Medical Engineering and Physics 96 (2021) 71–80

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

Intravascular imaging of coronary artery: Bridging the gap between clinical needs and technical advances

Atefeh Abdolmanafi [*,a,c], Luc Duong [a,c], Ragui Ibrahim [b], Nagib Dahdah [c]

[a] Department of Software and IT Engineering, École de Technologie Supérieure, Montréal, Canada
[b] Division of Cardiology, Hôpital Pierre Boucher, Longueuil, Canada
[c] Division of Pediatric Cardiology and Research Center, Centre Hospitalier Universitaire Sainte-Justine, Montréal, Canada

ARTICLE INFO

Keywords:
Coronary artery disease
Atherosclerotic plaque
Optical coherence tomography
Medical image analysis
Deep learning

ABSTRACT

Coronary artery disease is the leading cause of mortality worldwide. Almost seven million deaths are reported each year due to coronary disease. Coronary artery events in the adult are primarily due to atherosclerosis with seventy-five percent of the related mortality caused by plaque rupture. Despite significant progress made to improve intravascular imaging of coronary arteries, there is still a large gap between clinical needs and technical developments. The goal of this review is to identify the gap elements between clinical knowledge and recent advances in the domain of medical image analysis. Efficient image analysis computational models should be designed with respect to the exact clinical needs, and detailed features of the tissues under review. In this review, we discuss the detailed clinical features of the intracoronary plaques for mathematical and biomedical researchers. We emphasize the importance of integrating this clinical knowledge validated by clinicians to investigate the potentially effective models for proper features efficiency in the scope of leveraging the state-of-the-art of coronary image analyses.

1. Introduction

Atherosclerosis is recognized as the main cause of cardiovascular disease and the leading cause of death worldwide. Plaque development, progression, and rupture caused by atherosclerosis result in myocardial infarction and stroke, which are respectively the first and the fifth causes of death [1,2]. Advances in interventional cardiology, the catheter-based treatment procedure of heart disease, could improve the treatment strategy and contribute to assist millions of patients, thus avoiding coronary bypass surgery [3,4]. But before any treatment, cardiologists need to understand the type, location, and the level of progression of the atherosclerotic plaques to personalize their treatment strategy. Understanding the plaque morphology and its sub-components is fundamental to assist clinicians by providing them with the accurate information of plaque progression. This is where advanced cardiovascular imaging systems play the role of providing automatic plaque morphology assessment. Investigating the performance, effectiveness, advantages, and limitations of the cardiovascular imaging systems in plaque morphology accuracy as well as the clinical needs are the first important steps to define the effective scientific research projects. As we take these first steps firmly and correctly, new image analysis computational models and artificial intelligence algorithms come into play to fulfill the needs efficiently.

The main goal of this review article is to strictly underline a very critical fact that technical and clinical needs in development of medical imaging systems are tightly linked to each other. The focus of the survey is not only to assess the existing computational models proposed for analyzing the OCT images, but also to highlight a significant factor to be considered in the field of research and development, which is understanding the clinical aspects of the problem prior to developing any computational model. This is important since most of the time, the proposed models are not useful in clinical applications although they are all grounded on very strong mathematical concepts. The reason is that the clinical needs have not been targeted correctly or the clinical features of the tissues under review have not been investigated and understood for designing an applicable analytical model. This is a repeating cycle which is taking our research far from being advanced in terms of clinical use. In this review, we aim to provide a reference for clinical aspects of the atherosclerotic coronary artery, and the features of such atherosclerotic tissues in OCT images.

We review the trending clinical needs, display the difference between various coronary artery sequelae and plaques, and we review the

* Corresponding author at: Department of Software and IT Engineering, École de Technologie Supérieure, Montréal, Canada.
E-mail address: atefeh.abdolmanafi.1@ens.etsmtl.ca (A. Abdolmanafi).

https://doi.org/10.1016/j.medengphy.2021.09.003
Received 24 September 2020; Received in revised form 13 August 2021; Accepted 13 September 2021
Available online 16 September 2021

emerging technical solutions for identifying, characterizing, and predicting the rupture of the vulnerable plaque. We address the issues from the following angles:

- Explore the existing intravascular imaging systems and their limitations (Section 2).
- Describe the normal structure of coronary artery and visualization of various arterial wall tissues in OCT images (Section 3).
- Review the process of atherosclerotic plaque development and clinical features of plaques and other atherosclerotic tissues in OCT images (Section 3).
- Discuss the technical innovations, which should be considered to improve the imaging systems.
- Review the existing technical studies to investigate the needs and further technical improvements (Section 4).
- The limitations of recent studies, the clinical needs, and possible future development of the state-of-the-art intravascular imaging is discussed in Section 5.
- Section 6 is a summary with conclusion remarks on findings from the body of the paper.

Sections 2, 3, and 5 present specifically the interventional cardiologists' views. For related technical studies, we considered sixteen related works, which were performed in 2019–2021 to improve the plaque indication in intravascular Optical Coherence Tomography imaging. The studies are assessed based on targeted clinical needs, and the designed computational models based on machine learning and deep learning approaches in various stages of the disease.

2. Review of the intravascular imaging systems

Intravascular imaging evolved in response to the limitations of the cardiac imaging systems to indicate intracornay plaque morphology and their sub-components. For X-ray based imaging systems, the penetration depth is inversely proportional to tissue density. Intravascular structures cannot be determined by radiography unless they become calcified to attenuate more radiation and are visualized radiopaque. This is the main limitation of invasive coronary angiography (CA), and non-invasive coronary computed tomographic angiography (CCTA), which are both in the category of cardiovascular anatomic imaging systems. Consequently, both systems are limited to indicate intracoronary plaque sub-components [5–8]. Compared against X-ray-based imaging systems, Magnetic Resonance Angiography (MRA) should have better soft-tissue characterization as well as lacking harmful radiation. Despite the strength, in coronary circulation, MRA is not recommended to be used. High quality coronary image acquisition using MRA is challenging considering its motion artifacts caused by extended acquisition time, low spatial resolution, and low volumetric coverage [5,6,8,9].

Detailed indication of plaque morphology is possible by imaging the arterial wall in cross-sectional view. Intravascular Ultrasound (IVUS) is a catheter-based imaging system. The IVUS catheter generates sound wave in the range of 20–60 MHz and provides gray-scale cross-sectional images of arterial wall tissues. IVUS is limited to indicate plaque components. Using virtual histology (VH-IVUS), spectral analysis of back-scattered IVUS radio-frequency data, characterization of four plaque types is possible. Although VH-IVUS can indicate fibrous, fibrofatty, necrotic core, and dense calcium, but detection of the thin cap fibroatheroma, which is the most important predictor of plaque rupture is not possible using VH-IVUS. The limitation is due to noise enhancement, system artifacts, and low spatial resolution of the system (100–150 μm) [5,10]. Optical Coherence Tomography (OCT) is an interferometric imaging modality with high resolution that maps the back-scattered near-infrared light to create cross-sectional images of the tissues under review. OCT is a turning point in medical imaging techniques. Intravascular OCT has become an increasingly powerful tool in interventional cardiology with the highest resolution of 10–15 μm to provide detailed intracoronary tissue information, including various elements of vascular wall infiltration, and indication of atherosclerotic plaque morphology. Despite its high resolution, there is no harmful radiation involved, and image acquisition is very fast with minimum risk for patients (excluding the risk inherent to the invasive nature of the image acquisition). Compared against other intracoronary imaging systems, this state-of-the-art imaging system has incredible advantages. But OCT has some important limitations to be addressed [5,11,12]. Various generations of the OCT system were developed to ease the interpretation of the OCT images such as multi-modality IVOCT imaging and dual-modality catheter endoscope. Although the new generations of the OCT system could improve the quality of the acquired images, but interpretation of various pathological tissue types remains challenging [13,14]. As the main limitation, interpretation of the acquired images is operator dependent, which is not only very time-consuming but also highly error prone from one observer to another. The gap is identified as being the lack of a precise and accurate automated technology for analyzing OCT images of coronary artery, which would enable widespread use of this technology for diagnosis and intervention purposes. Being innovative to design a technique, which can accurately address this issue of the OCT imaging system, we have to understand the exact mechanism and clinical features of the atherosclerotic plaques. Full understanding of the plaque formation mechanism depends on comprehensive knowledge of the structure and functionality of normal arterial wall.

