Review article

Intracoronary near-infrared spectroscopy: an overview of the technology, histologic validation, and clinical applications

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ABSTRACT

Intracoronary near-infrared spectroscopy (NIRS) imaging, which is now clinically available in a combined NIRS and intravascular ultrasound catheter, is a novel catheter-based imaging modality capable of identifying lipid core plaque within the coronary arteries of living patients. The present manuscript provides an overview of intracoronary NIRS imaging with a focus on several concepts essential to individuals seeking to better understand this novel imaging modality. One of the major assets of NIRS is that it has been rigorously validated against the gold standard of histopathology and has been shown to accurately identify histologically-proven fibroatheroma. Clinical studies of NIRS have demonstrated its ability to accurately identify large lipid core plaques at culprit lesions across the spectrum of acute coronary syndromes. NIRS has also been shown to detect lesions at increased risk of causing peri-procedural myocardial infarction during PCI. With regards to predicting future risk, NIRS is seemingly capable of identifying vulnerable patients at increased risk of experiencing subsequent patient-level cardiovascular events. In addition to these clinical applications of NIRS, there are several large prospective observational studies underway to determine if NIRS imaging will be able to identify vulnerable plaques at increased risk of triggering site-specific future coronary events. These studies, once completed, are anticipated to provide valuable data regarding the ability of NIRS imaging to identify plaque vulnerability.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a widely used technique in analytical chemistry to identify organic substances. NIRS can be simplified into three basic components: (1) a light source; (2) a light detector; and (3) a computer capable of deciphering exiting light into clinically relevant information[1]. NIRS utilizes the attenuation, scatter, and absorption of light emitted at wavelengths of 700–1000 nm to detect a unique optical signature produced by any given unknown molecule[2]. NIRS was first applied *in vivo* in 1977 by Jobsis *et al* who devised a method to monitor oxygenation by detecting the particular optical signature of oxygenated and de-oxygenated hemoglobin via NIRS[3]. Since that time, NIRS has been described in a multitude of other *in vivo* applications, including the recent application of NIRS to detect lipid core plaque (LCP) in the coronary arteries of living patients. Although intracoronary NIRS imaging has been recently reviewed in detail elsewhere[4–6], we provide an overview of intracoronary NIRS imaging with a focus on three aspects essential to individuals seeking to better understand this novel imaging modality: (1) NIRS technology and its interpretation; (2) studies validating NIRS findings against the gold standard of histopathology; and (3) clinical applications of NIRS imaging in contemporary practice.

OVERVIEW OF NIRS TECHNOLOGY

Intracoronary NIRS imaging device

The intracoronary NIRS imaging catheter (TVC Insight Catheter, Infraredx, Burlington, Massachusetts) has applied the same principles of NIRS commonly used in analytic chemistry to identify lipid-rich coronary plaques *in vivo*. The current NIRS imaging system enacts a dual-modality catheter that houses both NIRS and intravascular ultrasound (IVUS) technologies to provide the user with information on both the composition and structure of plaques within the coronary arteries[7–9]. Using a 6 French or larger guide catheter, a combined NIRS-IVUS catheter is manually advanced into a coronary artery over a 0.014 inch guidewire. By pressing a start button on the device, the operator initiates an automated pullback and the catheter scans the target artery at a rate of 5 mm per second[7]. During the automated catheter pullback, more than 30,000 NIRS measurements are obtained within each 100 mm segment of vessel that is imaged[7]. Upon completion of the automated pullback, a NIRS "chemogram" is generated and displayed on the imaging console.

