Neoatherosclerosis, a recently recognized phenomenon in which lipid-rich plaques (LRPs) develop within pre-existing stents, represents an emerging cause of stent failure that can trigger stent thrombosis years after implantation. Originally described in postmortem studies, neoatherosclerosis has more recently been detected by intracoronary imaging. Given its association with stent failure, additional methods to identify neoatherosclerosis in vivo are needed.

Intracoronary near-infrared spectroscopy (NIRS) is a catheter-based imaging modality developed and validated for the specific purpose of LRP detection in the coronary arteries. Given its ability to detect coronary LRP, NIRS has been proposed as a method to detect neoatherosclerosis in pre-existing coronary stents, although NIRS has not been validated for this purpose. This study was undertaken to compare NIRS findings in pre-existing stents, in which an increased lipid signal has been speculated to indicate neoatherosclerosis, and NIRS findings in a control group of freshly implanted stents, in which any lipid signal originates from fibroatheroma under the stent.

Methods

Study Population
The Spectrum NIRS-IVUS registry (NCT01694368) is a single-center observational registry of prospectively enrolled patients undergoing combined NIRS-IVUS imaging at the Frederik Meijer Heart and Vascular Institute (Spectrum Health, Grand Rapids, MI). Inclusion criteria for participation in the registry are age ≥18, referral to the catheterization laboratory for clinically indicated invasive coronary angiography or percutaneous coronary intervention, and performance

Results

Among 60 pre-existing stents implanted 5.5±4.0 years earlier, NIRS detected LRP in 33%. At the site of LRP, intravascular ultrasound found no neointimal tissue in 35% of cases. NIRS findings in pre-existing stents were indistinguishable from those of freshly implanted stents (lipid-core burden index: 50±72 versus 42±58; \( P = 0.40 \) and maximum lipid-core burden index in 4 mm: 156±184 versus 155±203; \( P = 0.69 \)).

Conclusions
The detection of LRP in a pre-existing stent by NIRS alone is not reliable evidence of neoatherosclerosis, as the lipid signal may originate from fibroatheroma underlying the stent. By identifying the presence or absence of neointimal tissue at the site of LRP detected by NIRS, intravascular ultrasound may provide some insight into the potential source of the lipid signal in pre-existing stents.

Registration Information
of NIRS-IVUS imaging within the index target vessel. Consecutive registry participants having at least 1 pre-existing stent that was implanted >4 months before the time of NIRS-IVUS imaging were included in the present analysis. This time frame was selected because neointimal hyperplasia has been described as early as 111 days after stent implantation.11 Data on the type of pre-existing stent, date of implantation, and indication for stent implantation were obtained retrospectively from medical records. In all registry participants, clinical outcome data are collected prospectively after NIRS-IVUS imaging by study personnel blinded to the NIRS-IVUS imaging findings with phone calls at 6 months after the index procedure, 1 year after the index procedure, and then annually for a total of 5 years. This study was approved by the Institutional Review Board of Spectrum Health, and all participants provided written informed consent.

NIRS-IVUS Imaging and Analysis
The decision to perform NIRS-IVUS imaging at the time of invasive angiography was at the discretion of the operating physician. The NIRS-IVUS catheter (TVC Imaging System, Infraredx, Burlington, MA) was advanced into the target vessel, and motorized pullback was performed at 0.5 mm/s.

NIRS-IVUS images were interpreted offline. Images were considered uninterpretable and excluded from further analysis if the corresponding block chemogram was black in color, indicating the absence of reliable data. The proximal and distal margins of all coronary stents were identified and marked on the IVUS images. This resulted in marking the stent edges on the NIRS chemogram as well, as NIRS images are automatically coregistered to IVUS images at the time of image acquisition.

Quantitative IVUS analysis was performed along the entire length of each stent on cross-sectional images spaced 1 mm apart using commercially available software (CAAS IntraVascular, Pie Medical Imaging, Maastricht, Netherlands). The external elastic membrane (EEM), luminal contours, and stent contours were traced on each image. Residual plaque burden under the stent was calculated as (EEM area–stent area/EEM area)×100. Remodeling index was calculated as maximal EEM area in the stented vessel divided by reference segment EEM obtained within 5 mm of the stent edge. Minimal stent area and minimal luminal area within each stent were also recorded.

