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Imaging Atherosclerosis and Risk of Plaque Rupture

Eric A Osborn, MD PhD^{1,2} and Farouc A Jaffer, MD PhD^{2,3}

¹Cardiology Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

²Cardiovascular Research Center, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA

³Center for Molecular Imaging Research and Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

Atherosclerosis imaging strategies can delineate characteristics of plaques at risk of rupture and thrombosis. Structural plaque imaging identifies high-risk plaque features including lipid pools, thin fibrous caps, and intraplaque hemorrhage, among others. New molecular imaging techniques complement structural imaging approaches by illuminating important features of plaque biology, with a prominent focus on detecting inflammation as a high-risk phenotype. As we unravel the molecular and structural characteristics underlying thrombosis-prone plaques, there is significant promise for eventual early identification and prediction of atherosclerotic plaque complications before they occur. Here we focus on recent imaging insights into high-risk arterial plaques, the etiologic agent of acute myocardial infarction (MI), stroke, and sudden cardiac death.

Keywords

atherosclerosis; plaque rupture; imaging; molecular imaging; myocardial infarction; thrombosis; vascular injury

Introduction

Atherosclerosis is a leading cause of cardiovascular morbidity and mortality worldwide. Plaque complications occur most commonly from plaque rupture, and also from plaque erosion and calcified nodule formation. In the last several years, advanced structural and molecular imaging technologies have emerged and offer new windows into atherosclerosis pathophysiology. Recently, an expert working group summarized the current knowledge base for high-risk plaque imaging, and provided directions for future research [1]. While recognizing that atherosclerosis is a systemic disease requiring systemic treatment [2], MI, stroke, and death occur from specific lesion complications, offering a sound rationale for pre-complication imaging. The development and clinical translation of structural and molecular plaque imaging approaches will refine our ability to identify high-risk plaques,

Correspondence: Farouc Jaffer, MGH Cardiovascular Research Center, Simches Research Building 3206, 185 Cambridge Street, Boston, MA 02114, Tel: 617.724.9353, Fax: 617.860.3180, fjaffer@mgh.harvard.edu.

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Conflict of Interest

Eric A. Osborn and Farouc A. Jaffer declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

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with important implications for risk prediction, drug development, and personalized medicine.

Extensive post-mortem histopathological studies of coronary and carotid plaques have identified key features of high-risk plaques (HRP, aka “vulnerable” plaques) including: 1) a thin fibrous cap, 2) lipid-rich necrotic core, 3) inflammation, 4) neovascularization, 5) intraplaque hemorrhage 6) microcalcifications and potentially 7) cholesterol crystals. Plaques with thin fibrous caps and large thrombogenic lipid cores, known as thin-cap fibroatheromas (TCFAs), are the prototypical substrate for plaque rupture and atherothrombosis. Inflammation due to macrophage infiltration and destabilizing activated tissue proteases can weaken the fibrous cap. Hemorrhage into the plaque itself has been implicated in progression to more advanced lesions. Finally, small calcified nodules may induce plaque disruption due to local mechanical stress on softer adjacent tissue structures. These features may be present alone or in combination in a particular HRP, and can evolve as the plaque matures into a more vulnerable phenotype or stabilizes in response to effective treatment. Importantly, many high-risk features are increasingly detectable by clinical structural and molecular imaging tools.

A recent invasive and non-invasive imaging autopsy study of 295 coronary atherosclerotic plaques obtained from 213 sudden cardiac death patients identified cap thickness $<55\mu\text{m}$ as the best concomitant discriminator of plaque rupture, followed by inflammation (macrophage infiltration) and necrotic core [3]. Although highly informative, histopathological investigations are limited by single timepoint, cross-sectional associations. *In vivo* imaging studies that visualize the structure and biology of HRP ahead of plaque disruption are critically needed to understand its complex and dynamic pathophysiology, such as serial rupture, inflammation, regression, and erosion.

Structural Plaque Imaging

Multidetector CT coronary angiography (MDCTA)

MDCTA has emerged as the leading platform for non-invasive coronary plaque imaging due to its high speed and resolution. Current generation 320-slice MDCTA systems can image the entire heart with a single gantry rotation in seconds at sub-millimeter resolution. MDCTA can detect both lumen stenosis (sensitivity and specificity $>90\%$ compared to invasive imaging), and plaque composition based on tissue density measured in Hounsfield units (HU), potentially discriminating high-attenuation calcification from low-HU fibrofatty plaques.

