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A Review of Intravascular Ultrasound–Based Multimodal Intravascular Imaging: The Synergistic Approach to Characterizing Vulnerable Plaques

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Abstract

Catheter-based intravascular imaging modalities are being developed to visualize pathologies in coronary arteries, such as high-risk vulnerable atherosclerotic plaques known as thin-cap fibroatheroma, to guide therapeutic strategy at preventing heart attacks. Mounting evidences have shown three distinctive histopathological features—the presence of a thin fibrous cap, a lipid-rich necrotic core, and numerous infiltrating macrophages—are key markers of increased vulnerability in atherosclerotic plaques. To visualize these changes, the majority of catheter-based imaging modalities used intravascular ultrasound (IVUS) as the technical foundation and integrated emerging intravascular imaging techniques to enhance the characterization of vulnerable plaques. However, no current imaging technology is the unequivocal “gold standard” for the diagnosis of vulnerable atherosclerotic plaques. Each intravascular imaging technology possesses its own unique features that yield valuable information although encumbered by inherent limitations not seen in other modalities. In this context, the aim of this review is to discuss current scientific innovations, technical challenges, and prospective strategies in the development of IVUS-based multi-modality intravascular imaging systems aimed at assessing atherosclerotic plaque vulnerability.

Keywords

intravascular ultrasound; high frequency ultrasound; atherosclerosis; multimodal imaging

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Introduction

Coronary heart disease (CHD) remains the leading cause of deaths in the developed nations. Acute coronary syndromes (ACS) are the clinical manifestations of a sudden reduction in perfusion and oxygenation to the myocardium, typically resulting in heart attacks. Each year, more than 20 million patients worldwide with CHD experience ACS, and one-third of these individuals die from complications of ACS.¹ Atherosclerosis, a chronic disease typically asymptomatic at early stages, is characterized by the thickening of the arterial vessel wall due to the buildup of atheromatous plaque in the inner lining of arteries.^{2,3} Vulnerable atherosclerotic plaque, a particularly risk-laden plaque vulnerable to sudden rupture, is widely recognized to be the main “trouble maker” underlying ACS.^{4,5} Although the understanding of vulnerable plaques remains to be elucidated, histological studies have demonstrated that thin-cap fibroatheroma (TCFA) is the most common phenotype of vulnerable plaques (shown in Figure 1). TCFA is composed of a lipid-rich necrotic core with an overlying thin cap rich in macrophages (white blood cells that attack foreign substances).⁶ Quantitatively, TCFA is further defined as an atherosclerotic plaque with a fibrous cap <65 μm in thickness associated with macrophage infiltration (>25 cells per 0.3 mm diameter field) and a large lipid-rich necrotic core occupying nearly 35% of plaque volume.⁷ Therefore, both the thickness of TCFA and the size of the lipid-rich necrotic core are considered to be the major predictors of ACS. As a corollary, the presence of the inflammatory molecules and cells, such as increased macrophages, are useful in both identifying and staging the vulnerable plaques. Additional markers of TCFA are micro-calcifications and proliferation of the *vasa vasorum* (vessels that supply the walls of large arteries). To precisely identify intravascular TCFA *in vivo*, the imaging techniques used must recognize key morphological structures as well as biological features of the TCFA. Thus, early detection and staging of TCFA will not only guide the interventional or pharmacological strategy to prevent plaque rupture, but also contribute to the study of epidemiology of vulnerable plaques.

Therefore, an optimal intravascular imaging technology for plaque characterization, especially for the identification of vulnerable plaque with TCFA, should meet the following requirements¹: visualizing the endoluminal structure in details and scaling the degree of stenosis²; quantifying the entire plaque volume and plaque burden³; identifying plaque components such as calcification, lipid-rich necrotic core, fibrous tissue, and inflammatory markers⁴; providing adequate spatial resolution to measure the thickness of thin fibrous cap⁵; and monitor plaque rupture and thrombus formation. Each intravascular imaging technology possesses unique features that yield valuable information while exhibiting inherent limitations that can be difficult to overcome; therefore, an integration of multiple imaging modalities seems a synergistic solution.⁸⁻¹³