NIRS chemograms in the stent were interrogated for the presence of LRP, defined as ≥1 bright yellow block on the NIRS block chemogram.14 To quantify the amount of lipid present in each stent, the lipid-core burden index (LCBI) was calculated, defined as the fraction of pixels indicating lipid within a region multiplied by 1000.14 Each stent was also denoted by study personnel blinded to the NIRS-IVUS imaging findings with phone calls at 6 months after the index procedure, 1 year after the index procedure, and then annually for a total of 5 years. This study was approved by the Institutional Review Board of Spectrum Health, and all participants provided written informed consent.

Statistical Analysis
All continuous data were explored graphically using Q–Q plots to determine conformance to a normal distribution. Non-normally distributed continuous variables, which included LCBI, maxLCBI_4 mm, and triglycerides, are shown as median (interquartile range). All other variables were normally distributed and are reported as mean±SD. Categorical variables are shown as count (frequency). NIRS-IVUS findings were described using summary statistics. IVUS findings and measures of lipid burden, including LCBI, maxLCBI_4 mm, and frequency of maxLCBI_4 mm ≥400, were compared between pre-existing stents and freshly implanted stents. To evaluate an association between NIRS-IVUS findings and stent failure, the frequency of stent failure at the time of NIRS-IVUS imaging and the frequency of stent failure during follow-up were compared between stents with and without NIRS-IVUS patterns II or III. Differences in clinical characteristics of the study population and controls were assessed with Welch t tests and Fischer exact tests. Generalizing estimating equations were used to analyze stent-level observations to control for confounding correlation caused by multiple stent observations from individual patients. All fitted generalized estimating equations included 1 independent variable and were estimated using an exchangeable correlation structure. Each model was fit to assess the association between a single variable (eg, LCBI, stent diameter, etc) and group status (eg, either pre-existing versus freshly implanted). Wald tests using SEs from a robust jackknife variance estimator were used to compute P values. When examining associations between group status and a quantitative variable, a Gaussian link function was used and the quantitative variable was modeled as the dependent variable. When examining associations between group status and a categorical variable, a binomial link function was used and the group status was modeled as the dependent variable.

The correlation between residual plaque burden and LCBI and between remodeling index and LCBI were examined while controlling for multiple observations from individual patients and are reported as correlation coefficients and 95% confidence intervals (CIs). CIs for proportions were estimated using the Agresti–Coul method.19 Significance was assessed at P<0.05. All analyses were performed using the R statistical software environment version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results
Patient Characteristics
Between January 10, 2012, and August 3, 2014, 454 patients were approached for consent to participate in the Spectrum NIRS-IVUS registry. Of these, 145 patients did not meet inclusion criteria based on angiographic findings or declined to participate. Among the remaining 309 registry participants, 41 patients were identified as having at least 1 pre-existing stent evaluated with NIRS-IVUS imaging >4 months after stent implantation. Among these 41 patients, a total of 61 pre-existing coronary stents were present at the time of NIRS-IVUS imaging. Of these, a single stent was excluded from further
analysis as the NIRS block chemogram was black in color indicating the absence of reliable NIRS data. The remaining 60 stents constitute the study cohort and underwent NIRS-IVUS imaging 5.5±4.0 years after stent implantation. Pre-existing stents consisted of 10 (16.7%) bare-metal stents and 50 (83.3%) drug-eluting stents, which were first generation in 26 (52.0%) and second generation in 24 (48.0%). The clinical characteristics of patients with pre-existing stents and those of the control group of patients with freshly implanted stents are presented in Table 1. Groups were well matched except for a lower total cholesterol in patients with pre-existing stents.

**NIRS-IVUS Findings in Pre-Existing Coronary Stents**

Comparative NIRS-IVUS findings in pre-existing stents and the control group of freshly implanted stents are presented in Table 2. Quantitative IVUS analysis did not reveal significant differences among pre-existing and freshly implanted stents with respect to minimal stent area or remodeling. Residual plaque burden was slightly less at the site of pre-existing stents (63.1±8.4% versus 66.8±7.3%; P=0.01). Because of the presence of neo-intimal tissue, pre-existing stents had a smaller minimal luminal area (4.5±1.7 versus 5.3±2.0 mm²; P=0.01).

