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NIRS-IVUS Imaging To Characterize the Composition and Structure of Coronary Plaques

David Rizik, MD1 and James A. Goldstein, MD2

It is a pleasure to introduce this supplement describing experience with a combination near-infrared spectroscopic (NIRS)-intravascular ultrasound (IVUS) coronary catheter. The findings already obtained with this novel device indicate that it is now possible to move beyond angiography toward the goal of full characterization of the causes of stent failures and identification of the vulnerable plaques responsible for spontaneous coronary events.

Limitations of Conventional Angiography for Plaque Characterization and Optimal PCI

Coronary angiography has been, and continues to be an invaluable tool for the detection and treatment of the coronary stenoses causing myocardial ischemia. It permits rapid assessment of the entire coronary circulation and can readily detect a localized stenosis as shown in Figure 1.

However the angiogram provides only limited information about the properties of the wall of the artery. As is apparent from Figure 2, a lipid-rich plaque (LRP) and a fibrotic and calcified plaque would produce identical images on an angiogram, which depicts only the lumen. Yet the LRP, which can be detected by NIRS imaging, is much more likely to cause a peri-procedural MI when stented, and such plaques have been associated with spontaneous coronary events.

Angiography also underestimates the magnitude of atherosclerotic burden, particularly in earlier stage disease in which positive vascular remodeling may allow maintenance of "normal" lumen caliber despite substantial vascular wall plaque. In the quest to detect vulnerable and frankly unstable lesions, angiography detects only gross plaque ruptures, which comprise only a subset of those coronary lesions that are truly unstable and provides no insight regarding non-ruptured "vulnerable plaques," the putative substrate for most acute coronary syndromes and many cases of sudden cardiac death. Furthermore, performance of PCI with guidance by angiography only is associated with sub-optimal stent expansion or lack of detection of edge complications in 15%-20% of cases, which has been associated with adverse events.18

Intravascular Imaging to Supplement the Angiogram

Intravascular imaging can fill part of the gap in information existing after the angiogram is reviewed. Intravascular ultrasound (IVUS) imaging can identify features of complex unstable plaques and measure stenosis severity, plaque burden, calcification, and remodeling.1,2 IVUS use can also facilitate optimal PCI by providing reference vessel diameter (for selection of proper stent size), identification of landing zones with diminished plaque burden, and confirmation that a stent has been optimally expanded. PCI guided by angiography plus IVUS has been associated with reduced stent thrombosis and restenosis compared to PCI guided by angiography alone.16,17

While IVUS provides useful information about plaque structure and stent expansion, the conventional grayscale images are of only limited value for detection of lipid-rich plaque. For this reason IVUS-based algorithms have been developed to identify necrotic core and other plaque features. In the PROSPECT Study, analysis of radiofrequency IVUS signals improved the prediction of events provided by plaque burden alone. However, PROSPECT failed to demonstrate that prediction by grayscale IVUS combined with radiofrequency IVUS

Figure 1. Conventional angiogram showing an isolated stenosis in the circumflex artery.
was sufficiently specific to warrant a change in diagnostic and treatment strategies. In addition, a later animal study, which compared the radiofrequency signs of necrotic core to results obtained with a histologic gold standard in a porcine autopsy study failed, calling into question the accuracy of radiofrequency IVUS as a method to detect necrotic core plaque.

Optical Coherence Tomography (OCT) is a novel intracoronary optical imaging technique that can provide much higher resolution structural imaging than IVUS. It is an excellent technique for identification of plaque rupture, thin-cap, and the causes of stent failure. OCT is also an excellent technique for investigating the causes of stent failure. However, OCT requires removal of blood from the field of view, cannot image deeply into tissue and lacks an automated, validated method of detection of lipid-rich plaque.

Angioscopy has been an excellent tool for advancement of knowledge of the causes of coronary events. However it is not in use in routine practice due to the need to remove blood from the field of view, and its limited ability to penetrate beyond the luminal surface of the vessel.

While not an imaging tool, fractional flow reserve (FFR) has been shown by outcome studies to be an excellent means to judge the functional significance of a coronary stenosis.

The Ideal Tool for Plaque Characterization and Optimal PCI

The ideal invasive tool for characterization of coronary plaque would provide a complete roadmap of atherosclerotic burden throughout the coronary tree and deliver lesion specific data characterizing the structure, composition, and dynamic biology of each plaque. It should provide information about: (1) Luminal stenosis; (2) Flow limitation; (3) Plaque burden and remodeling; (4) Plaque rupture; (5) Lesion length; (6) Plaque composition, including calcification, lipid content and inflammation; (7) Fibrous cap thickness and integrity; and (8) Intracoronary thrombus.

The ideal imaging tool should also be able to facilitate optimal PCI through determination that stents are fully deployed and edge dissections are not present.

While the instruments previously available were capable of achieving many of these goals in a reproducible, safe and cost-effective manner, several desired features have not been available, such as the ability to accurately identify LRP and a means to quantitate the degree of inflammation. This supplement features the newly available TVC Imaging System, which combines intracoronary IVUS and NIRS to provide true vessel characterization of both vessel structure and composition through the system's ability to co-register IVUS with lipid-rich plaque detection.

The Importance of Lipid-Rich Plaque Detection

The development of NIRS as a tool to detect LRP coincides with increasing evidence that LRPs play a major role in stenting complications and spontaneous events. NIRS has undergone a rigorous validation in autopsy studies conducted in 84 hearts. An example of the ability of NIRS to identify lipid core plaque is shown in Figure 3. Figure 4 demonstrates the manner in which this additional information adds to the data available from a conventional coronary angiogram.

NIRS and other imaging techniques have shown that dilation of a stenotic LRP is associated with an increased incidence of no-reflow and peri-stenting myocardial infarction. The combination of NIRS with IVUS in a single catheter permits the addition of IVUS benefits to the proven and potential benefits of NIRS. There are multiple ways in which the NIRS-IVUS catheter can provide value by helping to optimize PCI and perhaps, in the future, by playing a role in the prevention of spontaneous coronary events. As reported in this supplement, NIRS has identified large, often circumferential LRPs at the culprit site in most patients experiencing a STEMI.

The Importance of Lipid-Rich Plaque Detection

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NIRS and other imaging techniques have shown that dilation of a stenotic LRP is associated with an increased incidence of no-reflow and peri-stenting myocardial infarction. This stenting complication could possibly be prevented with the use of a filter device—a potential clinical benefit that is being evaluated in the NIRS-guided CANARY Study.

The combination of NIRS with IVUS in a single catheter permits the addition of IVUS benefits to the proven and potential benefits of NIRS. There are multiple ways in which the NIRS-IVUS catheter can provide value by helping to optimize PCI and perhaps, in the future, by playing a role in the prevention of spontaneous coronary events. As reported in this supplement, NIRS has identified large, often circumferential LRPs at the culprit site in most patients experiencing a STEMI. These cross-sectional data have led to the initiation of two large-scale prospective studies that will test the hypothesis that NIRS can enhance the prediction of cardiac events beyond the success achieved with plaque burden in the PROSPECT Study.

Goals, Purpose, and Future Directions

This supplement, authored by highly experienced interventional cardiologists expert in the field of coronary plaque characterization, contains a detailed description of the new NIRS-IVUS combination catheter, and the clinical information obtained during its use in over 90 hospitals in over 10 countries. Case vignettes, cohort outcomes, reviews, and plans for future studies are also presented. It is our hope that this information will be useful in the near term to those seeking to improve PCI. For the longer term, we believe that the NIRS-IVUS system is an excellent candidate for evaluation as a detector of vulnerable plaque. Success in the prospective studies that are planned will make it possible to detect vulnerable plaques and thereby enhance efforts to prevent coronary events.
4A

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Note from Dr. Rizik: I would like to express my gratitude to Dr. Jim Goldstein. Jim has been a long time teacher, mentor, and friend dating back to our Washington University days in St. Louis. When I first approached him about participating in this focus issue, he didn’t hesitate to take on this project. He guided the effort, bringing his knowledge of the subject and editorial expertise to this endeavor. If not for his leadership, this supplement would not be possible.

References

Figure 3. Demonstration of a NIRS chemogram and the underlying coronary histologic features in a human coronary autopsy specimen. The chemogram displays the results of several thousand NIR chemical determinations obtained through blood within 3 minutes. The x-axis shows the millimeter in pullback within the artery while the y-axis shows the degree of rotation within the artery from 0 to 360 degrees. Sites with a high probability of the presence of a lipid-rich plaque are shown in yellow. The figure shows the close correspondence between the yellow spots on the chemograms and lipid-rich plaques documented by histology. Movatt’s Pentachrome stain, data on file. Infraredx, Inc.

Figure 4. The angiogram shown in Figure 1 with additional data now provided by imaging with the NIRS-IVUS system. A stenosis is visible on the angiogram (A). The cross-sectional IVUS shows stenosis. The halo around the IVUS image represents the NIRS values obtained at that location; yellow indicates that a lipid-rich plaque is present, while red indicates the absence of a lipid-rich plaque (B). Other images (C, D, E, F) indicate that the lipid-rich plaque extends proximally in the artery. A large lumen is shown with no evidence of lipid core plaque (G). The entire chemogram is also shown (H). An angiogram showing correction of the stenosis by placement of a stent (I).
Imaging of Plaque Composition and Structure With the TVC Imaging System™ and TVC Insight™ Catheter

Brandie Shydo, BA, Michael Hendricks, BS, Grant Frazier, BS, MBA

Each year, nearly 4 million people worldwide undergo coronary stenting, a procedure that improves blood flow to the heart. While clinical results of stenting procedures have steadily improved, approximately 30% of individuals undergoing these procedures experience a significant adverse event. Stenting has traditionally been guided by x-ray angiography, which identifies the general location of the luminal narrowing but cannot reveal the composition of the vessel wall. Physicians are increasingly recognizing the limitations of relying on angiography alone and are turning to more advanced imaging solutions to optimize not only their stenting strategy, but also the overall care of their interventional cardiology patients.

Direct intracoronary imaging methods offer new insight into opportunities to improve PCI treatment of flow-limiting target lesions and identify the vulnerable plaques responsible for subsequent events (Table 1).

There is a growing awareness of the need to more effectively characterize the vessel by assessing not only its structure (by way of angiography and IVUS) but also its composition. The TVC Imaging System™ was developed to meet this need.

Revealing What You Need to Know

The TVC Imaging System (Infraredx) is the latest generation intravascular imaging system with the unique ability to assess vessel composition and structure via integrated near-infrared spectroscopy (NIRS) lipid core plaque detection and enhanced IVUS imaging technologies. The TVC Insight™ catheter provides simultaneous, co-registered acquisition of NIRS lipid core plaque (LCP) detection and grayscale IVUS that is available to the operating physician immediately upon completion of the catheter pullback procedure.

By obtaining a composite view of both vessel structure and composition (Figure 1), the TVC Imaging System provides interventional cardiologists with a more complete characterization of coronary plaques than has previously been possible. This true vessel characterization promotes optimal clinical decision-making and supports more effective treatment strategies. For example, NIRS will be able to better confirm LCP presence if high plaque burden and hypoechoic regions are found by IVUS, possibly indicating lesions at elevated risk of distal embolization during balloon dilation and stenting.

The system (Figure 2) is composed of a mobile console with an automated pullback and rotation device and the dual-modality TVC Insight™ catheter (Figure 3) for simultaneous NIRS LCP detection and IVUS imaging. The optical components of the system and catheter include a scanning infrared laser and optical fibers. The technical specifications of the TVC Imaging System and TVC Insight Catheter are summarized in Table 2.