3. Intracoronary plaque development & rupture

3.1. Normal coronary artery

Normal arterial wall has three-layered structure. Intima is the first and closest layer to the arterial lumen, which is covered by single layer of endothelial cells. Normal intima is nourished by oxygen diffusion of the lumen. Endothelial cells have significant responsibilities in arterial wall functionality. They are responsible to provide anti-thrombotic molecules to prevent blood clot. In addition, they secrete substances (vasodilators and vasoconstrictors) to adjust contraction of the smooth muscle cells (SMCs) in the media layer. To deal with the local inflammations and adjust the immune responses, endothelial cells resist leukocyte adhesion, which are white blood cells of immune system. It is very important to know that being exposed to different stressors, endothelial cells can produce pro-thrombotic molecules [1]. Intima is visualized as homogeneous signal-rich layer in OCT images. It is difficult to specify the exact thickness of the intima layer by pathology since intima thickness depends on various factors such as age, gender, and bio-mechanical characteristics. But, in OCT, the thinnest intima is defined as intima layer with the thickness of 4 5 μm, which becomes thicker by age. Intima layer with the thickness of 300 600 μm is considered as non-atherosclerotic intimal thickening [15]. Media is the second and thickest layer of normal arterial wall, which is mainly responsible of elastic functions of the artery. It is nurtured by vasa vasorum in the outermost layer of arterial wall, adventitia. Two boundaries of elastin called internal and external elastic lamina separate media from intima, and adventitia respectively. Media composed of SMCs and extracellular matrix (ECM), which they tightly work together. SMCs not only provide vasoactive and inflammatory mediators, but also they synthesize the collagen, elastin, and proteoglycans, which form the bulk of ECM. ECM is responsible for retaining the structural integrity of the arterial wall, which composed of collagen, and elastin. Collagen provides the bio-mechanical strength of the artery to avoid failure at high pressure, while elastin provides flexibility and control the reversible extensibility of the arterial wall during cardiac cycles [1,16]. Media layer is characterized as a signal-poor layer in OCT images with the thickness of 125–350 μm. Internal and external elastic lamina are signal-rich bands in OCT images with the thicknesses < 3 μm, and 3–6 μm respectively (Fig. 1) [15].

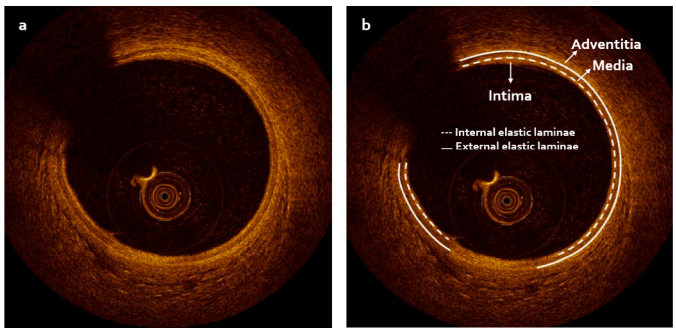

Fig. 1. OCT image of normal arterial wall: Intima is visualized as a signal-rich layer, Media is shown as a signal-poor layer by OCT, adventitia is characterized as a signal-rich layer. Internal and external elastic laminae are shown as signal-rich bands with dashed and filled lines respectively [15].

3.2. Atherosclerosis and plaque development

Atherosclerosis initiates by accumulation of low-density lipoprotein (LDL) in the arterial wall, which results in an active inflammatory process. Various factors contribute to the inflammatory process of atherosclerosis, which can be categorized accordingly: Endothelial dysfunction, accumulation of lipids in the intima layer, deployment of leukocytes and SMC to the vessel wall, foam cell formation, and deposition of ECM [1]. Based on the classification of atherosclerotic lesions by the American Heart Association (AHA) [17], development of atherosclerosis includes various stages: 1. Non-atherosclerotic intimal thickening as a result of SMCs accumulation in the intima while lipid or macrophage foam cells are not developed in this stage. 2. Fatty streak or intimal xanthoma which appears as a result of accumulation of foam cells in the luminal side of the arterial wall while no necrotic core and fibrous cap are seen in this stage of the disease. 3. Pathological intimal thickening is defined as accumulation of SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation while there is no sign of necrotic core. This stage of the disease can be followed by the luminal thrombus 4. Fibroatheroma (fibrous cap atheroma) is developed as a result of the necrotic core formation with an overlying fibrous cap. This stage can be followed by luminal thrombus. 5. Thin cap fibroatheroma (Thin fibrous cap atheroma) which is characterized by infiltration of macrophages and lymphocytes with SMCs and an underlying necrotic core. This stage can be followed by plaque rupture. 6. Fibrocalcific plaque which is a collagen-rich plaque with large calcification and few inflammatory cells. This results in a severe stenosis with or without necrotic core development. The process of plaque development is explained in the following sections.

3.2.1. Intimal thickening

Non-atherosclerotic intimal thickening Accumulation of SMCs and proteoglycan-rich ECM results in intimal thickening. In the absence of the inflammatory infiltration, lipid accumulation, and macrophage foam cells, the intimal thickening is considered as non-atherosclerosis. Although this type of intimal thickening occurs in atherosclerosis-prone arteries including coronary artery, but they do not result in atherosclerosis necessarily. In OCT, non-atherosclerotic intimal thickening is visualized as signal rich region with the thickness of 300–600 μm [1,15]. Fig. 2 shows partial intimal thickening with partial media disappearance in OCT images.

Pathological intimal thickening Pathological intimal thickening (PIT) is the earliest stage of the atherosclerotic lesion formation. In histological point of view, PIT is characterized by intimal thickening > 600 μm with small area of lipid pool (< 1 quadrant of the OCT cross-sectional image), which may follow by macrophage accumulation in luminal side of the lipid pool (Fig. 3). Micro-calcification emanated by SMCs, and free cholesterol crystals can be found in lipid pools as well (Fig. 4) [1,15,18,19].

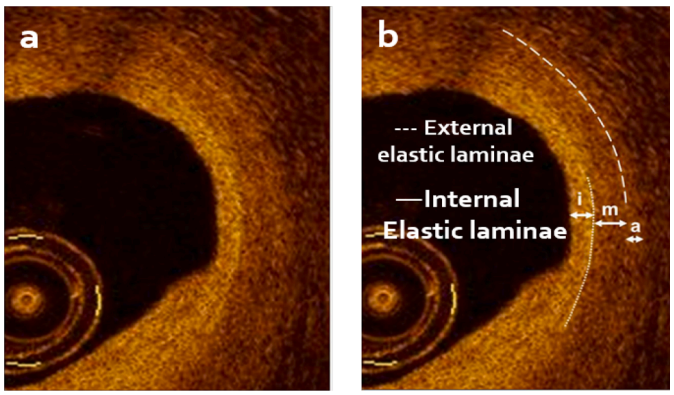

Fig. 2. Part of OCT coronary cross-section with partial intimal thickening and media disappearance [15].

3.2.2. Fibrocalcific plaque

Intimal calcification is the most common type of calcification. The process of calcification formation and progression is not completely known. Apoptosis of SMCs and macrophage may contribute in development of fibrocalcific plaques. Lowest grade of calcification is seen in pathological intimal thickening close to internal elastic lamina and healed plaque rupture followed by fibroatheroma show the highest grade of calcification. It is important to mention that stable plaques are more calcified than vulnerable plaques. Calcification is visualized in OCT images as sharply delineated signal-poor regions (Fig. 6) [1,15,19,20].

