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Intravascular imaging for characterization of coronary atherosclerosis

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Abstract

This short review surveys recent developments in coronary intravascular imaging technologies. We present an outline of the applications of intravascular imaging for guidance of percutaneous coronary interventions and imaging of atherosclerosis, along with emerging clinical evidence for use. Imaging of tissue composition is important for understanding the relation between the presence of a lesion and clinical sequelae. We describe the recent innovations to enable imaging of unstable atherosclerotic plaques, focusing on the emergence of experimental multimodal imaging technology.

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Introduction: objectives of intravascular imaging

Guidance of percutaneous coronary intervention

Intravascular imaging has earned its place at the table in interventional cardiology practice. Its present role is primarily in a posteriori checking of the result of percutaneous coronary interventions (PCI), as an add-on to conventional angiography.[1] In PCI, one or more stents are implanted to resolve myocardial ischemia. PCI shows adequate acute success rates, but sees a persistent recurrence of symptoms in approximately 10% of patients in the first year (including periprocedural complications), rising to around 20% at three years [1–3]. Around half of those repeat catheterizations address the target site.

In recent years, features on intravascular imaging have emerged that correlate with adverse events such as stent thrombosis and restenosis: inadequate stent expansion, dissections and thrombus [4,5] can all be visualized with intravascular imaging. Catheter-based imaging is also used prior to intervention, to obtain measurements of vessel and lumen size, and length without the projection artifacts inherent to angiography. For these purposes, it is important to deliver high-contrast, easily interpretable images of the lumen and stent, as well as visualization of the vessel wall in high resolution.

Current commercially available technologies do this very well: Intravascular ultrasound (IVUS) [6] and intravascular optical coherence tomography (IVOCT; also called optical frequency domain imaging, or OFDI) [7] in particular are in practical use. The latter delivers higher resolution and higher image contrast, but at the cost of the necessity to flush blood from the artery. This step, combined with the inherently limited ranging depth, make IVOCT less reliable in large vessels, near major side branches, and in patients with kidney dysfunction (who do not tolerate the flush medium well). IVUS is easier to use and more versatile, but the images contain fewer details, less contrast, and require a longer learning curve to interpret. For the purpose of this review, we will assume familiarity with these techniques.

Recent meta-analyses, based on a range of registries and a number of randomized studies that compare intravascular imaging guidance to angiography alone, demonstrate a clear benefit from intravascular imaging on hard endpoints like death and myocardial infarction (MI), and also on repeat revascularization [8,9]. Data also show improved procedural outcome metrics, like larger post-intervention minimal lumen area (MLA) [10], and effect on therapeutic decisions, such as

[1] The clinical use as discussed in this review reflects the European and North American situations. Japan is an exception, with almost universal use of intravascular imaging in PCI.

number of implanted stents and stent length [11,12]. OCT demonstrated a favorable effect on functional assessment of the treated vessel [13]. These observations have led to proposals for intravascular imaging guided stenting [14,15], criteria for which are currently being investigated in clinical trials.

Current techniques for plaque imaging

Despite promising recent indications for the clinical utility of current technology, the intravascular imaging field has always aspired to a higher goal: detecting atherosclerotic plaque for predicting future events and pre-emptive intervention. This ability is extremely valuable in the scenario of a patient presenting for coronary revascularization, who has one or more non-culprit lesions in addition to the one that generates his/her symptoms. These patients make up the other half of repeat revascularizations mentioned before: symptoms arose from a different site than was treated originally. Clinically, this target of "vulnerable plaque" [16] imaging has so far remained elusive. The key to finding vulnerable plaques is detecting the composition of plaques, in addition to their morphology. Unstable plaques are characterized by the presence of a heterogeneous lipid-rich necrotic core, covered by a thin fibrous cap (in the order of 50–100 μm) that is weakened by inflammation (thin-cap fibroatheroma; TCFA). These lesions frequently feature microcalcifications, increased microvessel density, and outward remodeling of the vessel. Vulnerable plaques can trigger events spontaneously, but also lead to higher complication rates in interventions. Detection is important for pre-emptive treatment as well as stent placement. Every defining characteristic of plaque vulnerability (thin cap, microvascularization, inflammation, lipids, plaque volume) has been investigated as a marker for detecting vulnerable plaque, driving technology development in catheter-based tissue composition imaging. Plaque burden (the ratio of plaque area and area enclosed in the outer vessel wall) is another important indicator of plaque stability, with plaques occupying >70% of the vessel being predictive of events [1,17].

Angioscopy was the first optical technique to be applied to plaque imaging [18], but is rarely used today. It provides a video endoscopy image of the (flushed) vessel, showing thin-cap lipid-rich plaque as yellow, and has very good sensitivity for thrombus. It was also the first technique to show a prognostic association of imaging with cardiovascular events in small studies [19].

IVOCT has adequate resolution and useful tissue type contrast [20] for visualizing plaque microstructures, resulting in a rich literature on IVOCT imaging of coronary atherosclerosis. Cap thickness can be measured, and the presence of IVOCT-derived TCFA is a predictor of peri-procedural MI (PMI) [21,22], a condition that is associated with worse long-term outcomes. IVOCT-measured cap thickness is associated with the prevalence of plaque rupture [23]. IVOCT-derived lipid-rich plaque was recently shown to be predictive of adverse cardiac events arising from non-culprit sites [24]. The technique also shows features of inflammation [25] and frequently plaque microchannels [26], but the reliability of these findings is unknown and their evidence level is low.

IVUS initially demonstrated the shortcomings of coronary angiography, by showing atherosclerosis in the vessel wall in addition to luminal narrowing. Because of its large penetration depth, it is the only intravascular technique that can directly quantify plaque burden. IVUS-derived plaque volume has been applied as the primary outcome measure in pharmaceutical interventions [27,28]. Even though plaque volume changes are typically small, there appears to be a robust association with clinical events [29]. IVUS remains a highly useful technique for PCI guidance, but lacks image contrast and resolution for vulnerable plaque characterization. IVUS signal analysis techniques [30,31] have attempted to add tissue type information to the grayscale image, most prominently in the form of an analysis called IVUS-VH (virtual histology). IVUS-VH has been used extensively in plaque and drug studies [1,17,32] but has not achieved widespread clinical use, which can be at least partially attributed to its limited validation [33].

The clinical breakthrough of IVUS for imaging of lipid-rich plaque came with the introduction of a combined IVUS/near-infrared reflection spectroscopy (NIRS) device [34]. This combination catheter was the first commercial multimodal intracoronary imaging device. NIRS was developed and validated for intracoronary sensing of plaque lipid [35,36], aiming for vulnerable plaque detection [37]. In small scale studies, coronary lipid as detected by NIRS was indeed found to be predictive of event risk [38,39], more frequently involved in acute coronary syndrome (ACS) [40] and also associated with PMI [41]. Large clinical trials to establish criteria for intervention guidance are ongoing [37].

New developments in catheter technology: multimodal imaging

Associations between imaging markers and subsequent events exist on a population level, but may not be strong enough to direct interventions in individual patients. In more than a decade of vulnerable plaque imaging, no single technology has demonstrated the ability to predict whether a particular plaque will trigger an MI in the months or years following the index procedure. Different technologies are sensitive to different plaque components, as illustrated in Figure 1. The natural response of the engineering field has been to combine complementary technologies in a single catheter [42].