The TVC System is FDA cleared (July 2010) and CE marked (April 2011) for the ultrasonic imaging of the coronary arteries as well as the detection of lipid-core containing plaques of interest (LCP) and the measurement of the Lipid Core Burden Index (LCBI). LCBI is a quantitative summary metric of the total LCP detected in the segment of artery scanned. LCBI correlates with fibroatheroma volume and has been shown to have clinical implications for the risk stratification of certain adverse peri-procedural PCI events.

Near Infrared Spectroscopy (NIRS)

Spectroscopy is a classic and highly trusted method within the field of analytical chemistry for the identifica-

<table>
<thead>
<tr>
<th>Table 1. Imaging methods for detection of intravascular plaque.</th>
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<tbody>
<tr>
<td>Cap Thickness</td>
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<tr>
<td>Expansive Remodeling</td>
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<tr>
<td>Plaque Volume</td>
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<tr>
<td>Calcification</td>
</tr>
<tr>
<td>Thrombus</td>
</tr>
<tr>
<td>Inflammation Macrophages</td>
</tr>
<tr>
<td>Lipid Core</td>
</tr>
<tr>
<td>Requires Blood-Free FOV</td>
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● Direct, robust, and/or validated; ○ Indirect, inferred, and/or unvalidated

Disclosure: The authors are employees of Infraredx Inc.

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Figure 1. TVC Composite™ View of co-registered near infrared spectroscopy lipid core plaque with intravascular ultrasound.

Figure 2. TVC Imaging System.

The combination of scattering and absorption of near infrared light by the organic molecules in the artery wall and plaque produces a unique chemical signature. The TVC Imaging System’s proprietary algorithm analyzes the detected signal for signs of cholesterol. In this way, the TVC Imaging System measures and interprets the chemical signals and identifies the composition of plaque to directly identify lipid cores, which is one of the most important characteristics of a plaque vulnerable to rupture and thrombosis.

NIRS-IVUS Combination with the TVC Imaging System

The TVC Imaging System augments the lumen and anatomical information obtained via angiography by using IVUS and NIRS to provide additional information about vessel size, lumen diameter and cross-sectional area, plaque volume, and composition of the plaque. Combining two complementary techniques that do not require a blood free field of view allows the most complete assessment of the patient’s arteries.

With the TVC Imaging System, NIRS-IVUS data is obtained via a monorail imaging catheter system similar in design and profile to a standard mechanical IVUS catheter. The catheter can be inserted via a 6 Fr guide and over a 0.014-inch guide wire. IVUS is acquired via a rotating transducer operating at 40 MHz. IVUS can be acquired either during an automated pullback for simultaneous co-registered NIRS measurement or by allowing the user to obtain live IVUS images via manual manipulation of the catheter. The TVC Imaging System provides a full suite of IVUS data analysis tools for border contouring, area and volume measurements, and case annotation.

To acquire LCP data, the catheter is advanced to a point distal to the target anatomy and scanning is initiated at a speed of 0.5 mm/s via the Nexus Controller™, an automated rotational pullback unit. The system performs more than 30,000 chemical measurements per 100 mm of artery scanned through the blood. Each measurement interrogates 1-2 mm² of tissue at a depth of about 1 mm. The sensitivity and specificity of the LCP measurements exceeds 85% ex vivo.4

At the completion of the scan, the NIRS LCP data is automatically displayed on a map of the vessel called a chemogram (Figure 4).

The chemogram and block chemogram provide easily interpreted visual representations of the spectroscopic assessment of the artery and plaques. Utilizing a simple two-color pseudo-color map, the chemogram graphically displays the probability of lipid prediction scores to the user in a two-dimensional map of the artery. The x-axis is millimeters of pullback (0.0 mm-120.0 mm). Degrees of catheter rotation (0-360 degrees) is represented on the y-axis. The chemogram displays low
probability of lipid as red and high probability as yellow. With a rapid transition from red to yellow at a prediction score of 0.6, shades of orange are minimized resulting in an easy to read near binary display. The block level chemogram summarizes the chemogram in 2 mm increments. These 2 mm increments correspond to 2 mm histology segments analyzed during the validation of the lipid prediction algorithm. The blocks are colored with a four-color scale based on the 90th percentile lipid core prediction value within the corresponding 2 mm of the chemogram. The blocks may be colored red ($x<0.57$), orange ($0.57 \leq x \leq 0.84$), tan ($0.84 < x \leq 0.97$), or yellow ($x>0.97$).

Immediately upon completion of the automated pullback procedure, the TVC Imaging System’s Composite View™ simultaneously presents the chemogram with the grayscale IVUS data images in both longitudinal and transverse views (Figure 1). In the longitudinal view, the grayscale IVUS data has the co-registered block chemogram displayed within the representation of the catheter to provide the physician with an overall perspective of both the structure of the vessel together with its lipid core content.

The individual frames of the IVUS data are displayed in a transverse view on the left side of the TVC composite. The co-registered NIRS lipid core data corresponding to each transverse IVUS frame is presented as a halo or ring around the perimeter of the IVUS image. This view enables the physician to better understand the extent of lipid core involvement within a very specific region of interest, such as within the culprit lesion or near a bifurcation or side-branch.

The TVC Composite View, with its longitudinal and transverse perspectives, provides the interventional cardiologist in the cath lab with a view of both vessel structure and composition necessary for true vessel characterization to optimize clinical decision-making and support optimal treatment strategies.

Clinical Validation of NIRS for Detection of LCP

Calibration and validation studies of near-infrared
Table 2. Technical Specifications of TVC Imaging System and TVC Insight Catheter.

<table>
<thead>
<tr>
<th></th>
<th>Operating System</th>
<th>Windows 7 Embedded</th>
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<tbody>
<tr>
<td>Processor</td>
<td>Intel Quad Core i7</td>
<td></td>
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<tr>
<td>Memory</td>
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</tr>
<tr>
<td>Hard Drive Capacity</td>
<td>500 GB (1000+ scans)</td>
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<td>Digital Archiving Options</td>
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<tr>
<td>Data Archive Formats</td>
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<tr>
<td>DICOM Services Supported</td>
<td>DICOM Store</td>
<td></td>
</tr>
<tr>
<td>Image Acquisition Modes</td>
<td>Live IVUS (Manual) or automated pullback (0.5 mm/s)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TVC Insight™ Catheter</th>
<th>Minimum Guide Catheter</th>
<th>6 French (2 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Guide Wire</td>
<td>0.014” (0.36 mm)</td>
<td></td>
</tr>
<tr>
<td>Catheter Crossing Tip Profile</td>
<td>3.2 French (1.1 mm)</td>
<td></td>
</tr>
<tr>
<td>Maximum Imaging Depth</td>
<td>16 mm</td>
<td></td>
</tr>
<tr>
<td>Catheter Working Length</td>
<td>120 mm</td>
<td></td>
</tr>
<tr>
<td>Operating Frequency</td>
<td>40 MHz</td>
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</table>

spectroscopy (NIRS) for detection of LCP were first performed in human autopsy specimens of the coronary arteries. Coronary arteries were obtained from specimens with a broad range of patient characteristics and causes of death. The arteries were mounted in a tissue fixture and connected to a blood circulation system with physiologic pressure, temperature, and flow. Approximately 5,000 NIRS measurements were taken from the coronary tissue samples and then compared to histology from the corresponding locations (Figure 3). A total of 86 coronary segments from 33 hearts were used to calibrate the system algorithm for detection of LCP. A further 126 coronary segments from 51 hearts were used to validate the data in a double blind, prospective study. For the purposes of calibration and validation, LCP of interest was defined as a fibroatheroma containing a necrotic core at least 0.2 mm thick with a circumferential span of at least 60° on cross-section.

In order to collect in vivo data, the SPECTroscopic Assessment of Coronary Lipid (SPECTACL) pivotal study was conducted to determine if the spectra recorded in patients (in whom tissue is not available for validation), were equivalent to the spectra recorded in autopsy specimens (in which tissue was available for histologic validation). The study supported the feasibility of detection of LCP in patients by demonstrating that NIRS signals similar to those collected in human autopsy specimens could be obtained from living patients.

Based on data from these two studies, the system obtained an FDA label claim specific to detection of LCP. The TVC Imaging System is the only intravascular imaging system available today with FDA 510(k) market clearance for the detection of lipid core plaques.

The robust technique of diffuse reflectance near infrared spectroscopy and the automated interpretation of the signals are very reproducible. Intra-catheter and inter-catheter agreement of NIRS result show the value of this method for longitudinal studies of natural history or treatment effects on arterial plaque.

**True Vessel Characterization with the TVC Imaging System**

Full characterization of the state of coronary artery disease must take into account structure, function, and composition. Imaging techniques such as angiography, IVUS, OCT, and fractional flow reserve provide invaluable insights into structure and function, but have not been able to provide accurate, easily obtainable information about plaque composition. The TVC Imaging System has been rigorously, prospectively validated for detection of one of the most important composition parameters related to stenting safety and the risk of rupture of a given plaque—the presence of a lipid core. The ability to detect LCP by NIRS and the use of this information to guide major stenting decisions may help improve the safety and efficacy of PCI. Outcome studies are planned to determine if NIRS-IVUS detection of LCP can identify plaques more likely to result in future coronary events.

**References**

Comparative Intravascular Imaging for Lipid Core Plaque: VH-IVUS vs OCT vs NIRS

Eric Fuh, MD and Emmanouil S. Brilakis, MD, PhD

The most common cause of acute coronary syndromes is believed to be coronary artery thrombosis due to rupture of a lipid-rich plaque (LCP).\textsuperscript{1,2} The goal of the present review is to compare three intravascular imaging modalities [virtual histology-intravascular ultrasound (VH-IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS)] that are currently available for the \textit{in vivo} detection of LCP (Figure 1).

**Lipid Core Plaque: Pathology**

Since the introduction of the term almost 20 years ago,\textsuperscript{3} vulnerable coronary plaques have been linked to the development of acute coronary syndromes (ACS). Three plaque pathologies have been described to cause ACS: plaque rupture, plaque erosion, and calcified nodules.\textsuperscript{4} Plaque rupture is the most common ACS-causing lesion type\textsuperscript{4} and usually occurs in thin-cap fibroatheromas (TCFAs),\textsuperscript{5} which consist of a lipid-laden necrotic core with an overlying fibrous cap usually measuring <65\,µm, scant smooth muscle cells, and numerous macrophages. TCFAs are often associated with positive remodeling and are present in areas of mild or moderate luminal narrowing.\textsuperscript{6,7} Percutaneous coronary intervention (PCI) of LCPs has been associated with no reflow and peri-procedural myocardial infarction due to embolization of plaque components during mechanical plaque disruption.\textsuperscript{7}

In this review we will describe how VH-IVUS, OCT, and NIRS can be used for determining coronary plaque composition and discuss their respective strengths and weaknesses for LCP detection.

**Virtual Histology-Intravascular Ultrasound (VH-IVUS)**

In contrast to grayscale IVUS that provides two-dimensional imaging based on the intensity of the reflected ultrasound waves, VH-IVUS uses spectral analysis of the backscattered radiofrequency IVUS signals to determine coronary plaque composition.\textsuperscript{8,9} The technique was developed by Nair et al\textsuperscript{10} who examined 51 human left anterior descending (LAD) coronary arteries obtained at autopsy. VH-IVUS provided accurate detection of four lesion types: thin- and thick-cap fibroatheroma (VH-TCFA), pathological intimal thickening (PIT), fibrocalcific plaque, and fibrocalcific plaque. However, additional attempts at \textit{in vivo} validation of VH-IVUS have yielded mixed results.\textsuperscript{11-14} Two porcine studies demonstrated poor correlation between VH-IVUS findings and histology.\textsuperscript{12,14} Conversely, using a rabbit aorta model, van Herck et al found good correlation between VH-IVUS and histology.\textsuperscript{15} Nasu et al performed VH-IVUS on lesions prior to directional coronary atherectomy. The tissue sample from atherectomy was then sent for histopathologic assessment that demonstrated high correlation between VH-IVUS and histology.\textsuperscript{15}

In a large, prospective natural history study of coronary atherosclerosis, 697 ACS patients underwent 3-vessel IVUS and VH-IVUS imaging after PCI and were followed for a median period of 3.4 years. At 3 years, non-culprit lesion related events occurred in 11.6% of patients. Most non-culprit lesions responsible for follow-up events were angiographically mild at baseline (mean diameter stenosis was 32.3 ± 20.6%). However, on multivariate analysis, compared to non-culprit lesions not associated with recurrent events, non-culprit lesions that were associated with recurrent events were more likely to have plaque burden of ≥70% (hazard ratio, 5.3; 95% confidence interval [CI], 2.5 to 10.11; P=0.001), minimal luminal area of ≤4.0 mm\textsuperscript{2} (hazard ratio, 3.2; 95% CI, 1.61 to 6.42; P=0.001), or to be classified on the basis of VH-IVUS as thin-cap fibroatheromas (hazard ratio, 3.35; 95% CI, 1.77 to 6.36; P=0.001).