Catheter-based intravascular ultrasound (IVUS) has been used clinically over the last two decades to image coronary arteries for atherosclerotic lesions, to evaluate the lumen and plaque dimensions, and to guide intervention and stent deployment. The mechanically scanning IVUS transducer (20~40 MHz) or the radial array transducer (10~20 MHz), transmitting and receiving the high frequency ultrasonic waves, is capable of delineating the cross-sectional anatomy of coronary artery wall in real time with 70 to 200 μm axial

resolution, 200 to 400 μm lateral resolution, and 5 to 10 mm imaging depth.^{14,15} In the late 1990s, Bernard Sigel et al. first demonstrated the feasibility of using ultrasonic spectrum analysis to characterize vulnerable plaques of carotid arteries.¹⁶⁻¹⁸ Later on, the newly developed radiofrequency backscatter spectrum analysis algorithm, quantitatively analyzing the back-reflected ultrasonic signal in frequency domain and determining the tissue composition, was implemented in two commercial intracoronary artery imaging systems: Virtual Histology (VH-IVUS, Volcano Therapeutics, California) and iMap (Boston Scientific, California).¹⁹⁻²² The IVUS-based elastography technique, intravascular palpography, is able to assess local mechanical properties during arterial deformation caused by the intraluminal pressure, which can be used to perform high-risk plaque assessment.²³⁻²⁵ However, based on clinical studies in patients with ACS, the reliability of using ultrasonic spectrum analysis and intravascular palpography to detect vulnerable plaque was subpar.²⁶ This was caused by the insufficient resolution of IVUS to reliably characterize different tissue types and to precisely detect TCFA at such small scales. Nevertheless, IVUS remains an important tool for assessing plaque burden and monitoring artery remodeling.²⁷

Optical coherence tomography (OCT), considered as the optical analogue of ultrasound, utilizes back-scattered infrared light to achieve high spatial resolution (10-30 μm) and high-speed microstructural coronary artery images (>100 frames per second [fps], 20-40 mm/s pull-back speed).^{28,29} The optical pulse, or broad bandwidth infrared light, is irradiated into the tissue at different angular positions. 2D cross-sectional image can then be reconstructed based on the echo time delay and the intensity of the detected optical echo from tissue. Under rapid development in scientific research and proliferation in medical device industry, intravascular OCT has gained wide recognition in clinical practice and has become the top contender to challenge the status of IVUS in the intravascular imaging field. However, the major disadvantages of OCT are the limited penetration depth (1-2 mm) and lacking the reliability of tissue characterization as compared with IVUS. Moreover, similar to other optical intravascular imaging techniques, another important drawback of OCT is that it requires the temporal clearance of high-scattering luminal blood by using flushing agents such as iohexal and iodixanol, which may cause life-threatening reactions during or after the imaging procedures.^{30,31}

Recently, using chemical composition for tissue characterization has further increased the feasibility of assessing the metabolic state of vulnerable plaques in molecular level. Different tissue compositions have different optical absorption and scattering effect on near-infrared (NIR) light (400-2400 nm). Near-infrared spectroscopy (NIRS) is the first intravascular imaging technique to achieve lipid content characterization within plaques by analyzing absorbance of emitted NIR light at different wavelengths.^{32,33} However, this technology lacks the quantitative information about the size and location of the lipid core, which potentially limits its clinical utility. Intravascular photoacoustic (IVPA) detects the acoustic waves generated by thermal expansion induced by pulsed light to provide unique optical absorption contrast at ultrasound resolution. Because lipid has a distinct absorption spectrum in the NIR wavelength range, IVPA imaging is a promising technique for detecting and quantifying the amount of lipid in atherosclerotic plaques.^{34,35} Other emerging optical imaging techniques, such as near-infrared fluorescence (NIRF) imaging,³⁶ Raman spectroscopy,^{37,38} and fluorescence spectroscopic imaging,^{39,40} are advancing the field of

catheter-based technology by providing the contrast that involves chemical specificity, which can be used to identify tissue composition. However, these optical image techniques lack the capability to perform cross-sectional mapping for tissue structure; thus, IVUS and OCT remain essential.

Historically, IVUS has served as the de facto catheter-based intravascular imaging modality as the most established device in the clinical setting; however, it is by no means the “gold standard” for diagnosing coronary atherosclerosis and assessing plaque vulnerability. New intravascular imaging techniques are emerging to supplement deficiencies in IVUS, each with its own strengths and limitations. This review aims to expound on the different IVUS-based multi-modality intravascular imaging systems and address their innovations, challenges, and strategies for improvement.

