Nonangiographic assessment of coronary artery disease: a practical approach to optical coherence tomography and fractional flow reserve

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In an era of increased scrutiny of the appropriateness and safety of revascularization, interventional cardiologists must evolve by adding key tools to their armamentarium. This review highlights the utility of optical coherence tomography and fractional flow reserve in the catheterization lab and provides a practical guide for using these technologies during coronary intervention in various lesion subsets. We propose that fractional flow reserve informs the decision to intervene and optical coherence tomography guides the optimization of the outcome. ***Coron Artery Dis*** **25:608–618 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The modern era has seen improved diagnostic technology, adjunctive medical therapy, and safer revascularization procedures. Although intravascular ultrasonography (IVUS) has overcome many shortcomings of angiography, it is being surpassed by optical coherence tomography (OCT), which offers detail that was previously only possible with histopathologic evaluation. Fractional flow reserve (FFR) allows physiologic evaluation of potentially flow-limiting lesions. In an era of increased scrutiny of the appropriateness and safety of revascularization, interventional cardiologists must evolve by adding key tools to their armamentarium. This review highlights the importance of OCT and FFR in specific lesion subsets (Table 1) and provides a practical guide for the use of these techniques during percutaneous coronary intervention (PCI). We propose that FFR informs the decision to intervene and OCT guides the optimization of the outcome.

Fractional flow reserve

FFR, an index of physiological significance, is the ratio of the maximal myocardial blood flow in the presence of a stenosis to the maximal flow in a normal artery [1]. It is measured during coronary angiography by measuring the ratio of coronary pressure distal to a stenosis to aortic pressure in the guiding catheter using a pressure wire during adenosine-induced steady-state maximal hyperemia. FFR readings of 0.80 or lower identify potential ischemia-inducing lesions with sensitivity and specificity greater than 90% [2]. The ratio between FFR and ischemia is better validated than any previous test [1,3]. FFR-guided PCI carries a class 1 recommendation in European guidelines [4] and a class 2a recommendation in the US guidelines [5]. Similarly, current appropriate use criteria for coronary revascularization designate an FFR of 0.80 or lower in single-vessel or double-vessel coronary disease excluding proximal left anterior descending (LAD) as 'appropriate' [6] (Table 2).

Single stenosis

The greatest impact of FFR has been on intermediate, stable coronary lesions. Clinical event rates less than 10% for medically treated intermediate coronary stenoses have been documented for lesions without an ischemic FFR [3,7,8]. In cases of single-vessel disease with hemodynamically significant lesions, FFR not only supports the decision to perform PCI, but can assess the adequacy of stent deployment. Following PCI, an FFR greater than 0.94 has 91% concordance with IVUS in verification of optimal stent apposition and deployment [9].

FFR is performed following systemic anticoagulation and calibration of the pressure wire. If hemodynamics allow, 100–200 μg of intracoronary nitroglycerine is administered (alternatively, papaverine, adenosine 5′-triphosphate, or nicorandil). The wire is advanced to the tip of the guiding catheter, where equalization of aortic and pressure wire measurements is confirmed; it is then advanced into the coronary artery until the pressure sensor is located as far distal in the target vessel as possible. Adenosine is infused at 140 μg/kg/min for more than 2 min through central or peripheral venous access (intracoronary bolus dosing also available) before steady-state hyperemia is achieved, allowing for FFR calculation (Fig. 1).

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Table 1 Usefulness of FFR and OCT in various lesion subsets

Type of lesion	FFR	OCT
Moderate stable stenosis	Useful to decide whether physiologically significant	Useful to assess lesion characteristics, vessel sizing, and poststent assessment
Severe stable stenosis	Useful to decide whether physiologically significant	Useful to assess lesion characteristics, vessel sizing, and poststent assessment
Aorto-ostial coronary stenosis	Useful to decide whether physiologically significant (ensure guiding catheter does not dampen waveform)	Limited utility in ostial lesions (difficulty opacifying vessel)
Left main stenosis	Useful to decide whether physiologically significant (ensure guiding catheter does not dampen waveform)	Limited utility in ostial lesions (difficulty opacifying vessel). May be useful to assess lesion characteristics, vessel sizing, and poststent assessment
Bifurcation lesions	Can be useful to decide whether bifurcation intervention is required or whether a simpler provisional strategy may be used	Useful to assess lesion characteristics, vessel sizing, and poststent assessment
Coronary dissections	Not indicated	Useful to assess length of dissection to ensure that the proximal dissection flap is covered with stent
Acute coronary syndromes	Not indicated	Useful to assess lesion characteristics, vessel sizing, and poststent assessment
Stent thrombosis	Not indicated	Useful to assess mechanism of stent thrombosis and subsequent repeat intervention planning/assessment

FFR, fractional flow reserve; OCT, optical coherence tomography.

Table 2 Summary of ischemia-guided recommendations for using FFR in appropriate use criteria for coronary revascularization[a]

	Asymptomatic		CCS I or II		CCS III or IV	
	FFR ≤ 0.80	FFR > 0.80	FFR ≤ 0.80	FFR > 0.80	FFR ≤ 0.80	FFR > 0.80
One or two vessel borderline 50–60% CAD, excluding proximal LAD	Inappropriate	Inappropriate	Uncertain	Inappropriate	Appropriate	Inappropriate

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; FFR, fractional flow reserve; LAD, left anterior descending.
[a]The majority of the recommendations in the appropriate use criteria for coronary revascularization include noninvasive assessment of ischemia. This table represents those recommendations that include the use of fractional flow reserve to guide ischemia-driven revascularization.