PCI of necrotic core containing lesions has been linked to distal embolization in several studies. Kawamoto et al demonstrated that PCI of necrotic core containing lesions has been associated with more Doppler-detected high-intensity transient signals (HITS) during PCI.\textsuperscript{15} Similarly, Kawaguchi et al demonstrated that higher necrotic core area and volume were associated with higher risk for ST-segment re-elevation during PCI for ST-segment elevation acute myocardial infarction.\textsuperscript{16}

Two recent meta-analyses have confirmed those findings. In the first, Claessen et al demonstrated that the necrotic core plaque component, either by itself or as a constituent of a VH thin-cap fibroatheroma, was associated with distal embolization in all but 2 of the 11 reviewed studies.\textsuperscript{17} In the second study, Jang et al examined 16 studies showing that at the minimum lumen site, the absolute and relative necrotic core area was significantly greater in the embolization group than the no embolization group, whereas other plaque components were similar in the two groups.\textsuperscript{18}

In summary, VH-IVUS detected LCPs have been associated with higher incidence of clinical events and peri-procedural complications during PCI.

**Optical Coherence Tomography (OCT)**

OCT is a light-based intracoronary imaging modality with near-histologic resolution (5-20 µm).\textsuperscript{19,20} OCT directs near-infrared light into the vessel wall and measures the intensity of the reflected light waves to construct an image of the vessel wall. Because of the high speed of light the delay and magnitude of the reflected light cannot be measured directly, but
those who had no reflow after PCI had larger lipid arc (166˚ vs 44˚, P<0.001) and more often had TCFAs (50% vs 16%, P<0.005). Apart from lipid arc, the presence of plaque rupture\textsuperscript{33,34}, TCFA,\textsuperscript{33,34} intra-stent thrombus formation, and intra-stent dissection have been associated with post-PCI myocardial injury.\textsuperscript{35}

Unlike VH-IVUS and NIRS that both perform automated assessment for LCP (fully automated for NIRS, and semi-automated for VH-IVUS, as lumen and vessel border drawing is first required for the latter), OCT-based LCP detection requires image interpretation, which can sometimes be challenging (ie, in plaques containing both lipid and calcification).

Near-Infrared Spectroscopy (NIRS)

In NIRS, light from the near-infrared region of the electromagnetic spectrum (approximately 1300 nm) is directed to the coronary artery wall and the diffusely reflected light is collected and analyzed to provide an assessment on the presence of the LCP, based on its known NIRS signature. The NIRS algorithm for LCP detection was developed and validated in a large \textit{ex vivo} study of 84 autopsy hearts and 216 coronary segments that led to FDA approval of the device. In that study LCP was defined as a fibroatheroma containing a necrotic core at least 200 microns thick with a circumferential span of at least 60 degrees on cross-section and <450 µm fibrous cap thickness.\textsuperscript{36} The NIRS algorithm prospectively identified LCP with a receiver-operator characteristic area under the curve of 0.80. In a subsequent prospective clinical study (SPECTroscopic Assessment of Coronary Lipid (SPECTACL)), NIRS spectra were collected from patients (in whom tissue was not available for validation), and showed that these spectra were equivalent to the spectra recorded in autopsy specimens (in which histology was available for validation).\textsuperscript{37} NIRS measurements have been shown to be highly reproducible.\textsuperscript{38,39}

NIRS is currently available as a combined system with IVUS [True Vessel Characterization (TVC), InfraReDx, Inc] that consists of a console, a pullback and rotation device (PBR), and an intravascular catheter.\textsuperscript{40} IVUS-NIRS is the first clinically available hybrid intravascular imaging system, which is an area of rapid development and promise.\textsuperscript{41}

The NIRS console is comprised of a near-infrared scanning laser, computer, power system, and two monitors. The 3.2 Fr rapid exchange catheter consists of a tip with a 40 MHz ultrasound transducer and two mirrors, one for directing near-infrared light through blood onto the artery wall and the other for receiving the diffusely reflected light. The catheter imaging core rotates at 960 rpm with automated pullback at a linear rate of 0.5 mm/s, interrogating tissue in a helical pattern. The NIRS spectra are processed by the LCP detection algorithm to generate a longitudinal image (chemogram) of the scanned artery segment (Figure 1, panel C2). Each spectral measurement is assigned a probability of LCP by the detection algorithm and displayed in a false color map known as a block chemogram (Figure 1, panels c2 and c3). Blocks correspond to one of four discrete bins, each represented by a distinct color (red, orange, tan, and yellow, respectively).

Near-Infrared Spectroscopy (NIRS)

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### Table 1. Comparative studies of various LCP imaging modalities.

<table>
<thead>
<tr>
<th>Study</th>
<th>Compared modalities</th>
<th>Total lesions</th>
<th>In vivo / ex vivo</th>
<th>Correlation between modalities</th>
<th>Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugaletta et al (2011)</td>
<td>VH-IVUS, NIRS</td>
<td>31</td>
<td>In vivo</td>
<td>r: 0.149, P:0.002 NC to LCP</td>
<td>• Poor correlation between VH-IVUS NC and NIRS LCP detection</td>
<td>• Exact co-registration of NIRS vs VH-IVUS scanned ROI not possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Unable to identify TCFA due to resolution of VH-IVUS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Small sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No histologic comparator</td>
</tr>
<tr>
<td>Pu et al (2012)</td>
<td>VH-IVUS, NIRS</td>
<td>131</td>
<td>In vivo</td>
<td>r: 0.16, P:0.110 NC to LCP</td>
<td>• Poor correlation between VH-IVUS NC and NIRS LCP detection</td>
<td>• Exact co-registration of NIRS vs VH-IVUS scanned ROI not possible</td>
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<tr>
<td></td>
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<td></td>
<td>• Unable to identify TCFA due to resolution of VH-IVUS</td>
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<td>• Small sample size</td>
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<td></td>
<td></td>
<td>• No histologic comparator</td>
</tr>
<tr>
<td>Kubo et al (2011)</td>
<td>VH-IVUS, OCT</td>
<td>96</td>
<td>In vivo</td>
<td>Spearman rho not reported</td>
<td>• With OCT as gold standard, VH-IVUS provided acceptable sensitivity &amp; specificity for TCFA diagnosis</td>
<td>• Tortuous vessels with heavy calcifications excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• High false positive rate for VH-IVUS compared to OCT</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Small sample size</td>
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<td></td>
<td></td>
<td>• No histologic comparator</td>
</tr>
<tr>
<td>Sawada et al (2008)</td>
<td>VH-IVUS, OCT</td>
<td>126</td>
<td>In vivo</td>
<td>Spearman rho, sensitivity, specificity, NPV, PPV not reported 28 of 61 VH-IVUS TCFA correlated with OCT TCFA</td>
<td>• Plaques determined as TCFA by both VH-IVUS and OCT were larger by volume, %plaque volume</td>
<td>• Tortuous vessels with heavy calcifications excluded</td>
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<td></td>
<td>• High false positive rate for VH-IVUS compared to OCT</td>
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<td>• Small sample size</td>
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<td></td>
<td>• No histologic comparator</td>
</tr>
<tr>
<td>Kawasaki et al (2006)</td>
<td>IB-IVUS, OCT</td>
<td>128</td>
<td>Ex vivo; cadaver samples</td>
<td>Spearman rho not reported Sensitivity &amp; specificity for lipid pool by OCT (95%, 98%) and IB-IVUS (84%, 97%) compared to histology</td>
<td>• Using histologic gold standard, OCT offered better sensitivity &amp; specificity at detecting lipid pools compared to IB-IVUS</td>
<td>• Imaging performed ex vivo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cadavereic vessels perfused with saline and not perfused to physiologic pressure</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Small sample size</td>
</tr>
<tr>
<td>Miyamoto et al (2011)</td>
<td>IB-IVUS, OCT</td>
<td>81</td>
<td>In vivo</td>
<td>Spearman rho not reported 37 IB-IVUS diagnosed TCFA vs 40 by OCT 35 lesions met both IB-IVUS &amp; OCT criteria for TCFA</td>
<td>• TCFA as identified by both IB-IVUS and OCT had larger plaque burden with higher lipid, lower fibrotic content</td>
<td>• Tortuous vessels with heavy calcifications excluded</td>
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<td>• Small sample size</td>
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<td>• No histologic comparator</td>
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</tbody>
</table>

VH-IVUS = virtual histology-intravascular ultrasound; NIRS = near-infrared spectroscopy; NC = necrotic core; LCP = lipid core plaque; TCFA = thin-cap fibroatheroma; ROI = region of interest; OCT = optical coherence tomography; IB-IVUS = integrated backscatter-intravascular ultrasound
Table 2. Comparison of three intravascular imaging modalities for the detection of coronary lipid core plaque.

<table>
<thead>
<tr>
<th></th>
<th>VH-IVUS (20 MHz)</th>
<th>OCT</th>
<th>NIRS-IVUS (40 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hybrid intravascular imaging</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Axial resolution, µm</td>
<td>200</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Imaging through blood</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Need for blood column clearance during image acquisition</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Imaging through stents</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Imaging through calcium</td>
<td>No</td>
<td>Yes</td>
<td>Yes for NIRS – No for IVUS</td>
</tr>
<tr>
<td>Imaging neovascularization</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Detection of non-superficial LCPs</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Evaluation of LCP cap thickness</td>
<td>+</td>
<td>++</td>
<td>*</td>
</tr>
<tr>
<td>Detection of thrombus</td>
<td>-</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Expansive remodeling</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Need for manual image processing for LCP detection</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

+++ = excellent; + = good; ± = possible; - = impossible; * = potential under investigation
VH-IVUS = virtual histology intravascular ultrasound; OCT = optical coherence tomography; NIRS = near-infrared spectroscopy; LCP = lipid core plaque

There is a growing body of evidence on the clinical utility of NIRS. PCI of large LCP lesions has been associated with distal segments free of LCP with high accuracy.56 Moreover, NIRS is a distinguished STEMI culprit segments from coronary artery autopsy

There are important differences in LCP detection using different intravascular imaging modalities. Comparative studies using histology as the gold standard will be required to reconcile these differences.