3.2.3. Fibroatheroma

In progressive atherosclerosis, secreting proteolytic enzymes particularly matrix metalloproteinases (MMPs) at luminal border of the plaques degrade the collagen and allow infiltration of SMCs. This results in thinning the fibrous cap and remodelling of the arterial wall. Macrophages act as mediators in response to the remodelling of the vessel, which leads to excessive infiltration of macrophages. Death macrophages create necrotic core, which is surrounded by fibrous cap. This is the most important characteristic of fibroatheroma as a sign of progressive stage of the atherosclerosis process. Fibroatheroma progression associates with different stages of the necrotic core formation, which results in either early-stage or late-stage fibroatheroma. Early-stage fibroatheroma is distinguished by presence of the proteoglycans in the lipid pool and macrophage accumulation (Fig. 7). Late-stage fibroatheroma is characterized by the excessive amount of cellular debris, free cholesterol, calcification, intra-plaque haemorrhage, and fully evacuated ECM (Fig. 8).

Fibroatheroma is distinguished in OCT images with signal-poor regions of lipid pool and necrotic core. Since necrotic core is not distinguishable by OCT, lipid pool/necrotic core is considered as a single signal-poor region in the OCT images and commonly this region takes > 1 quadrant of the arterial cross-section. Fibrous cap thickness is an indicator of plaque vulnerability and is categorized as follows: 1. Fibrous cap thickness < 55 μm is related to ruptured plaques. 2. Fibrous cap thickness > 84 μm is defined as stable fibroatheroma. 3. Fibrous cap thickness in the range of 55–84 μm is characterized as thin cap fibroatheroma (TCFA). TCFAs usually have necrotic core arcs $> 120^{\circ}$ (Fig. 9) [1,15,21–23].

3.2.4. Determinants of plaque rupture

Atherosclerosis is a complex inflammatory disease of coronary artery. Macrophage accumulation is the most important and the main factor and effector of the inflammatory process, which associates with almost all stages of the atherosclerotic plaque development and

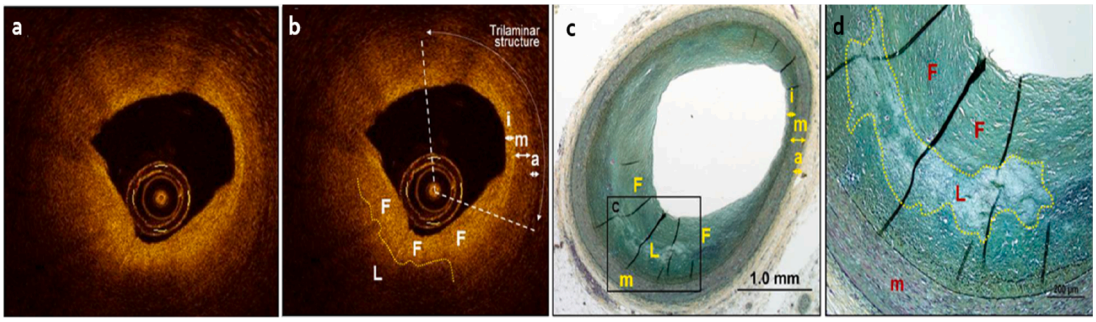

Fig. 3. Pathological intimal thickening/fibrous plaque. (a) shows the original OCT image. (b) is annotated OCT image: F:Fibrous tissue, L: Lipid pool, i: Intima, m: Media, and a: Adventitia. Corresponding histological sections are shown in (c) and (d) [15].

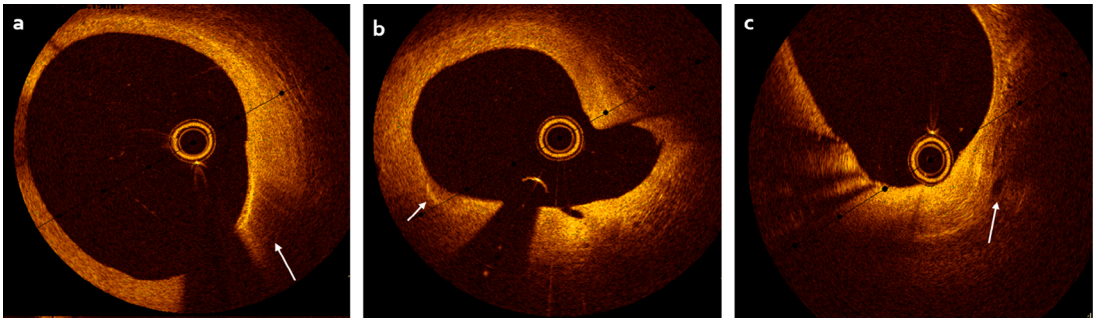

Fig. 4. Examples of intimal thickening with macrophage infiltration, cholesterol crystal, and micro-calcification, which are shown with arrows in (a), (b), and (c) respectively.

progression. In early stages of the disease, macrophages infiltrate in intima to respond the cholesterol uptake, and LDL phagocytosis, which results in foam cell formation. Macrophages are characterized by OCT as signal-rich bright bands or spots with a dorsal shadow in the direction of the light (one example is shown in Fig. 4) [1,15,24]. By progression of the atherosclerosis, in intimal thickening of about 500 μm, hypoxia, lack of optimal oxygen supply in intima, results in progression of micro-vessels. Micro-vessels density depends on chronic inflammatory cell infiltration. Due to their defective endothelial junctions, micro-vessels are characterized by weak and permeable structure, which results in invasion of lipids and inflammatory cells into the intima and intraplaque haemorrhage, which they can highly contribute in plaque vulnerability. Micro-vessels are shown in OCT images as rounded signal-poor structures (Fig. 5). Extensive macrophage infiltration results in plaque rupture, which causes coronary thrombosis and acute coronary syndrome. Coronary thrombus is categorized in two types: 1. White thrombus is composed of platelets and fibrin, which is visualized as homogeneous signal-rich region in OCT images. 2. Red thrombus is composed of the red blood cells, and characterized by OCT as signal-poor region since blood highly attenuates the light (Fig. 10) [1, 15,25].

As it was mentioned previously in this review article, medical imaging systems play significant role in early detection, diagnosis, effective decision-making and treatment of the disease. Interpretation of the medical images by human experts including radiologists, clinicians, and trained technicians is non-accurate and highly challenging considering high variation of pathological features of the disease and possible human errors. We investigated the state-of-the-art imaging system for coronary plaque indication and understood the mechanism of plaque development and clinical features of the coronary plaques. Now it is the time to integrate machine learning approaches and design proper computational models which can provide clinicians with a real-time fully analytical model of coronary artery with high precision. To this end, we refer to recent related technical studies to realize what needs to be done further considering the limitations of the existing studies in both technical and clinical aspects.

4. Review of algorithms & their applicability in image interpretation

Artificial intelligence, computer-aided models, is rapidly evolving in various medical fields. Due to their high fidelity and efficiency, these

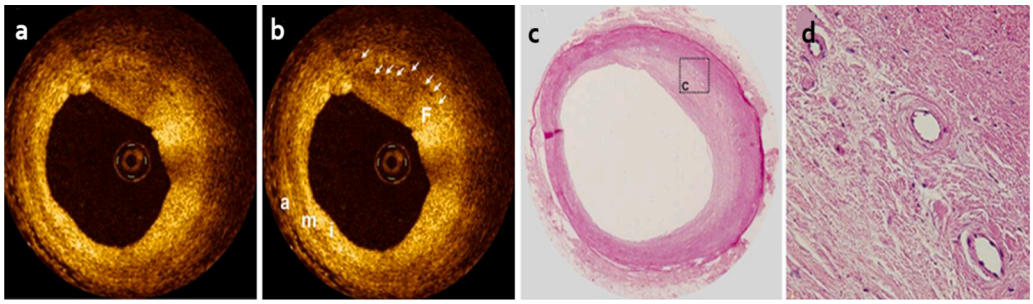

Fig. 5. OCT images with micro-vessels: (a) Original image, (b) annotated image. Corresponding histological sections are shown in (c) and (d) [15].