Integrated IVUS and OCT Imaging System

Three different studies have compared the diagnostic accuracy of IVUS versus OCT for characterizing different tissue components within coronary atherosclerotic plaques by using the imaging systems to individually process and fuse acquired IVUS and OCT images.⁴¹⁻⁴³ They suggested that, generally, OCT had a higher diagnostic accuracy for lipid-rich plaques and fibrous plaques than does IVUS. However, IVUS is better for characterizing deep tissue components such as intimal thickening and deep calcifications. Thus, it was hypothesized that the complementary information provided by IVUS and OCT may enhance the assessment of high-risk plaques associated with TCFA as compared with a single imaging modality.^{44,45} An integrated IVUS-OCT imaging system allows the high resolution of OCT to precisely measure the thickness of thin fibrous cap and to delineate the morphology and boundary of luminal structure while incorporating the penetration depth of IVUS to visualize the whole plaque volume and to monitor the plaque burden. The collaboration between the University of Southern California (USC) Ultrasonic Transducer Resource Center and University of California–Irvine (UCI) OCT group have culminated in several integrated IVUS and OCT imaging systems and different hybrid IVUS-OCT catheter designs for both *in vitro* and *in vivo* assessment of lesions (Figure 2).⁴⁶⁻⁵³ There are two key criteria for the design of a clinically compatible IVUS-OCT catheter: (a) small size (outer diameter [OD] and length) to ensure a smooth catheter advance through the branching points of the tortuous cardiovascular system and (b) automatic image co-registration to shorten the imaging procedure time in synchrony with each cardiac cycle. Most previously reported hybrid IVUS-OCT catheter designs either suffered from increased size or inaccurate image co-registration due to the offset between the IVUS transducer and OCT probe. The newly developed hybrid IVUS-OCT by the USC and UCI groups has solved these problems by arranging the IVUS transducer and OCT ball lens in a back-to-back configuration. This configuration enabled the catheter to provide automatically co-registered IVUS and OCT images fused in real time as well as to maintain a micro-dimension at 0.9 mm in OD and 1.5 mm in length (Figure 3).⁵⁴ However, the current integrated IVUS-OCT system needs further improvements prior to clinical trials. The current integrated IVUS-OCT catheter performs at only 20 fps, which is much lower than the commercial OCT imaging speed (>50 fps). This slower imaging speed is nonideal because an increased amount of flushing contrast will be needed to obtain clear co-registered IVUS-OCT images. Moreover, a higher

imaging speed will allow for a faster pull-back imaging speed as well as a faster 3D volumetric image reconstruction, which will provide a more comprehensive visualization of entire plaque volume and shorten the procedure time. Thus, the future development of integrated IVUS-OCT should try to increase the current imaging speed of IVUS and bridge the imaging speed gap between IVUS and OCT. The mechanical design and electrical signal coupling of the hybrid catheter, especially for the transducer and electrical slip ring, should be further strengthened to maximize the efficacy of the hybrid IVUS-OCT. In addition, the hardware and data acquisition of the combined IVUS-OCT system is currently at the research stage. An integration of the hardware between the two systems along with the development of parallel computing algorithm to meet the high imaging speed requirement will advance the imaging system to the pre-clinical stage. Finally, successful translation of this technology to the clinical arena will require an explicit guideline for using the co-registered IVUS-OCT image pairs in assessing atherosclerosis and in guiding percutaneous coronary interventions (PCI).

Multi-frequency IVUS Imaging System

The genesis for the development of an integrated IVUS-OCT system was prompted by the significant gap in the image resolution and penetration depth between IVUS and OCT. Ultra-high frequency IVUS (>80 MHz), investigated previously, has been proven to provide improved resolution over conventional IVUS with a predictable trade-off of imaging depth to fill the gap between conventional IVUS and OCT.⁵⁵ A multi-frequency IVUS imaging system, which integrates a conventional IVUS transducer (35 MHz) with an ultra-high frequency IVUS transducer (80-150 MHz) into one single catheter, was recently reported to successfully image human coronary artery *in vitro*.⁵⁶ Shown in Figure 4, a clinically compatible size catheter (0.95 mm OD) and an integrated dual-channel ultrasonic system were prototyped and evaluated for *in vitro* human coronary artery imaging, with back-to-back arrangement of the two transducers to achieve image co-registration. The multi-frequency IVUS system was able to achieve a more comprehensive visualization of the coronary artery as compared with the integrated IVUS-OCT system by imaging the whole plaque volume using the low frequency transducer with deep penetration and by measuring the thin fibrous cap using the ultra-high frequency transducer with finer resolution. Although it is challenging to further increase the center frequency and bandwidth of the ultra-high frequency IVUS to reach the resolution level of OCT, the multi-frequency IVUS system is a promising alternative to the integrated IVUS-OCT system because of its low cost and the relative simplicity of integrating an ultrasonic-only system. As discussed in the study, the ultrasonic wave at ultra-high frequency experienced a much stronger attenuation from the luminal blood, significantly limiting the imaging depth and downgrading the quality of the ultra-high frequency IVUS images. Furthermore, increasing the imaging speed is necessary before implementing this preliminary multi-frequency IVUS system for the pre-clinical studies in which clearance of luminal blood during the imaging procedure may turn out to be a prerequisite. However, the use of radial-shape ultrasonic array transducer for IVUS application has the unique advantages of providing high-speed cross-sectional images of coronary arteries without mechanical scanning of ultrasonic transducer. Even though it will be difficult to develop an intravascular radial ultrasonic array more than 20 MHz, it is

anticipated that the fabrication of a multi-frequency intravascular array can be achieved on the further advancement of micro-fabrication techniques. Such multi-frequency imaging would not only provide the multi-scale morphological information of vessel wall, but also open up a new window for contrast enhanced molecular imaging and acoustic angiography to image the proliferation of *vasa vasorum* in the atherosclerotic plaques.⁵⁷

