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INTRAVASCULAR IMAGING (A TRUESDELL, SECTION EDITOR)

Role of Near-Infrared Spectroscopy (NIRS) in Intracoronary Imaging

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Abstract

Purpose of Review The purpose of this article is to review the basic principles of near-infrared spectroscopy (NIRS) and its contemporary role in intracoronary imaging.

Recent Findings NIRS has been demonstrated to effectively detect culprit lesions in acute coronary syndromes (ACS) and to potentially identify vulnerable plaque. Lipid-rich plaques detected by NIRS are also associated with higher incidence of future adverse cardiac events. Plaques with high lipid content detected by NIRS have been shown to predict periprocedural myocardial infarction during percutaneous coronary intervention (PCI). The beneficial effects of high-intensity statin therapy in terms of plaque regression and plaque stabilization have also been demonstrated using NIRS.

Summary NIRS is a valuable intracoronary imaging tool to assess lipid burden in atherosclerotic plaques and has been validated against histopathologic data. The commercially available dual-modality NIRS-intravascular ultrasound (IVUS) catheter further provides complementary data regarding lesion and vessel characteristics, thereby facilitating planning and optimization of PCI. Finally, the ability of NIRS to detect vulnerable plaque opens up potential new opportunities for risk stratification and intensification of secondary preventive measures.

Keywords Near-infrared spectroscopy (NIRS) · Intracoronary imaging · Lipid core plaque (LCP) · Lipid core burden index (LCBI)

Introduction

Although coronary angiography provides valuable information regarding coronary anatomy and may grossly estimate the degree of stenoses, it fails to reliably assess the size of the vessel and nature of atherosclerotic burden. It provides no information about the composition and severity of the atherosclerotic plaque and provides little information regarding optimal stent expansion and apposition post-percutaneous coronary intervention (PCI). For these reasons, intracoronary imaging modalities such as optical coherence tomography (OCT), intravascular ultrasound (IVUS), and near-infrared spectroscopy (NIRS) are valuable supplemental tools to coronary angiography for diagnostic evaluation and optimization of intervention. Intravascular imaging with IVUS has been shown to improve clinical outcomes post-PCI, particularly in complex groups of patients such as those undergoing PCI of left main coronary artery [1, 2]. Figure 1 shows a coronary lesion in the left anterior descending artery and its assessment by multiple modalities of intracoronary imaging.

NIRS has been demonstrated to accurately identify the presence of lipid core inside atherosclerotic plaques [4]. It has also been used to evaluate the morphologic differences in coronary atherosclerotic plaque based on sex [5] and clinical presentation [6–9]. NIRS has additionally been evaluated for prediction of periprocedural myocardial infraction (MI) during PCI [10, 11], detection of vulnerable plaque [12], demonstrating the effect of statin therapy [13, 14], and for predicting the prognosis of coronary lesions [15, 16]. In this review article, we describe the principle of near-infrared spectroscopy and elaborate on its application in intracoronary imaging. Table 1