Serial stenoses

Diffuse coronary atherosclerosis with consecutive lesions along the same artery is common. The FFR equation remains accurate for evaluating the significance of both stenoses, provided no large intervening arterial branches are present. Predicting the hemodynamic significance of each individual stenosis was addressed by De Bruyne *et al.* [2], and it is calculated using equations seldom used in daily practice. For two or more stenoses, it is common to identify the stenosis associated with the largest pressure drop on wire pullback (Fig. 2). After stenting of the most significant lesion identified, repeating the FFR with maximal hyperemia reveals residual pressure gradients attributed to the other lesion.

Multivessel disease

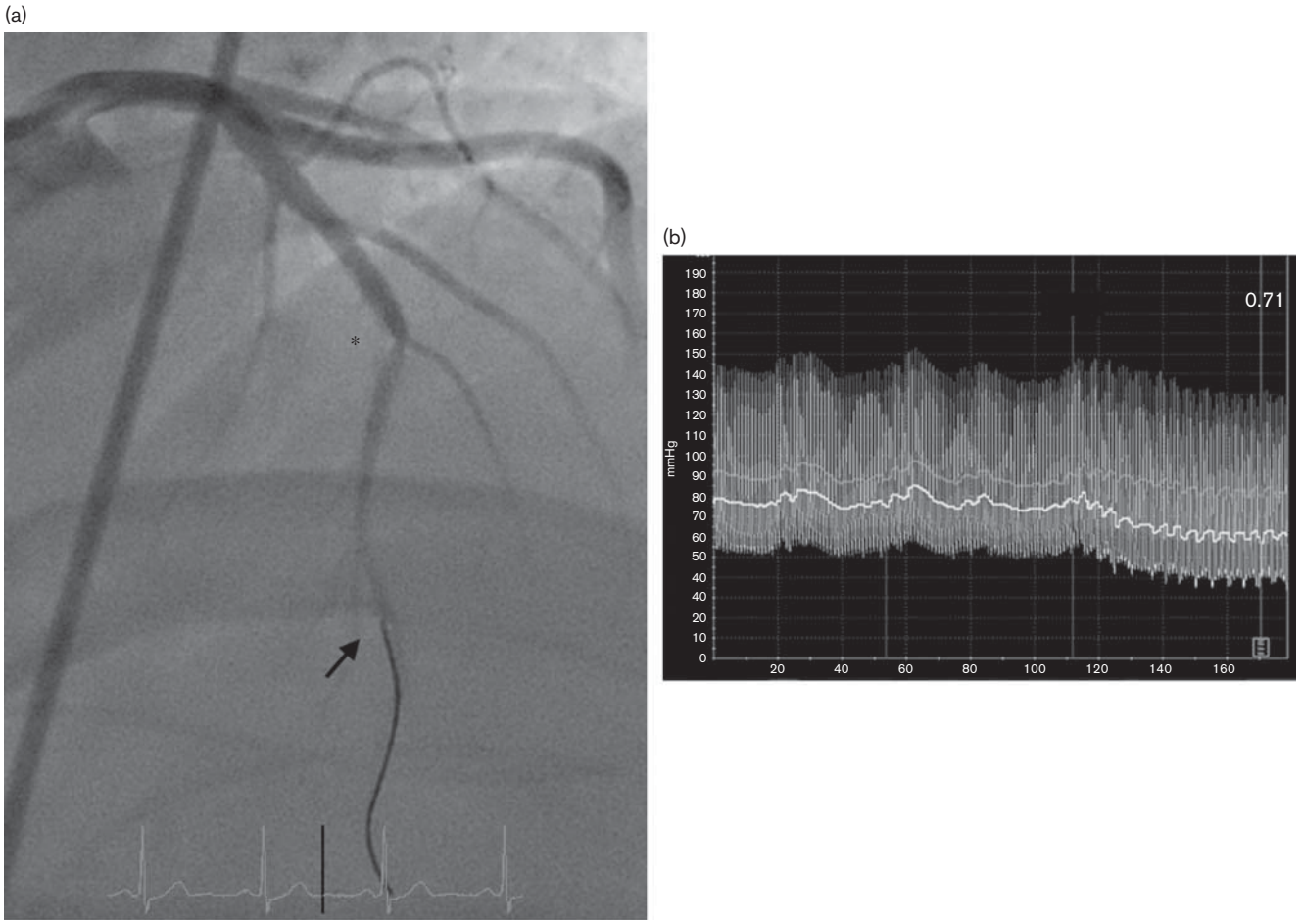
The Fractional Flow Reserve (FFR)-Guided Percutaneous Coronary Intervention Plus Optical Medical Treatment vs. Optical Medical Treatment Alone in Patients with Stable Coronary Artery Disease (FAME 1) trial illustrates the benefit of FFR-guided intervention over angiography-guided for multivessel coronary artery disease [8,10]. This multicenter trial demonstrated increased numbers of stents deployed and a higher contrast use for angiography-guided compared with FFR-guided groups. Major adverse cardiac event (MACE) rates at 1 year favored FFR-guided intervention (22.4% in the angiography group and 17.9% in the FFR group), as did all-cause mortality rates (3.8 and 2.6%, respectively). At the 2-year follow-up, the fate of the lesions deferred due to FFR greater than 0.80 were benign (0.2% presented as myocardial infarction). The advantage of FFR-guided PCI is explained by the selection of ischemic stenoses (FFR ≤ 0.80) in which the benefit of alleviating coronary ischemia outweighs the potential risk for drug-eluting stent (DES) thrombosis or restenosis. These data support revascularization strategies for stable ischemic coronary stenoses and medical management of nonischemic stable lesions.

