REVIEW

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In vivo imaging of complicated atherosclerotic plaque – role of optical coherence tomography (OCT)

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Abstract

Cardiovascular diseases are the main cause of death worldwide, with coronary artery disease (CAD) being the predominant underlying etiology. Coronary angiography (CA) is the current invasive method used for CAD diagnosis, as well as for defining the coronary interventional treatment strategy. However, CA offers sometimes-poor accuracy in estimating atherosclerotic plaque volume, morphology and degree of stenosis severity. Optical coherence tomography (OCT) is an intracoronary imaging technique, developed in order to overcome CA limitations and is considered to be an "optical biopsy" that provides *in vivo* imaging. OCT has an extremely high resolution, similar to that of a usual histological evaluation of a biopsy sample. One of the most important clinical research areas for OCT is represented by the study of the pathophysiology of coronary and carotid atherosclerotic disease, in order to improve diagnosis and optimize therapy. This article reviews OCT basic technical aspects related to its diagnosis efficacy, OCT morphological information offered in coronary artery disease, including acute coronary syndromes and non-atherosclerotic coronary disease, OCT use for morphological percutaneous coronary intervention (PCI) follow-up and stent-failure mechanisms, as well as the new three-dimensional (3D)-OCT approach for atherosclerotic plaque assessment.

Keywords: optical coherence tomography, *in vivo* optical biopsy, coronary artery disease, vulnerable plaques.

Introduction

Cardiovascular diseases continue to represent the main cause of death worldwide, coronary artery disease (CAD) being the predominant underlying etiology [1]. Coronary angiography (CA) is the current invasive method used for CAD diagnosis, as well as for defining the coronary interventional treatment strategy [2]. The main limitations of CA imaging are the two-dimensional (2D) view of the three-dimensional (3D) coronary artery lumen and wall structure, as well as, in some cases, the poor accuracy of estimating atherosclerotic plaque volume, morphology and degree of stenosis severity [3]. Optical coherence tomography (OCT) is an intracoronary imaging technique, developed in order to overcome CA limitations and was first used as a research tool [4]. Its indications for clinical use in current routine practice are under discussion [5], but OCT proved to be an extremely important tool in selected cases.

OCT has an extremely high resolution, similar to that of a usual histological evaluation of a biopsy sample and is considered to be an "optical biopsy" that provides *in vivo* imaging [6]. One of the most important clinical research areas for OCT is represented by the study of the pathophysiology of coronary and carotid atherosclerotic disease, in order to improve diagnosis and optimize therapy.

This article reviews OCT basic technical aspects related to its diagnosis efficacy, OCT morphological information offered in coronary artery disease, including acute coronary syndromes and non-atherosclerotic coronary disease, OCT use for morphological percutaneous coronary intervention (PCI) follow-up and stent-failure mechanisms, as well as the new 3D-OCT approach for atherosclerotic plaque assessment.

OCT basics

OCT evolved from optical one-dimensional low-coherence reflectometry to 2D imaging of the retina, due to addition of transverse scanning (B-scan) in 1991 [7] and, since that moment, OCT technique was applied in various medical and non-medical settings [8].

OCT uses a near-infrared light source with frequencies between 1250 and 1350 nm, while the modern OCT technologies employ a 1300 nm frequency. This wavelength allows a tissue penetration of up to 3 mm, smaller than that of up to 8 mm acquired with intravascular ultrasound (IVUS). Despite the fact that higher light frequencies allow deeper tissue penetration, there are other more important characteristics, such as tissue absorption and the refractive surface capacity that defines ideal frequency [8].

Because the speed of light (3×10^8 m/s) is much higher than that of sound (1500 m/s), OCT as a fiber optic system offers 10 times greater resolution and 40 times faster image acquisition as compared to IVUS [9].

The time-domain (TD)-OCT and the frequency/Fourier domain (FD)-OCT techniques are the two OCT systems used.

The first generation OCT system, TD-OCT, is provided with two arms: the reference arm that represents a moving mirror and the second arm that functions as a broadband light source. Erythrocytes, due to high iron concentration,

are an important source of artifacts and along with the fact that image-gaining process is slow, there is a need for proximal coronary artery occlusion. In order to selectively displace blood during image acquisition, an over-the-wire low-pressure occlusion balloon is used, but this process involves an adjacent procedural risk, related to myocardial ischemia, vascular perforation, arrhythmias and death [10].

The second-generation OCT system FD-OCT employs a fixed mirror with different wavelength light source that provides concomitant reflections acquisition. It allows better signal to-noise ratio and faster imaging processing time [11]. These technological improvements made unnecessary the previous coronary balloon occlusion, in order to produce a blood-free environment, replacing it with a contrast bolus injection. Procedural complications are thereby reduced [12].

OCT research purposes – coronary artery disease

OCT offers intravascular insights of the underlying coronary artery pathophysiology, complementary to CA. OCT is able to clearly identify not only all the atherosclerotic plaque components, with their spatial distribution, but also plaque complications, such as dissection, thrombus formation or recanalization. OCT represents therefore an important clinical research tool for the *in vivo* study of atherosclerotic disease, for guiding intravascular interventions and for evaluating their results.

Atherosclerotic plaque characteristics

OCT can be used for imaging and identification of the various features of each of the atherosclerotic plaque stages of progression, therefore contributing to *in vivo* pathological classification of atherosclerotic CAD [13].