Integrated IVUS and NIRS Imaging System

NIRS has been validated for its capability to characterize the lipid composition of plaque by analyzing the spectral response from the scattering and absorption of NIR light by the cholesterol.³³ The TVC Imaging System (Infraredx, Burlington, Massachusetts) is the first commercial multimodal intravascular imaging system to fully assemble an IVUS transducer and an optical NIRS fiber into a single catheter to provide simultaneously co-registered IVUS-NIRS image without flushing procedure needed (Figure 5). In this way, the presence of the lipid content from the chemogram of NIRS image can be mapped on to the coronary artery structural information captured by the IVUS transducer, allowing for a more accurate detection of vulnerable plaque. The integrated IVUS and NIRS system has been evaluated in more than 90 hospitals across 10 countries, and extensive clinical data and case reports have validated its ability to identify lipid core plaque with improved accuracy.⁵⁸⁻⁶² However, the integrated IVUS-NIRS system also has several limitations: the NIRS can only display the lipid distribution along the lateral or transversal direction, which has poor resolution, and it does not contain axial resolution to determine the location and to quantify the size of the lipid-rich core. Moreover, it is still uncertain whether the penetration depth of NIRS is able to cover the entire field-of-view (FOV) of an IVUS image, especially to predict the lipid presence at a location relatively further away from the catheter tip. Therefore, to determine the treatment strategy for patients diagnosed with vulnerable plaques by the integrated IVUS-NIRS system, a prospective multi-center observational study of patients undergoing NIRS via TVC imaging system (COLOR Registry) is needed.⁶¹

Integrated IVUS and IVPA Imaging System

The principle of IVPA is based on the detection of acoustic waves generated by vascular tissue components when irradiated by a pulsed laser light. The unique optical absorption of different tissues when excited at a specific wavelength opens a new frontier for atherosclerotic plaque characterization. Lipid components within coronary arteries have a distinct absorption spectrum in the NIR wavelength range; specifically, several groups have demonstrated that the enhanced overtone absorption of C-H bonds excited at the wavelength range of 1.2 and 1.7 μm can be used for imaging and mapping lipids in an atherosclerotic plaque.⁶³⁻⁶⁶ Moreover, spectroscopic IVPA imaging was also investigated as a tool for providing additional information to further differentiate lipid components of atherosclerotic plaques.⁶⁷⁻⁶⁹ The beauty of IVPA is that it not only quantifies the size of lipid components, a key indicator of vulnerable plaque, but also automatically incorporates the IVUS image to clarify ambiguity such as photoacoustic signals generated by calcification (Figure 6a-i).⁶⁷ Because IVPA originated from the combination of optical illumination and ultrasonic detection, the quality of laser source and ultrasonic transducers are the two key determining factors for this new promising technology. Most of the previously integrated IVUS and

IVPA systems suffered from low imaging speeds (>25 seconds per frame) because of low repetition rate lasers (10 Hz), which hindered the progress of clinical study of IVPA. Wang et al. recently overcame this low imaging speed barrier by demonstrating highspeed IVPA imaging (at 1-4 fps) of lipid-laden plaque with nearly two orders of magnitude speed increase (Figure 7a-d). Meanwhile, the safety of IVPA will garner increased attention as advancement in IVPA imaging speed matches that of current commercial IVUS systems. To alleviate concerns over the safety of IVPA systems, modifications of the hybrid IVUS-IVPA catheter are required to increase the sensitivity of ultrasonic transducer and to improve the overlap of optical illumination and ultrasonic detection pathways to reduce the optical illumination power. Most commonly used miniature IVPA catheter designs have either a lateral or a longitudinal offset between the optical illumination path and the ultrasonic detection path (Figure 6j-m). This not only creates inaccuracy in the IVUS-IVPA images co-registration, but also limits the FOV of IVPA along the axial direction.^{34,63,70} An alternative is a confocal IVUS-IVPA catheter by using a miniaturized ring-shaped transducer in the high-speed IVPA system to enable an enlarged FOV with increased sensitivity. As a result, the IVPA system modified with the improved transducer requires significantly lower pulse energy (80 μ J) than those with traditional catheter designs.⁷¹ Other innovations on the horizon to further miniaturize the size of ring-shaped transducers are to switch to high-performance piezoelectric material for ultrasonic transducer fabrication, using laser dicing method and focused light illumination.