A LRP was detected by NIRS in 20 (33.3%; 95% CI, 22.7–46.0) of the 60 pre-existing coronary stents. NIRS characterized the lipid burden of pre-existing stents as an LCBI of 50±72 and a maxLCBI<sub>4</sub> of 156±184. The frequency of a large focal lipid burden, indicated by a maxLCBI<sub>4</sub> of ≥400, within pre-existing stents was 16.7%. The lipid burden in pre-existing stents was not significantly different among stable patients and those presenting with an ACS (LCBI: stable 58±102 versus ACS 90±101; P=0.62 and maxLCBI<sub>4</sub>: stable 174±239 versus ACS 209±189; P=0.53). Among pre-existing coronary stents, no significant correlation was detected between residual plaque burden and LCBI (r=0.05; 95% CI, −0.22 to 0.32) or between remodeling index and LCBI (r=0.07; 95% CI, −0.19 to 0.31).

NIRS findings in pre-existing stents were not significantly different from those of freshly implanted stents, regardless of whether lipid burden was assessed as LCBI (50±72 versus 42±58; P=0.40) or maxLCBI<sub>4</sub> (156±184 versus 155±203; P=0.69). The frequency of a maxLCBI<sub>4</sub> of ≥400 was also similar in pre-existing stents and freshly implanted stents (16.7% versus 16.7%; P=1.00). Similarities of NIRS findings in pre-existing and freshly implanted stents are depicted in Figure 1.

**Patterns of NIRS-IVUS Findings in Pre-Existing Stents**

Interrogation of the IVUS findings at the site of LRP detected by NIRS within pre-existing coronary stents revealed 3 distinct patterns (Figure 2) as follows:

Pattern I: In 35.0% (95% CI, 18.0–56.8) of cases, IVUS revealed no neo-intimal tissue at the site of the LRP. Pattern II: In 35.0% (95% CI, 18.0–56.8) of cases, IVUS revealed both neo-intimal tissue and the presence of plaque underneath the stent at the site of LRP. Pattern III: In 30.0% (95% CI, 14.3–52.1) of cases, IVUS revealed either neo-intimal tissue containing attenuated plaque that obscured the underlying stent struts at the site of the LRP or neo-intimal tissue covering stent struts that were immediately adjacent to the underlying media (ie, no underlying plaque) at the site of LRP.

In 21.7% of pre-existing stents, NIRS-IVUS pattern II or III was detected. Patterns II or III were found in all types of stents examined, including 20.0% of bare-metal stents, 19.2% of first-generation drug-eluting stents, and 25.0% of second-generation drug-eluting stents. NIRS-IVUS patterns II or III occurred with similar frequency in stable patients and in patients with an ACS (stable 23.1% versus ACS 21.3%; P=0.77). Pre-existing stents having NIRS-IVUS patterns II or III were associated with a significantly greater focal lipid burden compared with other pre-existing stents, as evident in a greater maxLCBI<sub>4</sub> (462±187 versus 129±131; P<0.001) and a greater frequency of a maxLCBI<sub>4</sub>≥400 (61.5% versus 4.3%; P<0.001). IVUS detected a disrupted neo-intima in 23.1% of pre-existing stents having NIRS-IVUS patterns II or III and in only 4.3% of stents lacking patterns II and III (P=0.20).

**NIRS-IVUS Findings and Stent Failure**

At the time of NIRS-IVUS imaging, 16 (26.7%) pre-existing stents demonstrated stent failure, including 11 cases of in-stent restenosis and 5 cases of stent thrombosis. Pre-existing stents with NIRS-IVUS pattern II or III were marginally more often associated with stent failure at the time of NIRS-IVUS imaging compared with other pre-existing stents (46.1% versus 21.3%; P=0.053; Figure 3). Among the 16 cases with...
stent failure at the time of NIRS-IVUS imaging, percutaneous intervention resulted in transient angiographic no-reflow in 2 cases, one of which had NIRS-IVUS pattern III present and another had no detectable lipid by NIRS.

