI4mm $\geq$500 was 12 (95% confidence interval [CI], 3.3–48) (Figure 4).

The 10th, 25th, 50th, 75th, and 90th percentile maxLCBI4mm values were 33, 85, 232, 453, and 670, respectively. Seven of 9 MIs (78%) that occurred in the study population occurred in treatment zones with a maxLCBI4mm $\geq$500. No significant trends were observed for maxLCBI4mm versus coronary vessel (left anterior descending, right coronary artery, circumflex).

The sensitivity and specificity of varying thresholds of maxLCBI4mm for prediction of periprocedural MI are shown in Figure 5. The dotted vertical line shows the threshold of 500 used in this study. The AUC of the ROC curve (not shown) of sensitivity versus false-positive rate is 0.83. A lipid core with a maxLCBI4mm $\geq$500 would correspond to an LCP that, on average, is 4 mm in length and extends for 180° of the vessel circumference.

Figure 6 shows a box plot of maxLCBI4mm grouped by occurrence of periprocedural MI, displaying the predictive ability of maxLCBI4mm within this data set. The median

<table>
<thead>
<tr>
<th>Parameter $^a$</th>
<th>Threshold $^b$</th>
<th>Relative risk of peri-procedural MI (95% CI) $^c$</th>
<th>$p^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>maxLCBI4mm</td>
<td>$\geq$500</td>
<td>12 (3.3 to 48)</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDL – mg/dL</td>
<td>$&gt;100$</td>
<td>5.4 (1.4 to 23)</td>
<td>0.03$^f$</td>
</tr>
<tr>
<td>Complex Plaque</td>
<td>$Y$</td>
<td>3.5 (0.91 to 14)</td>
<td>0.15</td>
</tr>
<tr>
<td>Degree Stenosis</td>
<td>$&gt;75$</td>
<td>3.1 (0.92 to 11)</td>
<td>0.14$^{**}$</td>
</tr>
</tbody>
</table>

$^a$ Non-significant $p$ value ($p>0.1$) for Age, Sex, BMI, Race, Prior CAD, Prior MI, DM, Smoking, HTN, HLD, HDL, HLD R, Lesion Length

$^b$ For continuous variables, a threshold was selected using a ROC analysis.

$^c$ Fisher’s Exact Test two-sided $p$

$^d$ $N=44$ due to missing data

$^{**}$ $N=61$ due to missing data
The primary finding of the present study is that in patients with coronary artery disease, PCI of lesions with a large lipid core (maxLCBI_{4 mm} \geq 500 by NIRS) is associated with a 50% risk of periprocedural MI (95% CI, 28–62), compared with only a 4.2% risk (95% CI, 0.8–11) for lesions without a large lipid core (maxLCBI_{4 mm} <500 by NIRS). NIRS provided rapid, automated detection of these high-risk LCPs associated with culprit stenoses. Conversely, lesions without a large lipid core had a low risk of periprocedural MI.

The use of NIRS permitted the identification and quantification of LCPs whose presence could not be determined by coronary angiography. Baseline variables also correlated poorly with the presence of a large LCP, with elevation of plasma LDL levels as the only statistically significant association. A maxLCBI_{4 mm} \geq 500 identified plaques with a 12-fold increase in relative risk (95% CI, 3.3–48; \(P=0.0002\)) of periprocedural MI (Figure 4). In contrast, plaque complexity identified on coronary angiography, a finding often considered to be an index of increased risk of a PCI-induced complication, was associated with a relative risk of only 3.5 (95% CI, 0.91–14), a difference that was not statistically significant.

Intracoronary Imaging and LCP

The results of the present study are in accord with prior findings with other intracoronary imaging methods. Angioscopy, grayscale IVUS, integrated backscatter IVUS (IB-IVUS), virtual histology IVUS (VH-IVUS), and even noninvasive computed tomography angiography (CTA) have all demonstrated an association between PCI of LCP and periprocedural MI.\(^{23–25,32,34–36}\) A prior study of NIRS in a small number of patients also indicated that dilation of a large, circumferential lipid core lesion was associated with a high risk of periprocedural MI.\(^{26}\) The results of the present study are thus consistent with these prior observations. Comparative studies would be required to determine whether one imaging tool is superior to another in identifying lesions at risk for periprocedural MI.