Atherosclerotic plaque

Atherosclerotic plaque (Figure 1A) is represented by the disappearance of the normal three layer (intima, media, adventitia) disposition of the vessel wall, usually associated with focal intimal thickening. In some cases, due to intimal thickening and short tissue penetration of the OCT, media and adventitia may not be recognized [4].

Intimal thickening

Intimal thickening is often considered to be the first hallmark of CAD [14] and consists of a lipid pool (Figure 2B), an aggregation of fatty molecules and proteoglycans to its external part [13] and a proteoglycan and collagen-rich extracellular structure, covered by smooth muscle cells, to its internal part, without presence of inflammatory cells. Intimal thickening definitely progresses over time, but there are insufficient data on prevalence and speed of progression.

OCT enables an excellent view of the intimal thickening, intima appearing as a highly backscattering signal at its internal layer, with progressive loss of reflected signal towards the external layers [15].

Fibrous plaque

Fibrous plaque (fibroatheroma) is characterized by fibrous tissue that encircles a lipid-rich necrotic core and is considered to be the initial truly recognizable sign of the atherosclerotic plaque [13]. The natural evolution of fibroatheroma is outspread through two periods. The first period, asymptomatic, is similar to that of the intimal thickening described earlier, the difference being represented by the presence of macrophages infiltration into the lipid pool. The second period consists of a fibroatheroma coronary artery stenosis, evolving from clinically asymptomatic to stable angina pectoris. Neo-vascular proliferation that may cause intraplaque hemorrhage and continuous accumulation of cellular debris and free cholesterol represent the mechanisms of luminal narrowing [15].

The OCT description of both stages of fibroatheroma is similar to that of an intimal thickening, differentiation being made by the almost complete loss of light signal in the external layers, most probably due to both bigger size of fibroatheroma and its macrophages infiltration [15, 16].

Thin-cap fibroatheroma

Thin-cap fibroatheroma (TCFA) (Figure 1B) has all the components of fibroatheroma, is characterized by the presence of a very thin luminal layer, easily predisposed to rupture and is considered to be the hallmark of a vulnerable plaque [17]. A cap thickness of less than 65 μm is usually associated with plaque rupture, as demonstrated by post-mortem studies [18]. OCT investigations showed that intimal rupture may also appear at thicker diameters. In one study [19], in patients with exertion triggered acute myocardial infarction, 93% of the culprit coronary atherosclerotic plaques had a 90-μm average cap thickness. In patients with acute myocardial infarction who experienced symptoms at rest, 57% had plaque ruptures in areas of 50-μm average cap thickness. In a recent study, OCT provided objective evidence of plaque stabilization in patients taking statins, by precise identification of intimal fibrous cap thickening [20].

Fibrocalcific plaque

Fibrocalcific plaque (Figure 1C) is basically a fibroatheroma along with clear evidence of calcium deposits presence [4], but is considered to be a more advanced stage of atherosclerotic disease and appear more frequently in older, diabetes and renal failure patients [15]. It consists of a nodule shape calcium mass situated on a fibrous tissue layout rich in macrophages infiltration and microchannels [15].

OCT enables a high-resolution image of fibrocalcific plaque, due to the light ability to penetrate calcium. Thereby, calcified nodules are extremely well outlined from other plaque components [8]. In one study, OCT proved very high sensitivity (96%) and specificity (97%) for the detection of calcified nodules [21].

Inflammation

Inflammation (Figure 1D) is associated with plaque complications, since macrophage activation can cause plaque rupture and a subsequent pathological cascade leading to vascular thrombosis [22]. The OCT aspect of inflammation is represented by hyper-intense background speckle signal reflected by different sized areas located nearby fibroatheroma. They demand differentiation from

cholesterol crystals, elastic lamina or calcium deposits [4]. It is important to know that OCT signs of inflammation can be interpreted only in presence of a fibrous plaque, because there is no proved information related to the relevance of images suggestive for macrophage accumulation elsewhere in the vascular wall [4].

Cholesterol crystals

Cholesterol crystals (ChCs) (Figure 2A) are an important feature of atherosclerotic plaque and are strongly related to its vulnerability [23]. ChCs are defined on OCT as linear, highly backscattering structures within the plaque [4]. There are strong data that confirm the link between ChCs and acute coronary syndromes (ACS) culprit lesions [23]. Inflammation and plaque rupture are correlated to ChCs formation. Culprit lesions of ST-elevated myocardial infarction patients contain more ChCs as compared to those in non-ST-elevated myocardial infarction patients [23].

Necrotic core

Necrotic core (Figure 2B) represents the heart of a fibroatheroma and there are sufficient data to support the its OCT correlation to a low signal area. Other OCT characteristics of a necrotic core are represented by an imprecise bordering, along with no backscattering signal and its fast drop-off. It is to take into account that a poorly made procedural pullback, with incomplete blood removal, can cause pseudo-necrotic core appearance. There are several studies demonstrating that the culprit lesion in patients with ACS contain such necrotic cores, their incidence being higher as compared to patients with stable angina [4].

Microchannels

Microchannels (Figure 2C) are defined by a new, disorganized network of thin vessels that invade the fibroatheroma. There is an important link between microchannels and plaque vulnerability. Microchannels are strongly correlated to TCFA and large necrotic core presence [24] and, due to their immature structure, are predisposed to intra-plaque hemorrhage [25]. Plaque neovascularization is observed on OCT as a low signal, well bordered, network within the fibroatheroma [4].