During a follow-up period of 471±269 days after NIRS-IVUS imaging, stents having NIRS-IVUS pattern II or III at baseline developed subsequent stent failure in 4 (30.8%) of 13 cases, including 2 cases of subsequent very late stent thrombosis and 2 cases of subsequent in-stent restenosis requiring revascularization (Figure 4). By comparison, subsequent stent failure occurred in only 1 (2.1%) of 47 stents that lacked NIRS-IVUS pattern II or III (P=0.034).

Discussion

This study makes several novel observations on NIRS-IVUS imaging within pre-existing coronary stents. First, no significant differences were observed in the NIRS findings of pre-existing stents, in which lipid signals have been previously speculated to represent neoatherosclerosis, compared with a control group of freshly implanted stents, in which any lipid signal likely originates from fibroatheroma under the stent. The observation that NIRS findings in these 2 groups were indistinguishable highlights the inability of NIRS to determine the depth of an LRP and thereby to accurately differentiate lipid within the neointima from lipid within fibroatheroma underneath a pre-existing stent. Second, this study demonstrates that IVUS, by identifying the presence or absence of neointimal tissue at the site of LRP detected by NIRS, may provide insight into the potential source of the lipid signal. Hence, the lack of visible neointimal tissue by IVUS at the site of the lipid signal, a pattern found in more than one third of LRP in this study, likely indicates that the lipid signal originated from a fibroatheroma underlying the stent and not from neatherosclerosis. Taken collectively, the observations of this study suggest that the detection of LRP in a pre-existing stent by NIRS alone is not reliable evidence of neoatherosclerosis.

In addition to the above findings, this study observed that neointimal tissue was evident by IVUS at the site of

Table 2. Quantitative Near-Infrared Spectroscopy-Intravascular Ultrasound Findings in Pre-Existing Stents and a Control Group of Freshly Implanted Stents

<table>
<thead>
<tr>
<th></th>
<th>Pre-Existing Stents, n=60</th>
<th>Freshly Implanted Stents, n=60</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent diameter, mm</td>
<td>3.1±0.5</td>
<td>3.2±0.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Minimal stent area, mm²</td>
<td>5.5±1.8</td>
<td>5.3±2.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Residual plaque burden, %</td>
<td>63.1±8.4</td>
<td>66.8±7.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Remodeling index, ≥1.10</td>
<td>54 (90.0)</td>
<td>50 (83.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>LCBI</td>
<td>50±72</td>
<td>42±58</td>
<td>0.40</td>
</tr>
<tr>
<td>MaxLCBI&lt;sub&gt;max&lt;/sub&gt;</td>
<td>156±184</td>
<td>155±203</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Values shown are mean±SD except for LCBI and MaxLCBI<sub>max</sub>, which are shown as median ± median absolute deviation, and remodeling index ≥1.10, which is shown as number (frequency). LCBI indicates lipid-core burden index; and maxLCBI<sub>max</sub>, maximum lipid-core burden index in 4 mm.

Figure 1. Near-infrared spectroscopy (NIRS) findings in pre-existing stents and freshly implanted stents. For all NIRS chemograms, proximal and distal stent edges are represented by blue lines. A, NIRS chemograms demonstrate lipid-rich plaques (LRPs) in pre-existing stents (right). The detection of LRP by NIRS in a pre-existing stent should not be considered adequate evidence of neoatherosclerosis, as NIRS findings do distinguish the LRP of neoatheroma from the LRP of fibroatheroma underneath the stent. NIRS chemograms obtained from freshly implanted stents (left), in which the detected LRP is presumed contained within fibroatheroma underneath the stent, are indistinguishable from the chemograms of pre-existing stents. B, Baseline angiogram in January 2013 demonstrates a culprit lesion (arrow) causing ST-segment–elevation myocardial infarction (left). NIRS chemogram and combined NIRS-intravascular ultrasound (IVUS) image (top) obtained after stent placement show LRP underneath a freshly implanted stent. Repeat imaging 21 months later (bottom) demonstrates persistence of the LRP on the NIRS chemogram. Combined NIRS-IVUS image shows the absence of neointima overlying the lipid signal, indicating that the LRP signal in the stent is unlikely neoatherosclerosis.
Madder et al  NIRS-IVUS Findings in Pre-Existing Stents

