Near-infrared spectroscopy-intravascular ultrasound: scientific basis and clinical applications

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Coronary angiography underestimates the magnitude of the atherosclerotic burden and cannot detect the presence of disease in the early phases. Recognition of these inherent limitations of angiography has been an impetus for the development of other coronary imaging techniques. The novel near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) catheters can detect and quantify the presence of lipid core in the atherosclerotic plaque and associate it with other features such as lumen size and plaque architecture. Lipid-rich plaques are known to pose a higher risk of distal embolization during interventions and plaque disruption. The aim of this manuscript is the review of the potential clinical and research applications of this technology as highlighted by recent studies.

Keywords near-infrared spectroscopy • intravascular ultrasound • lipid core • vulnerable plaque

Introduction

An ideal invasive coronary imaging tool should provide a complete road map of atherosclerotic burden throughout the coronary tree, delineate the architectural and compositional nature of each plaque, and determine lesion severity. Unfortunately, coronary angiography alone falls far short of providing the complete information to inform and guide management decisions. Although it is a crucial tool to delineate the gross presence of disease, locate likely culprit lesions responsible for the current clinical presentation, and quantify per cent stenosis, angiography underestimates the magnitude of atherosclerotic burden, particularly in earlier stage disease in which positive vascular remodelling may allow 'normal' lumen calibre despite substantial vascular wall plaque. Moreover, in any stage, angiography provides little or no information regarding plaque composition and biological activity.[1] Intravascular imaging has been developed to address these limitations of angiography.

This manuscript reviews the potential uses of near-infrared spectroscopy (NIRS), a novel technique to quantitatively and qualitatively assess lipid cores through their unique spectroscopic fingerprints.

Principles of near-infrared spectroscopy

Spectroscopy can be broadly defined as the measurement of the wavelength-dependent interaction of electromagnetic radiation with matter. Several spectroscopic methods have been investigated for the purpose of identifying the composition of the atherosclerotic plaques. The currently commercially available catheter uses diffuse reflectance NIRS. Alternative spectroscopy techniques that reached some stage of research or development for intravascular applications include nuclear magnetic resonance spectroscopy, Raman spectroscopy, and fluorescence spectroscopy.[2,3]

NIRS has a strong fundamental basis for compositional measurement and is widely used in many fields to identify the chemical composition of unknown substances.[4] In this technique, a sample of interest is illuminated with near-infrared (NIR) light, and the molecular interactions of the sample with the light are probed. The term 'near' indicates the section of infrared that is closer to the visible light region with a longer wavelength (780–2500 nm) and hence a lower energy than visible light. At this wavelength, there is reasonably low absorbance of haemoglobin, the main chromophore in the visible range and water, the main absorber of mid-to-long infrared wavelength.[5] After NIR emission, a detector measures the proportion of diffusely reflected light returned as a function of wavelength. Two quite different processes determine the amount of light that returns to the detector—scattering and absorption. 'Scattering' occurs when the path of the light is altered by cellular and extracellular structures that are larger than the wavelength of light in the material. 'Absorption' occurs when light energy is absorbed by chemical bonds of the constituent molecules. Absorbed light is mainly

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transformed into molecular vibrational energy in the form of oscillations of atoms within their chemical bonds. The bonds that are responsible for the major absorption of NIR light are C–H, N–H, and O–H bonds. In similar fashion to unique variation between each individual's fingerprints, each functional group of large complex molecules has a specific absorption and the unique pattern of those absorptions is known as its spectroscopic fingerprint. Therefore, by evaluating absorption patterns and spectroscopic fingerprints, robust sample recognition and tissue classification is possible.

NIR spectra taken in biological systems are often complex due to the wide variety of biochemicals and tissue-scattering properties, and the measured spectra usually require sophisticated techniques for data analysis. A typical strategy is that predictive models are constructed using the spectra of known materials, guiding and teaching the system how to recognize the same desired component in unknown samples.[6] The science of applying such multivariate statistical data analysis is called chemometrics.

NIRS has several figures of merit that make it uniquely suited for analysis of lipid core plaques (LCP) in coronary arteries *in vivo* since it (i) can penetrate blood, (ii) can penetrate several millimetres into the tissue, (iii) can be done with an ultrafast scanning laser, overcoming the problem of cardiac motion, (iv) is capable of acquiring the tens of thousands of spatial measurements required to create an image of the artery, and (v) provides a positive and specific chemical measure of LCP, since cholesterol has prominent features in the NIR region that can distinguish it from other tissue constituents such as collagen.

The NIRS-IVUS catheter system

A single modality NIRS catheter system (Lipiscan™, InfraRedx Inc., Burlington, MA, USA) was originally developed for invasive detection of LCP. Recognizing the need to provide multimodality imaging, the NIRS-intravascular ultrasound (IVUS) catheter was recently introduced (TVC Imaging System™, InfraRedx Inc.), providing simultaneous, co-registered acquisition of structural and compositional data. In addition to the established value of IVUS alone, the complementary nature of the NIRS compositional and IVUS structural information allows more complete characterization of coronary plaques than has previously been possible. This system is CE marked and has an FDA clearance for LCP detection.