Clinical Implications

There are important differences in the three imaging modalities used to detect LCP, which are summarized in Table 2. OCT has the highest resolution (allowing detection of cap thickness and the presence of thrombus) but the least penetration, limiting assessment of plaque burden and overall plaque volume. Moreover, unlike the other two modalities OCT also requires clearance of the blood column for image acquisition. In contrast to VH-IVUS and OCT that require image interpretation for the detection of LCP, NIRS provides automated LCP detection without the need for manual image processing (Table 2), facilitating its use for clinical decision-making during cardiac catheterization and percutaneous coronary intervention. OCT and NIRS can image through calcified lesions, whereas IVUS cannot. LCPs are often accompanied by neovascularization, which can only be visualized by OCT. Finally, VH-IVUS may misclassify stents,
which usually appear white (misclassified as “calcium”) surrounded by red (misclassified as “necrotic core”), although this does not appear to be a limitation for NIRS and OCT.54

Conclusions

VH-IVUS, OCT, and NIRS can assist in the detection and evaluation of lipid core plaque. Comparative studies have shown important differences between modalities, but are all limited from lack of comparison with the gold standard of histology. Given the different strengths and weaknesses of each modality, combination imaging will likely provide the best results.55 Further refinement of the clinical implications of LCP detection and its impact on optimizing treatment strategy selection will stimulate advances in LCP detection imaging.

References


4. Kotani J, Nanto S, Mintz GS, et al. Plaque gruel of atheromatous coronary lesion may contain lipid-rich necrotic core, although this does not usually appear white (misclassified as “calcium”) surround ed by red (misclassified as “calcium”) although this does not appear to be a limitation for NIRS and OCT.


9. Madder RD. Presented at the 2012 Transcatheter Cardiovascular Therapeutics meeting, Miami, Florida.


37. Madder RD. Presented at the 2012 Transcatheter Cardiovascular Therapeutics meeting, Miami, Florida.

38. Madder RD. Presented at the 2012 Transcatheter Cardiovascular Therapeutics meeting, Miami, Florida.
NIRS-IVUS Imaging Identifies Lesions at High Risk of Peri-Procedural Myocardial Infarction

James A. Goldstein, MD, Simon R. Dixon, MBChB*, Gregg W. Stone, MD

ABSTRACT: Percutaneous coronary intervention (PCI) is associated with distal embolization complications, including peri-procedural myocardial infarction (PPMI), including no-reflow, in 3%-15% of cases. These complications are predominantly related to distal embolization of lipid core plaque (LCP) components. Catheter-based near-infrared spectroscopy (NIRS) provides rapid, automated detection of LCPs, the magnitude of which appears associated with a high-risk of PPMI. Employing this technique may facilitate development of preventive measures such as embolic protection devices (EPDs).

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Key words: Distal embolization, lipid core plaque, near-infrared spectroscopy, peri-procedural myocardial infarction

Although percutaneous coronary intervention (PCI) routinely achieves excellent angiographic success, 3%-15% of cases (depending on the definition) are complicated by peri-procedural myocardial infarction (PPMI) and no reflow, which are associated with adverse long-term outcomes.1-3 Embolization of the lipid core contents of such lesions during PCI has been implicated as an important cause of PPMI and no reflow.4-11 Lesions at greatest risk for distal embolization complications are those with larger atheroma burden and lipid core plaque (LCP) composition.

The efficacy of embolic protection devices (EPDs) in preventing embolic complications after PCI of saphenous vein grafts suggests that PPMIs occurring during dilations of stenoses in native coronary arteries may be prevented if lesions most prone to these complications could be accurately identified.3 This paper reviews the utility of intracoronary near-infrared spectroscopy (NIRS) to identify coronary LCP.

NIRS Detection of LCPs at High Risk of Distal Embolization Complications

Prior NIRS studies10,11 document distal embolization complications associated with dilation of NIRS detected LCP, dramatically illustrated by a case of abrupt and severe no reflow and PPMI following dilation of a large, circumferential LCP (Figure 1).10 Observations from a larger cohort described the relationship between the presence of a large LCP detected by NIRS and PPMI.11 Stabilized patients undergoing stenting were identified from the COLOR Registry, an ongoing prospective observational study of patients

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Disclosures: Dr. Goldstein is a consultant for and owns equity in Infraredx, Inc. Dr. Stone is a consultant for Infraredx, Inc., Volcano Corp., Medtronic, and Boston Scientific, and is a member of the scientific advisory boards for Boston Scientific and Abbott Vascular. Dr. Dixon reports no financial relationships or conflicts of interest regarding the content herein.

Figure 1. A 62-year-old man with stable angina underwent coronary angiography, which demonstrated a complex hazy ulcerated culprit lesion in the mid-right coronary artery (Figure 1A, solid arrow). Neither the angiogram nor an intravascular ultrasound image indicated the presence of thrombus. NIRS demonstrated a large yellow signal spanning the circumference of the culprit site (Figure 1B, white rectangle), indicating the presence of a napkin-ring LCP; a smaller LCP was evident distally (Figure 1, open arrow).

Figure 2. Balloon angioplasty was performed (Figure 2A, arrow), which led to prompt no-reflow (Figure 2B, arrow) associated with severe bradycardia and profound hypotension (Figure 2C). After brief cardiopulmonary resuscitation and pharmacological support with atropine and dopamine, physiologic rhythm and blood pressure were restored and stenting resulted in excellent angiographic outcome. However, the patient developed a peri-stenting non-transmural infarction (peak creatine kinase of 512 ng/mL) and required an additional day of hospital care in an intensive care unit. (Goldstein JA, et al. JACC Cardiovasc Imaging. 2009;2(12):1420-1424. Reproduced with permission.)
undergoing NIRS prior to 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 large LCP (maxLCBI$_{4mm}$ ≥ 500) in 14/62 lesions (22.6%) and PPMI were documented in 9 (14.5%) cases. Importantly, PPMI occurred in 7/14 patients (50%) with maxLCBI$_{4mm}$ ≥ 500, compared to 2/48 patients (4.2%) patients (P=0.0002). PPMI occurred in 50.0% of lesions with maxLCBI$_{4mm}$ ≥ 500, but only 2/48 patients (4.2%) with lower maxLCBI$_{4mm}$ (P=0.0002) (Figure 3). The relative risk of PPMI for patients with maxLCBI$_{4mm}$ ≥ 500 was 12 (95% CI, 3.3 to 48), and the odds ratio of a PPMI occurring during dilation of stenoses with maxLCBI$_{4mm}$ ≥ 500 was 23 (95% CI, 4.3 to 117).

Figure 4 illustrates a case in which stenting of an extensive circumferential LCP (maxLCBI$_{4mm}$ = 591) resulted in PPMI. Interestingly, comparison of pre- and post-PCI NIRS scans reveals substantially decreased LCP following PCI, suggesting that stenting resulted in disappearance of “yellow,” which embolized downstream.

Clinical Implications of Pre-procedural Detection of LCP Lesions at Risk

Based on prior observations, the key morphologic features that might be expected to influence the predilection of a given lesion to distal embolization complications is the absolute magnitude of intra-lesional LCP, which may be estimated by combining measures of lesion atheroma volume (by IVUS) with plaque composition (LCBI) over the full length of a lesion. Other factors that may influence proclivity to distal embolization complications may include intramural location of LCP within the arterial wall (ie, distance of LCP contents from the lumen), fibrous cap thickness, and intra-lesion thrombus. Based on available data, the absolute magnitude of LCP is likely to be a key determinant of risk. The recent advent of multi-modality imaging with a combined NIRS-IVUS catheter provides the capability of simultaneous co-registered data on plaque architecture and composition. The additive insights provided by IVUS determined plaque volume to the maxLCBI$_{4mm}$ ≥ 500 should provide even more insight into lesions at greatest risk for PPMI.

The ability to predict PPMI may facilitate efforts to reduce distal embolization complications after PCI. The use of embolic protection devices (EPDs) to prevent distal embolization of plaque contents, a strategy established to reduce...
such complications in patients undergoing PCI of stenotic vein grafts and carotid stenoses, is a particularly promising approach. The potential ability of NIRS-guided use of an EPD to prevent peri-procedural 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 this pilot trial, 54 lesions with a max-LCBI_{mean} ≥ 600 are being randomized to PCI with the FilterWire EZ (Boston Scientific) vs PCI alone. The primary endpoint is the incidence of peri-procedural MI (defined as a new troponin rise post-PCI to >3x ULN). An additional 54 lesions with max-LCBI_{mean} < 600 will undergo PCI alone, and serve as a control arm to determine prospectively for the first time if indeed a high LCBI is associated with PPMI.

Summary

The NIRS-IVUS system provides an accurate, rapid, and automated means to identify atheroma volume and plaque composition, data that can be used to identify large, stenotic LCPs believed to be at greatest risk of PPMI. Lesion risk assessment prior to coronary stenting may provide the opportunity to prevent distal embolization complications. A randomized trial of EPD as a means to enhance the safety of coronary stenting in high-risk, stenotic LCPs associated by NIRS is underway.

References


Multiple Plaque Ruptures in a Patient with ST-Segment Elevation Myocardial Infarction: Does Infrared Spectroscopy Evidence Explain a Significant Change in the Angiogram?

Michael J. Lim, MD and Joshua M. Stolker, MD

Case Report

A 63-year-old man developed sudden onset of left-sided chest pain radiating to his back and left shoulder associated with diaphoresis and dyspnea. He was found to have ST segment elevation in the inferior leads of his electrocardiogram after arriving in the emergency department. He was treated with aspirin, ticagrelor, and intravenous bivalirudin before being taken emergently to the cardiac catheterization laboratory for primary angioplasty. He had a complete thrombotic occlusion of the proximal right coronary artery. Angioplasty was performed, and the offending lesion was treated with a single stent, resulting in restoration of normal flow into the distal vessel. Upon interrogation of the left coronary bed, we found a 70%-80% mid left anterior descending (LAD) coronary artery lesion just prior to an aneurysmal segment, as well as a 95% lesion in the distal circumflex (Figure 1). The patient was sent to the intensive care unit for monitoring, including continuation of dual antiplatelet therapy and consideration of further revascularization in 48-72 hours.

During this time, he remained stable without arrhythmias or further chest discomfort. His troponin peaked at 6.73 ng/mL; 48 hours after his initial intervention, he was brought back to the catheterization laboratory for interrogation and revascularization of his left-sided lesions. At the time of angiography, the LAD lesion looked unchanged from the previous images but the circumflex lesion was no longer as prominent. We decided to further interrogate both lesions with intravascular ultrasound and near-infrared spectroscopy to guide further revascularization therapy (Figure 2). The images of the LAD showed that there was an aneurysmal segment in the mid-portion of the vessel, just distal to a narrowing that never reached less than 4 mm² in luminal area. There was almost no lipid accumulation within the mid and proximal portions of this vessel. The circumflex interrogation showed no obstructive luminal lesions, particularly...
Multiple Plaque Ruptures in STEMI Patient

around the area of the previously tight stenosis within the obtuse marginal branch. However there was significant accumulation of lipid core plaque within the region of interest as well as the entire circumflex itself.

This case illustrates several unresolved questions regarding the behavior and management of multivessel coronary atherosclerosis in a patient with acute coronary syndrome: (1) Was the angiographic variation in the distal circumflex territory caused by vasospasm, or did this change represent a second ruptured plaque, thereby providing evidence that lesions with high lipid burden are those more likely to rupture and cause acute coronary syndromes? (2) What is the best long-term outcome and potential treatment for the circumflex coronary artery, particularly the area with the tight angiographic stenosis on initial angiography? (3) How would the LAD be managed, with its lack of lipid core plaque by near-infrared spectroscopy, particularly if the stenosis had been slightly more severe?

Figure 1. Initial coronary angiography demonstrating thrombotic occlusion of the right coronary artery, and severe stenoses of the mid left anterior descending and distal circumflex arteries (arrows).

Figure 2. Follow-up angiography demonstrating moderate stenosis and aneurysmal dilation of the left anterior descending artery, with no lipid core plaque (right-hand intravascular ultrasound images), but moderate stenosis with significant lipid core plaque throughout the proximal, mid, and distal left circumflex artery by near-infrared spectroscopy (yellow color on lower intravascular ultrasound images).
Missing the Culprit Yellow Plaque

David Erlinge, MD, PhD

Case Example
An 86-year-old man presented with chest pain and an acute anterior STEMI. He suffered from diabetes with nephropathy (GFR 30), retinopathy, and polyneuropathy. His medical history included abdominal aortic aneurysm and asbestosis. He was treated with morphine, aspirin, and ticagrelor in the ambulance. His blood pressure was 140/90; heart rate was 80 bpm at arrival.