MDCTA plaque composition and cardiovascular events—Nance et al. studied 458 subjects at low-to-intermediate cardiac risk seeking acute care for chest pain who underwent coronary MDCTA and then were followed for major adverse cardiovascular events (MACE) including MI, revascularization, cardiac death, or angina requiring hospitalization [4]. Overall, 15% of patients experienced MACE at 13 months median follow-up, with plaque extent independently strongly predicting MACE (hazard ratio (HR) of 1.52 for 4 segments of plaque compared to no plaque, $p<0.001$), MACE rates were highest in fibrofatty and mixed calcified plaques (HR 87), followed by purely non-calcified (HR 58) and calcified (HR 33) lesions (all $p<0.05$).

Nonobstructive CAD and acute MI—Aldrovandi et al revealed a new association of non-obstructive coronary atherosclerosis ($<50\%$ stenosis) and subjects with acute MI, a difficult clinical scenario including a differential diagnosis of myocarditis, coronary vasospasm, and plaque disruption with thromboemboli. The authors performed MDCTA in 50 MI patients with nonobstructive CAD at invasive coronary angiography (ICA), but

evidence of MI by MRI late-gadolinium enhancement [5]. First, the authors noted that MDCTA identified many plaques not visible on ICA. Of MDCTA-detected plaques, 60% were located in the infarct-related artery (IRA), and these plaques exhibited significantly more non-calcified and mixed calcified/fibrofatty composition than non-IRA plaques (64% vs. 32%, $p=0.005$). These results suggest that nonobstructive CAD could be the etiological cause of many acute MIs, warranting greater secondary prevention therapies. Further insights are expected in this very important patient subgroup using intravascular imaging.

Magnetic resonance imaging (MRI)

Advantages of MRI include excellent inherent soft-tissue contrast, good resolution and no ionizing radiation exposure. In the carotid arteries, multi-contrast weighted MRI readily detects lipid-rich necrotic core plaques, plaque erosion and rupture, and intraplaque hemorrhage (IPH), in addition to determining percent luminal stenosis. Serial plaque MRI has emerged as an imaging endpoint in outcomes and drug development clinical trials.

MRI plaque composition and cardiovascular risk factors—The association of cardiovascular risk factors and MRI carotid plaque composition was evaluated in 1006 subjects with carotid ultrasound intimal thickening [6]. Carotid MRI revealed that IPH and lipid-core were most common, and occurred in 25% of all subjects but more often in men. On multivariate analysis, IPH associated with age, smoking and hypertension (OR 1.8, 1.6, and 1.4, respectively), while lipid-cores were more common in only hypercholesterolemic patients (OR 1.4). Since the high frequency of HRP features observed would be expected to far outpace the number of clinical events, this study highlights the need to develop combinatorial risk scores for individual plaque risk, and of course prospective studies to validate such criteria.

Associations between cryptogenic stroke and complicated, nonobstructive plaques—Analogous to the coronary arteries, the link between nonobstructive carotid plaques and stroke is incompletely understood. In 32 patients with non-obstructive carotid stenosis <50% and cryptogenic stroke [7], complicated HRP (MRI-identified AHA Type VI lesions with thrombus, fibrous cap rupture, and/or IPH) were found in 37.5% of carotid arteries ipsilateral to the stroke, in contrast to 0% in the contralateral carotid ($p=0.001$). In a second study, 41 patients with TIA or stroke demonstrated a 54% rate of MRI-defined complex AHA Type VI lesions in the ipsilateral culprit vessel, also with IPH as the predominant feature. Remarkably, over half of these lesions were <70% stenosed [8]. These data strengthen the concept that severe stenosis is not a prerequisite for carotid plaque-induced thromboembolism and subsequent stroke or TIA.