This NIRS-IVUS system comprised a scanning NIR laser, a pullback and rotation unit, and a catheter similar in size to traditional IVUS catheters. The 3.2F rapid exchange catheter has an entry profile of 2.4F and a shaft profile of 3.6F, and is compatible with 6F guiding catheters. It can be inserted over a 0.014-inch guide wire while its passage through the lesion is facilitated by the hydrophilic coating present on the flexible distal 50 cm end. IVUS images are acquired during an automated rotational pullback at a speed of 0.5 mm/s together with simultaneous co-registered NIRS measurements. The catheter's imaging core rotates at 960 rpm with a maximum imaging length of 12 cm. The majority of the NIRS tissue information is obtained from a depth of 1 mm or less in the direction from the luminal surface towards the adventitia. The system acquires >30 000 NIRS spectra per 100 mm. The latest iteration of commercial NIRS-IVUS utilizes a novel method of higher bandwidth transducer excitation frequencies and tailored send/receive electronics to purportedly produce an image with higher resolution and better contrast resolution. The new system is currently being released in the marketplace, and a formal comparison study is in progress to compare images obtained with the new system to various other currently available IVUS systems (SAVOIR2, NCT02154295).

After pullback, NIRS lipid core data are automatically displayed on a two-dimensional map of the vessel revealing the probability of the presence of an LCP with the pullback position in millimetres on the *x*-axis and the circumferential position on the *y*-axis; this chemical display is known as the 'chemogram'. For each pixel of 0.1 mm length and 1° angle, the lipid core probability is calculated from the spectral data collected and quantitatively coded on a colour scale from 0 (red) to 1 (yellow). Whenever a pixel lacks sufficient data, for instance if the guidewire is shadowing, the resultant image pixel appears black.

The 'block chemogram' is a semi-quantitative summary of the results for each 2 mm section of the artery and provided for straightforward 1:1 comparison of the chemogram with a binary histologic reference (presence or absence of LCP) during validation. The numerical value of each block in the block chemogram represents the 90th percentile of all pixel values in the corresponding 2 mm chemogram segment. The display uses four discreet colours to aid in the visual interpretation of the algorithm probability that an LCP is present in that 2 mm block analysis [red ($P < 0.57$), orange ($0.57 \leq P < 0.84$), tan ($0.84 \leq P < 0.98$), and yellow ($P \geq 0.98$)]. The block chemogram has been described more fully elsewhere.[7,8] Additionally, the NIRS spectral data are mapped and paired with corresponding IVUS frames, ultimately presented as a ring around the IVUS image (*Figure 1*).

While chemogram helps in visual interpretation, the lipid core burden index (LCBI) is provided as a semi-quantitative summary metric of LCP presence in the entire scanned region. LCBI is computed as the fraction of valid pixels within the scanned region that exceed an LCP probability of 0.6 per million (‰, multiplied by 1000). Since the chemogram colour-scale transitions from red to yellow near an LCP algorithm probability of 0.6, the LCBI can be viewed as a quantitative measure of the amount of yellow present on the chemogram. Various related measures can be computed on the chemogram image, such as the LCBI of a region of interest (ROI), or the maximum LCBI of narrow segments within an ROI (i.e. $\text{maxLCBI}_{4\text{mm}}$). The $\text{maxLCBI}_{4\text{mm}}$ computation accentuates LCP that are relatively short, but high angular extent.

Validation

The earliest use of NIRS in atherosclerotic plaque classification dates back to 1993, when Cassis and Lodder demonstrated the ability of NIRS to accurately characterize low-density lipoprotein cholesterol accumulation in the aortas of hypercholesterolaemic rabbits.[9] Since then, many studies were carried out using experimental models to test NIRS, all verifying its utility and safety, until eventually reaching the stage where it was acceptable to use on humans.[2,10,11,12]

To validate the accuracy of the NIRS catheter for detection of LCP in humans, two pivotal studies were carried out (*Figure 2*). First, the NIRS system and algorithm were developed and validated using measurements from 84 human heart specimens. The first 33 hearts were utilized to develop NIRS algorithms and produce