The benefit of PCI for stable coronary disease was questioned in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which randomized patients to PCI plus optimal medical therapy (OMT) versus OMT alone and demonstrated no difference in MACEs at the 4.6-year follow-up [11]. De Bruyne and colleagues addressed this in FAME 2 by randomizing patients with functionally significant lesions for ischemia (FFR ≤ 0.80) to PCI plus OMT versus OMT alone. Recruitment was halted early because of significant differences in the composite endpoint of death, myocardial infarction and urgent revascularization, driven by lower rates of urgent revascularization in the PCI group (1.6 vs. 11.1%) at a mean follow-up of ~7 months [12].

Left main disease

Evaluating FFR of the left main coronary artery (LMCA) is similar to evaluating other territories except that the guiding catheter should be withdrawn from the coronary ostium to facilitate hyperemic blood flow and prevent dampening of the waveform. Given the risk for hypotension, guide dampening, or inaccurate delivery of adenosine

Fig. 1



Single lesion evaluated by FFR. (a) Angiogram showing the pressure sensor (arrow) distal to the lesion (star). (b) A tracing showing the FFR value for the lesion in question. FFR, fractional flow reserve.

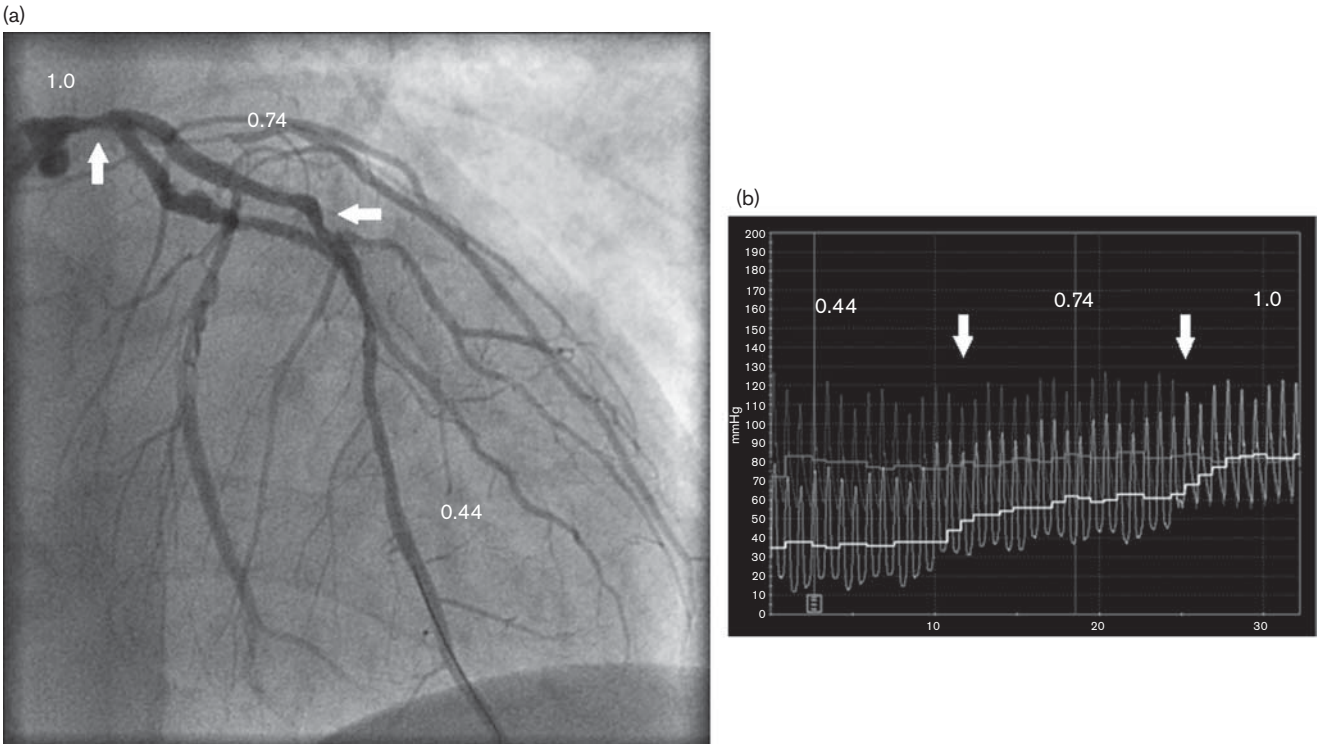
in the LMCA with intracoronary adenosine, central or peripheral infusion should be used.

Visual estimation of the angiographic severity of the LMCA is often under-reported or over-reported compared with FFR. Hamilos and colleagues examined the outcome of FFR-guided revascularization of the LMCA by recording quantitative angiographic and FFR data on all LMCA lesions. The long-term clinical outcome in patients for whom coronary artery bypass graft (CABG) surgery was deferred on the basis of FFR values greater than 0.80 was favorable and similar to that in patients undergoing CABG for physiologically significant stenosis, with an FFR of 0.80 or less. The 5-year survival estimates were 89.8% in the medically managed group and 85.4% in the group undergoing CABG ($P = 0.48$). Alarmingly, when visual estimation of angiographic severity of LMCA disease was reported in this study, 23% of LMCAs with angiographic stenosis of 50% or lower had a significant FFR of less than 0.80, whereas 6% of cases with angiographic stenosis greater than 50% had an FFR of 0.80 or higher. Incorrect decision-making in up to a third of the LMCA cases could thus arise if angiographic criteria alone were applied [13].

Good correlation exists between IVUS and FFR in the LMCA. A minimal luminal diameter of 2.8 mm and a minimal luminal area (MLA) of less than 6.0 mm^2 on IVUS predicts physiologically significant LMCA stenosis by FFR [14]. In one study, an MLA of 4.8 mm^2 was a predictor of ischemic FFR, although the population in that study had smaller coronary arteries at baseline [15]. A multicenter, prospective trial confirmed that MLA greater than 6.0 mm^2 confers excellent prognosis without revascularization, suggesting that FFR greater than 0.80 or MLA greater than 6.0 mm^2 identifies patients who do not require revascularization [16].