IPH and plaque progression—IPH may predict rapid carotid plaque progression. Sun et al. serially imaged twelve asymptomatic patients with 50–79% stenosed carotid arteries over 4.5 years [9]. Each patient developed IPH in at least 1 carotid artery. Plaque progression was initially low ($-20.5 \pm 13.1 \text{ mm}^3/\text{yr}$), but then rapidly accelerated after IPH appeared ($18.3 \pm 6.5 \text{ mm}^3/\text{yr}$, $p<0.02$). Despite enhanced plaque progression, no cerebral ischemic events occurred in this small study. However, a larger investigation of 114 symptomatic carotid stenosis patients reported that IPH strongly associated with stroke or TIA (OR 4.1) [10]. In addition, IPH predicted ischemic events (OR 6.7 for new symptoms within 2 weeks). Thus, MRI-detected IPH indicates evolving plaque risk, and may ultimately help reclassify patients.

Intravascular ultrasound (IVUS)

A widely utilized invasive imaging tool, IVUS has been a pillar of clinical structural plaque imaging technology for many years. IVUS employs miniaturized ultrasound transducers

(20–45 MHz) to obtain images of the vessel wall at up to 100 μ m resolution, and can not only determine lumen stenosis as observed by angiography, but also the positive expansive vessel remodeling that occurs in earlier stage plaques before luminal narrowing. Clinically, IVUS is used to guide coronary intervention, resolve ambiguous left main coronary artery lesions, and to evaluate atherosclerotic lesion length and plaque burden.

Grayscale IVUS calcified nodules and plaque progression—Plaque progression is linked to focal plaque calcification, a HRP feature readily identified by grayscale IVUS. Kataoka et al. performed serial IVUS on 1374 patients with stable CAD [11]. Plaques from 922 patients contained spotty calcification, defined as an arc of calcified plaque that encompasses $<90^\circ$ of the IVUS cross-sectional image. Spotty calcification existed in older, male, and diabetic subjects. Over time, plaques exhibiting spotty calcification progressed at rates *20-fold* greater (measured as increase in percent atheroma volume, $p=0.002$). Concerningly, plaque growth was more resistant to intensive cholesterol and blood pressure control when spotty calcifications were present.

Virtual-histology IVUS (VH-IVUS) plaque composition—While grayscale IVUS can effectively differentiate calcified (bright, high-density reflectors) from non-calcified plaque, it has limited capacity to determine non-calcified plaque tissue composition. However, spectral analysis of the IVUS backscatter signal has given rise to VH-IVUS, which can reasonably identify four distinct plaque components: calcified, fibrous, fibrofatty, and necrotic core. VH-IVUS can further differentiate plaques into thin- and thick-cap fibroatheromas, fibrocalcific plaques, and pathological intimal thickening. Recent evidence demonstrates that human coronary and peripheral atheroma show marked heterogeneity in VH plaque composition, with coronary and carotid arteries harboring more HRP phenotypes than the renal and iliac arteries [12]. Comprehensive definitions for grayscale and VH-IVUS plaque analysis have been published to standardize interpretation for future clinical studies [13].

VH-IVUS and prediction of coronary events—VH-IVUS was employed in the recent landmark PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree). PROSPECT evaluated the natural history of all 30% stenosed coronary plaques identified by ICA and 3-vessel grayscale- and VH-IVUS imaging, in 697 ACS patients [14]. At >3 years follow-up, one-half of new cardiovascular events were attributable to plaques distinct from the index culprit lesion. The adverse event rate related to IVUS was nontrivial at 1.6% (10 dissections, 1 perforation). Independent predictors of future non-culprit plaque adverse events included plaque burden $>70\%$, minimum lumen area $<4\text{mm}^2$, and VH-TCFA (defined as necrotic core that extends to the lumen surface). The presence of these plaque features were additive in their risk, and in combination predicted an 18% likelihood of MACE at 3 years compared to 0.3% in non-culprit plaques without these features. However, the predictive accuracy of VH-IVUS is currently too low for routine clinical risk prediction.