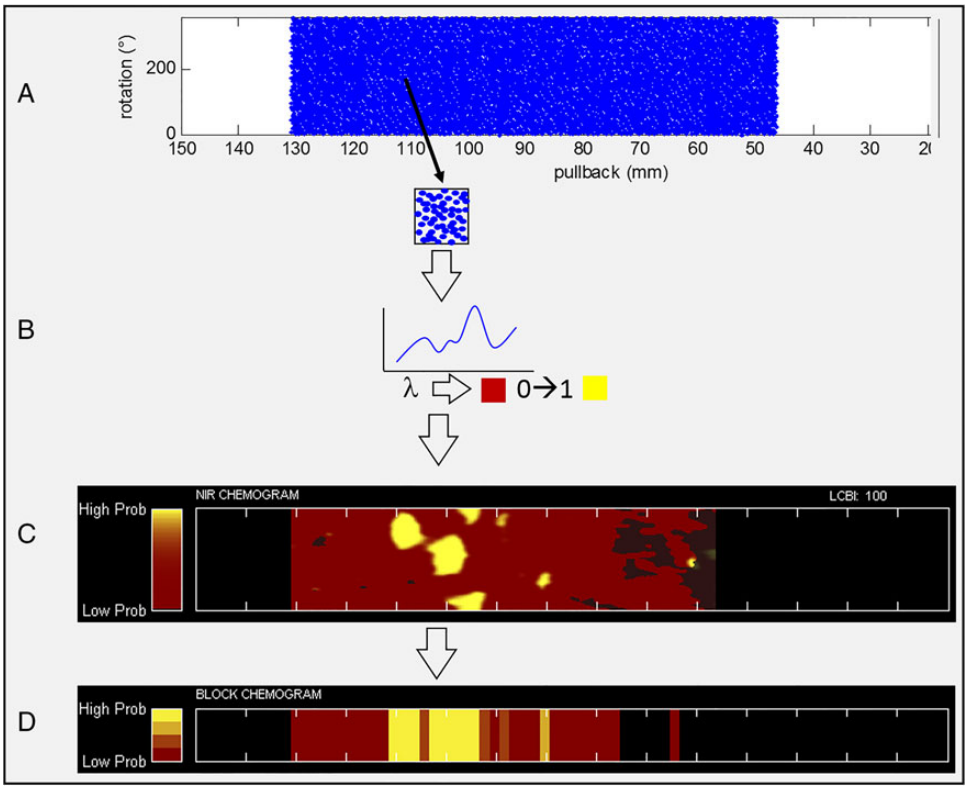

Figure 1 Formation of chemogram: during pullback, spectra acquired at discrete positions (*A*). Measured spectra are complex due to multiple components and variable scattering properties. Processing algorithms extract relevant spectral information and transform each measured spectrum into a probability of LCP (between 0 and 1) (*B*). High probability (>0.6) is mapped to yellow and low (<0.6) to red (*C*). Algorithm predictions from individual pixels are formed into the chemogram (*D*). Block chemogram is a vertical summary of the chemogram at 2 mm pullback intervals. Each value of the block chemogram is the 90th percentile probability for the corresponding 2-mm slice. It is mapped to the same colour scheme as the chemogram, binned into four discrete colours.

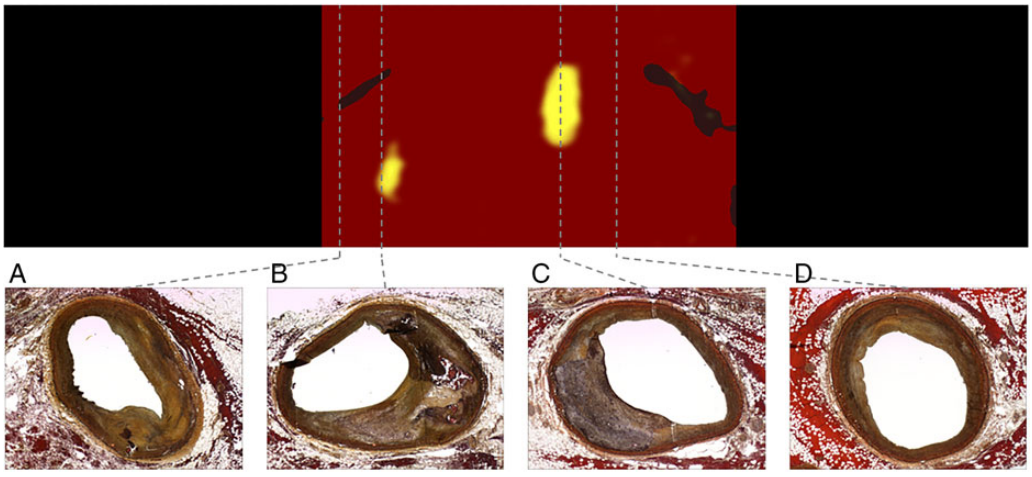

Figure 2 Example of correlation between NIRS chemogram and histologic findings. Vessel tissue lacking necrotic lipid core corresponds to 'red' in chemogram (*A* and *D*—fibrous PIT), whereas necrotic lipid core plaques correspond to 'yellow' (*B* and *C*—early stage fibroatheromas). Movat's pentachrome stain used for histologic evaluation.

prospectively defined endpoints. The following 51 hearts were used for prospective validation, in a double-blind manner, to evaluate the accuracy of NIRS in detecting LCPs. To formulate a suitable quantitative target to construct an algorithm and validate results, an LCP of interest was defined as a fibroatheroma with a lipid core $>60^{\circ}$ in circumferential extent, >200 μm thickness, and with a fibrous cap of mean thickness <450 μm. The primary analysis was conducted by comparing block chemogram readings with histologic classifications. Receiver operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.80 (95% CI: 0.76–0.85), confirming that the NIRS system accurately identified LCP.[7] Second, to validate the accuracy of LCP signals in patients, the **SPECT**roscopic **A**ssessment of **C**oronary **L**ipid (SPECTACL) clinical study was performed. The study met its primary endpoint of demonstrating that spectral data of coronary arteries could be safely obtained clinically and shown to be greatly similar to those gathered from autopsy specimens, verifying the feasibility of invasive detection of coronary LCPs with the NIRS system.[13] Intra- and inter-catheter reproducibility were later demonstrated in independent studies.[14,15]