Coronary artery disease is a diffuse condition – that is, the LMCA lesion seldom exists in isolation. The flow across the LMCA depends on the outflow to the LAD or the left circumflex (LCx). In-vitro and sheep models demonstrate

Fig. 2



Tandem lesions evaluated by FFR. (a) Angiogram showing the FFR value at each point along the left anterior descending artery. (b) A tracing showing the FFR value at each point during wire pullback. Arrows indicate the point of step-up during wire pullback. FFR, fractional flow reserve.

that in the setting of intermediate LMCA and downstream disease involving the LAD or LCx, FFR in the non-diseased limb of the bifurcation is not significantly affected until the FFR of the composite of LMCA and downstream disease in the diseased limb become severe (FFR < 0.65) [17,18]. Although these models suggest that left main (LM) FFR is reliable in the absence of severe and proximal downstream stenoses, IVUS/OCT measurement may be considered to confirm FFR findings.

In the drug-eluting stent era, LMCA intervention has been proven to be safe and offers enduring relief from symptoms of coronary ischemia, with a low rate of target vessel revascularization, particularly in disease of the ostium and the body of the LM [19]. Significant debate still rages on the best strategy for treating distal LM disease. FFR has a role in simplifying LM intervention in cases in which a single stent strategy is adopted. If the side branch of the bifurcation is free from disease or compromise on stenting across it and high-pressure postdilatation is uneventful, FFR can be repeated into the side branch and if negative, then no further intervention is warranted for the bifurcation [20].

Bifurcation intervention

Disease in the side-branch ostium before intervention is a predictor of functionally significant stenosis by FFR after stenting the main vessel; however, in one study, only 17.8% of side branches had functional significance requiring treatment, and only 13.5% of side branches had FFR less than 0.80 following provisional stenting [20]. It is reasonable to avoid side-branch PCI provided TIMI 3 flow is maintained. FFR measurement can be considered when the side branch subtends large regions of the jeopardized myocardium. Adjunctive invasive coronary imaging can also be utilized in this setting to predict side-branch compromise following bifurcation stenting and the need for final kissing balloon dilatation. An IVUS run of the side branch identifying significant ostial disease (MLA < 2.4 mm^2) can predict those cases that are likely to develop a significant obstruction (FFR < 0.8) following stent deployment and require postdilatation [21,22].

Nonculprit lesions in acute coronary syndrome

FFR evaluation is not indicated for culprit lesions in ST-segment elevation myocardial infarction (STEMI) but can be performed to evaluate nonculprit lesions on completion of the intervention of the culprit lesion. Ntalianis *et al.* [23] also dispelled the concern that microvascular dysfunction during acute coronary syndrome (ACS) in the nonculprit vessel impacts the accuracy of FFR. Therefore, nonculprit stenoses with an FFR less than 0.80 can be subjected to staged PCI.

Other lesion subsets

In addition to the severity and length of coronary stenoses, FFR is dependent on the extent of viable myocardium perfused. For the same percent stenosis, LAD lesions are more likely than a right coronary artery or LCx lesion to have an ischemic FFR [15]. As a result, even a modest stenosis in a donor artery providing collaterals to a chronically occluded arterial territory may have an ischemic FFR (≤ 0.8) and may normalize on recanalization of the chronic total occlusion [24].

Areas with insufficient data

FFR-guided CABG is associated with decreased numbers of graft anastamoses and rates of on-pump surgery compared with angiography-guided CABG, with no difference in MACE rates [25]. In a study evaluating the use of FFR-guided PCI in 223 patients with intermediate arterial and venous bypass graft stenoses, FFR-guided PCI was found to be associated with a significantly reduced primary endpoint of MACEs compared with angiographic-guided PCI [26]. Moreover, the FFR-guided strategy was associated with a lower total procedure cost. The findings of these two retrospective studies are encouraging; however, they will need to be confirmed prospectively.

There are few data supporting the use of FFR for evaluating culprit lesions in ACS. FFR is a diagnostic tool for physiologic assessment and does not provide information on plaque morphology, composition, vulnerability, local thrombogenicity, or shear stress.