Integrated IVUS, OCT, and Fluorescence Imaging System

Although the fully integrated IVUS-OCT system captures most of the morphological features of atherosclerotic plaques with both deep penetration and high resolution, it lacks molecular specificity for characterization of the plaque composition. To solve this problem, Liang et al. recently reported a tri-modality intravascular imaging system that combines IVUS, OCT, and fluorescence imaging as an improved extension of the integrated IVUS-OCT system.⁵⁰ A double-clad fiber combiner was used to resolve the OCT beam and fluorescence beam coupling in the optical subprobe, which was aligned side-by-side with an ultrasonic transducer to fabricate a miniature trimodality catheter (Figure 8a-c). The tri-modality system was able to simultaneously acquire IVUS, OCT, and fluorescence signals from a coronary artery stained with fluorescent-imaging agent Annexin V conjugated Cy5.5, which was used to target the presence of macrophages (Figure 8d-f). The combination of these three modalities is synergistic in detecting key features of a vulnerable plaque that cannot otherwise be accomplished with a single modality such as IVUS for visualizing the gross architecture, OCT for the detailed examination of luminal microstructure, and fluorescence imaging for inflammatory reactions. Besides further reducing the size and increasing the imaging speed for a clinically compatible catheter, some important validations are required before translating of this technology to *in vivo* human coronary artery imaging, including systematically quantifying the imaging depth of fluorescence imaging and evaluating the longterm safety associated with the use of fluorescent-imaging agents.

Other IVUS-Based Multi-modality Intravascular Imaging Systems

Notably, there are several other IVUS-based multi-modality intravascular imaging systems in early stages of development. Similar to fluorescence imaging, time-resolved fluorescence spectroscopy (TRFS) and fluorescence lifetime imaging (FLIM) are another two functional imaging modalities with molecular specificity to characterize the compositions of vulnerable plaques. Both an integrated IVUS-TRFS³⁹ and an integrated IVUS-FLIM⁷² imaging system have been reported. They enabled the mapping of biochemical information onto conventional IVUS images to evaluate the molecular composition of superficial plaques. These technologies can improve the characterization of vulnerable plaques when combined with existing imaging modalities; investing in the further improvement of the integrated system's performance and imaging quality will prove the foreseeable value of such integrations. Moreover, some emerging technologies based on micro-scale electric-sensors, such as electrochemical impedance spectroscopy (EIS), offer a feasible approach to identifying active metabolism inside atherosclerotic plaques. This technology also has the potential for implementation in a catheter-based device to help differentiate the cellular composition of vulnerable plaques.⁷³ Furthermore, it has already been proposed that a plaque's vulnerability can be predicted by assessing the biomechanical properties of the coronary artery wall.⁷⁴ For this reason, high-resolution elastography techniques are rapidly being developed toward this goal in offering precise mapping of the vessel wall's biomechanical information onto structural IVUS or OCT images to detect vulnerable plaques.⁷⁵⁻⁷⁷ Examples of these emerging technologies include acoustic radiation optical coherence elastography and high-resolution harmonic motion imaging.

Future Perspectives of IVUS-Based Multi-modality Intravascular Imaging

Despite challenges to its validity in characterizing vulnerable atherosclerotic plaques, IVUS imaging still forms the basis for most multi-modality intravascular imaging systems owing to its wide recognition and extensive scientific studies. But IVUS alone cannot meet the urgent need for improved diagnosis of atherosclerosis to prevent heart attack, mainly because it lacks the resolution capacity to identify features specific to vulnerable plaques such as TCFA. Instead, newly developed intravascular imaging techniques, namely, IVUS-OCT, multi-frequency IVUS, IVUS-NIRS, IVUS-IVPA, IVUS-FLIM/TRFS, and IVUS-OCT-fluorescence, must meet the challenge. Two candidates are the integrated IVUS-OCT and the multi-frequency IVUS imaging systems, which offer higher resolution imaging to visualize the microstructure of coronary arteries and the presence of thin fibrous caps. Integrating OCT with IVUS is considered superior to integrating an ultra-high frequency IVUS with a conventional IVUS because of OCT's unique optical scattering contrast and its maturity in the market. However, the multi-frequency IVUS imaging system, an ultrasonic-only solution, is more advantageous in terms of low cost and simplicity for integration. Infraredx's IVUS-NIRS is the only commercially available multi-modality intravascular imaging systems. Infraredx's IVUS-NIRS is undergoing prospective clinical trials worldwide to determine its ability to accurately detect vulnerable plaques. Hopefully, it will become part of the clinical practice for the diagnosis of vulnerable plaques and prevention of heart attack. Among all the innovative techniques that characterize lipid components inside vulnerable plaques based on molecular specificity, IVPA is capable of quantifying the size