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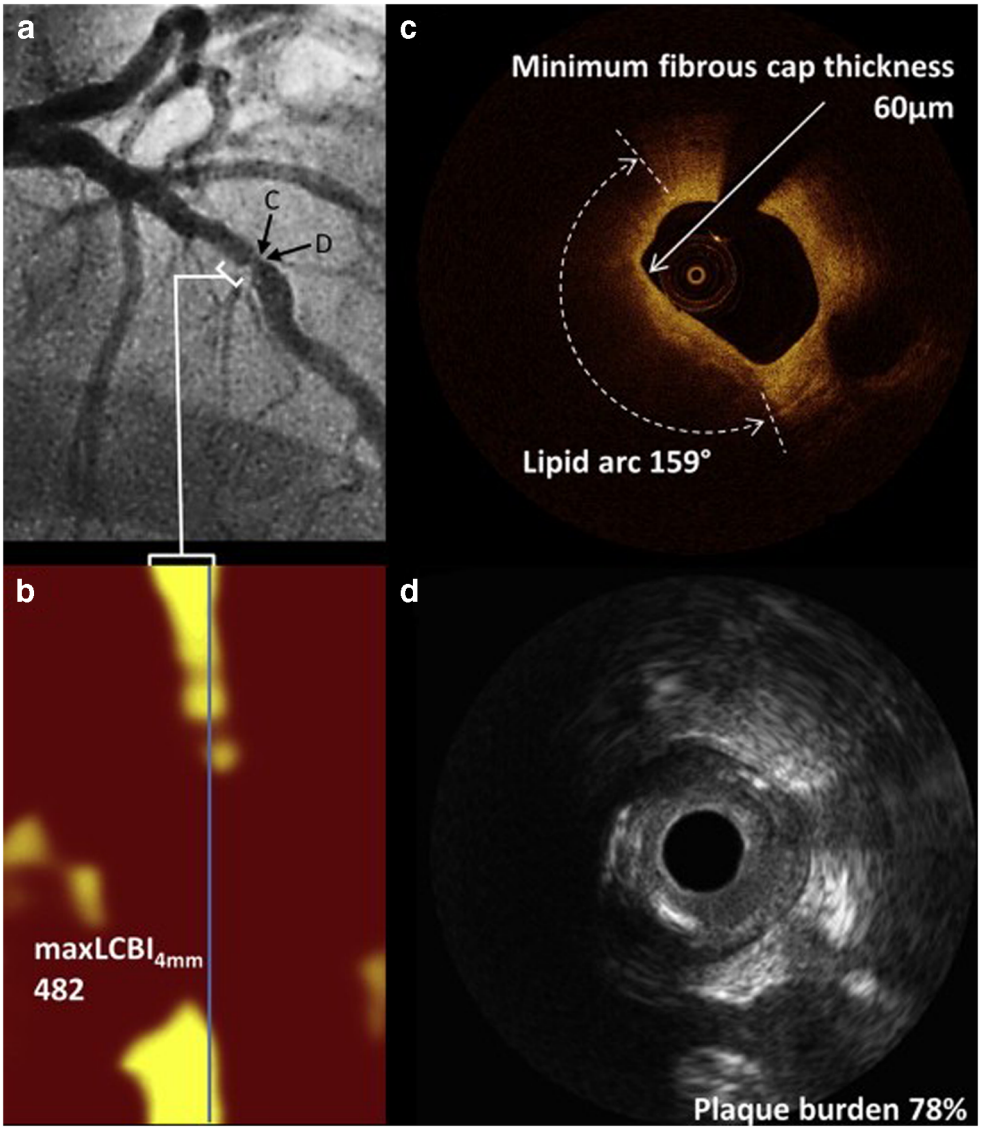

Fig. 1 Coronary angiography and multimodality imaging of a single coronary lesion. (A) Coronary angiography demonstrating a hazy focal lesion in the left anterior descending artery. (B) NIRS demonstrating a high lipid burden in the lesion (maxLCBI (4 mm) of 482). (C) Optical coherence tomography (OCT) demonstrating a lipid arc of 159° with thin cap fibroatheroma. (D) Intravascular ultrasound (IVUS) demonstrating a plaque burden of 78% (reprinted with permission from Kini et al. [3] with permission from Elsevier)

Summarizes the prominent studies utilizing NIRS in human subjects to demonstrate its application as an intracoronary imaging tool.

Basic Principles of NIRS

Spectroscopy involves the measurement of the wavelength-dependent interaction of electromagnetic radiation with matter. In its application as an intracoronary imaging tool, near-infrared light is emitted on the atheroma in the vessel wall and its molecular interactions with the light are probed. NIRS has been used to assess the lipid content of plaques by identifying the presence of cholesterol monohydrate and cholesterol ester. This has been validated in histopathological studies [4] and in comparison to OCT [17]. There are several characteristics of NIRS that make it an attractive intracoronary imaging tool. It has the ability to penetrate blood and several millimeters into the tissue. It uses an ultrafast scanning laser to acquire thousands of spatial measurements required to create an image of an artery, thereby overcoming the problem of cardiac motion. The specific utility of NIRS in assessing lipid core plaque (LCP) stems from the fact that cholesterol has prominent features in the near-infrared region. This property helps differentiate cholesterol from other tissue constituents such as collagen [20••].