The presumed mechanism of the MI after PCI of LCPs is distal embolization of lipid contents released during PCI. This pathophysiologic mechanism is supported by direct observations documenting lipid debris in fatal cases of distal embolization\(^{28}\) and by recent findings obtained with various techniques, including NIRS, that the extent of lipid core in the vessel wall is diminished after balloon inflation.\(^{17,18,36,37}\) The present study demonstrates a high relative risk of periprocedural MI in lesions with a maxLCBI_{4 mm} \geq 500, a quantitative measure determined on-line by the NIRS system that does not require subjective operator interpretation or postprocedure analysis.

The present study of periprocedural MI adds to accumulating evidence that LCPs are associated with complications of stenting. In addition to the relationship with periprocedural MI, autopsy studies have demonstrated that stent thrombosis and restenosis often occur at sites of LCP.\(^{39}\) Recent reports have documented the occurrence of acute stent thrombosis in association with a LCP as detected by NIRS\(^{39}\) and OCT.\(^{40}\) In aggregate, these findings support the concept that LCPs may be prone to complications after stenting. Conversely, the absence of a lipid core at a stenotic site may indicate a lesion at lower risk for both periprocedural MI and subsequent stent thrombosis. The ability to identify stenoses with varying levels of risk of complications when stented would indicate that LCP presence or absence might play a role in determining whether or not a lesion should be treated. Future studies in large numbers of patients are warranted to confirm these observations.
Implications for Prevention of Periprocedural MI

The ability to predict periprocedural MI may enable efforts to reduce this complication after PCI. Possible measures that have been advocated to reduce no-reflow and periprocedural MI include prophylactic use of vasodilators, statin loading, direct stenting, covered stents, glycoprotein IIb/IIIa inhibitors, and use of EPDs. The use of an EPD to prevent distal embolization of plaque contents, as is done for dilation of stenotic vein grafts and carotid stenoses, is a particularly promising approach. Lesions in both saphenous veins and carotid vessels are characterized by the presence of friable cholesterol-laden plaque prone to embolization. In both settings, EPDs are routinely used to prevent infarction caused by embolic particles.1–7 The rate of periprocedural MI associated with large LCP in native coronary arteries in the present study was high (50%), exceeding the rates reported for dilation of stenoses in saphenous vein grafts when embolic protection is not used.41,42 A randomized study would be required to determine whether NIRS is able to prospectively identify LCPs prone to a high rate of distal embolization and MI and whether pre-PCI use of an EPD is effective in preventing this complication. The potential ability of NIRS-guided use of an EPD to prevent periprocedural MI is being tested in the prospective, randomized CANARY trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow, ClinicalTrials.gov registered NCT01268319). In addition to prevention of periprocedural MI, the linkage of LCP with late stent thrombosis and new coronary events43 supports the need for research on the possibility that stents could be coated with a drug to prevent LCP rupture.

Limitations

Applicability to a larger population of catheterization patients is limited by potential selection bias in the formation of this small study subset. Most importantly, the analysis was restricted to patients in the COLOR Registry in whom post-PCI biomarkers were available. As such, selection bias relating to the treating clinicians’ decisions to obtain biomarkers cannot be excluded. Similarly, the number, type, timing, and frequency of biomarker determination were not standardized. The presence of intracoronary thrombus has
also been associated with distal embolization resulting in periprocedural MI. Although the present study was conducted in patients undergoing elective PCI (in whom thrombus is less likely to be present) and patients with angiographic evidence of thrombus were excluded, it is still possible that embolization of an undetected thrombus may have contributed to some of the periprocedural MIs. The selection of \( \text{max} \left( \frac{\text{LCB}_{\text{LCP}}}{\text{mm}} \right) \geq 500 \) as the threshold for prediction of periprocedural MI was a post hoc determination; hence, this should be viewed as hypothesis-generating, with a need for prospective validation in subsequent studies. Finally, the present study did not include routine IVUS evaluation and data were acquired before the availability of a combined NIRS-IVUS catheter. Therefore, we cannot comment on potential mechanistic contributors such as atheroma volume or extent of calcification.