Comparison with other methods for plaque characterization

Qualitative characteristics of signal drop-out and cross-sectional image texture are interpreted to characterize the atherosclerotic plaque by IVUS and OCT. For example, necrotic core plaques are identified as echo-attenuated or echo-lucent plaques by IVUS or with OCT plaques with a region of poor signals with poorly delineated borders, overall producing fast OCT signal drop-off alongside little or no signal backscattering.[16,17] These characteristics are suggestive of the presence of specific compositions, but do not visualize or determine actual composition. This explains the large intra- and inter-observer variability observed with both OCT and IVUS (*Figures 3 and 4*,[18] *Table 1*). Radiofrequency ultrasound data, from unprocessed backscattered signals, offer a potential alternative to grey-scale image analysis for measuring tissue properties and hypothetically could provide a more accurate and reproducible technique for measuring tissue properties as it is not dependent on operator interpretation.[19] While more sophisticated radiofrequency analysis methods have remained confined to experimental laboratories, a simplified algorithm using pattern analysis and called Virtual Histology (VH) became available on commercial phased-array-based IVUS console and has been widely studied. However, after a promising validation study on autopsy specimens and atherectomy samples,[20–22] doubts have been raised about its true sensitivity and specificity.[23,24] In a study in advanced lesions in the adult atherosclerotic-prone mini pig model, no correlation found between the VH-identified necrotic core and histology.[24] Nevertheless, this study also drew some criticism itself because of the differences between animal and human atherosclerosis.[25]

Signal loss behind calcium due to acoustic shadowing is another important limitation.[23,26,27] On the other hand, NIRS detects an unequivocal fingerprints from lipid core not affected by lower intensity due to attenuation, and the validation of NIRS included both calcified and non-calcified lipid cores in the 'truth definition' for lipid core.[7]

Many studies have compared NIRS and other morphologic techniques of intravascular imaging, highlighting possible synergies. A

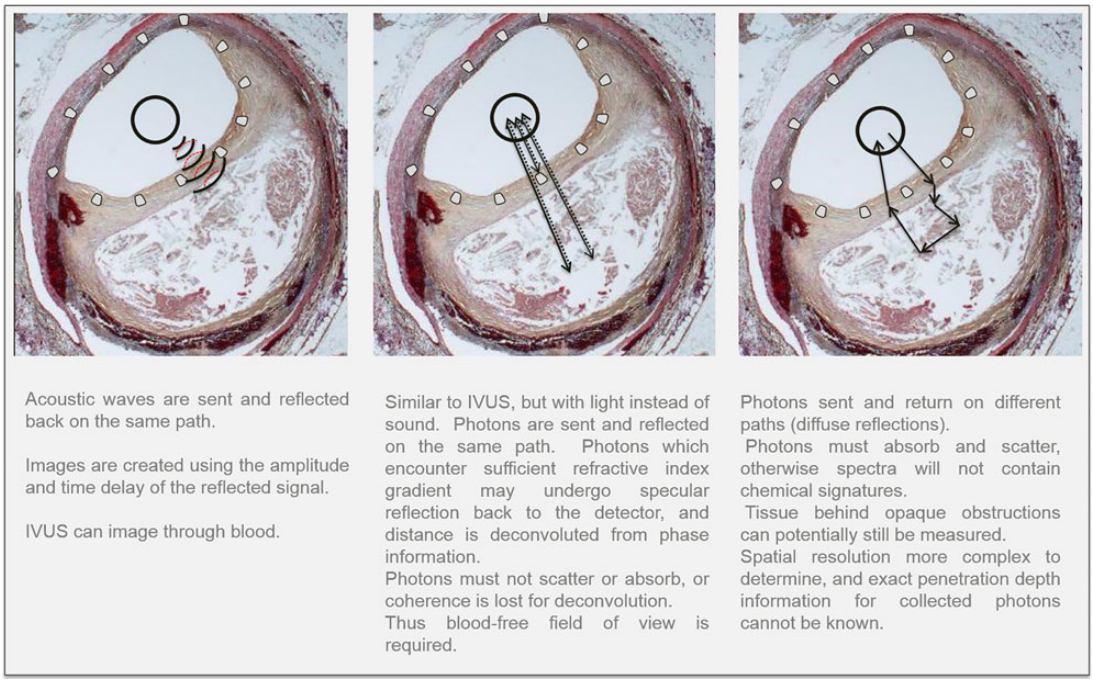

Figure 3 Comparison of image formation in IVUS, OCT, and NIRS.