Thrombus

Several histophatological and OCT imaging studies have concluded that OCT has a very good ability of identifying thrombus and differentiating red from white thrombus [26]. This OCT ability of differentiation is simply explained by the light penetration response through different iron concentration (Figure 2D). A red thrombus, rich in erythrocytes, will provide an intense backscattering signal, with high attenuation, in contrast to moderate backscattering signal and low attenuation, as provided by platelet-rich white thrombus [4]. Before OCT, angioscopy was considered to be the best procedure for *in vitro* thrombus identification, but OCT proved to be superior in terms of detection of thrombus and differentiation between red and white thrombus [27].

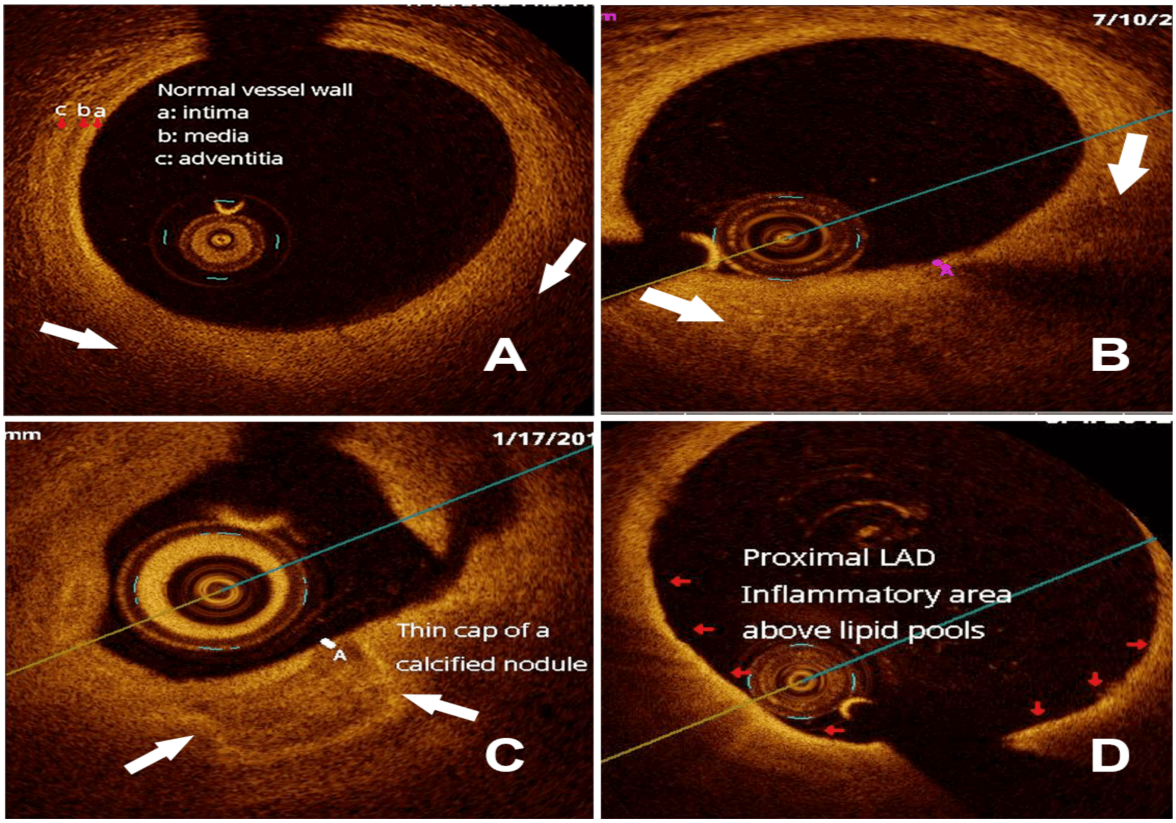

Figure 1 – ***(A) Transversal view of a coronary artery with an area of normal coronary structure (above) and, respectively, an area of lipid infiltration, below; (B) Atherosclerotic plaque, with loss of the layered structure of vessel wall (between white arrows) and a thin-cap fibroatheroma (red dot) overlying the large lipid pool; (C) Fibrocalcific plaque with well-defined boundaries (white arrows) and a thin cap, while a therapeutic dissection, following balloon predilatation, is present on the right upper corner; (D) Macrophage accumulation (red arrows) on a large circumferential lipid infiltration. LAD: Left anterior descending (artery).***