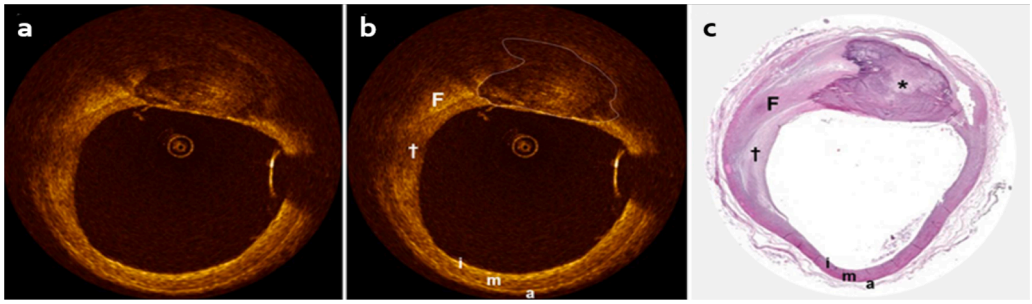

Fig. 6. Calcification in OCT imaging: (a) Original OCT image, (b) Annotated image: F: Fibrous tissue, t: Fibrous tissue with low signal intensity, i: Intima, m: Media, a: Adventitia, (c) Corresponding histological image [15].

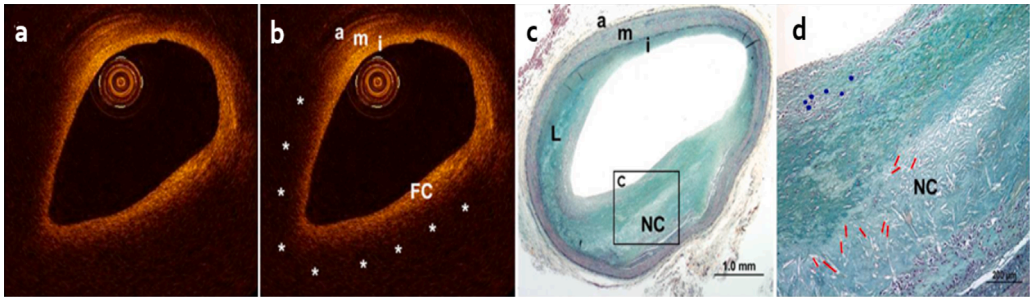

Fig. 7. Example of early-stage fibroatheroma with lipid pool/necrotic core. (a) Original OCT image. (b) Annotated OCT image: FC: Fibrous cap, i: Intima, m: Media, a: Adventitia, L: Lipid pool, start shows lipid pool/necrotic core. Corresponding histological images are shown in (c) and (d) [15].

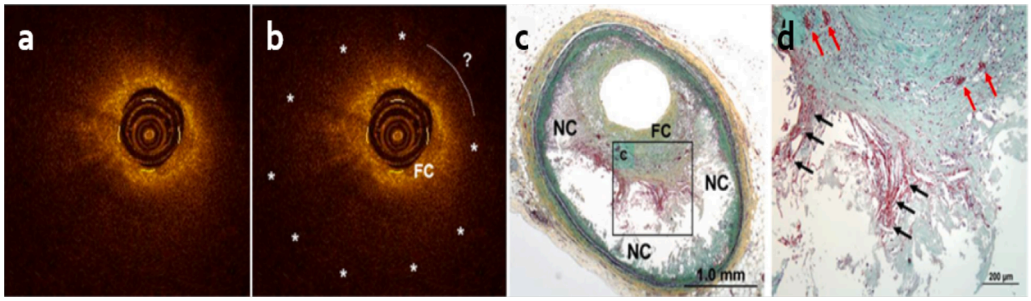

Fig. 8. Example of late-stage fibroatheroma with necrotic lipid pool/necrotic core, micro-vessels, and intra-plaque haemorrhage. (a) Original OCT image. (b) Annotated OCT image: FC: Fibrous cap, and star shows lipid pool/necrotic core region. Corresponding histological images are shown in (c), and (d): NC: Necrotic core, red arrows show micro-vessels, and black arrows represent intra-plaque haemorrhage [15]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

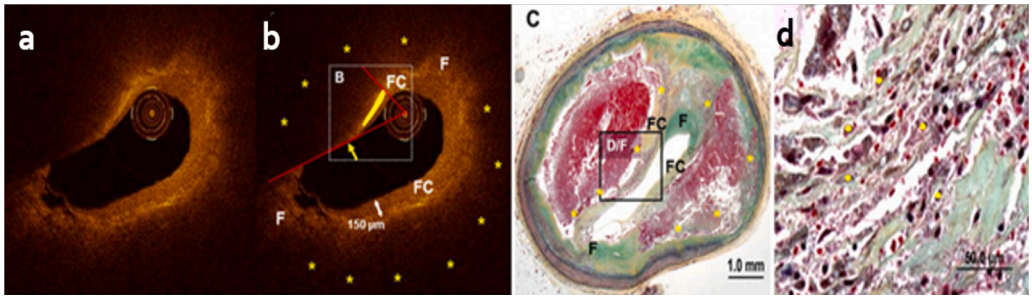

Fig. 9. Example of thin-cap fibroatheroma with fibrous cap thickness of 65 μm. (a) Original OCT image. (b) Annotated OCT image: FC: Fibrous cap, F: Fibrous tissue, stars show lipid pool/necrotic core region, direction of light beam is shown in red, and signal rich band is shown in yellow. Corresponding histological images are shown in (c), and (d): Yellow dots show macrophages [15]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

machine learning-based, and specifically deep learning-based techniques can improve medical image analysis for fast and accurate interpretation of the medical images [26,27]. Therefore, deep learning is widely used to provide accurate analysis of the images in various medical fields. The most important characteristic of deep learning models is their strength to extract features, which can accurately provide distinctive descriptions of various tissue types [28–31]. In this section, we focus on reviewing the most recent studies related to the coronary plaque characterization using OCT imaging.

A CNN-based approach was used by Athanasiou et al, for patch-based classification of coronary plaques including calcium, lipid, fibrous, mixed tissues, and non-pathological tissues. Training and validation was

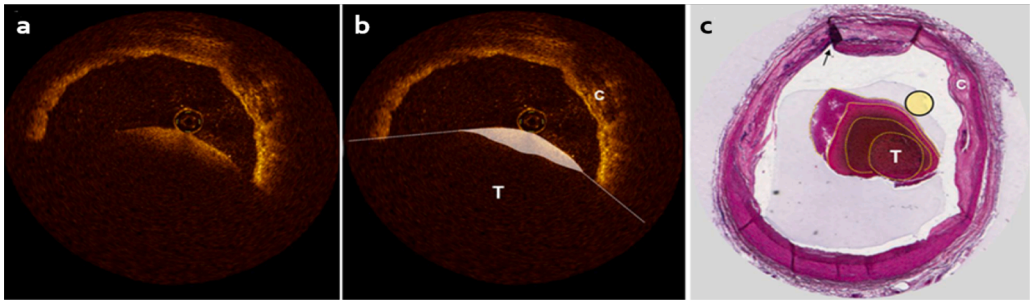

Fig. 10. Example of thrombus: (a) Original OCT image. (b) Annotated OCT image: C: Calcification, T: Thrombus. Corresponding histological image is shown in (c) [15].

performed on OCT images of 26 patients (the total of 700 cross-sections). Pre-processing was performed using bilateral filtering, and K-means approach to detect the arterial wall prior to applying CNN for tissue classification [32]. Although the work is interesting to classify different plaques, but there are some limitations to be considered. In clinical point of view, definition of non-pathological arterial wall should be clarified. Also, there are other significant factors of plaque development and rupture such as macrophage infiltration, type of fibroatheroma and micro-vessels that are not considered in this study. In technical point of view, pre-processing steps are time-consuming and may result in losing important information. It is difficult to generalize the pre-processing steps to all the cases considering the artifacts of the system, and disease progression stage, which can completely deform the arterial wall. Also, patch-based CNN has some limitations. Pre-processing steps are required considering the huge computation time, patch size selection is challenging, and redundant feature extraction process because of overlapping patches is another limitation of the patch-based classification using CNNs. Ren et al proposed another patch-based classification approach using CNN to detect lipid and fibrous plaque. As pre-processing steps, intensity based approaches were used to detect catheter. Lumen boundary was detected by applying dilation and erosion. Then, the images were cropped based on the lumen boundary to reduce the image size and make the feature extraction process faster. Proposed CNN model was inspired by the VGG architecture [33].