NIRS Catheter System

The first NIRS catheter system (Lipiscan™) was originally developed by InfraRedx Inc. (Burlington, MA, USA) for invasive detection of LCP. In order to provide multimodality imaging, a combined NIRS-IVUS catheter was subsequently developed (TVC Imaging System™, InfraRedx Inc.). This provides simultaneous, co-registered data with the two imaging modalities complementing each other. This NIRS-IVUS

Table 1 Summary of the prominent studies utilizing NIRS in human subjects to demonstrate its application as an intracoronary imaging tool

Application of NIRS	Study/authors/year	*N*	Study details	Conclusion
Prediction of periprocedural MI	COLOR Registry (subgroup); 2011 [11]	62	Association of presence of large LCP (maxLCBI (4 mm) ≥ 500) and occurrence of periprocedural MI were analyzed	Higher occurrence of periprocedural MI was noted during PCI of lesions with large LCP
	CANARY Trial; 2015 [10]	85	Multicenter study, used maxLCBI (4 mm) ≥ 600 as the cutoff to study the association of large LCP and periprocedural MI *Subgroup study of 31 randomized lesions also evaluated the utility of a distal protection filter to prevent periprocedural MI	Lipid-rich plaques identified by NIRS were associated with higher incidence of periprocedural MI. Use of a distal protection filter did not prevent periprocedural MI
	Raghunathan et al.; 2011 [18]	30	Angular extent of LCP, LCBI, and block chemogram were evaluated for association with periprocedural MI	Lipid-rich plaques identified by NIRS were associated with higher incidence of periprocedural MI
Identification of culprit lesion	Madder et al.; 2012 [9]	68	Composition of culprit lesions in ACS versus stable angina were evaluated by identifying LCP	ACS lesions were more often composed of LCP than lesions causing stable angina. However, a half of the lesions causing stable angina also contained LCP
	Madder et al.; 2016 [8]	75	NIRS was performed on lesions causing STEMI after establishment of flow but prior to stent placement	maxLCBI4mm ≥ 400 was established as a threshold to identify culprit lesions in STEMI (sensitivity 64%, specificity 85%)
	Madder et al.; 2015 [7]	81	NIRS was utilized to analyze lesions causing NSTEMI and unstable angina	NSTEMI culprit lesions had a 3.4-fold greater maxLCBI (4 mm) than non-culprits as opposed to unstable angina lesions which had a 2.6-fold higher maxLCBI (4 mm) than non-culprits
Detection of vulnerable plaque	Lipid Rich Plaque (LRP) Study; 2018 [12]	1563	NIRS-IVUS was used to evaluate plaque morphology. Patient- and plaque-level events were monitored for 2 years	At patient level, having maxLCBI (4 mm) ≥ 400 was associated with 87% higher risk of MACE at 2-year follow-up At plaque level, the risk of experiencing an event was 45% higher with each 100 unit increase in maxLCBI (4 mm)
Prognostication of coronary lesions	Oemrawsingh, R. M et al.; 2014 [19]	203	NIRS was performed in non-culprit coronary artery in patients referred for coronary angiography	Patients with LCBI ≥ the median of 43.0, as assessed by NIRS in a non-culprit artery, had a 4-fold risk of MACE during 1-year follow-up
	Schuurman, A. S et al.; 2018 [15]	275	NIRS was performed in non-culprit coronary artery in patients undergoing coronary angiography, median follow-up of 4.1 years	LCBI was associated with higher MACE in CAD patients independent of clinical risk factors and plaque burden during follow-up
	ORACLE-NIRS Registry; 2017 [16]	239	Data analysis of registry patients who underwent NIRS; median follow-up of 5.3 years	High LCBI in non-target vessel was associated with higher incidence of MACE
Demonstration of the effect of statins	YELLOW Trial; 2013 [13]	87	Patients with multivessel CAD undergoing PCI with at least 1 other obstructive lesion were randomized to either high-intensity (rosuvastatin 40 mg daily) or standard of care statin therapy	Greater reduction in lipid content (median LCBI (4 mm)) in obstructive plaque was achieved with high-intensity statin therapy at 7-week follow-up
	YELLOW II Trial; 2017 [14]	85	NIRS (maxLCBI (4 mm) > 150) was used to select lesions to demonstrate the plaque-stabilizing effect of high-intensity statin therapy	High-intensity statin therapy led to increase in fibrous cap thickness (demonstrated by OCT) and improved cholesterol efflux capacity which likely leads to plaque stabilization

system is similar in characteristics to a traditional IVUS catheter and is compatible with 6F guiding catheters with an entry profile of 2.4F and a shaft profile of 3.6F [20••]. The Dualpro™ IVUS+NIRS catheter and its accompanying Makoto™ Intravascular Imaging System are current state-of-the-art FDA-approved dual-modality catheter and imaging system indicated for the detection of LCP. This catheter acquires approximately 1300 NIRS spectra per millimeter of vessel scanned. The acquired NIRS signals are then analyzed and each spectrum is assigned a probability score from 0 to 1, depending on the presence of LCP. All probability scores are mapped on a continuous color scale from red to yellow [21]. A chemogram is a two-dimensional map of the vessel with its *x*-axis representing millimeters of pullback in the artery and the *y*-axis representing degrees of rotation (0° to 360°). A probability score is used to indicate the presence of LCP and is represented by a color scale from red to yellow. The "block chemogram" provides a summary of the results for each 2-mm section of artery. The color-coding scheme is as follows:

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

The lipid core burden index (LCBI) is used to provide a quantitative measure of the LCP present in the entire scanned segment of the artery. LCBI is calculated as the fraction of valid pixels within the scanned segment that exceed an LCP probability of 0.6, multiplied by 1000 [11].

Clinical Applications of NIRS

Prediction of Periprocedural Myocardial Infraction

Periprocedural MI complicates nearly 3 to 15% of all PCIs [22]. One of the most common causes of periprocedural MI is distal embolization of lipid-rich material from the target lesion during angioplasty and stenting, resulting in microvascular obstruction. Intraprocedurally, this can result in angiographic slow flow or no-reflow with resultant chest pain and EKG changes [11, 23]. In a subgroup of the COLOR (Chemometric Observation of Lipid Core Plaques of Interest in Native Coronary Arteries) registry, 62 patients undergoing coronary stenting were evaluated for periprocedural MI. A large lipid core plaque (defined as a maxLCBI (4 mm) ≥ 500) was present in 14 of 62 lesions. Periprocedural MI occurred in 7 of these 14 patients (50%) with a maxLCBI (4 mm) ≥ 500, compared with 2 of 48 patients (4.2%) with a lower maxLCBI (4 mm) ($P = 0.0002$) [11]. The CANARY (Coronary Assessment by NIR of Atherosclerotic Rupture-prone Yellow) study was a multicenter trial, which evaluated 85 patients with stable angina who underwent NIRS and IVUS to assess the lipid burden prior to PCI. Of the 21 patients who had periprocedural MI, maxLCBI (4 mm) was significantly higher compared to those who did not suffer periprocedural MI (481.5 versus 371.5, $P = 0.05$) [10]. Similar findings were reported in yet another study where creatine kinase-MB increase > 3 times the upper limit of normal was observed in 27% of patients with ≥ 1 yellow block versus in none of the patients without a yellow block within the stented lesion [18].

In an attempt to prevent periprocedural MI, NIRS has been used to identify lesions with large LCPs for the potential use of embolic protection devices. Brilakis et al. reported that use of embolic protection devices frequently resulted in embolized material retrieval after stenting of native coronary artery lesions with large LCPs [24]. However, in a subgroup of the CANARY study undertaken in 31 randomized lesions with maxLCBI (4 mm) ≥ 600, there was no difference in the rates of periprocedural MI irrespective of the use of a distal protection filter, although the modest sample may have made the study underpowered to detect small effect sizes [10].

Guiding PCI Procedure

Intracoronary imaging with NIRS has also been shown to detect the presence of significant atheroma beyond the length of the target lesion identified by angiography. Dixon et al. in their analysis of 75 lesions reported that LCP extended beyond the margin of angiographically defined target lesion in 16% of cases [25]. However, when NIRS-IVUS dual-modality imaging was used in addition to angiography, atheroma (defined as the presence of LCP by NIRS or a plaque burden of > 40% by IVUS) extending beyond the margin of angiographically defined target lesion was reported in 90% of cases [26]. In this study, LCP extending beyond the angiographic margin was found in 52% of the lesions. NIRS-IVUS guidance during PCI will help land the stent edge in a relatively healthy segment of the artery, thereby potentially preventing stent edge dissections and future adverse clinical outcomes [27•].