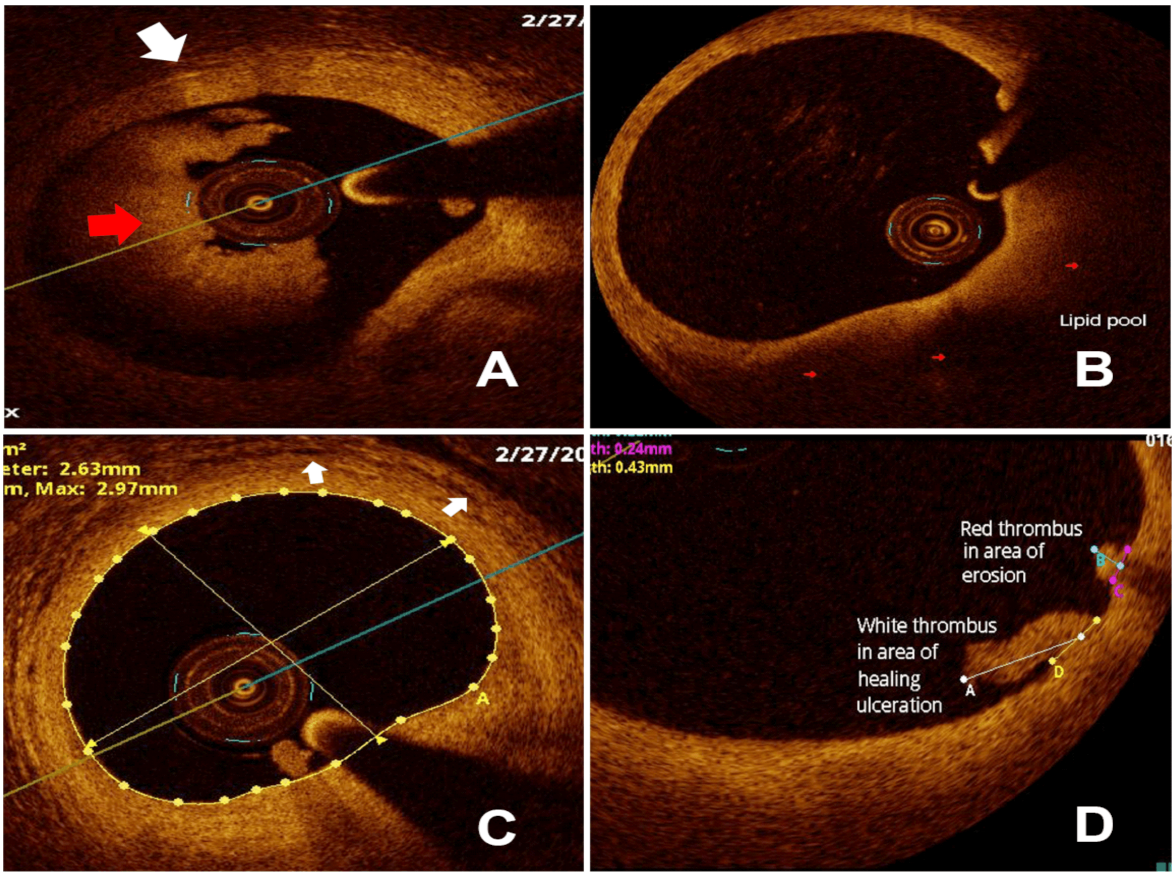

Figure 2 – ***(A) Cholesterol crystals (white arrow) frequently associated with characteristics of vulnerable plaques (red arrow – red thrombus); (B) Large lipid pool or necrotic core (red arrows); (C) Microchannels (white arrows); (D) Red and white thrombus.***

Vulnerable plaques

Ruptured plaques

Ruptured plaques consist of an intimal discontinuation, produced by either dissection or tearing of TCFA. Ruptured plaques are often covered, on the luminal side, by a thrombus (Figure 3A) [4]. The underlying necrotic core is usually large in size, covering more than one third of plaque surface [13]. The TCFA of a ruptured plaque is formed from type I collagen, with sporadic distribution of smooth muscle cells, and has signs of inflammation [15]. According to multiple morphology studies, the place of intimal rupture occurs at the mid-portion of the fibrous cap, especially in stress related events, in contrast to the general belief that rupture occurs at the fibrous cap thinnest point [28]. Thrombus formation is the result of direct contact between circulating cellular and non-cellular blood elements and, respectively, the highly thrombogenic components of the necrotic core, due to luminal disruption of the thin fibrous cap [15]. The white thrombus appears at the rupture site, while red thrombus encircle it and both of them are composed of a proteoglycans and type III collagen structure, infiltrated by inflammatory, smooth muscle and endothelial cells [15].

Intra-plaque cavity, observed on OCT, differ from the plaque rupture identified by histology [15]. In the histopathology studies, presence of intra-plaque cavity is not mandatory [15]. The intra-plaque cavity observed on OCT may be explained by possible embolization of the necrotic core material [15].

Plaque ulceration

Plaque ulceration (Figure 3B) is defined as "a recess in the plaque beginning at the luminal-intimal border" [29]. The pathogenesis of coronary ulcerated lesion is represented by a plaque rupture followed by the washing away of the necrotic core content [30]. Ulcerated plaques are infrequent in autopsy studies in the coronary arteries [31], as compared to carotid arteries. However, recent developments of intravascular imaging modalities have shown an increase in the prevalence of plaque ulcerations in ACS patients [30].

Coronary plaque ulceration covered with homogeneous high intensity tissue, without an OCT aspect of mobile thrombus, is not associated with future clinical events. Such lesions may not require further coronary stent implantation, if the lumen is adequately preserved [30].

Plaque erosion

Plaque erosion (Figure 3C) is represented by an intimal area with little or no evidence of endothelium, infiltrated by proteoglycans and smooth muscle cells, covered by few macrophages and T-lymphocytes and enveloped by a thrombus [15]. It represents the second most prevalent cause of coronary thrombosis [15]. The absence of fibrous cap disruption is the key differentiation from ruptured plaques [32]. Another important differentiation is that, in contrast to ruptured plaques, which appear on advanced atherosclerotic lesions, erosions appear on early plaques [15].