Subgroup analyses of PROSPECT have yielded further interesting findings. 220 patients with at least one plaque burden $>70\%$ had overall higher residual atherosclerotic disease with more VH-IVUS necrotic core and TCFA [15]. This population had significantly higher non-culprit lesion MACE compared to those without (20.8% vs. 7.7%, $p<0.0001$), supporting the concept that greater residual coronary disease attributes greater future risk. Significant lesion progression was also evaluated as a marker of future adverse events in the 72 patients that experienced non-culprit lesion events in PROSPECT [16]. Despite similar baseline IVUS metrics, the 44 patients with evidence of lesion progression 20% by ICA at the time of their event accounted for all of the 6 MIs observed in the 3-year study period. In contrast, events in patients without significant lesion progression were solely unstable

angina without MI. Therefore, understanding individual plaque characteristics that predispose to lesion growth and maturation may be most important to prevent infarction. While in PROSPECT lesion palpography did not provide further discrimination of future MACE [17], a separate study demonstrated that low local endothelial shear stress in combination with larger IVUS plaque burden independently predicted plaque progression [18].

Optical coherence tomography (OCT)

Intravascular OCT, and the high-speed 2nd generation form termed optical frequency domain imaging (OFDI), uses reflected near-infrared light at 1320nm to obtain unsurpassed high-resolution (~10µm) images of the vessel wall. OCT requires a blood-free imaging field through brisk saline or contrast flushing for image visualization. OFDI acquires data rapidly at rates up to 40 mm/sec. OCT/OFDI can evaluate intravascular thrombus, macrophage infiltration, and subintimal lipid accumulation, and can even image the thin fibrous caps of TCFA that are unresolvable by IVUS. OCT outperforms MDCTA and IVUS in discriminating early from advanced lesions in donor heart coronary arteries, where lipid-rich OCT plaques significantly predicted advanced atheroma at histopathology (OR 31.2, $p<0.0001$) [19]. Consensus standards for OCT acquisition and measurement have been recently formulated by an international working group [20].

OCT plaque composition, positive remodeling, and the influence of diabetes—

Positively remodeled or expansive atherosclerotic plaques are implicated as having a higher-risk of plaque rupture. Rathore et al. employed OCT and IVUS in 47 patients to assess relationships between plaque remodeling and structural features [21]. Positively remodeled plaques exhibited greater lipid, thinner fibrous caps, and more TCFAs, thrombus, and sites of plaque rupture. In 98 patients with diabetes, OCT plaque analysis demonstrated greater plaque lipid content, calcification, and thrombus compared to non-diabetic subjects [22], consistent with recognition that diabetic subjects have more complex and diffuse coronary disease. When stratified further by blood glucose, poorly controlled diabetics (HgbA1c 8.0%) had even greater plaque lipid and thinner fibrous caps ($p<0.02$ for both trends), with more TCFAs and plaque macrophage infiltration.

OCT and VH-IVUS plaque composition as measures of statin efficacy—In a prospective study of 42 patients with coronary revascularization for stable angina and then randomized to 4 mg daily pitavastatin or dietary changes, serial OCT, grayscale IVUS, and VH-IVUS were performed at baseline and at 9 months follow-up [23]. In the statin-treated group, grayscale IVUS plaque volume and VH-IVUS lipid volume index both significantly decreased at 9 months in contrast to the dietary change group ($p<0.05$). By OCT, plaque fibrous cap thickness was also greater after statin therapy (189 ± 46 vs. 140 ± 42 µm, $p=0.001$). These results demonstrate the effects of statin treatment on HRP characteristics, and the potential of using advanced plaque imaging to provide surrogate coronary efficacy biomarkers for novel atherosclerosis therapeutics.

OCT plaque analysis in acute coronary syndromes versus stable CAD—Three-vessel OCT was employed to assess 248 non-culprit plaques in 17 ACS and 87 stable CAD patients [24]. Compared to stable CAD, plaques from ACS patients demonstrated greater lipid accumulation, thinner fibrous caps, and more TCFAs (65% vs. 15%, $p<0.001$), as well more macrophages and thrombus content. Non-culprit lesion neovascular microchannels were detected at similar frequency in the two groups, but they could be observed significantly closer to the vessel lumen in ACS patients, which in theory could make these plaques more susceptible to disruption.