and location of the lipid-rich necrotic core. On continued refinement of the integrated IVUS-IVPA imaging system, it is likely that this technology will become a “game-changer” in the near future by providing clinically crucial information. An alternative direction in determining the plaque vulnerability by evaluating the molecular composition of coronary arteries is via fluorescence imaging TRFS and FLIM. Due to the complexity of the fabrication process, most of the intravascular multi-modality used in clinic and research were made by hand with an OD around 1 mm. No doubt, further minisculizing of the multi-modality intravascular catheter will be beneficial when delivering such catheters into the complex and confined coronary circulation system. However, the current major technological barrier limiting the further downscaling of the IVUS-based multi-modality catheters is the size of ultrasonic transducer. Because further reducing the aperture size of IVUS transducer would sacrifice the FOV of the IVUS image, implementation of an advanced signal processing algorithm, such as chirp coded excitation, could potentially compensate for the lost imaging depth from reduced aperture size.⁷⁸

Based on the current understanding of markers in TCFA-phenotypic vulnerable plaques, the comparisons of various IVUS-based multi-modality intravascular imaging systems reviewed in this article are listed in Table 1. Given that each intravascular imaging modality has its own distinctive advantages and limitations, future advance is to further integrate more than two imaging modalities to complement each other's deficiencies and to significantly enhance the characterization of vulnerable plaques. However, the complexity of optimal combination of various imaging techniques remains to be determined. An ideal multi-modality intravascular imaging technique would be operated in a clinically compatible manner and, more importantly, would identify the most number of morphological structures as well as the metabolic state distinctive to vulnerable plaques. The current IVUS-based multimodal intravascular imaging techniques still operate at a relatively low imaging speed with long imaging acquisition time, posing a safety concern. The integrated IVUS-OCT and integrated FLIM is attempting to solve this problem by reaching a satisfactory imaging speed of 20 fps for *in vivo* studies.^{47,79} Further strengthening the mechanical design of imaging, improving the electrical signal coupling, and optimizing the data processing algorithm are strategies for providing a 3D visualization of entire coronary artery within several seconds. Recently, the imaging speed of integrated IVUS-IVPA system has been improved with two orders of magnitude (1 fps), but this is still not fast enough for the clinical setting. The main technical barrier hindering the imaging speed of IVPA is the shortage of high repetition rate pulsed laser at 1200 nm and 1700 nm; thus, the successful development of such lasers will allow the integrated IVUS-IVPA imaging system to bridge the above-mentioned speed limit.

From a sociological perspective, a successful clinical translation of multi-modality intravascular imaging will require acceptance by the greater medical community of its diagnostic value and willingness for clinicians to acquire training in interpreting the co-registered images.²⁷ Currently, the operational procedures IVUS and OCT were fit into the clinical work flow of PCI in the catheterization lab equipped with x-ray angiography. The recent clinical studies showed that the procedure time of IVUS-guided PCI is around 14 minutes longer than that of the angiography-only guided PCI, and there was no significant procedure time difference between OCT-guided PCI and angiography-only guided PCI.^{81,82} Thus, the operation time by using IVUS-based multi-modality intravascular imaging will not

exceed the operation time of IVUS-guided PCI, which will be significantly shortened compared with using multiple catheter separately. Generally, an IVUS imaging console and one-time use disposable IVUS catheter cost \$100,000 to \$200,000, and \$600 to \$1000, respectively. The commercially available intravascular OCT catheter is also priced around \$600. It is anticipated that the estimated cost of the integrated imaging system console and catheter will be higher than that of a single IVUS imaging system. Among all the IVUS-based intravascular imaging discussed in this review, the multi-frequency IVUS would be the most cost-effective technology because it only requires a moderate refinement of current IVUS system without the need of adding an optical laser source. However, the estimation of absolute cost of these IVUS-based multimodal intravascular imaging systems is a quite complex process, which should weigh on the time to achieve the regulatory certificates such as US Food and Drug Administration (FDA) approval, reimbursement plan, and the business development strategy of the companies or individuals who are commercializing these technologies. The longterm cost-effectiveness analysis and clinical-outcome evaluation are still needed to further investigate whether the foreseeable benefits of using multi-modality intravascular imaging to guide PCI, such as minimizing the use of iodine contrast, providing more precise stent implantation, and reducing the possibilities of restenosis, are able to outweigh the increased cost. Last, but not the least, investment interests in biomedical device innovation and proper handling of the intellectual property rights are essential to accelerating the future development of multi-modality intravascular imaging.