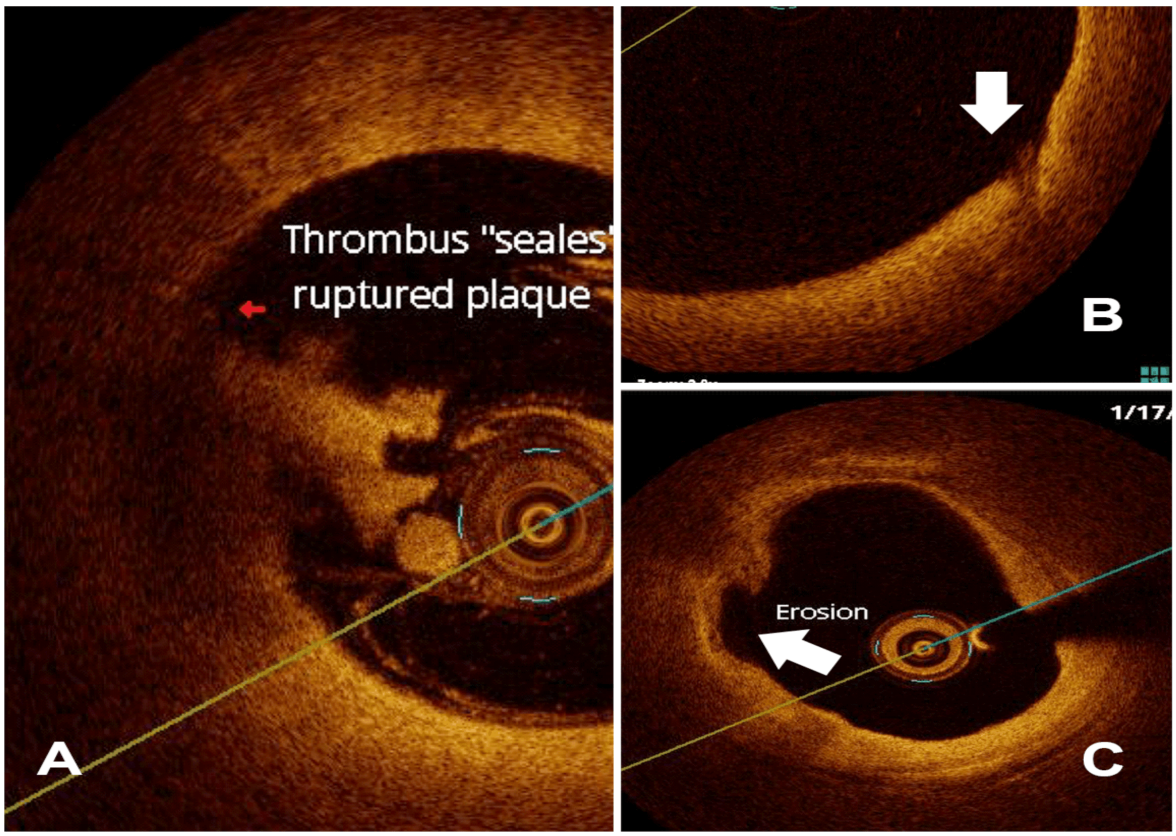

Figure 3 – ***Vulnerable plaques: (A) Ruptured plaque; (B) Plaque ulceration; (C) Plaque erosion.***

Plaque erosions are characterized, on OCT, by the presence of luminal thrombus that envelopes an intact, disorganized intimal area [4]. The hallmark of plaque erosion is represented by a thrombus covering a non-disrupted fibrous cap [33].

OCT imaging in acute coronary syndromes

In ACS patients, as compared to stable patients, there is a two times higher incidence of ruptured plaques, as compared to erosions or ulcerations. The information came from OCT studies in ACS patients and from pathology studies in sudden death individuals [17, 34].

The current management of ACS patients is mostly performed by percutaneous revascularization, with stent implantation at the site of a culprit lesion on angiography [35]. It is well known that a percutaneous coronary revascularization has a slight risk of stent failure, with subsequent symptom recurrence. OCT may identify culprit non-significant stenosis, with signs of plaque instability [35]. This non-significant stenosis, even though with signs of plaque instability, may not be treated by stent implantation. In one OCT study [36], ACS patients with eroded but intact fibrous cap culprit lesions were evaluated by comparing interventional treatment, with stent implantation, to medical treatment alone. After a follow-up of more than two years, none of the medically treated patients required an additional revascularization [36]. These findings suggest that knowing the underlying mechanism of culprit lesion vulnerability, provided by OCT imaging, can improve ACS management, by avoiding stent placement and, thereby, procedure-related complications [36].

OCT imaging of non-atherosclerotic coronary artery lesions

There are non-atherosclerotic pathological coronary entities that cause ACS, with potentially devastating outcome, and there is need for a valid differential diagnosis to complicated atherosclerotic plaques. OCT represent the perfect tool for the identification of these entities, therefore providing aid for an optimal therapeutic approach.

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) (Figure 4, A–D) is represented by coronary wall layers detachment, with intramural hematoma or false lumen formation. Anterograde blood flow decreases and symptoms may occur. SCAD is differentiated from other types of coronary dissections, traumatic or iatrogenic. In patients presenting with ACS, SCAD occurs in 3–4% of the cases, as compared to stable patients presenting for routine CA, in which SCAD is found in 0.3% of the cases. OCT may provide diagnosis [37], even in some difficult cases of SCAD [38]. The coronary revascularization with stent implantation is difficult in SCAD cases, due to intimal fragility and the possibility of guidewire traveling through the false lumen. In these cases, OCT can be an important PCI guidance tool [39].