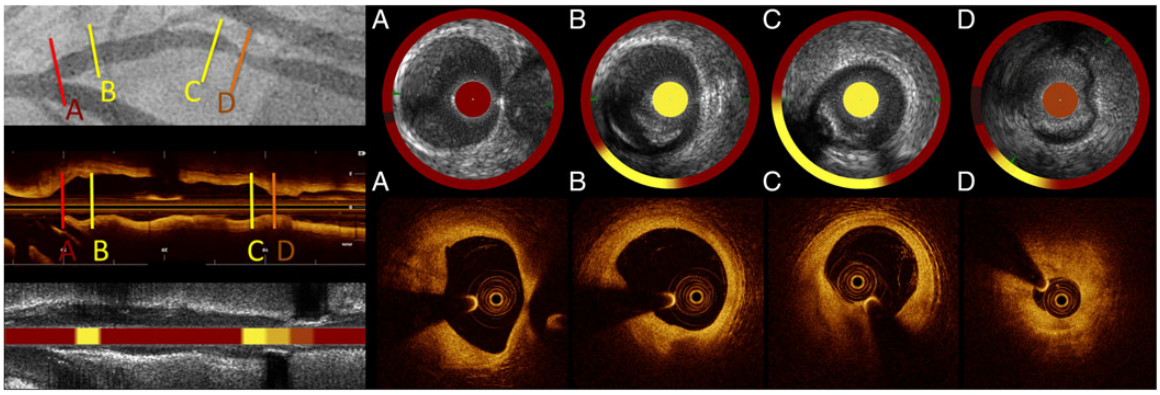

Figure 4 Multi-modality imaging of coronary artery disease in a large diagonal artery. (*A*) It shows fibrotic plaque. In (*B* and *C*), lipid arc corresponds to echo-lucent areas in IVUS and signal-poor areas in OCT. In the minimal lumen area in *D*, there is a limited amount of lipid by NIRS despite significant plaque burden by IVUS and severe stenosis apparent on both IVUS and OCT (modified from Fabris *et al.*[18]).

Table 1 Comparison of different intravascular imaging modalities

	OCT	IVUS	RF-IVUS	NIRS
Thin cap detection	++	−	+	−[a]
Positive remodelling	−	++	[b]	[b]
Plaque volume	−	++	[b]	[b]
Calcification	++	++	++	−
Thrombus	++	+	−	−[a]
Neovascularization	+	−	−	−
Macrophages	+	−	−	−
Lipid core	+	+	+	++

OCT, optical coherence tomography; IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; RF-IVUS, radiofrequency intravascular ultrasound.
[a]Under investigation.
[b]Like IVUS.

larger plaque burden measured with IVUS is associated with lipid accumulation detected by NIRS.[28,29] Dohi *et al.*[30] reported that a large lipid-rich plaque (LRP; $\text{maxLCBI}_{4\text{mm}} \geq 500$) was only found in plaques with plaque burden $\geq$70% and multivariate analysis established that plaque burden was the best predictor of the extent of LRP. However, ~60% of the plaques with plaque burden $\geq$70% had a $\text{maxLCBI}_{4\text{mm}}$ of $<$500. Additionally, one histological study showed that the highest probability of NIRS-derived LCP was found in echo-attenuated plaques, followed by echo-lucent plaques and spotty calcifications by IVUS.[31]

Regarding the comparison of NIRS and VH-IVUS, Brugaletta *et al.*[28] found a weak correlation between the VH necrotic core content of the plaque and the block chemogram probability values ($r = 0.149$). In a slightly larger study, similar results were found ($r = 0.16$, VH-NC% and LCBI); however, only after separation of the plaques according to grey-scale IVUS morphology, significant and modest relationships between VH-derived maximum % necrotic core and LCBI were obtained in the attenuated ($r = 0.50$, $P = 0.006$) and echo-lucent plaque ($r = 0.42$, $P = 0.076$) groups, respectively.[32]

Plaque LCBI showed modest correlation with maximum lipid arc and lipid index by OCT.[33] In a study of the comparison of OCT and combined NIRS/IVUS, researchers found that the greatest accuracy for OCT-defined TCFA detection was achieved by using $\text{LCBI}_{2\text{mm}} > 315$ with a remodelling index of >1.046 as a combined criterion value.[34] OCT-defined thin-cap fibroatheromas were characterized by positive vessel remodelling with a thicker plaque and higher lipid core burden.

NIRS-IVUS: clinical applications

Precise lesion length and optimal stenting

Visual estimation or quantitative angiographic analyses of lesion lengths is frequently inaccurate because of foreshortening and underestimation of plaque burden. IVUS provides accurate length measurements during motorized pullback at constant speed and allows cover of the entire diseased segment. NIRS adds a new dimension as it allows to cover all the segments with high lipid burden. Dixon *et al.*[35] demonstrated that in 16% of the lesions assessed in their study, the lipid core plaque extended beyond the angiographic margins of the initial target lesion. Employing guidance by NIRS-IVUS, a 'red-to-red' strategy can be adopted with longer stents to extend into the vessel free of LCP or conversely the choice of a shorter stent could be supported by the absence of LCP in a given landing zone. However, long-term studies are required to determine whether NIRS-IVUS informed stent length decisions result in better clinical outcomes.