The NIRS chemogram, block chemogram, and lipid burdens
NIRS chemogram

Following automated pullback of the NIRS catheter within the target artery, acquired spectra are analyzed to determine the probability of LCP presence at each site within the vessel[4–6]. The probability of LCP presence is displayed visually as a chemogram and a block chemogram, which are automatically generated within a few seconds of completing the NIRS pullback in the artery. The chemogram is oriented such that longitudinal position in the long axis of the vessel is depicted on the x-axis and circumferential position from 0–360 degrees around the inside of the vessel is depicted on the y-axis. For locations in the artery in which NIRS spectra indicate a low probability (i.e. less than 0.6) of LCP presence, the corresponding pixels are depicted as red. For locations in the artery in which NIRS spectra indicate a probability of LCP exceeding 0.6, the corresponding pixels are depicted as yellow. An example of a NIRS chemogram and a description of its orientation are provided in Figure 1.
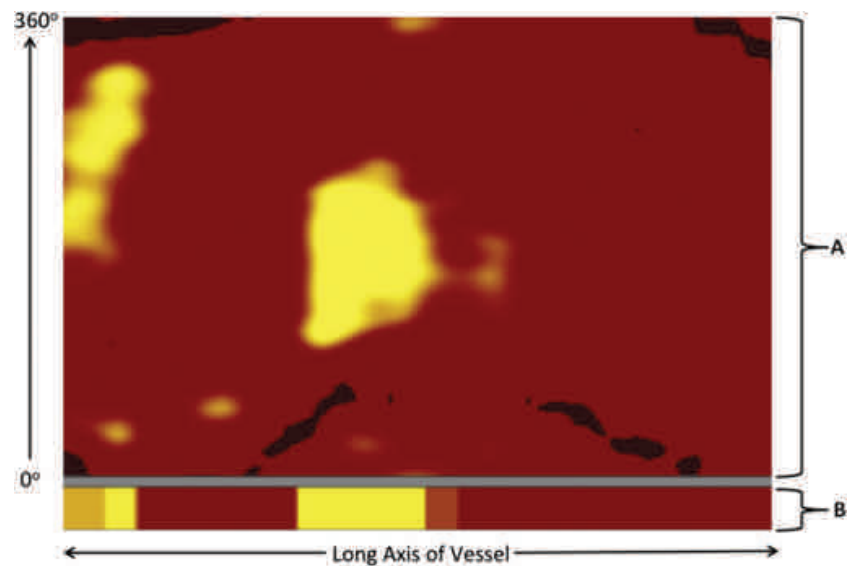
Figure 1. Intracoronary NIRS chemogram. An example of a NIRS chemogram (A) and a corresponding block chemogram (B) are shown. The chemogram is oriented such that distal vessel is located on the right side of the image and the proximal vessel is on the left. The x-axis represents the position along the long axis of the vessel (usually shown with a corresponding scale in millimeters) and the y-axis represents the circumferential position from 0 to 360 degrees. Yellow regions of the chemogram indicate the presence of lipid whereas red regions indicate the absence of lipid. In this example, two lipid cores are present, one of which is in the center of the vessel and the other is in the proximal segment of vessel. NIRS = near-infrared spectroscopy.

NIRS block chemogram

The contemporary NIRS imaging system also provides a block chemogram that can be found beneath the chemogram on the imaging display[4–6]. When the imaging software creates the block chemogram, the imaged vessel is divided longitudinally into contiguous non-overlapping 2mm segments termed blocks. Each 2mm block is assigned one of four colors based upon the 90th percentile probability of all NIRS measurements within that 2mm segment of vessel:

- Red indicates the probability of LCP is <0.57
- Orange indicates the probability of LCP is 0.57–0.83
- Tan indicates the probability of LCP is 0.84–0.97
- Yellow indicates the probability of LCP is 0.98 or greater

An example of a block chemogram is presented in Figure 1.

Lipid core burden index

In addition to providing information regarding the probability of LCP presence at any location within an imaged artery, NIRS is also capable of providing a semi-quantitative estimate of the amount of LCP present within any selected region of interest. This estimate of lipid quantity is termed the lipid core burden index (LCBI) and is calculated as the number of yellow pixels divided by the total valid pixels (red plus yellow) in any region of interest multiplied by 1000[4–6]. The LCBI is reported on a 0 to 1000 scale. In clinical studies of NIRS imaging, lipid burden has frequently been reported as the maximum LCBI in any 4mm section of the artery ($maxLCBI_{4mm}$)[10–14]. Because a 4mm section of vessel is rather narrow, the $maxLCBI_{4mm}$ metric can be considered a surrogate of the circumferential extent of a lipid core. Accordingly, a plaque having a $maxLCBI_{4mm}$ of 700 indicates that the lipid core occupies approximately 70% of the circumference of the vessel at that site.