Identification of Culprit Lesion in Acute Coronary Syndrome

Studies utilizing NIRS have demonstrated that high lipid burden exists in plaques that result in acute coronary syndromes [6–9]. A study by Madder et al. evaluated the composition of culprit lesions in ACS versus stable angina by identifying LCP. LCPs were defined as a 2-mm segment on the NIRS block chemogram having a strongly positive reading denoted by a bright-yellow color. They reported that while culprit lesions in patients with ACS were more often composed of LCP than culprits in patients with stable angina (84.4% versus 52.8%, $P = 0.004$), approximately one half of culprit lesions in patients with stable angina also contained LCP [9]. A study

of 20 patients who presented with STEMI demonstrated in vivo that a maxLCBI (4 mm) > 400, as detected by NIRS, was characteristic of the culprit ruptured plaques that contributed to STEMI [6]. These findings were later confirmed in a larger study of 75 patients who were enrolled at two centers in the USA and Sweden. These patients underwent NIRS intracoronary imaging after establishment of thrombolysis in myocardial infarction 3 flow but before stent deployment. The culprit segment was defined as the 10-mm segment distal to the proximal angiographic culprit margin. The remainder of the vessel was divided into contiguous 10-mm non-culprit segments. The maxLCBI (4 mm) of culprit segments was 4.4-fold greater than non-culprit segments ($P < 0.001$). The study validated the ability of NIRS to accurately differentiate STEMI culprit from non-culprit segments and confirmed the threshold of maxLCBI (4 mm) ≥ 400 to be a predictor of STEMI lesion [8]. Similarly, large lipid cores have also been reported in plaques causing NSTEMI and unstable angina. In a study including 81 patients, NSTEMI culprit lesions had a 3.4-fold greater maxLCBI (4 mm) than non-culprits ($P < 0.001$) and unstable angina lesions had a 2.6-fold higher maxLCBI (4 mm) than non-culprits ($P < 0.001$). NIRS detected a maxLCBI (4 mm) ≥ 400 in 63.6% of culprit lesions in NSTEMI and in 38.5% of culprit lesions in unstable angina [7]. Figure 2 depicts the NIRS findings in various types of ACS presentations.

Detection of Vulnerable Plaque

Retrospective autopsy studies of patients who suffered fatal myocardial infarction have been used to derive information on the histopathologic characteristics of culprit lesions [28]. The presence of a large necrotic core with either a non-existent cap or a thin fibrous cap (< 65 μm) and enzymatically active macrophages near the fibrous cap has been described as the characteristic histopathologic appearance of "vulnerable plaques" [28, 29]. Figure 3 depicts the correlation between NIRS imaging and histopathologic findings in a coronary artery by autopsy of a patient who suffered fatal myocardial infarction. In a prospective animal study, intracoronary imaging with NIRS and IVUS has been used to elucidate the characteristics and predict future development of unstable fibroatheromas as confirmed by subsequent histopathologic data. Histology confirmed that NIRS-positive lesions (yellow, tan, or orange coregistered chemograms) were significantly more likely to be a high-risk fibroatheroma containing larger plaque and necrotic core areas and thinner fibrous caps. Additionally, NIRS positivity also correlated with a higher concentration of inflammatory cells exhibiting protease activity as well as proliferating and apoptotic cells within the fibrous cap [30].

As described above, several human in vivo studies have demonstrated that culprit lesions causing ACS have a lipid-rich core as defined by a maxLCBI (4 mm) ≥ 400 [7, 8]. The LRP (Lipid Rich Plaque) Study evaluated the role of NIRS in identifying vulnerable plaque. This study enrolled 1563 patients from 44 centers in the USA and Europe with suspected CAD who underwent cardiac catheterization with PCI [12]. Intracoronary imaging with NIRS-IVUS was performed in two or more arteries and patient- and plaque-level events were monitored for 2 years. Patient-level analysis after adjustment revealed that the risk of experiencing non-culprit major adverse cardiovascular events within 24 months was 18% higher with each 100 unit increase in maxLCBI (4 mm). Specifically, a patient with maxLCBI (4 mm) > 400 was at 87% higher risk than a patient with < 400 maxLCBI (4 mm). With respect to vulnerable plaque-level analysis, the risk of experiencing an event in a coronary segment within 24 months was 45% higher with each 100 unit increase in maxLCBI (4 mm).