Prevention of distal embolization and peri-procedural myocardial infarction

The necrotic core of the atherosclerotic plaque is highly thrombogenic and contains fragile tissues such as lipid depositions within foam cells as well as intramural bleeding and/or cholesterol crystals.[36] These elements may initiate and aggravate in-stent thrombus

formation[37] or can be easily released into the blood stream during coronary interventions.[38–40] Peri-procedural myocardial infarction (MI) is mainly attributed to distal embolization of these LCP contents and/or intracoronary thrombus.

In a sub-study of the COLOR (Chemometric Observation of Lipid Core Plaques of Interest in Native Coronary Arteries) registry, the cardiac biomarkers in 62 stable patients undergoing stenting were evaluated. Findings revealed that 7 out of 14 (50%) patients with a $maxLCBI_{4mm} \geq 500$ suffered peri-procedural MI in comparison with the occurrence of this in only 2 out of 48 (4.2%) patients with a $maxLCBI_{4mm} < 500$.[41] Such data were concordant with the study of Raghunathan *et al.*,[42] in which a post-procedural creatine kinase-MB increase >3 times the upper normal limit was observed in 27% of patients with a ≥1 yellow block as opposed to none of the patients without a yellow block within the stented lesion. The CANARY (Coronary Assessment by NIR of Atherosclerotic Rupture-prone Yellow) studied 85 stable angina patients with pre-intervention NIRS and found that in the 21 patients with a significant peri-procedural MI, $maxLCBI_{4mm}$ was significantly higher (481.5 vs. 371.5, $P = 0.05$).[43] Brilakis *et al.*[44] reported anecdotal cases of successful use of an emboli protection device for retrieval of embolized material in eight of nine patients with large LCPs. However, in the randomized arm of CANARY study, in which 31 patients with a $maxLCBI_{4mm} \geq 600$ received PCI plus a distal emboli protection device or PCI alone, results failed to show the benefit of this adjunctive treatment in reducing the risk of peri-procedural MI, but it is difficult to know whether this was due to limitations of NIRS, of the cut-off criterion used or to shortcomings of the filters used for distal vessel protection, notoriously not the most efficient technique. More reliable alternatives represented by dedicated stents covered by pericardium, polytetrafluoroethylene, or polyurethane membranes or by a fine fabric mesh are being considered for future studies.

Assessing plaque vulnerability

Despite the lack of prospective evidence from natural history studies, retrospective autopsy studies have revealed the relevance of certain underlying histological culprit morphologies in patients suffering MI and sudden coronary death, thereby provides the foundation for the characterization of suspected vulnerable plaque thought to underlie ACS events.[45,46] 'Vulnerable' or 'rupture-prone' plaques are typically characterized by large necrotic cores with either a non-existent or a thin fibrous (<65 μm caps and enzymatically active macrophages near or within the fibrous cap.[46,47]

In a recent prospective animal study, NIRS and IVUS imaging detected and predicted the characteristics and future development of unstable fibroatheromas. These features of rupture-prone plaques included increased plaque and necrotic core areas, thinned fibrous cap, increased concentration of activated inflammatory cells, and proliferating and apoptotic cells within the fibrous cap.[48]

In a study conducted in 60 patients, consecutive patients undergoing coronary angiography and NIRS, Madder *et al.*[49] showed that the target lesions responsible for ACS were in most cases LCPs (84.4%) and that patients with ACS also commonly harboured remote, non-target LCPs. In a study of 20 patients with ST-segment elevation MI, $maxLCBI_{4mm} > 400$ in NIRS accurately distinguished culprit from non-culprit segments within the artery.[50] Similar results were replicated in a larger patient group during a multicentre trial.[51] NIRS also allowed *in vivo* demonstration of large lipid cores in culprit segments present in a small group of sudden cardiac death survivors.[52] It is of necessity to remark, however, that approximately one half of the target lesions in stable patients are LCP.[49] It may well be the case that some clinically 'stable' patients harbour lipid-rich potentially unstable plaques that may be the precursor for future ACS.

Risk stratification

A prospective observational study, assessing the non-culprit artery in stable and acute patients, found that the 1-year cumulative incidence of all-cause mortality, non-fatal ACS, stroke, and unplanned coronary revascularization was significantly higher in patients with an LCBI equal to or above the median value (43.0) compared with those with an LBCI value below the median. The association of the LCBI value with primary endpoint was similar in both stable and ACS patients.[53] De Boer *et al.*[29] studied the relationship between the LCBI in a non-culprit segment and clinical characteristics, blood lipids, and hs-CRP and found that only 23.2% of LCBI variability was linked to clinical characteristics reflecting a high cardiovascular risk profile while blood markers contributed little. In this cohort, the LCBI was also similar in patients presenting with ACS and those with stable angina. LCBI was not associated with the Framingham Risk Score in another study by the same group.[54]