NIRS VALIDATION AGAINST HISTOPATHOLOGY

Histologic evaluation of coronary autopsy specimens represents the gold standard for LCP detection. One of the major strengths of NIRS imaging is that NIRS has been validated against histopathology for the detection of LCP in several studies. In the first study to validate intracoronary NIRS against histology, Gardner *et al* applied a histologic definition of LCP as a fibroatheroma containing lipid core $\geq$ 200 µm thick, having a $\geq$60° circumferential distribution, and having an overlying fibrous cap thickness <450 microns, a definition mandated by the FDA[15]. In this study, the NIRS block chemogram differentiated segments with and without histologically-proven LCP with an area under the receiver-operator characteristic (ROC) curve of 0.80. This study also demonstrated that a tan or yellow block on the NIRS block chemogram identified a histologically-proven LCP with a specificity of 90%. The high specificity of a tan or yellow block on the NIRS block chemogram for the presence of a histologically-proven fibroatheroma has since been confirmed[16]. NIRS positive lesions have also been demonstrated at autopsy to have larger necrotic cores, more inflammatory cells, and thinner fibrous caps compared to NIRS negative lesions[17].

Two autopsy studies have demonstrated the incremental benefit of combined NIRS-IVUS imaging compared to the use of either NIRS or IVUS alone for the identification of histologically-proven fibroatheroma[16,18]. Compared to superficial attenuation by IVUS, Kang *et al* demonstrated that a tan or yellow block on the NIRS block chemogram was associated with a similarly high specificity, but a greater sensitivity for fibroatheroma detection[16]. Importantly, the combination of the NIRS and IVUS findings increased the sensitivity of fibroatheroma detection and improved the positive predictive value compared to ether imaging modality alone[16]. Puri *et al* demonstrated that plaque burden by IVUS and LCBI by NIRS differentiated coronary segments with and without histologically-proven fibroatheroma with similar accuracy[18]. However when plaque burden and LCBI were used together, these combined NIRS-IVUS findings resulted in significant improvement in the accuracy of fibroatheroma detection and were associated with a net reclassification index of 43%. Examples of combined NIRS-IVUS images are provided in Figure 2.

CLINICAL APPLICATION OF NIRS IMAGING

In addition to the use of NIRS imaging in the autopsy studies described above, there are several lines of clinical research that have reported NIRS findings in living patients. In general these NIRS studies have focused on the identification of culprit lesions in patients with acute coronary syndromes (ACS), the detection of lesions at greater risk for periprocedural myocardial infarction during percutaneous coronary intervention (PCI), and the identification of patients at greater risk for future patient-level cardiovascular events. The following sections will describe each of these lines of research in more detail.

NIRS findings at culprit lesions in patients with ACS
STEMI
Post-mortem studies of patients suffering fatal myocardial infarction have shown that most culprit lesions are ruptured thin-capped fibroatheromas with overlying thrombus[19–21]. Considering that an essential component of such thin-capped fibroatheromas at autopsy is a large necrotic lipid core[19–21], it would be expected that NIRS would likewise identify a large LCP at the culprit site of living patients suffering an acute myocardial infarction.