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Figure 1. Scheme of the phenotype of vulnerable atherosclerotic plaque—TCFA. Morphologic and biologic function markers distinctive to TCFA are illustrated, including thin fibrous cap, large lipid-rich necrotic core, macrophages infiltration, *vasa vasorum* proliferation, and spotty calcifications.⁷ TCFA = thin-cap fibroatheroma.

Figure 2.

Representative images acquired by the fully integrated intracoronary OCT-IVUS system. (Top row) *in vivo* imaging of a normal swine coronary artery with OCT and IVUS systems. (a) IVUS image, (b) OCT image, and (c) corresponding hematoxylin and eosin (H&E) histology that mainly colors the nuclei of artery tissue cell. Guidewire (G) artifact is denoted by * in (b). Yellow boxes denote the left anterior descending branch. From the center of the OCT image, there is a high-signal, thin band corresponding to the intima, followed by a high-signal strip corresponding to the external elastic lamina, and finally a low-signal area corresponding to the adventitia. (Bottom row) imaging of a coronary artery with a lipid plaque. (d) IVUS images, (e) OCT images, (f) co-registered IVUS-OCT pairs, and (g) corresponding histological images. Insets in (g) are highly magnified images of the histology slides: left inset, stained with H&E; right inset, stained with cluster of differentiation 68, which binds to the low density lipoprotein and expresses macrophages. Arrows denote the location of plaques. A low echogenicity region from 5 o'clock to 7 o'clock in (d) and a diffusive-boundary, signal-poor region from 5 o'clock to 7 o'clock in (e) indicate a lipid plaque. The histology results confirm the classification of plaque types by the OCT and IVUS images: In (g), foam cells and dark brown staining in the cluster of differentiation 68 stain slide verify that this is a lipid plaque. Note for (g): because this excised tissue is older (~10 months post-mortem), the degraded nuclear material did not stain well with hematoxylin. Although the tissue is predominantly pink in color, the structure and architecture are preserved. Scale bar = 1 mm. A = adventitia; E = external elastic lamina; I = intima; T = tissue; V = vessel. Adapted from Li et al.⁴⁷ OCT = optical coherence tomography; IVUS = intravascular ultrasound.

Figure 3.

(a) Schematic of the integrated imaging system. The dashed box illustrates the OCT subsystem, a swept-source OCT system. Black lines, a green line, and a blue line denote the optical path, the ultrasound path, and the electrical trigger signal, respectively. (b) Schematic of back-to-back OCT-IVUS probe. (c) Photo of back-to-back probe, showing the transducer. Inset: photo showing the OCT subprobe. (d) Schematic of cardiovascular system. Adapted from Li et al.⁵⁴ OCT = optical coherence tomography; IVUS = intravascular ultrasound.

Figure 4.

(a) Diagram of back-to-back multi-frequency IVUS catheter. Middle: 3D drawing. Left-bottom: sectional drawing. (b) Photograph of a multi-frequency IVUS catheter prototype. Enlarged photograph: side view (top) and front view (bottom) of catheter tip. (c) Fused IVUS images of human coronary artery captured by 35 MHz (grayscale)/90 MHz (orange) multi-frequency IVUS catheter: with the 90 MHz transducer, the three-layer structure (intima, media, and adventitia) more clearly identified because of the improved axial resolution. (d) Fused IVUS images of human coronary artery captured by 35 MHz (grayscale)/120 MHz (green) multi-frequency IVUS catheter: although the 120 MHz transducer can only image through the intima layer due to the limited penetration depth, an improvement in both axial and lateral resolution is achieved with a reduced speckle size in the image of intima layer. Dynamic range: 50 dB. Scale bar: 1 mm. Adapted from Ma et al.⁵⁶ IVUS = intravascular ultrasound; OD = outer diameter.

Figure 5.

(a) Photograph of integrated IVUS-NIRS imaging system (TVC imaging system™, Infraredx, Inc) including a TVC Imaging System™ console, a TVC Nexus™ Controller, and a TVC Insight™ Catheter. (b) Multi-modality TVC Insight Catheter core assembly. (c) TVC Composite™ View of co-registered NIRS lipid core plaque with IVUS. (d) Chemogram of the NIRS image. The yellow-red color-coded map illustrates the probability of the presence of a lipid core (yellow corresponds to high probability and red to low probability). (e) Co-registration of IVUS and NIRS data. Adapted from website of Infraredx, Inc. (<http://www.infraredx.com/>). IVUS = intravascular ultrasound; NIRS = near-infrared spectroscopic.

Figure 6.