Sign stenosis in proximal left main artery (LM) is shown in Figure 1. There was an occlusion in mid-left anterior descending artery (LAD). We performed thrombectomy with excellent result and found no remaining stenosis post-procedure. Solid single thrombus was retrieved. Two questions in this case are: (1) Is the emboli from proximal culprit site? and (2) Is the significant LM really the culprit?

We implanted a drug-eluting stent in the distal LAD despite the excellent result with thrombectomy. The heart team decided to defer PCI of the left main for 6-8 weeks and the patient was subsequently transferred to a local hospital but experienced repeated chest pain episodes during the hospital stay. After 10 days, it was evident that the patient was suffering from chest pain accompanied with repeated ST-depressions. He was transferred to our University Hospital in Lund, Sweden.

We then performed re-angiography (Figure 2), which is where the left main stenosis appeared to be the culprit lesion. However, NIRS did not show any lipid core in LM and MLA was borderline (7.5 mm²). Despite this the LM was stented according to the heart team decision.

NIRS/IVUS detected a large lipid-rich plaque in mid-LAD with MLA 2.7 mm², plaque burden 70%, and maxLCBI 4.55. maxLCBI 4mm >400 is a signature for plaques causing STEMI¹ and plaque burden of >70% is the most important IVUS-based risk indicator according to the PROSPECT study.² Mid-LAD was therefore considered to be the real culprit site and was stented with a drug-eluting stent measuring 3.0 x 38 mm. After treatment, the patient was free of chest pain, had no further ST-depressions and left the hospital a few days later.

Conclusion
The distal occlusion seen on angiogram was probably an embolus from the mid-LAD. The left main artery was probably not physiologically significant and had no lipid-rich plaque.

References

From the Department of Cardiology, Lund University.
Disclosure: Dr. Erlinge reports no financial relationships or conflicts of interest regarding the content herein.
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Figure 1. Sign stenosis in proximal left main artery.

Figure 2. Re-angiography after primary PCI.

This case illustrates how lipid core detection with NIRS-IVUS imaging can help identify the culprit site (ruptured lipid-rich plaque) in patients with an acute coronary syndrome.
The Use of Near-Infrared Spectroscopy to Optimize Stent Length

George A. Stouffer, MD

Case Report

A 61-year-old female with hypertension and hyperlipidemia developed subacute onset of exertional shortness of breath and palpitations. She was hospitalized for treatment of pneumonia and ECG monitoring showed non-sustained ventricular tachycardia. Following discharge, her symptoms worsened to a point where she could not walk from her car into her house without stopping to rest. Cardiology consultation was obtained and reported that physical examination and ECG were unremarkable. Echocardiogram showed normal left ventricular function. Coronary angiography showed severe multi-vessel coronary artery disease including a long 80% lesion in the right coronary artery (RCA) and severe disease in the left anterior descending (LAD) involving the ostium of the first diagonal. She was referred for multi-vessel percutaneous coronary intervention.

The RCA had a long diffusely diseased segment with three sequential, focal stenoses in the proximal and mid-vessel (Figure 1). Evaluation with near-infrared spectroscopy (NIRS) showed variable lipid expression throughout the diseased segment but with a heavy lipid burden in the wall of the RCA proximal to the first focal stenosis (Figure 1B). The decision was made to use a slightly longer stent to cover this area and thus a 3.5 mm × 38 mm drug-eluting stent (DES) was implanted with a good angiographic result (Figure 1C). The next day the disease in the LAD and diagonal artery was successfully treated with DES implantation. Eight months after treatment, the patient is doing well and is symptom-free.

Discussion

NIRS identifies the chemical composition of atherosclerotic plaque and several studies have shown that it can accurately identify lipid-rich regions. In our patient, the highest lipid core burden index (LCBI) was observed proximal to the first focal stenosis in the RCA. Prior studies have shown that lipid core plaque (LCP) can extend beyond the angiographic margins of a target lesion. In particular, Dixon et al performed NIRS in 69 patients (75 lesions) undergoing native vessel percutaneous coronary intervention and found that LCP was present in 50 target lesions with LCP present only within the target lesion in 84% and extending beyond the angiographic margins of the lesion in the other 16%.

Clinically, large LCP has been shown to be associated with adverse cardiovascular events, especially peri-procedural myocardial infarction. Less is known about whether lipid burden influences long-term outcomes following stent implantation. Angioscopic studies have shown that vascular healing after stent implantation is delayed in lipid rich lesions, especially when a DES is used, with incomplete neointimal coverage evident more than a year after implantation. There are also reports of adverse cardiovascular outcomes when DESs are implanted into lipid rich regions. Thus we chose a slightly longer stent rather than landing the proximal edge of a DES in a region with a high lipid burden.

There is a strong theoretical rationale for implanting the edges of DESs into normal or near normal tissue. But since using longer stents carries a small increased risk of stent thrombosis and/or restenosis, additional studies will be necessary to determine whether routinely using NIRS to determine proper stent length will improve patient outcomes.

References

Avoiding Geographic Miss

Employing NIRS-IVUS to Guide Optimal Lesion Coverage—

Ivan Hanson, MD, Simon Dixon, MBChB, James Goldstein, MD

ABSTRACT: Failure to cover the longitudinal extent of coronary target lesions with stent, termed “geographic miss,” is associated with increased rates of stent thrombosis and restenosis.1,2 Particularly if the uncovered lesion segment contains lipid core plaque (LCP),3,4 While invasive coronary angiography remains the criterion standard for determining lumen stenosis, it notoriously underestimates plaque burden and is incapable of delineating composition (ie, LCP). Furthermore, LCP extends beyond angiographic target lesions in nearly 20% of cases.3,4 The present paper describes two cases in which a combined catheter employing near-infrared spectroscopy and intravascular ultrasound (NIRS-IVUS) (Infraredx, Inc.) documented significant plaque burden and LCP extending beyond angiographic lesion borders.

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Key words: IVUS, NIRS, angiography

Case 1
A 54-year-old man with history of Hodgkin’s lymphoma and chest radiation developed New York Heart Association class 3 angina. Diagnostic angiography demonstrated multi-vessel coronary artery disease. Circumflex stenosis was successfully treated with everolimus-eluting stent (EES), and he was referred for staged LAD intervention. Angiography revealed a long, irregular target lesion (Figure 1A). Pre-intervention NIRS-IVUS revealed bulky plaque in the distal left main (Figure 1B), proximal LAD (Figure 1C), and mid-LAD (Figure 1D). A near-circumferential LCP was identified in the proximal LAD extending into the left main (Figure 1E), without significant angiographic left main stenosis. A 2.75 x 23 mm EES was deployed in the mid-LAD, and a 3.5 x 13 mm sirolimus-eluting stent was deployed at the LAD ostium, overlapping with the first stent. A schematic of the stented segment is shown (Figure 1F). After high pressure post-dilation, angiography and IVUS confirmed excellent stent expansion and apposition, including complete coverage of LAD ostium. Six months later, he developed unstable angina. Repeat angiography revealed severe stenosis and hazy filling defect in the distal left main with slow flow in the LAD and circumflex, suggestive of stent thrombosis (Figure 1G). He was referred for urgent coronary artery bypass surgery.

References

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Figure 1. In the first case example, angiography revealed a long, irregular target lesion (A). Pre-intervention NIRS-IVUS revealed bulky plaque in the distal left main (B), proximal LAD (C), and mid-LAD (D). A near-circumferential LCP was identified in the proximal LAD extending into the left main (E), without significant angiographic left main stenosis. A schematic of the stented segment is shown (F). Repeat angiography 6 months later revealed severe stenosis and hazy filling defect in the distal left main with slow flow in the LAD and circumflex, suggestive of stent thrombosis (G).

Figure 2. In the second case example, the patient was diagnosed with non-culprit circumflex and obtuse marginal branch stenosis. The length of the target lesion by quantitative coronary angiography was 13 mm (A). NIRS-IVUS revealed bulky, eccentric, lipid core plaque extending beyond the angiographic lesion margins (B-G).
Peri-Procedural Myocardial Injury Unraveled: Combined Assessment by Optical Coherence Tomography, Near-Infrared Spectroscopy and IVUS

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Case Example
A 64-year-old male with stable angina pectoris, positive exercise test and single vessel disease was referred for elective revascularization of the proximal left anterior descending (LAD) artery (Figures 1A and 1B). Pre-interventional near-infrared spectroscopy (NIRS) and optical coherence tomography (OCT) revealed diffuse disease with a lipid-rich plaque at the proximal segment (a 4 mm sub-segment with lipid-core burden index [LCBI]=517 by NIRS and ≥2 lipid quadrants in all frames by OCT; Figures 2A and 2B). Immediately after direct implantation (Xience V 3.5 mm/12 mm; inflation pressure: 18 atm) (Figure 1C), OCT revealed malapposition at the proximal stent edge as well as tissue protrusion at lesion sites with high lipid content (Figure 2C). After post-dilation (4.0 mm/8 mm compliant balloon, 18 atm), a rupture of the underlying plaque with intra-stent thrombus formation was visualized at the sites of tissue protrusion (Figure 2, Panels D3-D6), despite an improvement in stent apposition (Figure 2, Panel D2). The patient experienced no chest pain during the procedure. Troponin was elevated to 53 ng/L (ULN: 13 ng/L) one day after the procedure, whereas the patient was chest pain-free.

Discussion
Increased lipid content, either by NIRS or OCT, has been associated with post-procedural rise in myocardial enzymes.¹² Current hypotheses implicate inadvertent side branch occlusions or exposure of highly thrombogenic plaque to the bloodstream, with either local thrombus or the plaque content itself providing the substrate for distal embolization and microvascular obstruction.³ Our clinical observation supports the latter pathomechanism by visualizing the morphological changes in a patient with peri-procedural myocardial infarction following stenting of a lipid-rich plaque. The elucidation of the pathogenesis of distal embolization following PCI could allow for the development of more effective tools for reducing the incidence of peri-procedural myocardial infarction.

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Peri-Procedural Myocardial Injury Assessment

References


Figure 2. Top-to-bottom: Near-infrared spectroscopy (NIRS) pre-procedural assessment of the culprit lesion. High probability of lipid-rich plaque is shown by the yellow color (A). Pre-procedural optical coherence tomography (OCT) examination of the culprit lesion. The presence of lipid-rich plaque is identified as signal-poor regions with high attenuation (white crosses) (yellow asterisk: macrophage infiltration) (B). OCT post-stent implantation. White arrowheads indicate initially malapposed struts. Tissue protrusion after stent implantation is shown by yellow arrowheads (C). Final OCT after post-dilation. Note the improvement in strut apposition (white arrowheads). Yellow arrows indicate the underlying plaque rupture (D). Left-to-right: 1: NIRS chemogram and L-mode OCT renderings. White lines indicate the location of matched cross-sections in 2-7. 2: Proximal stent ‘landing zone.’ 3-6: Sections from the culprit lesion. 7: Distal stent ‘landing zone.’
Long-term Consequences of a Lipid Core Plaque

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ABSTRACT: Cumulative evidence has demonstrated that the compositional characteristics of plaque play a significant role in the final act of atherosclerosis and influence atherosclerotic evolution and prognosis. Radiofrequency backscatter analysis of intravascular ultrasound data, near-infrared spectroscopy, and optical coherence tomography are intravascular imaging techniques that have been used in the clinical setting to detect plaque composition and allow us to study the atherosclerotic process in vivo. Today it is apparent that lipid-rich plaques and especially those with a thin cap fibroatheroma phenotype are related with future cardiovascular events and worse outcomes. In this review article we cite the currently available imaging modalities that allow evaluation of the composition of the plaque and present the data regarding the long-term consequences of lipid core plaques.