Miyagawa et al proposed a CNN-based approach to detect vascular bifurcation using OCT imaging. Although this study is not concentrated on the atherosclerotic plaque characterization, but the risk of atherosclerosis is higher in vessel bifurcation. This can be an important complementary study to be considered. In technical point of view, the pre-processing was performed in various steps including binarization, morphological gradient, Hough transform, and cropping. Then, combination of four different CNN architectures were used to detect the region with bifurcation in the images [34]. Normalized-intensity standard deviation (NSD) was used to detect regions of the arterial wall with macrophage accumulation by Rico et al. An intensity-based method was used to detect the punctuated signal rich areas of the arterial wall followed by the signal-poor area with high and low NSD value respectively [35]. Although macrophage infiltration is associated with every stage of the atherosclerotic plaque development, but it is not coronary plaque by itself. Moreover, intensity based characterization of macrophage is not accurate since residual blood, which highly attenuates the light, can create the same visualization as macrophage in the OCT images. The signal-poor area followed by the punctuated signal-rich area can be lipid pool, which is not necessarily followed by the macrophage infiltration, specifically in early stages of the atherosclerosis development. A deep residual U-net was designed for binary classification to discriminate between the areas in the OCT images with vulnerable plaques versus other tissues. Resnet101-based U-net was modified by adding the residual units to the network architecture. Loss function was replaced by a combination of weighted cross-entropy loss and dice coefficient to improve the segmentation performance. The results were compared against the results of the Resnet50-based U-net, Resnet101-based U-net, and VGG-based U-net [36]. Although the work is very interesting, specifically to detect vulnerable plaques, but plaque types and vulnerable plaque components should be considered in future studies to assist clinicians in decision-making and personalized treatment strategies. U-net is robust for binary classification. Although it is used for multi-class classification problems, but the performance is not as accurate as binary classification. The other work was focused on discriminating between OCT images with and without fibroatheroma. Pre-processing steps and cropping the images were performed to reduce the feature extraction computational burden. Then, three types of features including Local Binary Patterns, Haar-like, and Histogram of Oriented Gradients were extracted from the region of interest (arterial wall). Support Vector Machine was used for binary classification to distinguish between images with and without fibroatheroma [37]. Although hand-crafted features can provide a fair description of the tissues, but considering the challenges of the OCT images, detailed tissue information is required for better representation and evaluation of the intracoronary plaques. Lipid, fibrous, and calcified plaques were detected by Ren et al. An intensity-based approach was used for pre-processing to detect the catheter. Lumen border was detected by considering local maximum of standard deviation. Multi-layer model was proposed for classification task. Training and validation was performed using OCT images obtained from seven patients [38]. The other study focused on detection of lipid and calcified plaque from OCT images. Pre-processing was performed in five different steps to detect the lumen border, denoising, and extraction of the region of interest. Then, ResNet was trained to segment lipid and calcified tissues. Training and validation were performed on 57 OCT pullbacks obtained from different patients [39]. Using fully convolutional networks, pre-processing is not required. Accurate choice of parameters at each layer of the network and right choice of loss function, which is sensitive enough for the segmentation task create a fast and precise network configuration to avoid pre-processing steps. Secondly, the clinical need is not clear in this study. Pre-trained SegNet was used to detect calcification and lumen area in OCT images. Conditional Random Fields (CRFs) was applied to refine the classification results. The model was trained and validated on 34 OCT pullbacks [40]. The clinical need is not clear in this study since calcification can be detected using coronary angiography as well. Dong et al proposed a finite element method to evaluate stent placement in calcified coronary arteries. Cross-sectional area, angle, and maximum thickness of the intracoronary calcified regions were quantified to analyze stent implementation [41]. This work is interesting since such information is useful in accurate stent placement. Lack of information regarding the dimension, type, and location of the plaque in the process of stent placement can result in plaque rupture. In the other study, combination of deep features and hand-crafted features were used to detect lipid and fibrocalcific plaques versus other coronary tissues. Different pre-processing steps were performed to extract the region of interest (arterial wall). Then, a CNN with three convolutional and three fully connected layers was applied to extract deep features from the OCT

images. Combination of deep features and lumen morphology features were used for classification task using Random Forest. At the end CRF method was used to refine the classification result [42]. Combination of deep features and texture features were used to detect coronary plaques including lipid and calcification. Random forest was used as the classifier [43]. Since detailed texture information was included in deep features, this question should be investigated that how much it is efficient to combine texture or lumen morphology features with deep features to improve classification accuracy. Combination of U-Net- and residual learning-based model was used for segmentation of intima, media, lumen, guidewire shadow and plaques by [44]. The model does not characterize the plaque types. A clustering method to discriminate between calcified versus other tissues using auto-encoders were proposed by [45]. Although creating the ground-truth for supervised learning is time-consuming but this method is not validated on characterizing all types of atherosclerotic plaques. Attenuation coefficients are estimated for OCT images by [46]. These measurements and investigations are important for better understanding of the optical properties of various tissues, which is crucial in quantitative analysis of the OCT images. A complete model to analyze coronary artery in OCT imaging was proposed by our team. Combination of CNN and FCN was used to design the model not only to avoid pre-processing steps, but also to apply the end to end networks for segmentation instead of using patch-based CNN. The model starts by evaluating the arterial wall to distinguish between normal three-layered structure and intimal thickening with media disappearance. If the arterial wall is recognized as normal in the first step, various arterial wall layers (intima and media) will be detected for accurate evaluation of each layer thickness in early stages of the disease, which three-layered structure is maintained. If the arterial wall is recognized as pathological in the first step, a FCN model is used to detect all possible plaques and pathological formations to be characterized by type in the final step. Fig. 11 demonstrates all the steps of our model, which will be extended to characterize all types of the atherosclerotic plaques [47]. Recent studies to indicate coronary plaque morphology is summarized in Table 1.

5. Discussion

Deep learning and machine learning methods are evolving to meet many clinical needs. Before proposing mathematical solutions using physical concepts and deep learning models, technical researchers need to understand the problem in detail. Teamwork between mathematicians, physicists, machine learning and deep learning experts is required to converge with clinical needs. Conducting a successful and effective research project, which can be applicable to improve patient's outcome has significant requirements. Without understanding the process of plaque development and having adequate knowledge of clinical features of the plaque formation, it is hardly possible to propose a model, which can efficiently address this problem. The clinical needs in the opinion of the interventional cardiologists lay the ground for future works based on the computational models will help describing the exact features of the tissues under review with the means of deep learning algorithms. Although interventional cardiology created a new platform to help millions of patients avoid bypass surgery, the current upper edge need is as follows: 1. Understanding the clinical features of the various coronary plaques in OCT images can improve the inter-observer agreement in various degrees depending on the type of pathology [48]. This improved interpretation comes following extensive focused training, and yet remains sub-optimal to general practice. 2. Considering recent studies and discussing with different interventional cardiologists to understand the unmet needs, we realized that lack of an integrated automatic tissue characterization software system in OCT imaging for real-time high precision analysis of intracoronary tissues remains a major problem.