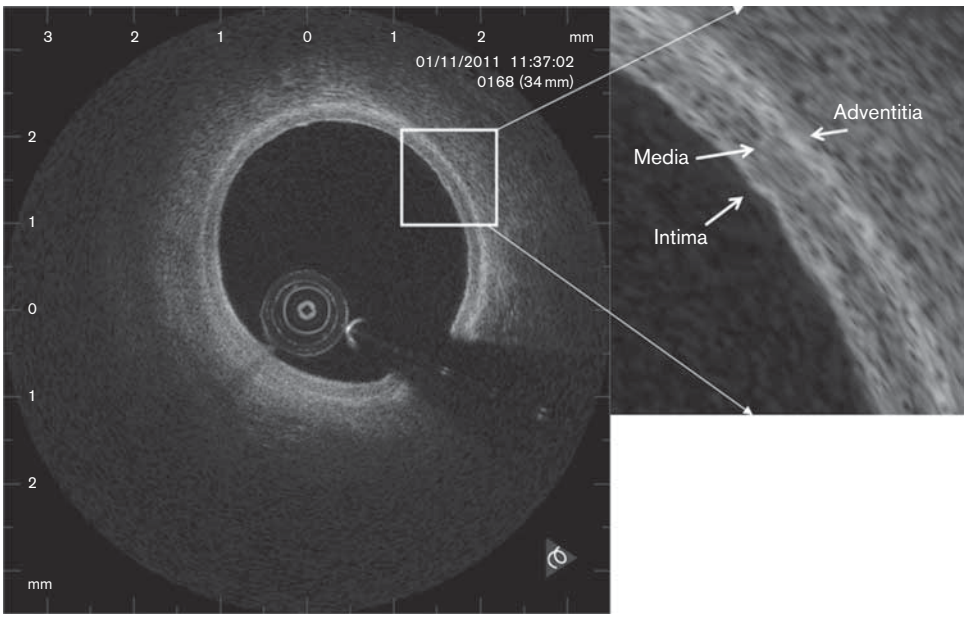
Optical coherence tomography

OCT is an imaging modality that creates high-resolution cross-sectional images based on measurement of reflection time and intensity of backscattered light [27]. Intravascular OCT uses light in the near infrared range and has an axial resolution of 10–15 μm and a lateral resolution of 20 μm, allowing detailed analysis of arterial wall and plaque characteristics. Light originating from the OCT system is split so that a portion travels to the patient through the catheter and the other portion travels a reference distance. A pattern of high and low intensities is detected and analyzed by the OCT system to determine the amount of backscattering, allowing the creation of an image.

Two main types of OCT systems exist: time domain and Fourier domain (frequency domain). Frequency domain is the most widely adopted, with advantages in imaging speeds and ease of use. OCT systems have evolved from requiring occlusion of the proximal vessel to rapid pullback during nonocclusive flushing of the vessel in modern systems. We will refer only to the frequency domain in this review.

Current OCT systems in the USA are produced by St. Jude Medical (Minneapolis, Minnesota, USA). The imaging catheter is a rapid exchange monorail system compatible with 0.014" coronary guide wires and 6F systems. To prepare the system, the imaging catheter is connected to the automated pullback device using the sterile technique. The catheter's inner lumen is flushed

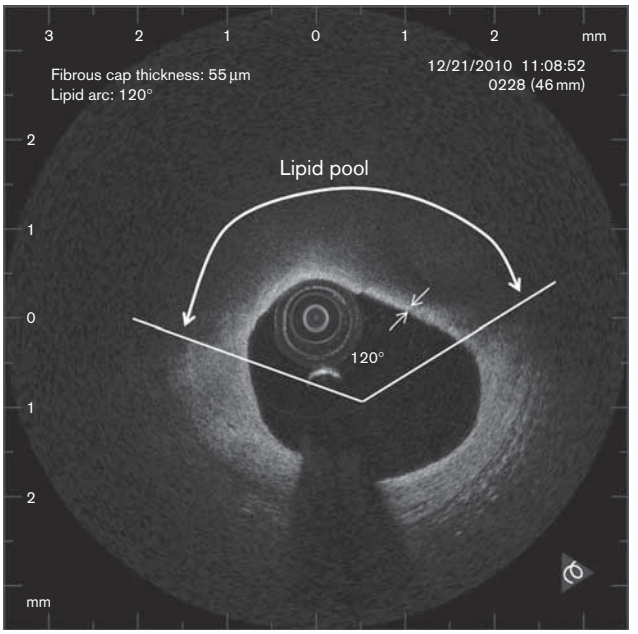
Fig. 3



OCT of a normal coronary artery. Normal vessel wall by OCT. Inlay, three layers of a normal vessel wall: intima (signal rich), media (signal poor), and adventitia (signal rich). OCT, optical coherence tomography.

with undiluted radiopaque contrast. Once the system is calibrated, the catheter is loaded onto the coronary guide wire and advance into the vessel. The imaging portion (prism) is located behind the middle of three radiopaque markers. The middle and most proximal marker identify the 50-mm segment of the artery imaged at 20 mm/s for 2.5 s. After positioning, the catheter may need to be flushed with contrast again and the guiding catheter should be properly seated in the vessel to optimize clearance of blood and image quality. The system is enabled, followed by coronary injection with contrast using a power injector (14 ml at 4 ml/s with 300 psi). Blood is cleared from the lumen, triggering the automatic pullback mechanism. Hand injections may be administered; however, the images may suffer if the vessel is not completely opacified. Dextran may be substituted for contrast if needed [28]. Terumo has launched a new system in Japan and Europe that is not yet available in the USA. It should be noted that OCT does not carry any recommendation in American PCI guidelines [5] or appropriate use criteria [6] and is only mentioned as a research tool in the European guidelines [4].

Fig. 4



Thin-cap fibroatheroma by OCT. Evaluation of thin-cap fibroatheroma: lipid pool with low signal, rapid attenuation (curved arrow), and thin fibrous cap (signal rich area between arrows, 55 µm). OCT, optical coherence tomography.

Evaluation of atherosclerosis

OCT has 10 times the resolution of IVUS, providing an unprecedented level of detail [29]. In addition to calculating vessel size, lesion severity, and lesion length, OCT allows for lesion characterization at a level close to that on histologic examination [30]. Evaluation of a normal vessel reveals a three-layer structure, shown in Fig. 3. The thickness of a normal intima is ~4 µm, which is beyond the resolution of OCT. However, it increases with age, and most adult coronary arteries show intimal thickening. The media is depicted as a dark band delimited by the internal and external lamina, with a thickness ranging from 125 to 350 µm, visualized clearly by OCT. The adventitia is a bright layer outside the media.

OCT identifies the histologic features of a vulnerable plaque: a thin fibrous cap overlying a large lipid pool, with/without macrophage accumulation. It is the only imaging modality with adequate resolution to measure the thickness of a fibrous cap (< 65 µm) associated with the thin-cap fibroatheroma (Fig. 4), an in-vivo equivalent of a vulnerable plaque [31]. In addition to plaque characterization (lipid, fibrous, and fibrocalcific plaques) [30, 32], other microstructures such as macrophages (20–30 µm), microvessels, and cholesterol crystals have been described [33,34].