Prognostication of Coronary Lesions

Data obtained from NIRS imaging of coronary lesions has been shown to predict cardiovascular outcomes. In a prospective, observational study of 203 patients who underwent coronary angiogram for stable angina or ACS, NIRS was performed in the non-culprit coronary artery and found that at 1 year follow-up, patients with an LCBI equal to or above the median in a non-culprit coronary artery were at a 4-fold higher risk of adverse cardiovascular events [19]. Similarly, a recent study by Schuurman et al. also evaluated LCBI as a prognostic indicator in 275 patients during a median follow-up of 4.1 years. The study revealed a statistically significant and independent continuous relationship between higher maxLCBI (4 mm) values and a higher risk of MACE. Each 100 unit increase of maxLCBI (4 mm) was associated with a 19% increase in MACE. Even after exclusion of target lesion-related events and exclusion of adverse events related to the NIRS-imaged coronary segment, continuous maxLCBI (4 mm) remained independently associated with MACE [15]. The ORACLE-NIRS registry analyzed outcomes in 239 patients who presented with stable angina and ACS. In this cohort of patients, non-target vessel LCBI of 77 was determined using receiver operating characteristic curve analysis to be a threshold for prediction of MACE. The adjusted hazard ratio for non-target vessel LCBI ≥ 77 was 14.05 (95% confidence interval 2.47–133.51, $P = 0.002$). The 5-year cumulative incidence of events in the above-threshold group was 58.0% versus 13.1% in the below-threshold group. The investigators concluded that at long-term