Monitoring effects of lipid-lowering therapy

Cholesterol is dynamically modulated in lesion regression or stabilization.[55] The pharmacological effects of specific agents that reduce free and esterified cholesterol can be tracked and evaluated using NIRS, as it feedbacks on the cholesterol content of plaque over time. The YELLOW trial recruited patients with multi-vessel CAD undergoing a percutaneous coronary intervention. Patients received baseline assessment via NIRS and IVUS imaging, and were then randomized to a treatment of either rosuvastatin 40 mg daily or the standard-of-care lipid-lowering therapy. After 6–8 weeks of short-term intensive statin therapy, a significant reduction in the plaque lipid content was found with $max\ LCBI_{4mm}$.[56] However, it is also important to note that in YELLOW study, baseline LCBI was significantly higher in patients randomly allocated to intensive vs. standard therapy. In the IBIS-3 study, the effect of rosuvastatin on coronary plaque composition and necrotic core was investigated in patients presenting with various manifestations and failed to demonstrate a significant reduction of necrotic core volume or LCBI under high-intensity rosuvastatin therapy during 1 year.[57] The effects of high-dose statin therapy is also being tested in the YELLOW 2 using OCT in addition to NIRS and IVUS modalities.

Brugaletta *et al.*[58] reported the ability of bioresorbable vascular scaffold (BVS) implantation to promote the growth of neo-intimal tissue acting as a barrier to isolate vulnerable plaques. In the PROSPECT II ABSORB sub-study (NCT021711065), patients with a plaque at high risk of causing future coronary events (plaque burden ≥70%) are being randomized to receive an Absorb™ BVS alongside optimal medical therapy (OMT) or OMT alone. NIRS-IVUS will be used to evaluate the changes in the plaque at follow-up, 2 years after the baseline imaging.

Other applications

Previously, Kilic and Di Mario reported lipid deposition behind a calcified lesion in a young patient with a history of Kawasaki disease, indicating a link between inflammatory diseases and atherosclerosis progression.[59]

Another use of NIRS is the differentiation between the mainly fibrotic intimal thickening within stents and the development of neoatherosclerosis (*Figure 2*).[60] In one study, neoatherosclerotic tissue was evaluated with OCT and NIRS-IVUS, and in 28% stented vessels, NIRS-identified lipid was not detected by OCT; however, lipid deposition in these cases was minimal without a discernible lipid core or thin-cap neoatherosclerosis.[61] Therefore, clinical utility of NIRS in this setting requires further investigation.

NIRS can also be applied in cardiac transplant patients. A key obstacle in cardiac transplantation patients is the process of monitoring and preventing graft rejection. Coronary angiography remains the most common clinical screening method; however, the sensitivity of angiography is as low as 30%, compared with IVUS.[62] A study on heart transplant patients showed that despite having similar values in the lesions of a plaque burden of >40%, the cardiac allograft vasculopathy group showed a significantly higher max $LCBI_{4mm}$ in lesions with a mild plaque burden compared with atherosclerosis patients, suggesting early lipid accumulation in cardiac transplant vasculopathy.[63]

Limitations

Conventional grey-scale IVUS has 25 years of application in interventional cardiology and has produced a wealth of information in guidance of interventions. There is a growing body of evidence demonstrating that PCI performed employing IVUS achieves superior outcomes compared with angiographic guidance alone.[64–66] NIRS-IVUS obviously shares the same advantages of IVUS; however, the potential added value of NIRS for detection of plaques at risk of embolization and full coverage of LRPs remain speculative at this point.

NIRS offers a more reliable and quantitative detection of LCP than other intravascular imaging methods. However, both its value as an independent predictor and its incremental prognostic utility when associated with other IVUS negative prognostic indices (plaque burden, remodelling, MLCSA, etc.) remain to be investigated.[67] The optimal thresholds of LCBI (and its derived measures) for risk stratification or to drive potential clinical actions are also still under investigation. The clinical relevance of missing key aspects of vulnerable plaque, such as fibrous cap thickness and intra-plaque inflammation, better assessed with high resolution intravascular imaging techniques such as OCT, is also unclear, and no commercial systems combining the two techniques have been developed so far.

Finally, the main limitation of NIRS-IVUS is the invasiveness of the technique, which in general precludes its utilization in primary prevention in asymptomatic patients with subclinical disease. For secondary prevention, IVUS can be used to guide the stenting procedure and adding NIRS can provide information helpful for both the treatment of the culprit lesion and the identification of other plaques at risk in different segments.

Future trials and directions

The COLOR Registry (Chemometric Observation of LCP of Interest in Native Coronary Arteries Registry) is a prospective, multicentre observational study to identify the associations of LCP with angiographic or symptomatic presentations of coronary artery disease in a catheterization laboratory population (NCT00831116). It is finishing enrolment of around 2000 patients, and findings are expected to be reported soon after all patients have completed their 2-year follow-up. The prospective, multicentre PROSPECT II trial (NCT02171065) will randomize patients with non-flow-limiting lesions with LCBI >400 to optimal medical treatment of the implantation of a BVS. The LRP study has enrolled 700 out of the expected 9000 patients presenting for coronary angiography and a clinically indicated IVUS (NCT02033694). Patients and investigators will remain blinded to NIRS data acquired in the non-index culprit lesion and LCBI will be correlated to major adverse cardiac events at 3-year follow-up. Lipid c**OR**e plaque **A**ssociation with **CL**inical **E**vents (ORACLE-NIRS, NCT02265146) study is a multi-centre study that will examine treatment strategies and outcomes of patients who underwent clinically indicated NIRS over a very long follow-up period (15 years).