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Key words: Thin-cap fibroatheroma, prognosis, intravascular imaging

Numerous histology-based studies have shown that the morphology of plaque affects its natural course and determines the final act of atherosclerosis.1–2 Since the 1930s, it has been demonstrated that lipid-rich plaques that were covered by a thin layer of fibrous tissue were prone to rupture and could cause an acute cardiovascular event.3 More recent pathological reports have shed light onto the phenotypic characteristics of atherosclerotic plaques allowing their classification and an evaluation of the mechanisms that are involved in their evolution.4–6

The advent of intravascular imaging in the 1980s allowed us to study in vivo plaque morphology and its prognostic implications. Angioscopy and intravascular ultrasound (IVUS) were the first imaging techniques that provided information about the composition of plaque and allowed detection of its lipid component.7,8 However, the first applications of these modalities in the clinical setting not only underscored their potential value in the study of atherosclerosis but also highlighted their limitations in characterizing atheroma.9–11 Therefore an effort was made over the last few years to develop advanced techniques that would allow more reliable assessment of a plaque’s composition. Today several modalities are available for this purpose including: the radiofrequency analysis of the IVUS backscatter signal (RF-IVUS), near-infrared spectroscopy (NIRS), optical coherence tomography (OCT), magnetic resonance spectroscopy, intravascular magnetic resonance imaging, Raman spectroscopy, photoacoustic imaging, and time resolved spectroscopic imaging (Figure 1). Some of these modalities are still in their infancy, while others have already been used in the clinical setting providing robust evidence about the prognostic implications of the differing compositions of the plaque. The aim of this review article is to present the most recent evidence about the long-term consequences of the atheroma’s phenotype.

Current Evidence From RF-IVUS-based Clinical Studies

Integrated backscatter analysis

The first study that suggested a role for RF-IVUS in assessing the prognostic implications of the different plaque compositions was reported by Sano et al. In this analysis, 140 patients suffering from stable angina and treated with percutaneous coronary intervention (PCI), were enrolled and underwent integrated backscatter analysis (IB)-IVUS imaging. One hundred sixty non-flow limiting lesions were evaluated. Within a follow-up period of 30±7 months, ten of the studied plaques caused an acute coronary event. The lesions that caused these events had increased eccentricity, plaque burden, remodeling index, and were rich in lipid tissue.12 In a recent report, Amano et al used IB-IVUS to show that patients admitted with an acute coronary syndrome or stable angina symptoms and treated with PCI, were at a higher risk of sustaining a non-target lesion-related cardiovascular event if they had lipid-rich plaques in a non-culprit segment.13 Significant limitations of both studies were the small number of events reported and the fact that the composition of the atheroma was evaluated in one coronary artery and not in the whole coronary tree.

Virtual histology – IVUS

The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study was the largest prospectively designed study that used three-vessel virtual histology (VH)-IVUS to examine the prognostic implications of the atheroma’s burden and its composition in 697 patients who were treated for an acute coronary syndrome. At 3 years follow-up, 149 major adverse cardiovascular events (MACE) were reported, 106 of which were due to newly developed lesions. Fifty-five of these were studied with VH-IVUS at baseline. The baseline necrotic core burden was identified as a predictor of future non-culprit lesion-related MACE. In multivariable analysis increased plaque burden (>70%), a thin-capped fibroatheroma (TCFA) phenotype and a minimum lumen area (MLA) <4 mm² were independent predictors of future culprit lesions.14 Similar were the results of the VH-IVUS in Vulnerable Atherosclerosis study. One hundred patients admitted with stable angina or acute coronary syndrome underwent PCI and 3-vessel VH-IVUS imaging. Within a follow-up period of 2 years, 13 non-stenotic lesions at baseline progressed and caused MACE. Univariate analysis at a lesion-based level demonstrated that TCFA phenotype, a MLA <4 mm², and a plaque burden >70% were predictors of future events.15

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Lipid-Rich Plaques and Prognosis

Figure 1. Currently available imaging modalities developed for the characterization of the composition of the plaque. (A) Virtual histology intravascular ultrasound (IVUS). (B) Integrated backscatter IVUS imaging. (C) Output of a near infrared spectroscopic (NIRS) catheter. The yellow-red color coded map illustrates the probability for the presence of a lipid core (yellow corresponds to high probability and red to low) while the grey areas correspond to segments with poor NIRS signal. The block chemogram that provides a summary of the raw data is illustrated on the bottom of the panel. (D) An optical coherence tomographic image showing a lipid-rich plaque (E) Intravascular photo acoustic images of a diseased (I) and a normal (II) aorta. The unique photoacoustic characteristics of different tissues (eg, lipid tissue (I), normal vessel wall (II), and media-adventitia (III)) allow identification of atheroma’s composition (III). (F) Angiographic images showing the intravascular magnetic spectroscopy catheter (I-III) (M indicates the probe and B the balloon used to prevent flow) and color coded display of the acquired data (the yellow corresponds to lipid tissue and the blue to non-lipid tissue). (G) Output of a recently developed intravascular magnetic resonance probe (I-IV), the images were obtained in vitro from an atherosclerotic iliac artery. The dark areas at 9 (II, III) and 12 o’clock (IV) indicate the presence of calcific tissue, which was confirmed in histology by Van Kossa staining (V-VI) and by micro-computed tomography (VII). (H) Spread out plots of the data acquired by an intravascular Roman spectroscopy catheter. The first panel portrays the distribution of the total cholesterol throughout the studied vessel (in the y-axis the number of the sensors used to scan the vessel) with the yellow-red color corresponding to increased cholesterol whereas the second panel provides information about the non-esterified cholesterol, which was measured when the total cholesterol was >5%. (I) A carotid atherosclerotic plaque imaged using a fluorescence lifetime imaging apparatus, which allows time resolved fluorescence imaging of relatively large surfaces. The final output is a color-coded map, which provides information about the biochemical composition of superficial plaque, where the red corresponds to fibrotic plaque, the yellow color to fibro-lipid and the cyan to normal endothelium (II). Images obtained with permission and modified from Bourantas et al.23

The above studies not only provide robust evidence about the association between the compositional characteristics of the plaque and future MACE, but also demonstrate the weak predictive accuracy of VH-IVUS derived variables in estimating prognosis (ie, in the Prospect study only 18% of the plaques with plaque burden >70%, MLA<4 mm², and a TCFA phenotype caused a MACE). This finding can be, at least partially, attributed to inherent limitations of IVUS imaging (ie, moderate resolution, increased noise and artifacts) as well as to the limited reliability of VH-IVUS to characterize complex lesions.16-18

Current Evidence from NIRS-based Clinical Studies

NIRS relies on the principle that different organic molecules absorb and scatter NIRS light to different degrees and wavelengths. Recent advances in device technology enabled the development of a catheter suitable for assessing the plaque in human coronaries that is able to emit NIRS light and acquire the scattered signal. Spectral analysis of the obtained signal provides a color-coded display, called a chemogram (Figure 1C), which provides the probability that lipid core is present in the superficial plaque (studied depth approximately: 1 mm). Several studies have examined the reliability of this technique using histology as the gold standard and demonstrated a high overall accuracy in detecting lipid-rich plaques while others demonstrated its feasibility in the clinical setting.19-20

The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis (NCT01779411) – NIRS sub-study was the first prospective trial designed to evaluate the prognostic implications of an increased lipid component, as detected by NIRS, in coronary plaques. Two hundred three patients that underwent X-ray angiography, and PCI if it was indicated, had NIRS in a non-culprit coronary segment and were followed-up for 1 year. Twenty-eight patients sustained a MACE during the follow-up period; 21 of these events were non-culprit lesion related. Lipid plaque burden index appeared to be an independent predictor of MACE (hazard ratio: 4.04, 95% confidence interval: 1.33–12.29; P=0.01).

Currently, the Chemometric Observation of Lipid Rich Plaque of Interest in Native Coronary Arteries (COLOR, NCT00831116) registry is recruiting patients. This study is planning to recruit 2000 patients that will be investigated with NIRS imaging, and aims to examine the association between the presence of a necrotic core in the atheroma and subsequent coronary events. Preliminary results indicate that the absence of lipid-rich

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plaque pathophysiology and evolution, detect more accurate lipid component, and appreciate the long-term consequences of plaque composition on clinical outcomes.

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Pharmacological Therapy of Lipid Core Plaque

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A new group of terms is slowly creeping in to the atherosclerotic disease lexicon: “Lipid Arc,” “Lipid Core Plaque,” “Lipid-Rich Plaque,” “Lipid Core Burden Index” and other similar phrases. While clinicians and researchers have long been aware of the central importance of lipid in the biology of atherosclerosis, the growing use of these terms is driven by the recent widespread use of novel imaging modalities that provide accurate detection, and even quantification, of the extent of lipid that is contained within the core of an atherosclerotic plaque. Our ability to detect and quantify lipid in plaques is opening up new therapeutic opportunities for modifying the atherosclerotic disease process, which may ultimately be of benefit to patients.

At the present time there are 3 methods that are commonly used to measure the extent of lipid in atherosclerotic plaques. Perhaps most familiar of these is coronary computer tomographic (CT) scanning. While more commonly used to quantitate calcification or luminal stenosis, CT scanning is readily able to quantitate the extent of lipid associated with an atherosclerotic lesion. However, while several studies have reported various Hounsfield Unit (HU)-based criteria to distinguish lipid-rich from fibrous plaques, the HU cut-off points have so far been inconsistent. The use of CT for detecting lipid-rich plaque is further limited by its relatively low spatial resolution and the fact that the HU values for distinguishing between fibrous and lipid-rich plaques are overlapping. In contrast, optical coherence tomography (OCT) offers perhaps the greatest spatial resolution of all clinically available coronary imaging devices. OCT can offer exquisite detail of abluminal coronary artery anatomy, including detection of lipid core plaque. However, while automated systems are being developed, at the present time the quantitation of lipid by OCT is a somewhat specialized process that typically involves detailed off-line analysis.

A specific intra-coronary imaging catheter for the quantitation of coronary artery lipid content is now available and FDA approved: diffuse reflectance near-infrared spectroscopy (NIRS). The application of NIRS to identify lipid deposition within coronary arteries has been validated ex vivo and in vivo. Although NIRS itself is essentially only able to detect and quantitate lipid, design changes and technological advances to this catheter have now made it possible to combine intravascular ultrasound (IVUS) and NIRS technology on a single instrument. In one of the few clinical studies published to date using this device, NIRS has already shown that a high lipid burden in a target lesion undergoing percutaneous coronary intervention (PCI) is associated with an increased likelihood of peri-procedural myocardial infarction.

It is well known that the reduction of cholesterol levels by statin therapy is associated with significant decreases in plaque burden. REVERSAL, ASTEROID, and more recently the SATURN II trial showed that in patients with coronary artery disease (CAD), lipid lowering with high-dose statin therapy reduced progression of plaque atheroma burden, even causing plaque regression of some lesions. However, while reduction in atheroma burden and plaque size are important anatomical endpoints, a major unresolved question had been the mechanism of action of statins and the unanswered question of whether they reduce plaque lipid content. Indeed, a high burden of plaque lipid is one of the cardinal features of a rupture-prone vulnerable lesion. Therefore, the ability to reduce plaque lipid content may have important effects on lesion stability and therefore, might impact clinical endpoints.