In ST-elevation MI, OCT is providing new insights into the mechanisms of atherothrombosis, and informing new management strategies. Prati et al. studied 31 STEMI patients with OCT-defined plaque erosion (identified as a non-ruptured fibrous cap following aspiration thrombectomy) that were treated with coronary stents (40%) or dual-antiplatelet therapy alone [25]. Multimodality imaging was performed in a subset of patients, demonstrating different HRP imaging strategies (Figure 1). At 2 years follow-up, no MI or death occurred in either group, and only a single target-vessel revascularization was performed, notably in the stented group. Distinguishing plaque erosion from plaque rupture by OCT in ACS patients could spare erosion patients the infrequent, but important, risks of stent implantation such as restenosis and stent thrombosis.

Near infrared spectroscopy (NIRS)

NIRS is a newer clinical intravascular imaging modality that detects lipid-rich plaques based on the absorption pattern of near-infrared light by cholesterol moieties. Since NIRS provides minimal anatomic information, NIRS has been coupled with IVUS to display co-registered structural plaque data. Following automated catheter pullback, the NIRS data is displayed on a color-coded scale in blocks that ranges from red (no lipid) to yellow (lipid-rich). NIRS has been extensively validated against histopathology in detailed human coronary studies, and its uses in patient care are still under active investigation.

A recent longitudinal preclinical study examining the evolution of at-risk coronary fibroatheromas in diabetic, hypercholesterolemic pigs tested whether early NIRS-IVUS plaque features could predict the development of future lipid-rich vulnerable plaques [26]. Baseline NIRS-IVUS was repeated every 3 months for 9 months, and demonstrated progressive IVUS atherosclerosis and positive remodeling. Lipid-rich NIRS lesions were more likely to have multiple HRP histopathology features, including more necrotic core and inflammatory cells, and thinner fibrous caps with evidence of apoptosis (all $p < 0.05$). In total, nearly 90% of 3- and 6-month NIRS positive lesions evolved into histopathological fibroatheromas at 9 months ($p < 0.01$), and furthermore the presence of a NIRS lipid-rich plaque at 6-months was predictive of this development (OR 2.7). The concept of using imaging tools to predict which early lesions will evolve into HRP is of importance.

Molecular Imaging

Molecular imaging complements traditional structural plaque imaging through the use of targeted probes that identify specific molecules and/or biological processes in vivo. Preclinical molecular imaging has successfully identified nearly all HRP features including inflammation, thrombosis, neovessel formation, apoptosis, and hemorrhage, but clinical translation of molecular imaging has been slow compared to the rapid growth within the field. Recently, an expert panel commented on barriers and recommendations to foster greater clinical application of molecular imaging technologies [27]. Currently, clinical atherosclerosis molecular imaging is dominated by non-invasive PET metabolism/inflammation plaque imaging with ^{18}F -fluorodeoxyglucose (FDG), but other clinically available approaches such as ^{18}F -sodium fluoride (NaF) for PET are emerging.

^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)

FDG is a radiolabeled glucose analogue that concentrates in metabolically active cells, including atheroma, where it associates with macrophage infiltration as a surrogate for plaque inflammation or possibly plaque hypoxia. FDG PET inflammation imaging is generally restricted to large arteries, such as the carotids and aorta, although coronary artery imaging is being pursued. FDG PET has high sensitivity but low spatial resolution (3mm), and therefore requires anatomic imaging to localize the FDG signal. Traditionally, FDG

PET is performed with CT, however PET co-registered MRI is now available offering greater plaque contrast and reduced radiation [28].

Carotid plaque FDG signal and cardiovascular risk factors—In a recent study, FDG PET of 43 noninsulin-dependent diabetic subjects revealed a significant association between the corrected fasting glucose level and carotid FDG uptake [29]. Among this diabetic group, FDG signal was greatest in patients with obesity (BMI 30kg/m^2) and smoking. In a separate study of 21 peripheral arterial disease patients, however, there was no significant correlation between FDG PET activity and the macrophage content from catheter-based directional atherectomy plaque samples [30]. Although it is expected that FDG PET may provide different information in different atherosclerosis beds, a clear limitation of this study is the method of histopathology tissue collection, which makes exact co-registration problematic.