Among 20 patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), Madder *et al* performed combined NIRS-IVUS imaging in the culprit vessel after
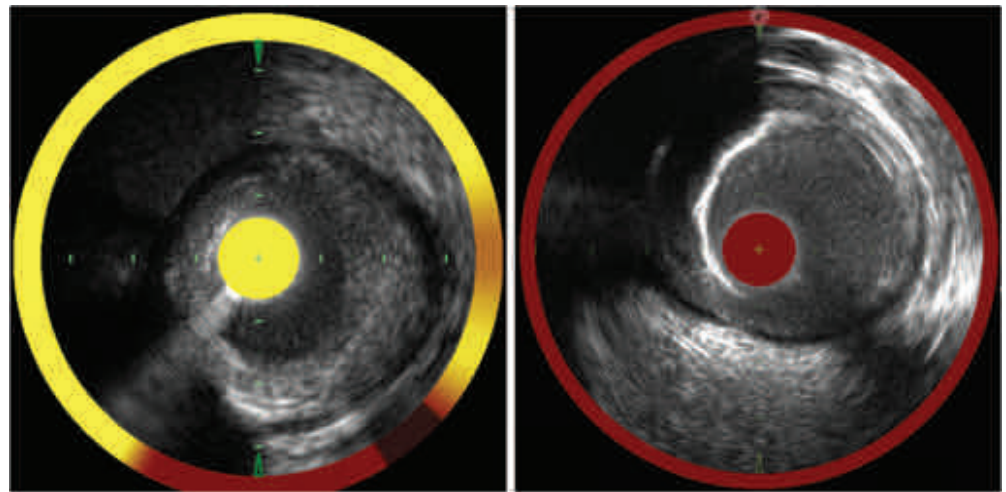
Figure 2. Combined NIRS-IVUS images. The current clinically available NIRS device provides combined automatically co-registered NIRS and IVUS images that are obtained during a single pullback within a coronary artery. Shown are two examples of combined NIRS-IVUS images. In each image the NIRS chemogram is located around the periphery of the greyscale IVUS image, whereas the block chemogram is shown in the central circle. Left: A plaque having a moderate plaque burden by IVUS is composed of lipid as demonstrated by the NIRS chemogram and block chemogram, both of which reveal yellow signal. Right: A calcified plaque by IVUS is shown to be devoid of lipid by NIRS, as both the chemogram and block chemogram are red. IVUS = Intravascular ultrasound; NIRS = near-infrared spectroscopy.

Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was established but prior to stenting[11]. NIRS identified a large, nearly circumferential LCP at the STEMI culprit site in the majority of these patients and STEMI culprit segments were found to have $maxLCBI_{4mm}$ that was 5.8-fold higher than non-culprit segments of the same vessel. Furthermore, the culprit segments had a $maxLCBI_{4mm}$ that was 87-fold higher than segments from an autopsy control group that were known to be free of LCP by histology.

In this study, a threshold $maxLCBI_{4mm}$ >400 identified STEMI culprit sites with specificity of 98% and a sensitivity of 85%. The significance of this finding is that the LCP generating the $maxLCBI_{4mm}$ >400 signal was likely present in the artery well before the onset of the STEMI. Hence, the $maxLCBI_{4mm}$ >400 signal may be a marker of a vulnerable plaque at increased risk of triggering a future myocardial infarction. A larger, multicenter study confirming these initial NIRS observations in STEMI patients is expected to be published in 2016. An example of typical NIRS findings in a patient with STEMI is provided in Figure 3.