approximately two thirds of LRP detected by NIRS. Given previous histological evidence that neoatherosclerosis is present in >20% of pre-existing stents, it is likely that the neointima detected at the site of the lipid-rich signal in some of these cases was neoatherosclerosis. However, the simultaneous detection of neointimal tissue and plaque underneath the stent at the site of LRP (pattern II) may also simply represent neointimal hyperplasia within a stent covering a fibroatheroma. Whether NIRS-IVUS pattern III, in which the neointimal tissue is of low attenuation or in which no plaque is visible underneath the stent struts, is more likely indicative of neoatherosclerosis remains unknown. Although these patterns of NIRS-IVUS findings should not be considered evidence of neoatherosclerosis without further validation, their observed association with the occurrence of stent failure in this study is provocative.

The concept that intracoronary imaging performed long after stent implantation might identify vulnerable stents at risk for future thrombosis or restenosis was recently demonstrated in an angioscopy study, in which stents harboring yellow plaques were associated with a significantly higher risk of subsequent very late stent failure. Given the small size of this study, caution must be applied in drawing firm conclusions on the ability of NIRS-IVUS to predict subsequent stent failure. The present observations should be considered hypothesis-generating only and require confirmation in additional studies.

In Vivo Detection of Neoatherosclerosis
Similar to the use of NIRS-IVUS in this study, previous studies have applied various intracoronary imaging modalities to detect neoatherosclerosis in pre-existing stents. Findings of

Figure 2. Patterns of near-infrared spectroscopy (NIRS)-intravascular ultrasound (IVUS) findings in pre-existing coronary stents. A, Pattern I: no neointimal tissue at the site of lipid-rich plaques (LRPs). IVUS reveals plaque (asterisks) underneath the stent struts (blue arrows) at the site of LRP by NIRS (white arrows). B, Pattern II: neointimal tissue (white asterisk) and plaque (green asterisk) underneath stent struts (blue arrows) at the site of LRP (white arrows). Pattern III: neointimal tissue containing attenuated plaque (asterisks) obscuring underlying stent struts in the absence of overlying calcification at the site of LRP (white arrows; C). Stent struts (blue arrows) are visible on the opposite side of the lumen from the attenuated plaque, or neointimal tissue (asterisks) with stent struts (blue arrows) immediately adjacent to the medial stripe at the site of LRP by NIRS (white arrows; D). E, Classic neointimal hyperplasia: neointimal tissue (asterisks) in the absence of LRP by NIRS (white arrows pointing to red chemogram). Stent struts are shown (blue arrows).
Neoatherosclerosis have been previously detected by angioscopy, as shown in a serial angioscopy study in which the development of yellow plaques was demonstrated within the lumen of bare-metal stents during a 4-year period. Virtual histology IVUS has been used to identify evidence of neoatherosclerosis, and a previous grayscale IVUS study demonstrated sites of plaque rupture within the lumen of remotely implanted stents in the setting of very late stent thrombosis. Ruptured plaque morphology within remotely implanted stents has been similarly demonstrated by optical coherence tomography (OCT), which may be the best imaging modality to detect ruptured neointima because of its superb spatial resolution. Further OCT evidence for the in vivo detection of neoatherosclerosis has been provided by the demonstration of LRP by OCT within the lumen of pre-existing stents.