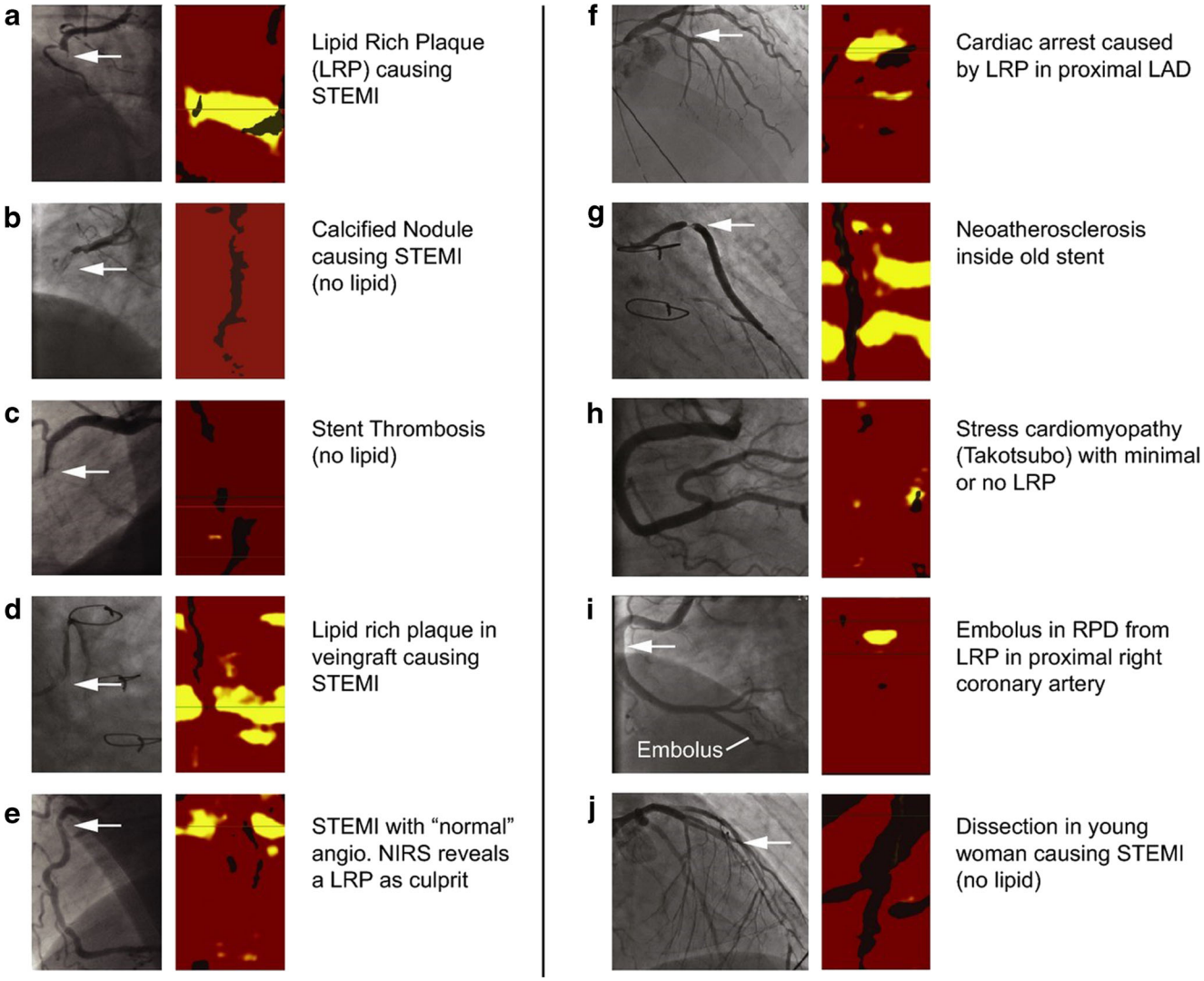

Fig. 2 Cases demonstrating the ability of near-infrared spectroscopy combined with intravascular ultrasound (NIRS-IVUS) to identify the culprit plaque and to discriminate between different causes of ACS. **a** A typical case of ST-elevation myocardial infarction (STEMI) with a circular lipid-rich plaque (LPR) in the proximal right coronary artery causing thrombotic occlusion. **b** A calcified nodule causing STEMI (approximately 5% of STEMI cases). No lipid is detected at the culprit segment. **c** A stent thrombosis caused by an under-expanded stent. This is a purely thrombotic occlusion, and as expected, the NIRS-IVUS chemogram is red (no LRP). **d** A STEMI caused by neoatherosclerosis in a vein graft with a circular LRP with a high maximum lipid core burden index demonstrating novel lipid accumulation in the graft. **e** An inferior STEMI with typical acute chest pain that disappeared during transport to the percutaneous coronary intervention center. Normal angiography, but a circular ulcerated plaque rich in lipid was detected in the proximal right coronary artery (RCA), which probably caused a thrombotic occlusion that was later dissolved by spontaneous thrombolysis. **f** A patient with cardiac arrest and STEMI with normal angiogram but LRP in the proximal left anterior descending artery (LAD), which may explain his cardiac arrest. **g** Stent neoatherosclerosis causing restenosis and non-ST-elevation myocardial infarction. **h** A case of Takotsubo cardiomyopathy. As expected, no major LRPs are detected. **i** An embolic thrombus was detected in RPD and PLA and aspirated with no residual stenosis. NIRS-IVUS revealed LRP in the proximal RCA as the probable source of the embolus. **j** A 36-year-old woman with a dissection of the LAD. As expected, no LRP was detected (reprinted from Erlinge [27] with permission from Wiley)

follow-up, high LCBI in a non-PCI target vessel was associated with a higher incidence of MACE [16].

Demonstration of the Effect of Statins

NIRS has been used to demonstrate the beneficial effect of statins in terms of reduction of free and esterified cholesterol within atheromatous plaque. The YELLOW trial by Kini et al. enrolled patients with multivessel CAD undergoing PCI. A baseline assessment was performed using NIRS and IVUS imaging and patients were randomized to a treatment of either rosuvastatin 40 mg daily or the standard-of-care lipid-lowering therapy. After 6 to 8 weeks of intensive statin therapy, a significant