Iatrogenic coronary artery dissection

Iatrogenic coronary artery dissection (ICAD) is a rare (<1%) complication of diagnostic CA, with potentially catastrophic outcomes. ICAD has a higher prevalence during coronary interventions, in relation to: use of Amplatz-

shaped catheters, deep intubation, unskilled manipulations and vigorous contrast ejection, especially in the presence of ulcerated plaques and variations in the coronary ostial anatomy. OCT provides the exact guidewire position and landing zones for therapeutic stent implantation, being an extremely helpful tool in managing an ICAD.

Honeycomb-like structure

Honeycomb-like structure (Figure 5, A and B) is seen on CA as an irregular linear filling defect. The general belief is that a honeycomb-like structure represents a spontaneous recanalization of a coronary thrombus. OCT aspect is that of multiple interconnected channels, surrounding and connecting to a larger central lumen, and converging, proximally and distally, into a single lumen [40]. OCT provides the anatomic confirmation of the diagnosis suspicion made on CA and offers support in the revascularization procedure [41].

OCT use for interventional procedures optimization

The rapid, intensive and continuous development of interventional cardiology, with technological improvements in percutaneous revascularization devices and procedures, lead to a total change in coronary revascularization management. Along with multiple clinical benefits, these advances also brought a new coronary pathology, namely stent failure. OCT offers the *in vivo* possibility of performing stent healing follow-up imaging and, respectively, of studying the mechanisms underlying stent failure.

PCI late outcome/follow-up

OCT strut coverage

The high-resolution of OCT make it able of visualizing tissue overlying struts (Figure 6A) and these properties can be used for long-term stent follow-up. OCT covered and uncovered struts are considered struts with or without evidence of tissue visualized above them [42]. In one recent study [43], this OCT ability was used to compare stent healing, for different type of stents and showed that second-generation drug-eluting stents (DES) are superior to first generation DES, as well as to bioresorbable vascular scaffolds and bare-metal stents. From the DES category, Everolimus covered stents proved to be the best option for up to one-year follow-up [43].

Restenosis

The mechanism of restenosis is not entirely clear, but there are data suggesting that the persistent intimal injury, caused by metal stent structure, lead to chronic inflammation and continuous fibrin luminal layering [44]. The OCT aspect of in-stent restenosis is represented by important tissue proliferation, with different signal intensity, covering stent struts (Figure 6B) [4].

Stent thrombosis and very late stent thrombosis

OCT played a central role in a study which investigated the potential causes of very late stent thrombosis (VLST) [45]. It is known that normal healing neo-intima is the desirable process after stent implantation, leading to safe double antiplatelet anti-aggregation discontinuation, thereby avoiding stent thrombosis. The usual cause for insufficient neo-intima formation is represented by mal-apposition of stent struts (Figure 6C). Another important cause for stent thrombosis is due to neo-atherosclerosis. There is a strong correlation between the size of stent area without neo-intima with the probability of stent thrombosis, but no significant statistical difference between early- and new-generation DES [45].

Neo-atherosclerosis

Neo-atherosclerosis (Figure 6, C and D) is defined by appearance of atherosclerotic components on stents surface and it is differentiated from the native one by its rapid progression. The underlying mechanisms remain unclear, with theories suggesting chronic and intense inflammation process, due to the intimal injury following non-resorbable metal struts implantation. As in native atherosclerosis, plaque rupture represents the main athero-thrombosis process. It can have all the morphological aspects of native coronary atherosclerosis. OCT is able to detect neo-atherosclerosis, providing an excellent tool for the positive *in vivo* diagnosis. It also allows the differential diagnosis to late stent thrombosis induced by other causes [46].

Post drug-eluting balloon intervention

Post drug-eluting balloon (DEB) intervention has the advantage of both local anti-proliferative drug delivery and absence of stent related chronic injury and inflammation. DEB is an excellent stent restenosis revascularization option. There is insufficient information about *de novo* lesions DEB interventions. OCT is used to evaluate safety and intravascular outcome of DEB interventions following cutting balloon dilation and, respectively, PCI with DES implantation [47].

3D-OCT

OCT enables an excellent 3D reconstruction of coronary vessels and stent struts, due to fast frame rate acquisition, with unrivalled resolution and pullback speed [48]. The development of 3D reconstruction software has promptly translated into OCT clinical use, for bifurcation lesions treatment, assessment of jailed side branches, and acute myocardial infarction management [49]. 3D-OCT is used to describe and differentiate all atherosclerotic plaque characteristics [50], offering novel information about atherosclerotic disease or stent healing process. OCT is safe and feasible in highly selected patients and clinical settings, as well as in unselected patient populations referring to a routine Cath Lab practice [51]. Still, 3D-OCT is under clinical and research development.

Conclusions

Morphological features of atherosclerosis were once identified post-mortem, with stained histological sections studied by white-light microscopy, in the department of pathology. Use of OCT, a very high-resolution invasive imaging procedure, enable these histopathological features to be identified *in vivo*, following coronary angiography. Use of diagnosis data provided by OCT has the potential to optimize interventional procedures of percutaneous coronary dilatation and stenting.