Detection of Neoatherosclerosis by NIRS

The ability of NIRS to detect LRP within pre-existing stents was originally demonstrated in a previous study by Ali et al in which 65 pre-existing stents with in-stent restenosis were imaged with combined NIRS-IVUS and OCT. In this previous study, which found the NIRS lipid burden to be inversely correlated to the fibrous cap thickness of the overlying neointima, LRP was detected by NIRS in 89% of pre-existing stents. The lower frequency of LRP reported in this study is likely attributable to the stringent definition of LRP used and to the inclusion of stents in the study population regardless of whether clinically significant stent failure was present. This study extends the findings of Ali et al by demonstrating that LRP detected by NIRS within pre-existing stents can be further differentiated based on the corresponding IVUS findings. Accordingly, approximately one third of LRP detected by NIRS in this study had no associated neointimal tissue by IVUS and were, therefore, unlikely to represent neoatherosclerosis. On the basis of this observation, many of the LRP detected by Ali et al may have represented fibroatheroma under the stent and not neoatherosclerosis. Importantly, the present findings and those of Ali et al suggest that NIRS alone, which cannot differentiate the lipid signal of neointima from that of fibroatheroma underneath the stent, is unlikely suitable as a stand-alone technique to accurately identify neoatherosclerosis. Rather, multimodality imaging that combines the NIRS findings with either IVUS or OCT are likely required to determine the position of the NIRS lipid signal relative to the underlying stent struts. Given the greater spatial resolution of OCT compared with IVUS, OCT may be preferred in this regard.

Limitations

This study is limited by a small sample size and single-center design. However, this study, which has a sample size similar to previous intracoronary imaging studies of neoatherosclerosis, is only the second study to evaluate NIRS findings in pre-existing coronary stents and is the first to describe patterns of combined NIRS-IVUS findings. By studying only those patients having a clinical indication for catheterization, and because the performance of NIRS-IVUS imaging was at the discretion of the operating physician, the present observations are likely affected by selection bias. Furthermore, this cross-sectional approach, in which imaging was performed on pre-existing stents that varied in their duration from the time of original implantation, is not ideal for delineating the true incidence of neoatherosclerosis or its pattern of temporal development. The significant difference in baseline cholesterol of cases and controls represents another limitation. Validation of the present NIRS-IVUS observations, with particular focus on whether patterns II or III indicate the presence of neoatherosclerosis, is needed. Finally, uncertainty on the effect of the present observations on contemporary patient care represents
an additional limitation. Future studies will be required to determine the clinical relevance of NIRS-IVUS findings in pre-existing stents.

Conclusions

The detection of LRP in a pre-existing stent by NIRS alone is not reliable evidence of neoatherosclerosis. By identifying the presence or absence of neointimal tissue at the site of LRP detected by NIRS, IVUS may provide some insight into the potential source of the lipid signal in pre-existing stents.

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Disclosures

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CLINICAL PERSPECTIVE

Neoatherosclerosis, a recently recognized phenomenon in which lipid-rich plaques (LRPs) develop within previously implanted coronary stents, represents an emerging cause of stent failure that can trigger stent thrombosis years after implantation. Given its ability to detect coronary LRPs, intracoronary near-infrared spectroscopy (NIRS) has been proposed as a method to detect neoatherosclerosis in pre-existing coronary stents, although NIRS has not been validated for this purpose. In this study, combined NIRS and intravascular ultrasound imaging was performed in pre-existing coronary stents and in a control group of freshly implanted stents. No significant differences were observed in the NIRS findings of pre-existing stents, in which lipid signals have been previously speculated to represent neoatherosclerosis, compared with a control group of freshly implanted stents, in which any lipid signal likely originates from fibroatheroma under the stent. This observation highlights the inability of NIRS to determine the depth of an LRP and thereby to accurately differentiate lipid within the neointima from lipid within fibroatheroma underneath a pre-existing stent. Combined NIRS-intravascular ultrasound imaging might partially overcome this limitation, as intravascular ultrasound may provide insight into the potential source of the lipid signal by identifying the presence or absence of neointimal tissue at the site of LRP detected by NIRS. Hence, the lack of visible neointimal tissue by intravascular ultrasound at the site of the lipid signal, a pattern found in more than one third of LRP in this study, likely indicates that the lipid signal originated from a fibroatheroma underlying the stent and not from neoatherosclerosis.
Combined Near-Infrared Spectroscopy and Intravascular Ultrasound Imaging of Pre-Existing Coronary Artery Stents: Can Near-Infrared Spectroscopy Reliably Detect Neoatherosclerosis?

Ryan D. Madder, Mohsin Khan, Mustafa Husaini, Margaret Chi, Sarah Dionne, Stacie VanOosterhout, Andrew Borgman, J. Stewart Collins and Mark Jacoby

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