The advent of sensitive imaging tools for the evaluation of plaque lipid content has paved the way for the investigation of potential pharmacological therapies for lipid core plaque. In particular, the ability of NIRS to provide an automated quantitation of plaque lipid provides a ready-made platform for this task. We recently completed the YELLOW study of high-dose statin therapy for the potential reduction of coronary artery lipid content as assessed by NIRS. We randomized 87 patients with multivessel CAD undergoing elective PCI to rosuvastatin 40 mg daily vs conventional statin therapy. Following PCI of the culprit lesion, non-culprit lesions with a fractional flow reserve (FFR) <0.8 were interrogated using IVUS and NIRS. Changes in plaque composition were assessed after 6-12 weeks during follow-up angiography. The core finding of this study was that high-dose statin therapy was associated with significant reductions in the lipid content of coronary atherosclerotic plaques. Interestingly, despite reduced plaque lipid content, in this relatively short time period concordant changes in gross lesion characteristics such as total atheroma volume or % plaque burden were not observed. In short, the YELLOW study identified that even before gross atheroma regression occurs, lipid removal from plaques is an early event upon initiation of high-dose statin therapy. Furthermore, the results of the YELLOW study are concordant with the known acute benefits of statin therapy in patients presenting with acute coronary syndromes, where the early introduction of these agents is known to be of clinical benefit. While the YELLOW study was the first of this nature and the results remain to be replicated in a larger trial, these findings have revived interest in the concept of the “vulnerable plaque” because it appears possible that by causing lipid core reduction over a just few weeks, high-dose statin therapy may have rapid plaque stabilizing effects. We are now embarking on the YELLOW II study, where we will further explore the utility of high-dose rosuvastatin for the early reduction of plaque lipid content and potential mechanistic pathways.

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What other agents might have therapeutic efficacy for lipid core reduction? This question is perhaps more complex than it might first appear, because at the present time we do not know the specific mechanism whereby high-dose rosuvastatin causes lipid reduction in plaques. Theoretically it may be due to reduced LDL, increased HDL, other mechanisms or a combination of these effects. Potentially, other agents that are already available such as bile acid sequestrants, ezetimibe, and fibrates may have a weak lipid core reducing effect. However, we would underscore the fact that at the present time the utility of these agents is speculative, and no other agent (apart from high-dose rosuvastatin in the YELLOW study) has been shown to reduce lipid content in vivo in human plaques. Furthermore, given the fact that these other agents are far less potent in their overall effect than rosuvastatin 40 mg/day, it may be clinically challenging to determine if they have efficacy for lipid core reduction beyond that of statins.

In addition to pharmacotherapy, it must be remembered that we have several non-pharmacological treatments in our armamentarium that may impact lipid core reduction. For example, exercise is known to be associated with reduced plaque lipid content, and proper adherence to current guidelines with respect to lifestyle diet are of paramount importance in any patient in whom it is considered desirable to reduce plaque lipid content.

Looking ahead, there are several emerging and investigational agents that may hold promise for lipid core reduction. Microsomal triglyceride transfer protein (MTP) is expressed in the liver, intestine, and the heart and is required for the proper assembly of VLDL and chylomicrons. In animals, treatment with an MTP inhibitor leads to a rapid reduction in plasma lipid levels, with a significant decrease in lipid content and monocyte-derived (CD68+) cells in atherosclerotic plaques. On December 21, 2012, the first of the MTP inhibitors was approved for clinical use. Lomitapide (marketed as Juxtapid) was approved by the FDA as an adjunct to a low fat diet and other lipid-lowering treatments for patients with homozygous familial hypercholesterolemia. However, concerns have been raised due to hepatic side effects and liver toxicity. As a result, lomitapide will carry a boxed warning and will only be available through a restricted program. Another new drug that was recently given restricted approval in the US for homozygous familial hypercholesterolemia is mipomersen. This agent is an antisense therapeutic that targets messenger RNA for apolipoprotein B, leading to reduced apoB protein and LDL levels. While showing efficacy for lowering LDL, safety concerns have thus far prohibited this agent from gaining approval for use in Europe. PCSK9 inhibitors are yet another novel class of agents that may hold promise for reducing lipid core plaque. PCSK9 is involved in the degradation of the LDL receptor (LDLR), and by inhibiting PCSK9 it is believed that this permits more LDL receptors in the degradation of the LDL receptor (LDLR), and by inhibit

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The findings reported in this supplement demonstrate encouraging progress in the decades-long search for the vulnerable plaque. These novel imaging results, together with progress in other areas, increase the likelihood that identification and stabilization of high-risk plaque may further reduce the ongoing morbidity and mortality caused by coronary artery disease. As summarized, the maturation of the scientific and technical prerequisites for success has accelerated the effort to detect, and subsequently treat vulnerable plaques before they lead to catastrophic events.

Insights from Autopsy Studies

Observations in post-mortem specimens have clearly established the essential features of the histology underlying myocardial infarction and ischemic cardiac death. Post-mortem studies by Constantinides and others have documented that the majority of fatal acute coronary events result from rupture of an atherosclerotic plaque resulting in exposure of flowing blood to tissue factor, collagen and other pro-thrombotic agents. This leads to coronary thrombosis, ischemia, and infarction. In most cases these culprit lesions causing fatal myocardial infarctions have a large necrotic lipid core infiltrated with macrophages and covered with a thin fibrous cap (Figure 1).1-7 Autopsy studies have also shown that plaques with such features occupy only about 4% of the length of the coronary arteries, indicating that risk is likely to be focal and potentially amenable to local diagnosis and therapy.8

In Vivo Observations Using Advanced Coronary Imaging Techniques

The autopsy findings have now been supported by the results of advanced imaging with both invasive and non-invasive methods. IVUS studies have demonstrated that culprit lesions commonly have a large plaque burden, spotty calcification, and areas of attenuation compatible with the presence of a lipid-rich plaque (LRP).9-12 Angioscopy has also identified evidence of lipid at culprit sites,13 while OCT has revealed that thin fibrous caps and plaque rupture are common features of culprit lesions.14,41

Near-infrared spectroscopy (NIRS) imaging, which was developed for the explicit purpose of detection of LRP has detected LRP in >80% of acute coronary syndrome (ACS) cases.15 More recently, a NIRs-IVUS study evaluating culprit lesions in STEMI identified regions of LRP as the cause of acute myocardial infarction and highlight the role of LRP in culprit lesions across the spectrum of acute coronary syndromes.

Moving Beyond Culpritology

By 2010 the concordance of culprit lesion findings from autopsy and in vivo imaging studies generated a widespread belief that plaques sharing the morphologic characteristics of the culprit lesions were the “vulnerable plaques” at increased risk of rupture and thrombosis.20,21 An inflamed thin-capped fibroatheroma (TCFA) was often called a “vulnerable plaque.” While it is likely that a TCFA is a vulnerable plaque, the linkage at that time was largely based on circumstantial evidence. In legal terms an inflamed TCFA would have been “indicted” on the basis of circumstantial, cross-sectional evidence but not yet “convicted” through prospective studies with a large number of patients.

Prospective Documentation of Plaque Vulnerability

Direct evidence documenting the vulnerability of large coronary plaques in patients has now been obtained in 5 studies.25-26 An early study by Yamagishi et al in 106 patients demonstrated that a large plaque burden and echolucent plaque by IVUS (a sign of a LRP), were associated with the 12 events that occurred during a 2-year follow-up.25 The strongest support for the vulnerable plaque hypothesis was obtained by the landmark PROSPECT study. In PROSPECT, 697 patients presenting with an ACS underwent 3-vessel scanning with IVUS following treatment of the culprit lesion. Non-culprit, non-stenotic sites with a plaque burden >70% as measured
Increased plaque burden by IVUS, in addition to low shear stress, predicted site-specific lesion progression. Increased plaque burden by IVUS, in addition to low shear stress, predicted site-specific lesion progression. Patient level prediction has also been accomplished with a non-invasive CTA assessment of coronary plaques. Motoyama et al studied 1059 patients with a baseline CTA who were followed for a mean of 27 months. Patients with one or more plaques with positive remodeling and low Hounsfield units (a finding associated with lipid) experienced a 22% event rate, while patients without either feature had an event rate <0.5%. The results of these 5 studies confirm the vulnerable plaque hypothesis by demonstrating that focal sites with increased risk of causing future events exist, and can be identified with imaging before the events occur. However the findings are not of adequate specificity to currently warrant an alteration in diagnostic and treatment strategies. A marker more closely aligned with vulnerability is needed.

Future Prospective Vulnerable Plaque Studies

The success of 5 prior prospective studies plus the supporting data obtained in cross-sectional studies support the conduct of additional prospective studies using the novel intravascular imaging modalities that are now available. The combined NIRS-IVUS catheter and OCT systems are excellent candidates for prospective evaluation. The NIRS-IVUS catheter can assess plaque burden >70% with IVUS, a feature that has already been documented to predict coronary events while simultaneously identifying LRP with NIRS. This additive information regarding the presence or absence of LRP would be expected to enhance the predictive accuracy of plaque burden alone. OCT, which is an excellent method to determine cap thickness, might also show useful predictive capability in a prospective study.

Two large prospective NIRS-IVUS studies are planned. The first is termed PROSPECT II and will be conducted in 900 patients in Scandinavia, led by 2 coauthors of this manuscript (Stone and Erlinge). As in the first PROSPECT study, patients with ACS who are undergoing PCI for an initial culprit lesion will undergo 3-vessel imaging. The Scandinavian SWEDEHEART system of registers will be used to identify all subsequent acute coronary events with new angiographic examinations during the follow-up period, thereby permitting determination of the relationship between the suspected vulnerable plaques defined by NIRS-IVUS and the new culprit site causing the coronary event. In contrast to the original PROSPECT study in which radiofrequency IVUS alone was used, PROSPECT II will be conducted with IVUS plus NIRS imaging. In addition, the PROSPECT II Study will address the question of local treatment of the vulnerable plaques (plaque burden >70% by grayscale IVUS), which have been shown to be associated with a 10% 3-year event rate in PROSPECT I. Results of treatment will be examined at sites with large plaque burden with and without LRP identified by NIRS.

The second prospective NIRS-IVUS study is termed the Lipid-Rich Plaque (LRP) study and will be conducted worldwide in 9,000 patients undergoing PCI. This study, which will focus on...
Search for Vulnerable Plaque

patients found by NIRS imaging to have a large LRP at baseline, will also determine the link between suspected plaque vulnerability and outcomes. It is likely that both of these NIRS-IVUS studies, which build upon the predictive ability already demonstrated with the use of IVUS alone, will also demonstrate that vulnerable plaques can be detected. If these studies successfully identify a highly predictive NIRS-IVUS signature of vulnerability, interest would then switch to studies of preemptive treatment of plaques with large plaque burden and large quantities of lipid detected by NIRS.

Can You Treat Vulnerable Plaques?

It is likely that vulnerable plaques are more difficult to identify than to treat. Both pharmacologic agents and interventional techniques are likely to provide effective plaque passivation. Multiple IVUS studies have demonstrated that statin therapy decreases plaque burden, which is a proven index of vulnerability. More recently, it was demonstrated that therapy with rosuvastatin, an agent proven to reduce coronary events in clinical trials, is able to diminish NIRS evidence of LRP supporting the concept that rosuvastatin may achieve its beneficial clinical effect in part through a reduction in LRP. OCT studies demonstrated an increase in cap thickness in response to statins, which would be expected to reduce vulnerability. Novel pharmacologic agents such as Apo A1 Milano and PCSK9 inhibitors, might likewise be tested as systemic therapies for vulnerable plaques.

In addition to systemic pharmacologic treatment, focal treatment of vulnerable plaques may also be effective. The excellent long-term results of placing a stent in a ruptured LRP are already known from the numerous studies in which stents have been placed in culprit lesions of ACS patients. While traditional stents could be tested as focal therapy for vulnerable plaques, bioresorbable vascular scaffolds, which leave no metal behind, might be of particular benefit in such lesions.

Can Primary Prevention of Coronary Events be Achieved through Detection and Treatment of Vulnerable Plaques?