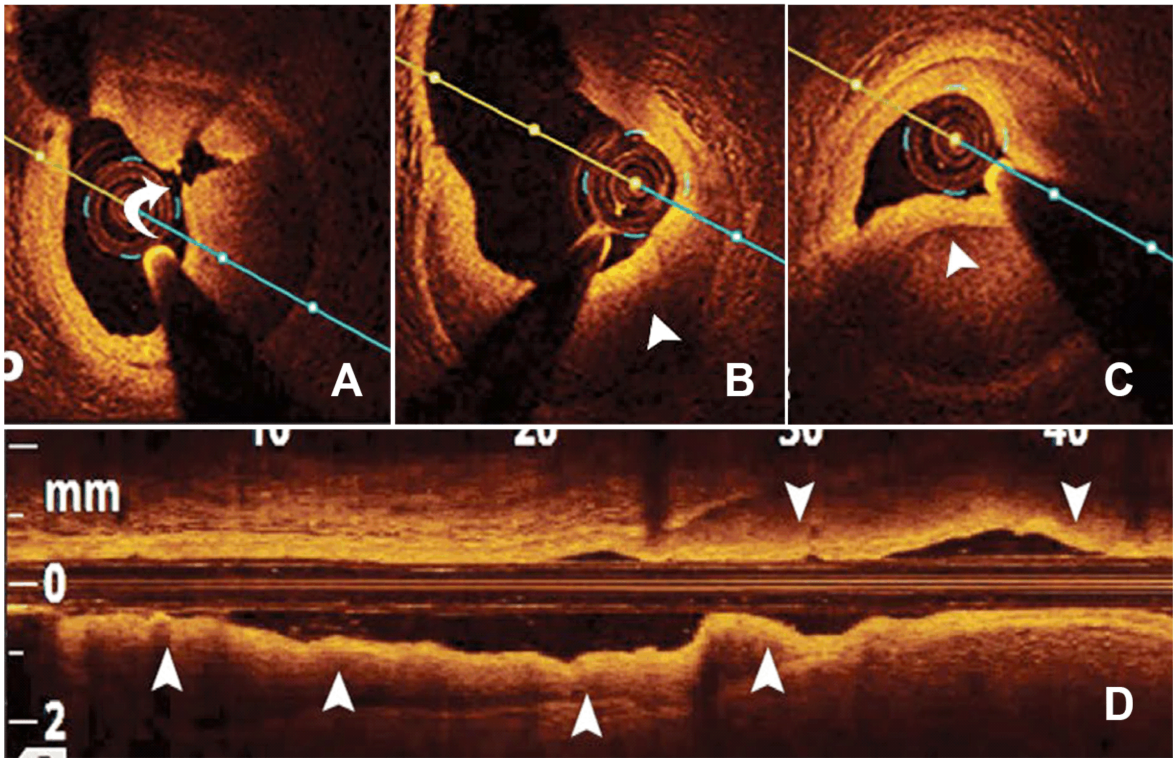

Figure 4 – ***Spontaneous coronary artery dissection: (A) Dissection entry point (curved arrow); (B and C) True and false (white arrows) lumens, in transversal view, false lumen with hematoma; (D) Dissection in longitudinal view false lumen (white arrows).***