Using the same spectroscopic principles, plaque components different from lipids can also be identified with NIRS.[68] Initial studies demonstrated the ability to differentiate between various LCP cap thicknesses. In contrast to a traditional dimensional thickness measurement, the NIRS predictive ability is likely due to sensitivity to the relative contribution of cholesterol and collagen towards the overall signal. A pilot study compared the NIRS interpretations with histology and showed accurate assessment of the fibrous cap thickness overlying LCPs through blood in coronary autopsy specimens.[69,70] NIRS detection of thrombus is also under investigation.

Co-registration of NIRS with other imaging modalities is also possible; the use of combined OCT-NIRS catheters has been recently demonstrated as a proof of concept.[71] Triple imaging catheters that include OCT, IVUS, and NIRS are also being developed.

Conclusion

NIRS is a promising tool in the detection of vulnerable plaque detection, guidance of revascularization procedures, and assessment of atherosclerotic therapies including lipid-lowering treatments. Ongoing NIRS trials may confirm its clinical usefulness in these applications and enlarge its use to a larger range of clinical settings.

Conflict of interest: S.M. is an employee of Infraredx Inc. J.G. is an Infraredx consultant and equity owner. P.R.M. owns shares of Infraredx Company. C.D.M. is an investigator for Lipid Rich Plaque Study, for which Royal Brompton Hospital receives research funding. I.D.K. was supported by a research grant from the 'The Scientific and Technological Research Council of Turkey (TUBITAK)'.

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IMAGE FOCUS

Non-invasive cardiac imaging to unmask a very uncommon aetiology of an embolic stroke

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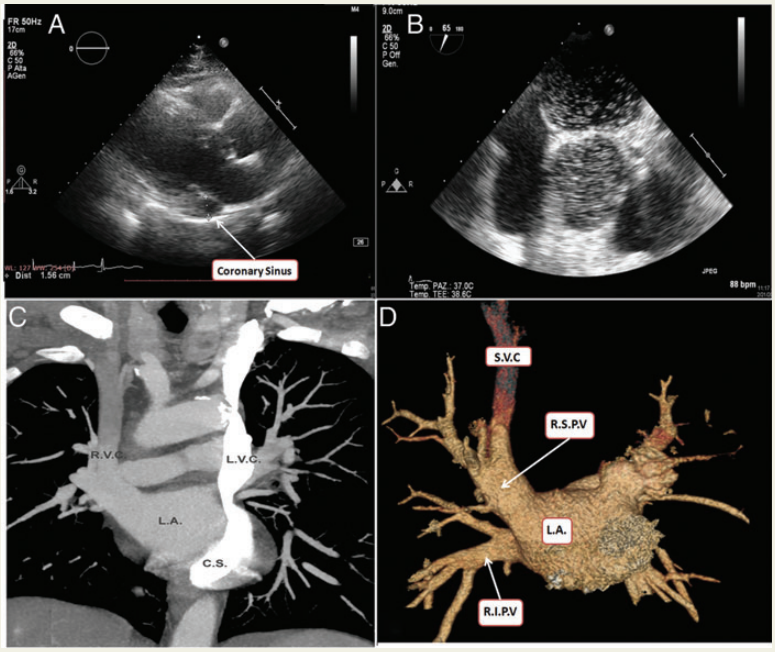

A 66-year-old healthy man admitted for an acute renal colic suddenly experienced a brief episode of loss of consciousness followed by persistent superior left arm hyposthenia during i.v. infusions of a non-steroidal anti-inflammatory drug using a standard antecubital right vein access (ARVA). A magnetic resonance imaging (MRI) scan showed a stroke with an embolic pattern. Carotid and vertebral Doppler scans, thrombofilic screening, and 24-h Holter were normal. Finally, an echocardiography was performed to rule out a cardiac embolic source. Dilatation of coronary sinus (CS; 15 mm) was evident after careful inspection of transthoracic parasternal long-axis view (*Panel A*). Therefore a transesophageal echocardiogram was performed during injection of agitated saline solution into the ARVA micro-bubbles unexpectedly filled directly the left atrium (LA) without passing through the right atrium (RA; *Panel B* and see Supplementary data online, *Video S1*), unmasking a partial anomalous systemic venous return into the LA contrast-enhanced CT angiography was performed demonstrating the presence of a right-sided Superior Vena Cava (SVC) meeting the right superior pulmonary vein before entering into the LA, and a persistent left SVC that drains into the RA via the CS. (*Panels C* and *D*). No other cardiac abnormalities were present. The strictly time-to-event relation between i.v. drug infusion in ARVA and occurrence of stroke during ED stay strongly supported the hypothesis of iatrogenic embolic event. A congenital isolated right SVC drainage into the LA is extremely rare: so far only 20 cases have been reported. This is the first case in which this anomaly was suspected and unmasked in a sudden iatrogenic stroke only by performing echo-imaging.

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