High-risk carotid plaque morphology and FDG activity—Carotid FDG PET activity has been associated with early recurrent cerebral events regardless of stenosis severity, such as reported in a 60 patient study with recent stroke or TIA [31]. At 90 days, 22% of subjects experienced recurrent events, with elevated ipsilateral carotid FDG signal being the only independent predictor identified (HR 6.1, $p=0.02$). Combining structural HRP with MDCTA may allow even greater risk-stratification of high-risk carotid plaques, as investigated by FDG PET/CT in 34 patients with carotid stenosis [32]. Positively remodeled, ulcerated, and non-calcified plaques had significantly greater FDG PET signal (TBR 2.2 vs. 1.7, $p<0.001$), with incremental increases in FDG activity for each high-risk component (trend $p<0.001$). Risk stratification based on combined structural and molecular imaging appears to be a sound strategy.

Coronary plaque FDG PET imaging—Coronary FDG PET imaging is challenging, in part due to the small size of coronary vessels and cardiac motion artifacts, but also because of the intense FDG uptake of the adjacent highly metabolic myocardium that obscures the coronary FDG signal. However, with dietary myocardial suppression protocols, detection of FDG PET signal in the left main and proximal coronary artery beds is sometimes achievable. Non-invasive coronary FDG PET activity was investigated in the stented culprit lesions of 20 ACS versus 7 non-ACS subjects within 1 week of stent placement [33]. Using a predetermined FDG target-to-background ratio (TBR) ≥ 2.0 to identify FDG positive lesions, ACS correlated positively with elevated stent FDG (OR 31.6, $p=0.044$). However, coronary FDG was interpretable in only one-half of ACS patients, signifying the need for further improvements in coronary FDG PET imaging.

Assessment of anti-inflammatory pharmacotherapy by FDG PET activity—Beyond statins, new anti-atherosclerosis therapies are being pursued, including anti-inflammatory agents hypothesized to stabilize vulnerable plaques. Ongoing clinical trials of the interleukin-1 inhibitor canakinumab (CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study) and low-dose methotrexate (CIRT, Cardiovascular Inflammation Reduction Trial) aim to explore whether inflammation reduction leads to fewer adverse cardiovascular events. New anti-inflammatory therapeutics are being tested by FDG PET, such as losmapimod, an inhibitor of the pro-inflammatory p38 mitogen-activated protein kinase pathway, and adalimumab, a TNF- α antagonist. 99 stable statin-treated patients randomized to losmapimod or placebo demonstrated significant FDG signal reduction following 3 months losmapimod [34]. Subcutaneous adalimumab significantly decreased maximum vessel TBR on serial FDG PET imaging in 30 randomized patients at 4 months, but failed to reach significance compared to placebo due to the small size [35]. FDG PET is likely to play an increasingly important role in the evaluation of

pharmacotherapeutics in phase II clinical trials, to determine if more costly phase III trials should be pursued.

Non-FDG nuclear molecular imaging strategies

Sodium ^{18}F -fluoride (NaF) PET imaging of coronary calcification—Plaque calcification is a hallmark of advanced atheroma that can be detected with non-invasive NaF PET imaging, a marker of active mineralization established clinically to detect cancer bone metastases. As opposed to FDG, background myocardial uptake of NaF is negligible, and therefore NaF can determine coronary osteogenic activity. A study of 119 patients revealed good correlation between coronary NaF and CT calcium score ($r=0.652$, $p<0.001$) [36]. NaF signal was greatest in subjects with atherosclerosis risk factors, angina, and prior cardiovascular events, but undetectable in patients with the highest CT coronary calcium scores (>1000) presumably due end-stage plaques lacking active calcium remodeling. Whether NaF activity can be reduced by medical therapy and its relationship to adverse outcomes is under investigation.