Applying artificial intelligence paradigms will overcome the following limitations inherent to subjective operator-dependent interpretation:

- Understanding the features of various plaques in OCT images requires intensive training and visual interpretation of the OCT images is still highly error prone.
- complete interpretation and manual detection of the various lesions may take weeks and even months for clinicians given the diffuse nature of the coronary artery disease sequelae, which postpones the diagnostic process, decision making, and possibility of the accurate personalized treatment strategy for better patient's outcome.
- The current cardiac imaging systems have many limitations when it comes to detecting vulnerable plaques, those types of plaques prone to rupture. Considering the advantages and incredible functionality

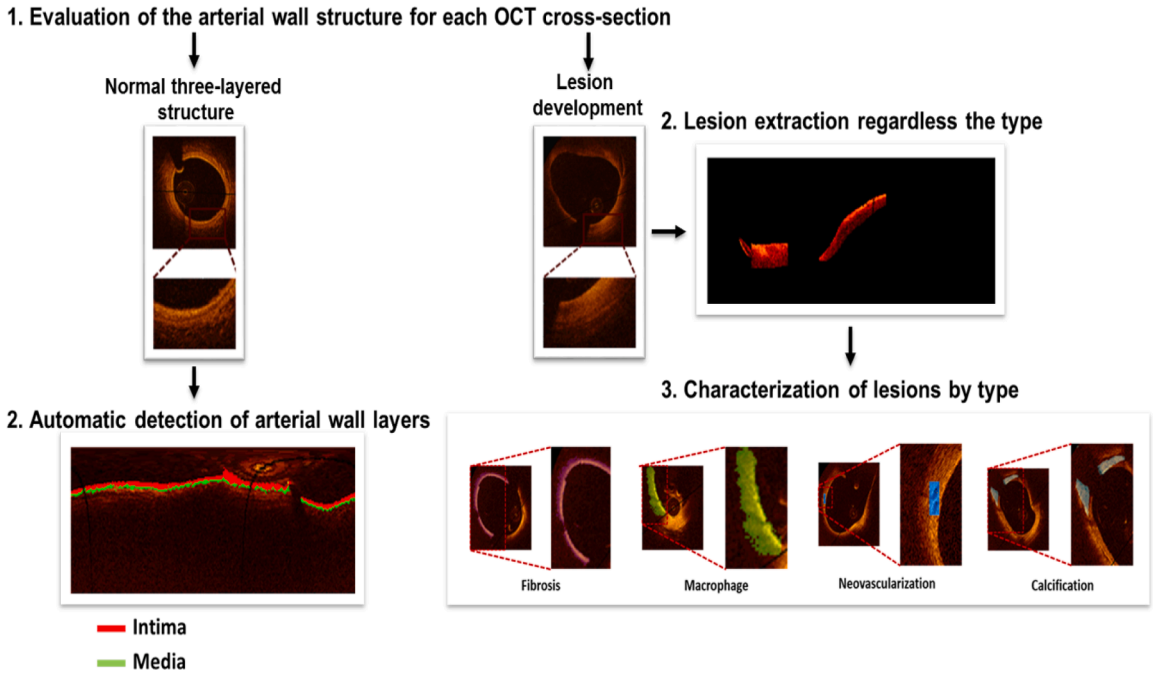

Fig. 11. Deep learning based model for fully analysis of coronary arteries in OCT imaging [47].

Table 1
Recent studies concentrated on indication of plaque morphology in OCT images.

Reference	Proposed method	Contribution	Model validation
[32]	Patch-based CNN for plaque classification.	Detection of calcium, lipid, fibrous, mixed and non-pathological tissues.	Accuracy varies from 73% to 93% based on the tissue type.
[33]	Patch-based CNN for plaque classification	Detection of healthy tissues, lipid and fibrous plaque.	Accuracy, precision, specificity, and sensitivity vary as follows respectively: 87% to 88%, 75% to 94%, 90% to 94%, and 61% to 90%
[34]	CNN-based classification	Detection of vascular bifurcation	Depends on the network architecture and in Cartesian coordinate, accuracy, specificity, and precision respectively vary as follows: 97% to 98%, 97% to 99%, and 96% to 98%
[35]	Normalized-intensity standard deviation (NSD)	Detection of macrophage accumulation	Using NSD, accuracy, specificity, and sensitivity vary as follows respectively: 53% to 88%, 54% to 89%, and 51% to 84%
[36]	Deep residual U-net for binary classification	Detection of vulnerable plaques versus other tissues	Using U-Net+ResNet101, mean accuracy, mean precision, mean IOU, and mean recall vary as follows respectively: 90%, 94%, 85%, and 91%
[37]	Combination of LBP, Haar-like, and HOG features for classification using SVM	Detection of fibroatheroma	Using all three types of features, accuracy, specificity, and sensitivity vary as follows respectively: 88%, 91%, and 89%
[38]	Multi-layer model for tissue classification	Detection of lipid, fibrous, and calcified plaques	Accuracy varies from 90% to 94% based on the plaque type
[39]	Pre-trained ResNet	Detection of lipid and calcification	Compared to other methods, sensitivity, specificity, and dice of the proposed method vary based on the plaque type, which are respectively reported as: 85% to 98%, 70% to 90%, and 82% to 90%
[40]	Pre-trained SegNet	Detection of calcification and lumen area	Sensitivity, specificity, and F1score respectively: Lumen: 97% to 100%, 97% to 99%, 89% to 91%, Calcification: 76% to 88%, 96% to 98%, 39% to 45%
[41]	Finite element method	Evaluation of stent placement in calcified coronary artery	Material coefficients were reported for this study.
[42]	Combination of deep CNN features and hand-crafted features to train Random Forest	Detection of lipid and fibrocalcified plaques	Different features and methods were compared against each other in this study.
[43]	Combination of deep features and texture features for classification using Random Forest	Detection of lipid and calcification	Sensitivity, specificity, and dice after applying CRF vary based on the tissue type as follows: 67% to 97% for sensitivity, 84% to 97% for specificity, 63% to 89% for dice.
[44]	Combination of U-Net- and Residual learning-based models was used in this study.	Detection of intima, media, lumen, guidewire, and plaques.	Metrics are not reported for all the tissue types.
[45]	A clustering method using auto-encoders.	Discrimination between calcified versus other tissues.	The best average precision of the model obtained for one-half clustered as 76%.
[46]	Estimation of attenuation coefficients for intracoronary OCT images.	Various optical parameters were estimated.	Only measured parameters were reported.
[47]	Combination of CNN and FCN models	Complete analysis of coronary arteries in OCT images	Accuracy, specificity, and sensitivity respectively vary as follows based on the plaque type: 90% to 95%, 95% to 97%, and 84% to 90%.

of the intravascular OCT imaging, evaluation and automatic indication of the vulnerable plaques in OCT images is another important clinical need.