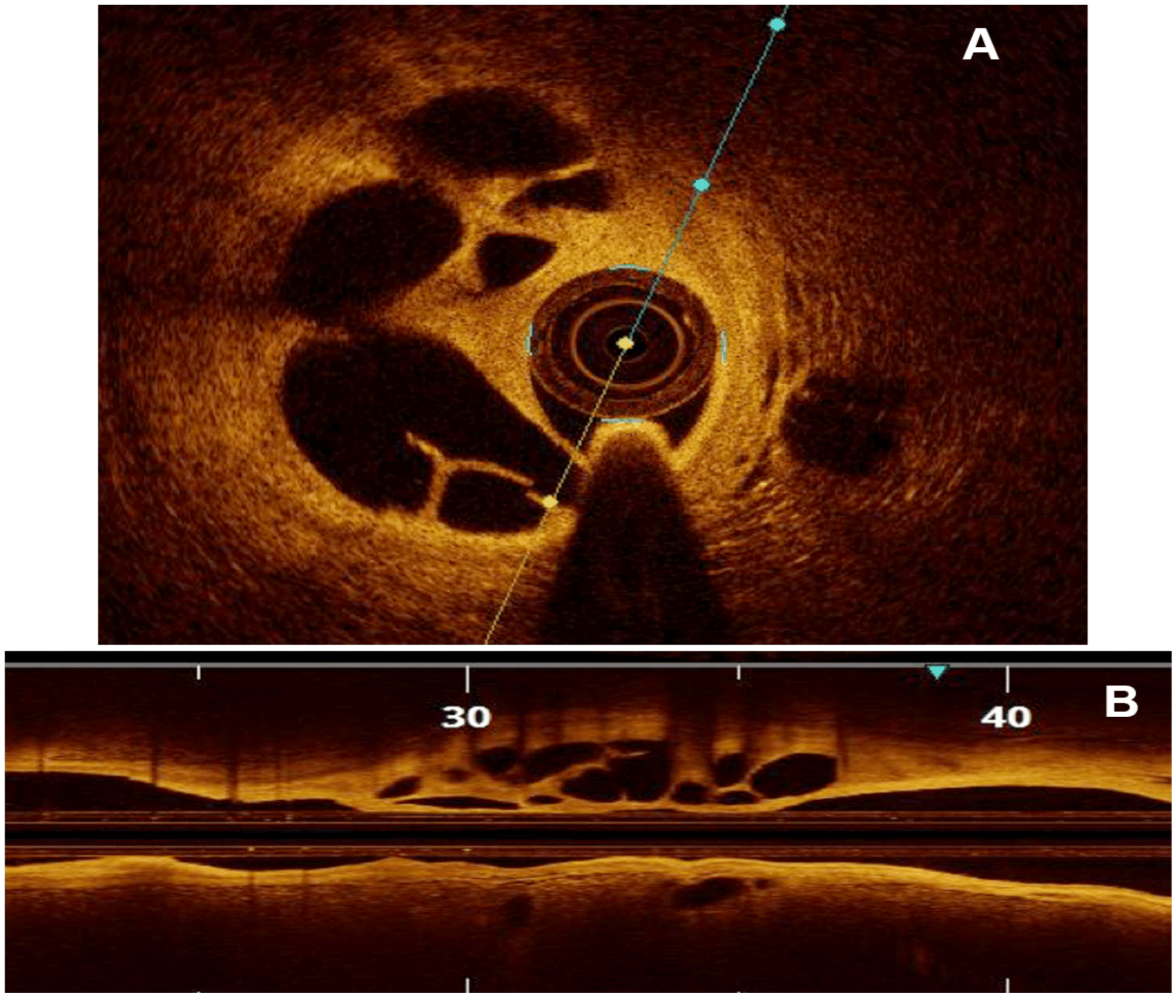

Figure 5 – ***(A) Honeycomb-like structure in transversal view; (B) Honeycomb-like structure in longitudinal view.***

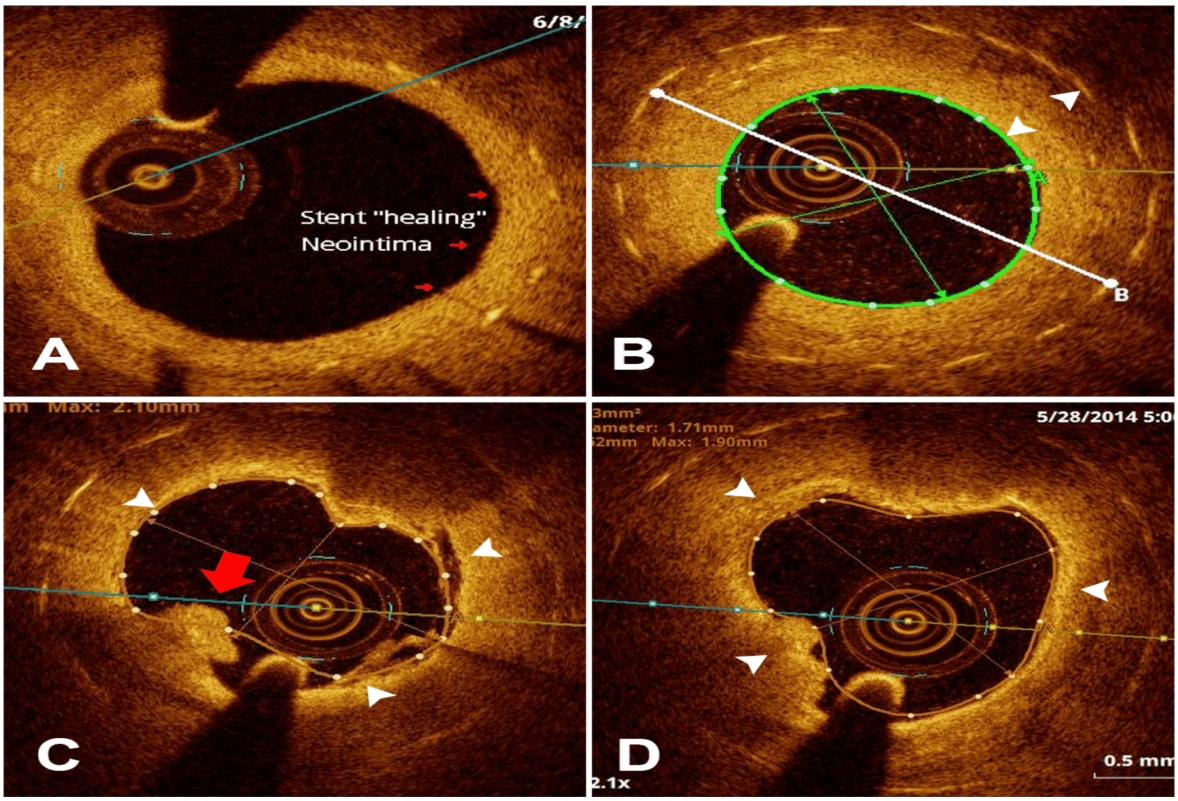

Figure 6 – ***OCT aspect of a bare-metal stent, 10 years evolution: (A) Normal stent neointima; (B) Restenosis (between white arrows); (C) Very late stent thrombosis (red arrow) due to neoatherosclerosis (white arrows); (D) Neoatherosclerosis (white arrows).***

Conflict of interests

The authors declare that they have no conflict of interests.

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