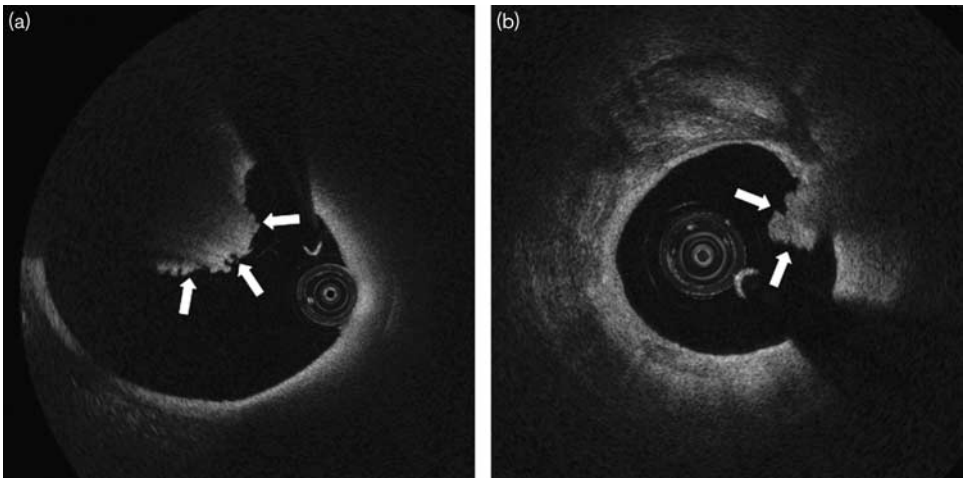
Lipid-rich plaques (defined by lipids occupying two or more quadrants of the cross-sectional area) were observed in 90% of patients with STEMI, 75% of patients with non-STEMI or unstable angina, and 59% of patients with stable angina. Interestingly, the fibrous cap was thinner in ACS as compared with stable angina [35]. In addition, OCT can differentiate between an erythrocyte-rich thrombus and a platelet-rich thrombus (Fig. 5) with high sensitivity and specificity by measuring light attenuation within tissue [36].

Preintervention lesion assessment

Pre-PCI OCT assessment informs decisions on adjunctive therapies, stent sizing, and inflation protocols. A high thrombus burden may influence adjunctive pharmacotherapy, such as the use of glycoprotein IIb/IIIa inhibitors or newer P2Y12 antagonists with more rapid onset of action [37,38], and mechanical thrombectomy [39]. High calcium burden could impact the need for rotational atherectomy. Similar to IVUS, OCT is useful in estimating vessel size, severity of stenosis, and lesion length (Fig. 6). Clear visualization of side branches helps facilitate lesion preparation and stent positioning.

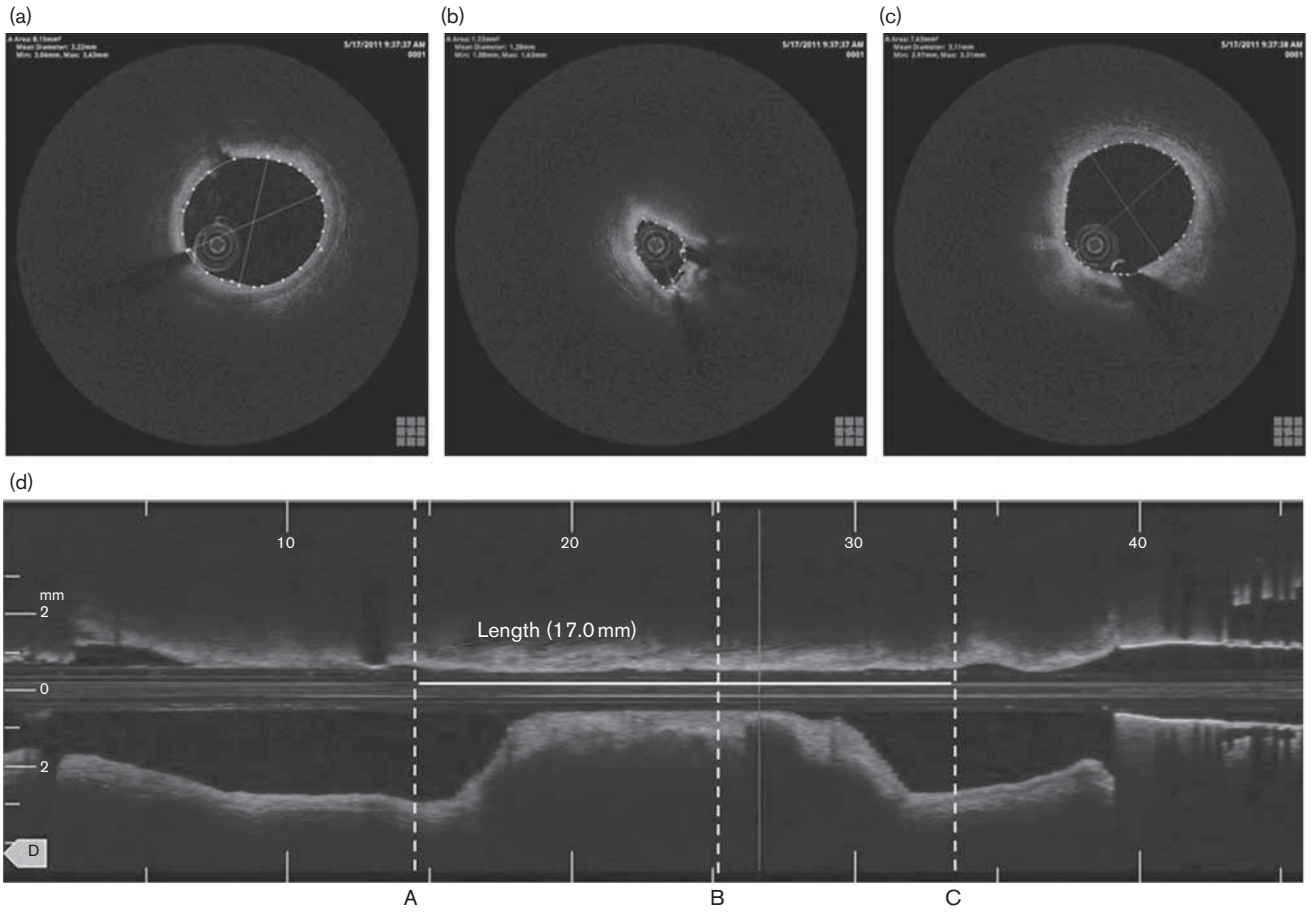
OCT assessment of lesion characteristics guides lesion preparation and stent deployment. Fibrous plaques have the lowest risk for post-PCI dissection, whereas lipid and calcific plaques are associated with higher risks [40]. Fibrocalcific tissue is most associated with stent edge dissection, followed by lipid-rich tissue [41]. Lipid arc size has been identified as an independent predictor of no-reflow after stenting in non-STEMI [42]. In addition, thin-cap fibroatheroma and intrastent thrombus have been associated with higher incidence of periprocedural myocardial infarction [43]. This type of lesion-specific prognostic information was not available previously and may have implications in the stent deployment