Considering the clinical features of the coronary plaques and various stages of disease progression. We should divide our technical solution into three different steps. Classification, segmentation, and prediction (Fig. 12). Since we need to have an automatic analytical model of coronary artery, which can be applied in real-time for immediate and accurate analysis of the images during intervention, the models with pre-processing steps are not desirable for the following reasons: 1. Pre-processing steps are additional computational burden. 2. We may lose some important information regarding tissue features during pre-processing. 3. Pre-processing steps are not certainly generalized to all the cases since we have vessel remodelling caused by the disease, which can result in complete deformation of the arterial wall. There are various types of deep learning architectures, which should be chosen wisely to design an appropriate model. Considering the related studies, CNNs are used in different studies for segmentation purpose. CNNs are very strong feature extractors and can be trained and used efficiently for classification purposes. Although patch-based CNN can be used for segmentation task, but it has some important limitations: 1. Path-based segmentation using CNN is computationally very expensive because patches are overlapped, which results in redundant feature extraction. 2. Pre-processing steps are inevitable since we need to extract the region of interest (arterial wall tissues) to reduce the computational time. 3. Choosing the right patch size, which is not too small or too large considering the max-pooling steps, is another challenge of using CNNs for segmentation task. Therefore, CNN models can be used mainly for feature extraction and classification, while we are characterizing various types of plaques or tissues. On the other hand, fully convolutional networks, which are trained end-to-end can be used for segmentation tasks. The advantage of using them is that the arbitrary size of the images can be used as the network input since there is no fully connected layer involved in the network architecture. Without involving the fully connected layers, the number of parameters will be reduced considerably. This can highly accelerate the process of network training. Therefore, the original images can be fed to the network for segmentation. For any other type of deep learning architectures, we need to investigate if they can properly be used to address the problems related to different stages

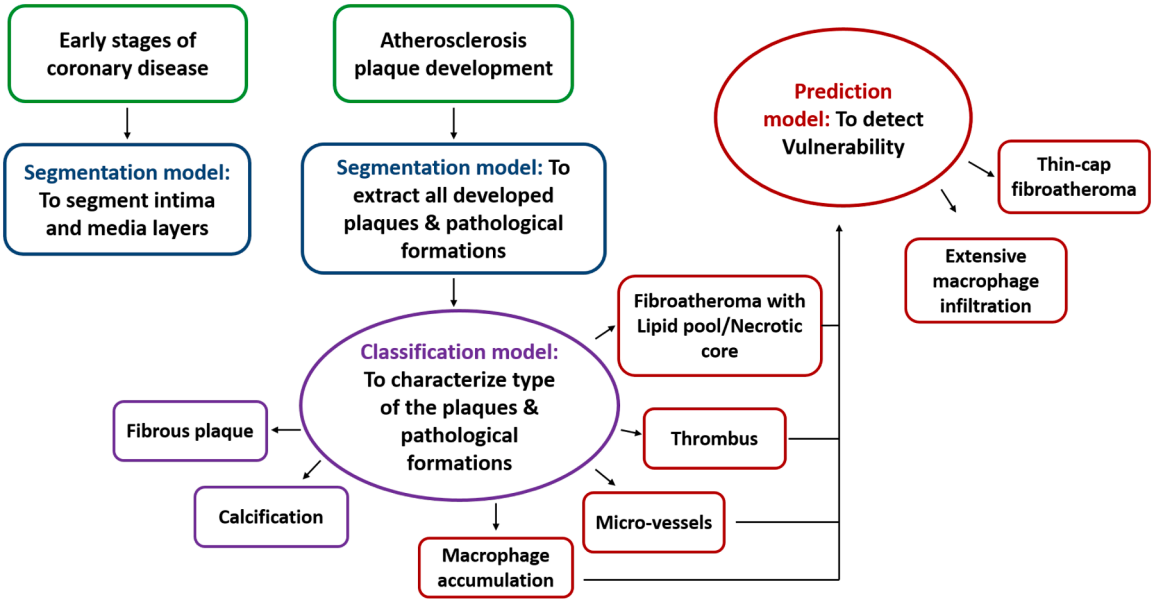

Fig. 12. Complete model to analyze coronary artery in OCT imaging. Deep learning models should be chosen by considering the step of problem solving to select appropriate networks for classification, segmentation, and prediction purposes.

of the disease (Fig. 12). It is also important to note that the quantitative evaluations that we report in research papers are important in research point of view but such measurements do not demonstrate the readiness of the proposed model for clinical applications. Research usually performs using limited data. The quantitative evaluations become important if the method will be applicable and it can be generalized to the challenging cases. These evaluations are useful not only by testing a method on large datasets, but also by evaluating its performance on various challenging cases.

6. Conclusion

In this review article, we investigate different aspects of the coronary artery disease from both clinical and technical perspectives. We aim to underline the importance of having thorough and detailed knowledge of the clinical features of the disease as well as the clinical needs to find the mathematical solution, which can address the problem accurately. Since OCT is a turning point and powerful tool in cardiovascular imaging for coronary plaque detection, we investigated its limitations to be addressed. Based on the discussions with different interventional cardiologists, we realized that there is a clear need for an automatic fully analytical model to accurately evaluate coronary artery in real-time using OCT imaging. By reviewing the existing technical studies, we divide different steps of the model into three categories of segmentation, classification, and prediction not only to detect coronary plaque morphology, but also to predict the plaques prone to rupture using various machine learning approaches. Future studies can be concentrated on the physics of the system during image acquisition and the limitations such as low penetration depth of the OCT imaging, and the need of blood clearance during image acquisition. We may also consider the optical properties of the various plaque sub-components for detailed analysis of the tissues.

Ethical approval

The ethical approval is not required for this study.

Funding

This study is supported by BoBeau Coeur-Fondation CHU Ste-Justine in Montreal.

Declaration of Competing Interest

Authors declare that they have no conflict of interest.

References

[1] Lilly LS. Pathophysiology of heart disease: a collaborative project of medical students and faculty. Lippincott Williams & Wilkins; 2012.
[2] Pahwa R., Jialal I.. Atherosclerosis. Statpearls. Treasure Island (FL). 2018.
[3] Cowley MJ. Tribute to a legend in invasive/interventional cardiology Melvin P. Judkins, M.D. (1922–85). Catheter Cardiovasc Interv 2005;64(2):259–61.
[4] Carreras ET, Williams DO. Interventional cardiology: the in and the out. Circulation 2018;11(4):e006709.
[5] Tarkin JM, Dweck MR, Evans NR, Takx RA, Brown AJ, Tawakol A, Fayad ZA, Rudd JH. Imaging atherosclerosis. Circ Res 2016;118(4):750–69.
[6] Daghem M, Bing R, Fayad ZA, Dweck MR. Noninvasive imaging to assess atherosclerotic plaque composition and disease activity: Coronary and carotid applications. JACC 2020;13(4):1055–68.
[7] Sandfort V, Lima JA, Bluemke DA. Noninvasive imaging of atherosclerotic plaque progression: status of coronary computed tomography angiography. Circulation 2015;8(7):e003316.
[8] Noguchi T, Nakao K, Asaumi Y, Morita Y, Otsuka F, Kataoka Y, Hosoda H, Miura H, Fukuda T, Yasuda S. Noninvasive coronary plaque imaging. J Atheroscler Thromb 2017:RV17019.
[9] Jansen CH, Perera D, Wiethoff AJ, Phinikaridou A, Razavi RM, Rinaldi A, Marber MS, Greil GF, Nagel E, Maintz D, et al. Contrast-enhanced magnetic resonance imaging for the detection of ruptured coronary plaques in patients with acute myocardial infarction. PLoS One 2017;12(11).
[10] Erglis A, Jegere S, Narbute I. Intravascular ultrasound-based imaging modalities for tissue characterisation. Interv Cardiol Rev 2014;9(3):151.
[11] Lee MW, Song JW, Kang WJ, Nam HS, Kim TS, Kim S, Oh W-Y, Kim JW, Yoo H. Comprehensive intravascular imaging of atherosclerotic plaque in vivo using optical coherence tomography and fluorescence lifetime imaging. Sci Rep 2018;8(1):1–12.
[12] Bouma BE, Villiger M, Otsuka K, Oh W-Y. Intravascular optical coherence tomography. Biomed Opt Express 2017;8(5):2660–86.
[13] Chen X, Kim W, Serafino MJ, Tan Z, Jo JA, Applegate BE. Dual-modality optical coherence tomography and frequency-domain fluorescence lifetime imaging microscope system for intravascular imaging. J Biomed Opt 2020;25(9):096010.
[14] Nishimiya K, Tearney G. Multimodality intravascular OCT imaging. Cardiovasc OCT Imaging 2020:163–74.
[15] Radu MD. The clinical atlas of intravascular optical coherence tomography for iPad. Eur Heart J 2012;33(10):1174.
[16] Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. J Cardiovasc Transl Res 2012;5(3):264–73.
[17] Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler, Thromb, Vasc Biol 2000;20(5):1262–75.