Newer imaging methods for detecting carotid plaque inflammation—Apart from FDG, agents targeted to inflammatory leukocyte subpopulations are also being tested in humans. ^{11}C -PK11195 PET, which identifies activated plaque macrophages by selective engagement of the macrophage translocator protein, exhibited greatest uptake in the ipsilateral carotid artery after recent stroke or TIA in 32 patients with $>50\%$ carotid stenosis [37]. When combined with high ^{11}C -PK11195 signal, lesions also demonstrating low-attenuation by CT suggestive of greater lipid content were $>90\%$ predictive of symptomatic carotid plaques. Although less abundant than macrophages, T-lymphocytes are also present in HRP and can be detected by surface interleukin-2 (IL-2) receptors with the selective SPECT agent $^{99\text{m}}\text{Tc}$ -HYNIC-IL-2. A small study of 28 end-stage renal disease patients revealed elevated $^{99\text{m}}\text{Tc}$ -HYNIC-IL-2 signals in 91% of subjects [38]. Further assessment of different leukocyte subpopulations in plaques will provide new insights into the evolution of plaque inflammation.

Intravascular near-infrared fluorescence (NIRF) imaging

Standalone and integrated NIRF-OFDI molecular imaging—Optical molecular imaging with NIRF catheters obtains high-resolution intravascular images with good sensitivity, making NIRF attractive for future intracoronary molecular imaging. An informative inflammation study by Jaffer et al. performed intravascular NIRF imaging in hypercholesterolemic rabbit aortas 24 hours after injection of Prosense VM110, a protease-activatable NIRF inflammation agent [39]. NIRF was detected through flowing blood, without vessel flushing or occlusion, demonstrating elevated NIRF in IVUS-verified atheroma. A separate study tested a new integrated NIRF-OFDI imaging catheter capable of exact molecular-structural imaging in rabbit models of thrombosis and atherosclerosis inflammation [40]. The NIRF-OFDI catheter system demonstrated excellent performance, with nanomolar NIRF sensitivity and ultra-high OFDI resolution ($7\text{ }\mu\text{m}$ axially), and has a high probability of clinical translation in the next few years.

NIRF imaging of inflamed, lipid-rich plaques—In addition to NIRF devices, clinical NIRF molecular imaging probes are needed. Indocyanine green (ICG), an FDA-approved NIRF retinal angiography agent, was recently demonstrated to target lipid-laden, inflamed lesions in atherosclerotic rabbits within 20 minutes of intravenous injection [41]. ICG localized to macrophages ex vivo, and accumulated within human CEA samples after incubation. In parallel with approval of the NIRF-OFDI intravascular imaging system, ICG may be a leading NIRF coronary molecular imaging agent to identify biologically HRP.

Conclusions

Atherosclerosis imaging remains pivotal in understanding its pathophysiology, and offers new insights into the relationships between plaque composition and structure, and risk. The addition of newer molecular imaging tools will continue to strengthen our understanding of the in vivo biology of HRP, are increasingly translating to clinical use, and in combination with structural imaging provide more comprehensive information to build risk-prediction tools. In the future, ongoing efforts to further non-invasive coronary imaging strategies must be pursued. Overall, with continued progress in molecular and structural atherosclerosis imaging, high-risk atherosclerotic plaques will be illuminated as never before.

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Figure 1.

Acute coronary syndrome multimodality plaque imaging in a 66 year old male with ST elevation MI and an intact fibrous cap by optical coherence tomography (OCT). (A) The patient presented with intermittent substernal chest discomfort over a period of 12 hours and anterior ST elevations on the electrocardiogram. Angiography demonstrated complete occlusion of the proximal left anterior descending (LAD) coronary artery. The patient was given intravenous heparin and half-dose thrombolytics prior to transfer to a tertiary care center. (B) On arrival, repeat angiography revealed the LAD to be widely patent without residual thrombus or obstructive stenosis by OCT (arrows identify locations of OCT cross-sectional images). (C) Trace red thrombus was observed by coronary angioscopy (left top

and middle panels), but OCT demonstrated plaque with an intact fibrous cap (right top and middle panels) consistent with plaque erosion as the etiology of coronary thrombosis. Grayscale and virtual histology intravascular ultrasound (IVUS) revealed mainly fibrous plaque (green) with scant fibrofatty tissue (blue) infiltrating the lesion (bottom panels). Ultimately, percutaneous intervention was deferred and the patient was treated with dual-antiplatelet therapy alone. (D) Before discharge, multidetector coronary CT angiography was performed (comparative reference angiography images on the left panels) showed non-obstructive coronary disease and no positive/expansive plaque remodeling at the site of the thrombotic culprit lesion. Reproduced with permission from [25].