Summary
The NIRS system, which provides an accurate, rapid, and automated means to identify LCP, can be used to identify large, stenotic, coronary LCPs, which in this study were associated with a 50% risk of periprocedural MI when dilated during PCI. Conversely, lesions without a large lipid core had a low risk of periprocedural MI. These findings demonstrate that large LCP identified by NIRS may provide improved risk assessment before coronary stenting. A randomized trial of EPD as a means to enhance the safety of coronary stenting in high-risk, stenotic LCPs as identified by NIRS is underway.

Acknowledgments
We are grateful to the multiple investigators and coordinators identified in the COLOR Registry Appendix who created the database used for the present study and to the patients for their informed consent.

Disclosures
Drs Muller, Sum, Madden, and Hendricks are employees of InfraReDx, Inc. Dr Goldstein is a consultant for and owns equity in InfraReDx, Inc. Drs Stone and Kern are consultants for InfraReDx, Inc. Dr Stone is also a consultant for Volcano Corp and Medtronic and a member of the scientific advisory boards for Boston Scientific and Abbott Vascular. Dr Brilakis has received speaker honoraria from St Jude Medical and Terumo, research support from Abbott Vascular and InfraReDx, and his spouse is an employee of Medtronic.

References


Detection of Lipid-Core Plaques by Intracoronary Near-Infrared Spectroscopy Identifies High Risk of Periprocedural Myocardial Infarction


_Circ Cardiovasc Interv._ 2011;4:429-437; originally published online October 4, 2011; doi: 10.1161/CIRCINTERVENTIONS.111.963264

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2011 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/4/5/429

Data Supplement (unedited) at:

http://circinterventions.ahajournals.org/content/suppl/2011/10/04/CIRCINTERVENTIONS.111.963264.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Interventions_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Interventions_ is online at:

http://circinterventions.ahajournals.org/subscriptions/
COLOR Registry Sites and Contributing Personnel

Veterans Affairs North Texas Health Care Systems, Dallas, TX  Emmanouil S. Brilakis MD PhD(Principal Investigator, PI), Subhash Banerjee MD, Holly Wise, Bavana V. Rangan, Abdul-Rahman R. Abdel –Karim, Katherine M. Harper; Scottsdale Healthcare, Scottsdale, AZ  David Rizik MD(PI), Joanne Saczynski RN, Deandra O’Connor RN; Moffitt Heart and Vascular Group, Harrisburg, PA  Brijeshwar Maini MD(PI), Anita Todd RN; Lisa M Moser RN; San Francisco Veterans Affairs Medical Center, San Francisco, CA  Kendrick Shunk MD PhD(PI), Jeffrey Zimmet MD PhD, Katherine Stanley RN; Medical University of South Carolina Hospital, Charleston, SC  Eric R. Powers MD(PI), Daniel H. Steinberg MD, Christina Russell RN; Mount Sinai School of Medicine, New York, NY  Annapoorna S. Kini MD(PI), Michael Kim MD, Pedro Moreno MD, Michael Fusilero, Kristin Falciglia; University of California Irvine Medical Center, Orange, CA  Pranav Patel MD(PI), Morton Kern MD, Elizabeth E. Michel RN; Piedmont Hospital, Atlanta, GA  William Ballard MD(PI), Nancy Flockhart RN; Columbia University Medical Center, New York NY  Giora Weisz MD (PI), Fernando A. Sosa; Mayo Clinic, Rochester, MN  Amir Lerman MD(PI), Abhiram Prasad MD PhD, Cindy Woltman RN; William Beaumont Hospital, Royal Oak, MI  Simon R. Dixon MD (PI), Dorothy Richardson; Washington Adventist Hospital, Takoma Park, MD  Mark A. Turco MD(PI), Denise M. Pond RN; Swedish Medical Center, Seattle, WA  John Petersen II MD(PI), Mark Reisman MD, Jennifer Nagel, Tracie Granger; Beth Israel Deaconess Medical Center, Boston, MA  Donald Cutlip MD (PI), Jenifer M. Kaufman RN; Massachusetts General Hospital, Boston, MA, Ik-Kyung Jang MD PhD(PI), Iris A. McNulty RN; University of Florida Gainesville Medical Center, Gainesville, FL, Carl J. Pepine MD(PI), R. David Anderson MD, Heather Herndon RN, Dana D. Leach NP.