[18] Otsuka F, Joner M, Prati F, Virmani R, Narula J. Clinical classification of plaque morphology in coronary disease. Nat Rev Cardiol 2014;11(7):379.
[19] Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R. Has our understanding of calcification in human coronary atherosclerosis progressed? Arterioscler, Thromb, Vasc Biol 2014;34(4):724–36.
[20] Saita T, Fujii K, Hao H, Imanaka T, Shibuya M, Fukunaga M, et al. Histopathological validation of optical frequency domain imaging to quantify various types of coronary calcifications. Eur Heart J 2017;18(3):342–9.
[21] Otsuka F, Kramer MC, Woudstra P, Yahagi K, Ladich E, Finn AV, de Winter RJ, Kolodgie FD, Wight TN, Davis HR, et al. Natural progression of atherosclerosis from pathologic intimal thickening to late fibroatheroma in human coronary arteries: a pathology study. Atherosclerosis 2015;241(2):772–82.
[22] Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, et al. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. J Am Coll Cardiol 2007;50(10):940–9.
[23] Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, Joner M, Virmani R. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. Nat Rev Cardiol 2016;13(2):79.
[24] Ganesan R, Henkels KM, Wrenshall LE, Kanaho Y, Di Paolo G, Frohman MA, Gomez-Cambronero J. Oxidized LDL phagocytosis during foam cell formation in atherosclerotic plaques relies on a PLD2–CD36 functional interdependence. J Leukoc Biol 2018;103(5):867–83.
[25] Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. Atherosclerosis 2015;239(1):260–7.
[26] Fourcade A, Khonsari R. Deep learning in medical image analysis: a third eye for doctors. J Stomatol, Oral Maxillofac Surg 2019;120(4):279–88.
[27] Shen D, Wu G, Suk H-I. Deep learning in medical image analysis. Annu Rev Biomed Eng 2017;19:221–48.
[28] Biswas M, Kuppili V, Edla DR, Suri HS, Saba L, Marinho RT, et al. Symtosis: a liver ultrasound tissue characterization and risk stratification in optimized deep learning paradigm. Comput Methods Prog Biomed 2018;155:165–77.
[29] Dong Y, Pan Y, Zhao X, Li R, Yuan C, Xu W. Identifying carotid plaque composition in MRI with convolutional neural networks. Smart computing (SMARTCOMP), 2017 IEEE international conference on. IEEE; 2017. p. 1–8.
[30] Lekadir K, Galimzianova A, Betriu À, del Mar Vila M, Igual L, Rubin DL, Fernández E, Radeva P, Napel S. A convolutional neural network for automatic characterization of plaque composition in carotid ultrasound. IEEE J Biomed Health Inform 2017;21(1):48–55.
[31] Menchón-Lara R-M, Sancho-Gómez J-L, Bueno-Crespo A. Early-stage atherosclerosis detection using deep learning over carotid ultrasound images. Appl Soft Comput 2016;49:616–28.
[32] Athanasiou LS, Olender ML, José M, Ben-Assa E, Edelman ER. A deep learning approach to classify atherosclerosis using intracoronary optical coherence tomography. Medical imaging 2019: computer-aided diagnosis. 10950. International Society for Optics and Photonics; 2019. p. 109500N.
[33] Ren X, Wu H, Chen Q, Kubo T, Akasaka T. A tissue classification method of IVOCT images using rectangle region cropped along the circumferential direction based on deep learning. International forum on medical imaging in Asia 2019. 11050. International Society for Optics and Photonics; 2019. p. 1105015.
[34] Miyagawa M, Costa MGF, Gutierrez MA, Costa JPGF, Costa Filho CFF. Detecting vascular bifurcation in IVOCT images using convolutional neural networks with transfer learning. IEEE Access 2019;7:66167–75.
[35] Rico-Jimenez JJ, Campos-Delgado DU, Buja LM, Vela D, Jo JA. Intravascular optical coherence tomography method for automated detection of macrophage infiltration within atherosclerotic coronary plaques. Atherosclerosis 2019;290:94–102.
[36] Li L, Jia T. Optical coherence tomography vulnerable plaque segmentation based on deep residual U-net. Rev Cardiovasc Med 2019;20(3):171–7.
[37] Yan Q, Xu M, Wong DWK, Taruya A, Tanaka A, Liu J, Wong P, Cheng J. Automatic fibroatheroma identification in intravascular optical coherence tomography volumes. J Ambient Intell Humaniz Comput 2019:1–7.
[38] Ren X, Wu H, Chen Q, Imai T, Kubo T, Akasaka T. A local multi-layer model for tissue classification of in-vivo atherosclerotic plaques in intravascular optical coherence tomography. IEICE Trans Inf Syst 2019;102(11):2238–48.
[39] Lee J, Prabhu D, Kolluru C, Gharaibeh Y, Zimin VN, Bezerra HG, Wilson DL. Automated plaque characterization using deep learning on coronary intravascular optical coherence tomographic images. Biomed Opt Express 2019;10(12):6497–515.
[40] Gharaibeh Y, Prabhu D, Kolluru C, Lee J, Zimin V, Bezerra H, Wilson D. Coronary calcification segmentation in intravascular OCT images using deep learning: application to calcification scoring. J Med Imaging 2019;6(4):045002.
[41] Dong P, Mozafari H, Prabhu D, Bezerra HG, Wilson DL, Gu L. Optical coherence tomography-based modeling of stent deployment in heavily calcified coronary lesion. J Biomech Eng 2020;142(5).
[42] Lee J, Prabhu D, Kolluru C, Gharaibeh Y, Zimin VN, Dallan LA, Bezerra HG, Wilson DL. Fully automated plaque characterization in intravascular OCT images using hybrid convolutional and lumen morphology features. Sci Rep 2020;10(1):1–13.
[43] Lee J, Kolluru C, Gharaibeh Y, Prabhu D, Zimin VN, Bezerra H, Wilson D. Automatic a-line coronary plaque classification using combined deep learning and textural features in intravascular OCT images. Medical imaging 2020: image-guided procedures, robotic interventions, and modeling. 11315. International Society for Optics and Photonics; 2020. p. 1131513.
[44] Haft-Javaherian M., Villiger M., Otsuka K., Daemen J., Libby P., Golland P., Bouma B.E.. Segmentation of anatomical layers and artifacts in intravascular polarization sensitive optical coherence tomography using attending physician and boundary cardinality lost terms. arXiv preprint arXiv:210505137 2021.
[45] Kolluru C, Lee J, Gharaibeh Y, Bezerra HG, Wilson DL. Learning with fewer images via image clustering: application to intravascular OCT image segmentation. IEEE Access 2021;9:37273–80.
[46] Ghafaryasl B, Vermeer KA, Kalkman J, Callewaert T, de Boer JF, Van Vliet LJ. Analysis of attenuation coefficient estimation in fourier-domain OCT of semi-infinite media. Biomed Opt Express 2020;11(11):6093–107.
[47] Abdolmanafi A, Cheriet F, Duong L, Ibrahim R, Dahdah N. An automatic diagnostic system of coronary artery lesions in kawasaki disease using intravascular optical coherence tomography imaging. J Biophotonics 2020;13(1):e201900112.
[48] Kini AS, Vengrenyuk Y, Yoshimura T, Matsumura M, Pena J, Baber U, Moreno P, Mehran R, Maehara A, Sharma S, et al. Fibrous cap thickness by optical coherence tomography in vivo. J Am Coll Cardiol 2017;69(6):644–57.