Non-STEMI and unstable angina

NIRS evaluations of culprit lesions in patients with non-STEMI and unstable angina have also been performed[12]. Similar to the findings previously reported in STEMI, patients with non-STEMI and unstable angina frequently have a large LCP detected by NIRS at the culprit site that is characterized by a $maxLCBI_{4mm} \geq 400$[12]. Accordingly, a threshold $maxLCBI_{4mm} \geq 400$ accurately differentiated culprit from nonculprit sites in non-STEMI and unstable angina while retaining the high specificity previously demonstrated in STEMI patients. Interestingly, culprit lesions in non-STEMI more often had a $maxLCBI_{4mm} \geq 400$ rather than a moderate ($maxLCBI_{4mm}$ 200–399) or small ($maxLCBI_{4mm}$ <200) lipid burden. In contrast, culprit lesions in unstable angina had lipid burdens that were more evenly distributed among lipid cores that were small, moderate or large. This observation suggests that the clinical presentation of a plaque rupture event may depend not only on the presence of a LCP, but also on the overall burden of lipid at the culprit site[12]. Additional
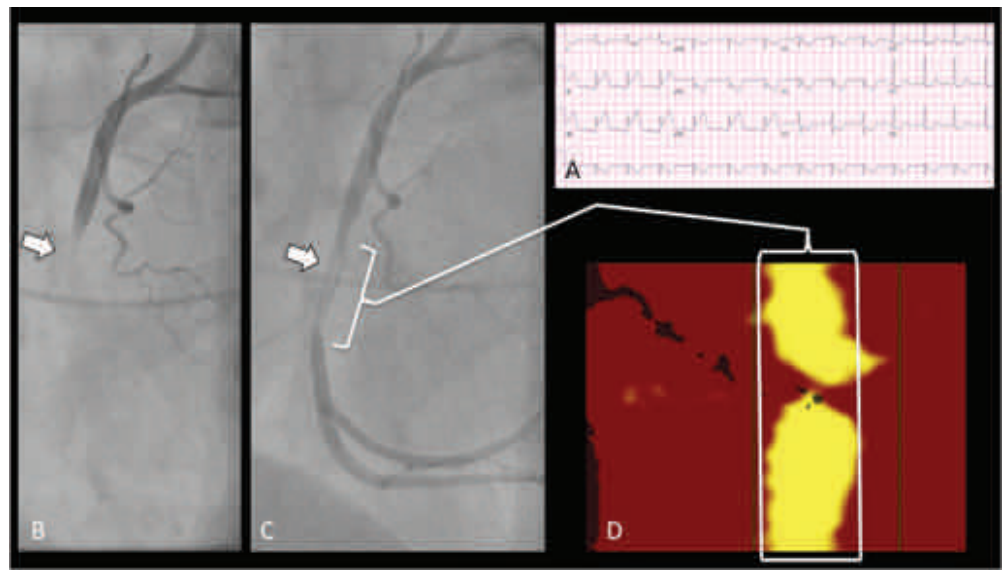
Figure 3.   Typical NIRS findings in STEMI. The electrocardiogram of a 54-year-old female presenting with acute chest pain is consistent with an inferior-posterior STEMI (A). The initial angiogram reveals complete occlusion of the mid right coronary artery (arrow, B). Angiography after establishing TIMI grade 3 flow reveals a filling defect consistent with thrombus at the culprit site (arrow, C). NIRS imaging performed prior to stent placement demonstrates a large, nearly circumferential LCP at the culprit site (white bracket, D). LCP = lipid core plaque; NIRS = near-infrared spectroscopy; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.

studies are needed to determine how the lipid burden impacts the clinical presentation of a plaque rupture event.

Sudden cardiac death

A small series of patients presenting with sudden cardiac death who were successfully resuscitated and subsequently underwent NIRS-IVUS imaging has been published[22]. In this small series of patients, a $maxLCBI_{4mm} \geq 400$ was detected by NIRS at each culprit site thought to be responsible for triggering ischemia and the resulting ventricular arrhythmia that lead to cardiac arrest. When considering this observation and those previously demonstrated in STEMI, non-STEMI, and unstable angina, NIRS has now been shown to identify large LCP at culprit sites across the entire spectrum of ACS clinical presentations. A larger study is needed to further evaluate the association between NIRS findings and sudden cardiac death.

NIRS to predict peri-procedural myocardial infarction

Peri-procedural myocardial infarction remains commonplace, complicating 3–15% of all PCI procedures[13]. One of the pathophysiologic mechanisms thought to account for some instances of peri-procedural myocardial infarction is embolization of lipid-rich material that is mechanically released from a target lesion during angioplasty or stent placement[23,24]. Hence, the identification of lipid at the target lesion prior to PCI may identify those lesions at greater risk of causing PCI-related complications. Although this concept has been demonstrated previously with IVUS[25–27], optical coherence tomography[28–30] and non-invasively with computed tomographic angiography[31], NIRS may offer an advantage over these techniques owing to its automated ability to identify LCP with high chemical specificity.

   In an analysis of cases from the COLOR registry, Goldstein *et al* studied target lesions undergoing NIRS imaging prior to PCI and demonstrated that lesions having a

maxLCBI$_{4mm}$ ≥ 500 had a 50% rate of peri-procedural myocardial infarction (13). This is in stark contrast to the observation that only 4.2% of target lesions having a maxLCBI$_{4mm}$ <500 were associated with a peri-procedural infarct. In this study target lesions having a maxLCBI$_{4mm}$ ≥ 500 prior to PCI had a 12-fold increased risk of developing a peri-procedural myocardial infarction during PCI[13].