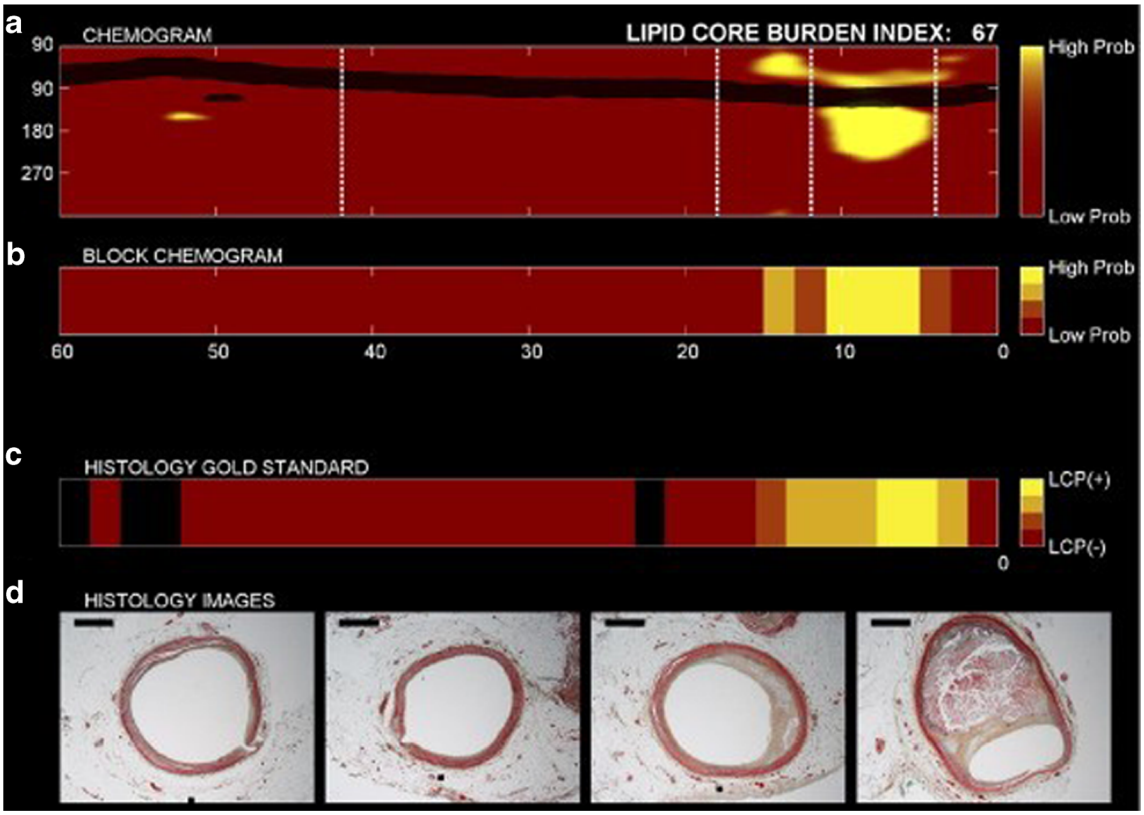

Fig. 3 A NIRS scan correlates well with histologic findings in coronary artery from an 85-year-old male with a history of MI. **a** Chemogram image indicating artery wall lipid content (*x*-axis = pullback in millimeters; *y*-axis = rotation in degrees). Each pixel is marked with red for low probability and yellow for high probability of lipid core plaque of interest (LCP). The lipid core burden index (top right) indicates amount of lipid in scanned artery on a 0 to 1000 scale. **b** Summary (block chemogram) of LCP presence at 2-mm intervals in 4 probability categories. **c** Map of histologic classifications (yellow = LCP; light orange = small or thick-capped fibroatheroma; dark orange = intimal xanthoma and pathologic intimal thickening; red = all other types). **d** Movat cross-sections from locations along the artery (dotted lines). Black bars denote 1 mm. Image interpretation: the chemogram shows prominent lipid core signal at 2 to 16 mm, occupying 180°. The block chemogram shows that the strongest LCP signals extend 5 to 11 mm. The NIRS signals at 18 and 42 mm correctly indicate absence of LCP (reprinted from Gardner et al. [4] with permission from Elsevier)

reduction in the plaque lipid content was demonstrated by NIRS [13]. In the YELLOW II Trial, NIRS was used to select lesions (maxLCBI (4 mm) > 150) to demonstrate the plaque stabilization afforded by high-intensity statin therapy utilizing optical coherence tomography imaging [14].

Conclusions

The different modalities of intracoronary imaging have their own relative merits and limitations. While OCT provides high-definition imaging of vessel wall and plaque morphology, NIRS by itself only assesses lipid content. The combined NIRS-IVUS system overcomes this limitation and the two modalities act complementary to each other. Assessment of lipid burden in coronary atherosclerotic plaques by utilizing NIRS has several clinical implications. For example, the ability of NIRS to predict distal embolization and intraprocedural MI in lesions with high lipid burden may guide decisions during PCI. Given that embolic protection devices have not shown clear benefit at this point [10], the operator may choose other strategies such as direct stenting and preemptive use of coronary vasodilators to prepare the distal vascular bed in an attempt to minimize distal embolization and prevent no-reflow phenomenon. Additionally, stenting "red to red" based on NIRS to cover the entire length of the lipid plaque may potentially prevent stent edge dissection and improve short- and long-term outcomes [27]. The information obtained from NIRS imaging in the YELLOW Trials [13, 14] underscores the importance of high-intensity statin therapy in patients with known coronary artery disease. Lastly, the ability of NIRS to detect vulnerable plaques and predict prognosis of coronary lesions opens up promising new frontiers for secondary prevention of adverse cardiac events.

Compliance with Ethical Standards

Conflict of Interest All authors have no conflict of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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