It is likely that the initial focus in vulnerable plaque detection and treatment will be the prevention of subsequent events in patients already undergoing coronary angiography for a primary event. As these patients are already undergoing PCI, intracoronary imaging can be performed without major increases in costs or risk of an adverse event. However, invasive imaging, given its risks and costs, is not suitable for use as the sole screening technique to detect vulnerable plaques in the general population. However intracoronary imaging could serve as a component of a primary prevention strategy as suggested by Eugene Braunwald (Figure 4). Such a strategy would utilize a sequence of evaluations including demographic factors, serum biomarkers, and non-invasive imaging to identify patients at sufficiently high risk to justify intracoronary imaging. Such an approach would be similar to the methods currently applied to screen for breast cancer (non-invasive imaging followed by an invasive biopsy). Advances in coronary CTA have indicated that this technique may well be capable of serving as a non-invasive screening technology for vulnerable plaque detection.

Will Vulnerable Plaque Detection and Treatment be Cost-effective?

Increasing healthcare expenditures generate the need to evaluate the cost-effectiveness of new technologies and strategies. Accordingly, there was an analysis to evaluate the theoretical cost-effectiveness of a strategy to detect and treat vulnerable plaques in patients already undergoing PCI. The analysis assumed the strategy was successful and that second coronary events, including myocardial infarction, were reduced. The results indicate that
### Table 1. Essential Components of a Strategy to Prevent Coronary Events by the Detection and Treatment of Vulnerable Plaques

<table>
<thead>
<tr>
<th>Essential Components</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathophysiology of Coronary Events</strong></td>
<td></td>
</tr>
<tr>
<td>• Are the causes of coronary events known?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Are LRPs focal?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Are LRPs stable over time?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Detection of Suspected Vulnerable Plaque by Invasive Imaging</strong></td>
<td>(For Secondary Prevention)</td>
</tr>
<tr>
<td>• Can invasive imaging safely detect LRP?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Do cross-sectional studies show increased LRP concentrated at culprit sites?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Do prospective studies show that suspected vulnerable plaque can be detected in advance?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Is more specific detection of vulnerable plaque possible?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Can Vulnerable Plaques be Treated?</strong></td>
<td></td>
</tr>
<tr>
<td>• Is systemic treatment of LRPs possible with current agents?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Is focal treatment of LRPs possible with current methods?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Can systemic treatment be enhanced with new agents?</td>
<td>?</td>
</tr>
<tr>
<td>• Can focal treatments be enhanced with new methods?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>• Can demographic and serum biomarkers be used as a first step in a screening strategy?</td>
<td>Yes</td>
</tr>
<tr>
<td>• Can non-invasive imaging with CTA detect LRP and increased risk?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost-Effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td>• Will a strategy of detection and treatment of vulnerable plaque, if proven to be successful, be cost-effective for secondary prevention?</td>
<td>Probably</td>
</tr>
<tr>
<td>• Will a strategy of detection and treatment of vulnerable plaque, if proven to be successful, be cost-effective for primary prevention?</td>
<td>?</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CTA = coronary computed tomographic angiography; LRP = lipid-rich plaque; TCFA = thin-capped fibroatheroma; VP = vulnerable plaque
implementation of an effective strategy to detect and treat vulnerable plaques for secondary prevention might even be cost saving — that is, it would improve health while reducing healthcare costs, representing an economically dominant strategy. Much of the cost reduction would be obtained by the prevention of myocardial infarction, which would also prevent heart failure and arrhythmia. Although more costly to implement, a primary prevention strategy might also be cost-effective.

Summary

The search for the vulnerable plaque has been a lengthy endeavor requiring the work of multiple individuals and institutions over many years. It is disappointing that in more than 2 decades since the “vulnerable plaque” concept was formulated, over 40 million coronary events have occurred. However, it is encouraging that positive answers are now available for most of the questions related to a vulnerable plaque detection and treatment strategy. As shown in Table 1, most of the essential preconditions of a successful vulnerable plaque strategy are present. This positive information has accelerated the pace of work in this area. The pathophysiology of coronary events is well-understood; powerful imaging methods are available; and therapies, both existing and novel, may well be effective (although appropriately powered randomized trials are required to demonstrate their safety and effectiveness). The time is approaching for the conduct of prospective outcome trials to determine the value of a vulnerable plaque strategy for more effective prevention of coronary events.

References

Observations from Intracoronary Near-Infrared Spectroscopy in Patients with ST-Segment Elevation Myocardial Infarction

Ryan D. Madder, MD, FACC

Intracoronary near-infrared spectroscopy (NIRS) has been developed to identify lipid core plaque (LCP) in the coronary arteries of living patients at the time of invasive angiography. NIRS has been validated for this purpose, is FDA approved, and has now been used in over 3,000 cases worldwide. NIRS has been previously applied to delineate the composition of culprit lesions in acute coronary syndromes and was more recently used to study the culprit vessels of patients presenting with acute ST-segment elevation myocardial infarction (STEMI). In the prior STEMI study, NIRS was used to image the culprit vessel after establishing TIMI 3 flow but prior to stent placement. This study found that STEMI culprit segments are frequently characterized by NIRS to have a large, nearly circumferential LCP at the culprit site. A NIRS signature of STEMI culprit lesions was identified, consisting of a maximum lipid core burden index in any 4-mm region (maxLCBI4mm) within the culprit margins of >400. This NIRS signature was found to be both sensitive and specific for the STEMI culprit site when tested against a background of non-culprit segments within the culprit vessel and against a background of coronary autopsy specimens from individuals having no history of coronary disease during their lifetimes.

The following case illustrates the typical NIRS findings within a culprit vessel of a patient presenting with STEMI.

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Disclosure: Dr. Madder reports no financial relationships or conflicts of interest regarding the content herein.

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Case History

A 56-year-old male presented to the emergency department with acute chest pain. An electrocardiogram revealed ST-segment elevation in leads V5, V6, 1, and aVL consistent with an acute lateral STEMI (Figure 1A). The patient was taken emergently to the catheterization laboratory for primary percutaneous coronary intervention. The initial angiogram revealed complete occlusion of the first obtuse marginal branch (Figure 1B, arrow denotes culprit site). Angioplasty was performed using an undersized balloon, which resulted in restoration of flow within the vessel (Figure 1C). Combined NIRS and intravascular ultrasound (IVUS) imaging was then performed. The NIRS chemogram revealed a large, circumferential LCP.
at the STEMI culprit site (Figure 1D, brackets). The proximal angiographic culprit margin is denoted by the proximal blue line (#1) on the chemogram. The maxLCBI4mm of the culprit lesion is 922, well in excess of the maxLCBI4mm >400 threshold demonstrated by the prior study of NIRS in STEMI patients. IVUS at the culprit site revealed a bulky lesion, hypoechoic plaque, and a large plaque burden (Figure 1E). The IVUS images were clinically useful for stent size and length selection. The patient underwent uncomplicated stent placement at the culprit site. The final angiogram showing TIMI 3 flow in the culprit vessel is presented in Figure 1F.

Conclusions

The observations in the present case and those from the prior study of NIRS in STEMI patients demonstrate that STEMI culprit lesions are frequently characterized by a large, often circumferential LCP. These observations are consistent with post-mortem studies implicating rupture of LCP in the pathophysiology of acute myocardial infarction. Importantly, it is highly likely that the large lipid cores observed by NIRS at STEMI culprit sites were present and detectable prior to myocardial infarction and may therefore have served as a target for preventive therapy. These observations require validation in a larger prospective study. Finally, further study is also needed to determine if NIRS can provide site-specific prediction of future myocardial infarction.

References


NIRS Imaging of Cardiac Allograft Vasculopathy

Giora Weisz, MD

Case Report

A 62-year-old man with history of orthotropic heart transplant presented for annual coronary angiographic surveillance. About 7 years earlier he suffered an extensive myocardial infarction complicated with cardiogenic shock, which was treated with a left ventricular assist device followed by heart transplant 4 months later. Since then he underwent routine post-transplant surveillance angiograms, starting at his first annual, and then every other year. The initial and next 2 angiograms were reported to show normal coronary arteries. The angiogram from 2 years prior to the current procedure showed a focal 60% stenosis in the mid segment of the right coronary artery (RCA). Repeat angiogram on this admission showed the same lesion unchanged, with a new 90% lesion distal to the first (Figure 1, right side). The chemogram of the near-infrared spectroscopy interrogation of the RCA demonstrated different findings in the two lesions (Figure 1, left side). By selecting manual landmarks, the chemogram was co-registered to angiogram. The distal new lesion was associated with bright yellow color indicating a lipid core plaque (arrow A). The older, angiographic stable lesion segment was completely red, excluding the presence of a significant lipid core plaque (arrow B). Interestingly, the segment between the two lesions, that looked normal angiographically, was also associated with large lipid core (arrow C).

Discussion

Cardiac allograft vasculopathy (CAV) is an important cause of morbidity and mortality among cardiac transplant recipients. CAV occurs in approximately 30% of patients by 5 years and 50% by 10 years and is a major cause of graft loss and death. Early detection of CAV is important because it may allow alterations in medical therapy before progression to the stage that revascularization is required. This has led to routine screening for CAV in transplant recipients, traditionally by coronary angiography.1,2

CAV is an accelerated fibro-proliferative process. The pathophysiology of CAV involves inflammation with persistent vascular injury and endothelial dysfunction. Histologically, there is subendothelial accumulation of lymphocytes, intimal proliferation of smooth muscles cells, development of lipid-laden foam cells, and perivascular fibrosis. Centric intimal hyperplasia leads to an obliteratorve process of the
intramural and epicardial coronary arteries. In contrast, traditional atherosclerotic disease typically evolves over a longer period of time, is focal and non-circumferential, and involves more calcium deposition during late stages. Although CAV typically manifests as diffuse luminal narrowing, lesions can also be focal and eccentric with an appearance similar to typical atherosclerosis. Since CAV can occur in combination with atherosclerosis, which may be present in allografts due to either de novo atherosclerosis or pre-existing donor atherosclerosis, distinguishing between these processes may be challenging. This distinction may be important from a clinical standpoint. Both processes lead eventually to decreased coronary blood flow and reduced vasodilatory capacity resulting in ischemia and ventricular dysfunction.

There are few possible explanations to the different findings between the two lesions. The first lesion was stable for at least 2 years, not calcified, and not associated with lipid core. This may represent a long-standing fibrotic stenosis that is the result of CAV. The second lesion was of shorter age, and was associated with large lipid core plaque that extended proximally. We speculate that these near-infrared spectroscopy findings of the distal lesion represent a rapidly progressive atherosclerotic lesion. Thus, this patient represents two distinct lesion types in the RCA—a chronic and stable CAV lesion (proximal), and a rapid progressive atherosclerotic lesion (distal).

Both lesions can be the result of the same disease process, either atherosclerosis or CAV. In the case of atherosclerosis, the proximal lesion is the long-standing fibrotic lesion and the distal is more acute. This is similar to the finding associated with acute coronary syndrome. There is higher prevalence of LCP in patients with acute coronary syndrome as compared to patients with stable angina. A third option is that both lesions represent CAV. This is unlikely, since in CAV lipid accumulation follows the fibrotic process. In the present case the lipid-core plaque lesion is younger.

Conclusions
Future research is needed to elucidate the role of near-infrared spectroscopy in the diagnosis and evaluation of patients after cardiac allograft transplantation. Hopefully, near-infrared spectroscopy will contribute to the differentiation between CAV and atherosclerosis, will permit stratification of CAV subsets and allow for earlier and perhaps specific interventions to prevent CAV progression, graft loss, and mortality.

References

Figure 1. Right panel: angiogram of the right coronary artery. Left: near-infrared spectroscopy chemogram, with corresponding segments co-registered to the angiogram by arrows (a, b, c).