Fig. 5



Evaluation of thrombus using OCT. (a) Red thrombus: high attenuation of light, poor tissue penetration/visualization behind thrombus. (b) White thrombus: low attenuation of light, strong tissue penetration. OCT, optical coherence tomography.

Fig. 6



OCT to determine stent size. (a) Distal reference diameter (3.2 mm), (b) lesion minimal lumen area, (c) proximal reference diameter (3.2 mm), (d) lesion length (17 mm). Stent deployed (3.00 × 18 mm), postdilation (3.25-mm balloon). OCT, optical coherence tomography.

strategy: higher-risk lesions might be best treated at lower inflation pressures, whereas lower-risk lesions could be safely treated with high pressures.

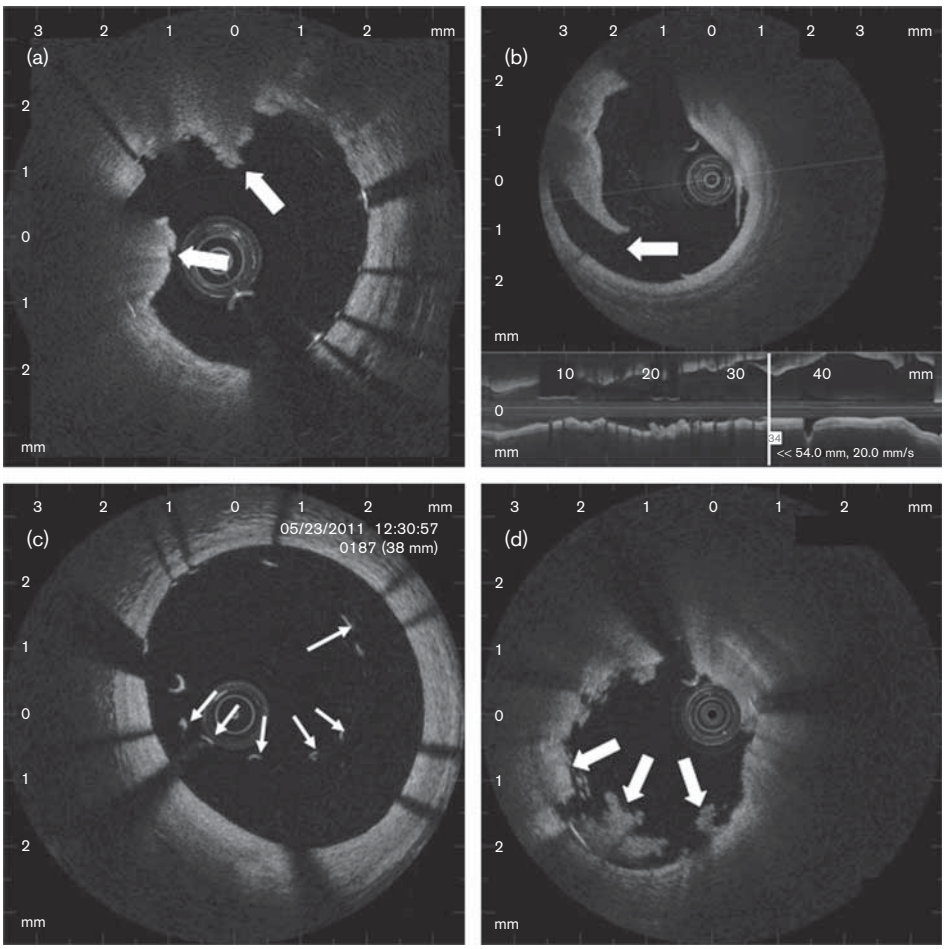
Immediate post-percutaneous coronary intervention optical coherence tomography findings

Post-PCI imaging using OCT provides a level of detail that was not previously possible with angiography or IVUS. It is unclear whether the findings from IVUS can be translated to OCT. For instance, post-PCI dissection seen on angiography or IVUS is associated with increased target vessel revascularization and stent expansion/malapposition [44]. OCT documents higher rates of plaque protrusion between stent struts, edge dissections, and stent malapposition (Fig. 7) [45,46]. However, there has been no increase in adverse clinical events early in follow-up, and there are discrepancies in the literature on the prognostic significance of these findings [47,48]. This uncertainty raises questions on the appropriate treatment, if any, for such complications. The Massachusetts General Hospital OCT Registry was launched in an attempt to answer these questions.