In the CANARY trial, Stone *et al* confirmed that large LCPs identified by NIRS imaging prior to PCI were significantly associated with a higher risk of peri-procedural myocardial infarction[14]. In this study lesions having a maxLCBI$_{4mm}$ ≥ 600 were associated with peri-procedural myocardial necrosis in 24.7% of cases. However, the CANARY trial, which randomized target lesions having a maxLCBI$_{4mm}$ ≥ 600 to undergo PCI either with or without a distal protection filter, failed to show benefit of distal protection. This finding was perhaps unexpected considering evidence from a prior small study that presented convincing evidence of debris capture using distal protection during PCI on large LCP[32] and also highlights the uncertainty regarding methods to reduce the risk of peri-procedural complications during PCI of large LCP. It is unknown if other methods shown to reduce the focal lipid burden, such as intensive statin therapy[33] or mechanical aspiration of lipid content from the target lesion[34], if performed prior to PCI will reduce the risk of PCI-related complications. Additional study in this area is clearly needed.

NIRS to identify the vulnerable patient

Whereas the identification of large LCP at heightened risk of triggering peri-procedural myocardial infarction represents one potential clinical use of NIRS imaging, another proposed application of NIRS is to identify patients at increased risk of future patient-level major adverse cardiovascular events. In the ATHEROREMO-NIRS study, investigators performed NIRS imaging within a non-culprit vessel after performing PCI elsewhere in the coronary tree. Patients having an LCBI in the non-culprit vessel above the median value of 43 for the population had a 4-fold increased risk of patient-level cardiovascular events during 1-year of follow up compared to those with an LCBI below the median[35]. Although prior studies have demonstrated a clear association of serum lipid content and cardiovascular risk[36–38], the observations of the ATHEROREMO-NIRS study suggests that the burden of lipid deposited within coronary tissues, as now detectable by NIRS imaging, also associates with cardiovascular risk. Additional studies examining the ability of NIRS imaging to identify patient-level vulnerability to cardiovascular events are forthcoming[39].

NIRS to identify the vulnerable plaque

Given the association of large LCP identified by NIRS with culprit lesions across the spectrum of ACS[10–12,22] and the propensity of such large LRP to trigger myocardial infarction at the time of PCI[13,14], it has been proposed that NIRS imaging may be a means to identify vulnerable plaques at increased risk of triggering future site-specific coronary events[4]. Whereas prior studies have demonstrated the ability of IVUS to detect plaques at increased risk of site-specific future events[40–43], it remains unproven if NIRS findings of a large LRP are in fact at increased risk of triggering future events. There are currently at least two large multicenter prospective observational studies testing the hypothesis that NIRS is capable of identifying vulnerable plaques. These studies include the Lipid Rich Plaque study being performed in the United States and Europe and the PROSPECT II study currently underway in Scandinavia[4]. These studies, once completed, are anticipated to provide valuable data regarding the ability of NIRS imaging to identify plaque vulnerability.

CONCLUSION

NIRS imaging, which is now clinically available in a combined NIRS-IVUS catheter, is a novel catheter based imaging modality capable of identifying LCP within the coronary arteries of living patients. One of the major assets of NIRS is that it has been rigorously validated against the gold standard of histopathology and has been shown to accurately identify histologically-proven fibroatheroma. Clinical studies of NIRS have demonstrated its ability to identify culprit lesions across the spectrum of ACS, to detect target lesions at increased risk of causing peri-procedural myocardial infarction, and to identify vulnerable patients. There are several large prospective observational studies underway to determine if NIRS imaging can identify vulnerable plaques.

COMPETING INTERESTS

Ryan D. Madder has received research support from Infraredx, Inc. Andrew O'Brien, Andrew Lacombe, and Aubrey Stickland have nothing to disclose.

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