(a-i) Lipid detection in an atherosclerotic human coronary artery using spectroscopic IVPA at 1.2 and 1.7 μm . (a) 1205 nm and (b) 1235 nm combined IVPA-IVUS images (IVPA 25 dB, IVUS 40 dB). (c) Lipid map based on 2-wavelength relative difference between the PA signal at 1205 nm and 1235 nm. (d) 1710 nm and (e) 1680 nm combined IVPA/IVUS images (IVPA 25 dB, IVUS 40 dB). (f) Lipid map resulting from the 2-wavelength relative difference between the photoacoustic signal at 1710 nm and 1680 nm. Both lipid maps are shown overlaid on the corresponding IVUS image. (g) Lipid histology stain (Oil Red O); lipids are stained red; calcification is stained black. (h) $5\times$ magnification of the part of the atherosclerotic plaque indicated as lipid rich by the lipid stains (area outlined in black in (g)) shows large extracellular lipid droplets, while the lipids in all other parts of the lesion are intracellular or contained in small extracellular droplets. (i) $4\times$ magnification of area outlined in black in (h). (j) Diagram of the experimental setup, including a detailed schematic of the catheter tip, showing the beam layout. (l) Photograph of the catheter tip on the edge of a 10 eurocent coin. White arrow indicates 1 mm. (m) Photograph of the catheter tip, showing the light beam exiting the catheter. Figure 6(a-i) are adapted from Jansen et al.,⁶⁸ Figure 6(j) is adapted from Jansen et al.,⁶³ and Figure 6(l-m) are adapted from Jansen et al.⁶⁷ IVPA = Intravascular photoacoustic; IVUS = intravascular ultrasound; AWG = arbitrary wave generator; DAQ = data acquisition; exp = expander; lim = limiter; bpf = bandpass filter; amp = amplifier.

Figure 7.

(a) High-speed IVPA and (b) IVUS imaging of an atherosclerotic artery. (c) Merged PA/US image. (d) Histology of the artery cross section of the area imaged by IVPA method. The 5-mm spatial calibration applies to all panels. Lipid deposition on the arterial wall, which is not seen in the IVUS image, shows clear contrast in the IVPA image. The white area in the histology image from hematoxylin and eosin staining shows the location of the lipid deposition. (e) Schematic and (f) photograph of the IVPA probe. (g) Photograph of the scanning assembly. Adapted from Wang et al.⁷¹ IVPA = Intravascular photoacoustic; IVUS = intravascular ultrasound.

Figure 8.

(a) Schematic of the tri-modalities integrated system and the probe. OCT and fluorescence systems were combined with a wavelength division multiplexer. US signal was synchronized with optical signal by the trigger from swept-source laser. (b) Structure of the tri-modality endoscopic probe: the optical probe and ultrasound transducer were placed side-by-side. (c) Photograph of the tri-modality catheter. The rigid portion of the probe is 7 mm and the diameter is 1.2 mm. The scale is in centimeters. *Ex vivo* images from human coronary artery (d) combined OCT and fluorescence image, (e) combined ultrasound and fluorescence image, and (f) combined tri-modality image. Adapted from Liang et al.⁵⁰ WDM= wavelength division multiplexer; DCF = double clad fiber; OCT = optical coherence tomography; US = ultrasound.

Table 1

Comparisons of Different IVUS-Based Multi-modality Intravascular Imaging Systems.

Integrated Multi-modality Imaging	Fibrous Cap Thickness	Lipid-Rich NC	Lipid-Content Mapping	Inflammation/Macrophages	Spotty Calcium	Thrombus Detection	Plaque Rupture	Flushing Required	Speed (fps)
IVUS-OCT ^{44,48,80}	☑☑	☑	☐	☐	☑☑	☑	☑☑	Yes	20
M-IVUS ^{55,56}	☑	☐	☐	☒	☑☑	☐	☑	TBD	TBD
IVUS-NIRS ⁵⁸⁻⁶²	☒	☑☑	☑	☑	☑	☐	☑	No	TBD
IVUS-IVPA ^{34,35}	☒	☑☑	☑☑	☑	☑	☐	☑	TBD	1
IVUS-OCT-FF ⁵⁰	☑☑	☑	☐	☑☑	☑☑	☑	☑☑	Yes	10
IVUS-FLIM/TRFS ⁷²	☐	☑	☐	☑☑	☑	☐	☑	Yes	20 ⁷⁹

The capability of identifying the key markers of vulnerable plaques is graded as excellent (☑☑), good (☑), possible (☐), and impossible (☒) IVUS = intravascular ultrasound; NC = necrotic core; OCT = optical coherence tomography; M-IVUS = multi-frequency intravascular ultrasound; NIRS = near-infrared spectroscopy; IVPA = intravascular photoacoustics; FI = fluorescence lifetime imaging; FLIM = fluorescence lifetime imaging; TRFS = time-resolved fluorescence spectroscopic; TBD = to be determined.