Late post-percutaneous coronary intervention findings

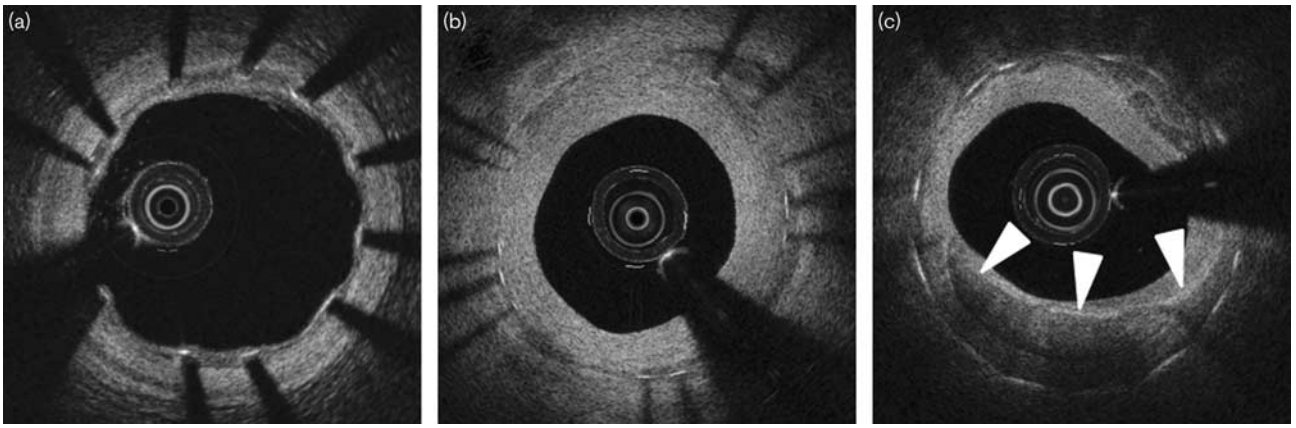
OCT evaluation of patients admitted with late stent thrombosis revealed more frequent malapposition and uncovered stent struts compared with matched controls [49], suggesting a role for OCT in understanding the mechanism of stent thrombosis. On identifying modifiable risk factors such as stent malapposition, further balloon inflations to achieve optimal stent apposition may avoid unnecessary conversion from one antiplatelet agent to another due to presumed antiplatelet failure. Another emerging use for OCT is the assessment of stent coverage as a marker of vascular response to stent implantation [50]; however, clinical outcomes to support its use are lacking despite the potential to determine the optimal duration of dual antiplatelet therapy following stent implantation.

Fig. 7



OCT findings: immediately after PCI. (a) Tissue protrusion, (b) stent edge dissection, (c) stent malapposition, (d) platelet-rich thrombus within stent. OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Fig. 8



Late post-PCI OCT findings. (a) Well-covered drug-eluting stent 15 months after implantation. (b) In-stent restenosis of a bare metal stent 2 years after implantation: homogeneous, high backscattering neointima. (c) Calcified neointima 11 years after implantation of a bare metal stent: signal-poor, heterogeneous region with a sharply delineated border (arrows). OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

The degree of in-stent neointimal hyperplasia assessed by OCT has been characterized in three patterns [51]. Homogeneous regions are rich in smooth muscle. Heterogeneous and layered patterns are rich in extracellular matrix. The development of atherosclerosis within the neointima (neoatherosclerosis) is a mechanism for late stent thrombosis. The presence of neoatherosclerosis (neointima > 100 μm) is more prevalent in DES versus bare metal stent in early (< 9 months) and intermediate (9–48 months) phases, with no difference in late follow-up (>48 months) [52]. The duration from stenting, the presence of a DES, and current smoking were identified as predictors of neoatherosclerosis, whereas the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was inversely associated with its development [53]. Clinical studies specifically targeting treatment of neoatherosclerosis are lacking and are an area for further research (Fig. 8).

Limitations of optical coherence tomography

Despite improved resolution, a major limitation of OCT is poor tissue penetration – limited to 2–3 mm – precluding imaging beyond the internal elastic lamina. In addition, because the dimensions of individual endothelial cells are below the resolution of OCT, it is not possible to fully assess stent coverage. It can be difficult to distinguish lipid from calcium using OCT. Evaluation of aorto-ostial lesions is challenging because of difficulty in opacification of the vessel. Caution should be exercised when interpreting OCT images in STEMI as red blood cell scatter artifact from red thrombus can obscure evaluation of the lesion. The most important limitation is the paucity of long-term post-PCI outcome data.

Conclusion

Emerging clinical trial data and the emphasis on cost-effective care are resulting in more FFR-guided PCIs. Further study of FFR in the setting of coronary bypass graft lesions, preoperative evaluation, and ACS will refine the use of the technology. OCT-guided PCI will increasingly be used as an adjunctive tool with the goal of decreasing adverse events. As long-term data become available, we will gain a deeper understanding of the clinical significance of plaque protrusion and edge dissections. Faster imaging platforms and combined catheter systems will incorporate both functional and imaging capabilities, facilitating the use of adjunctive tools during PCI. Interventional cardiology continues to evolve at a rapid pace. Successful interventional cardiologists must adapt to new tools as their clinical value is demonstrated.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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