Clinical Applications and Methods of Intravascular Imaging of Atherosclerosis
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Atherosclerosis is the leading cause of coronary artery disease, stroke and peripheral artery disease. The onset of atherosclerotic coronary lesions occurs through accumulation and oxidation of low-density lipoprotein (LDL). Oxidized LDL promotes the recruitment and activation of leukocytes, as well as cell death and generation of complex atherosclerotic plaques. These plaques have high necrotic core content, a thin fibrous inflamed layer, and intense accumulation of macrophages. In the initial stage of the formation of atheroma, remodeling of the vessel wall generally prevents the plate from invading the lumen, thereby masking the presence of atheroma in angiography. Advances have contributed to the study of atherosclerosis by intravascular imaging. Methods such as intravascular ultrasound, optical coherence tomography, intravascular magnetic resonance spectroscopy, infrared spectroscopy, Raman spectroscopy, fluorescence spectroscopy, intravascular magnetic resonance imaging and infrared fluorescence have been used in the intravascular evaluation of atherosclerosis. Intravascular ultrasound can assess the extent of the disease in the axial and longitudinal plane and contribute to the understanding of the pathophysiology of coronary artery disease. This manuscript describes the characteristics and clinical applications of the methods of coronary intravascular imaging.

Introduction

Coronary angiography has been the gold standard technique for the evaluation of coronary artery disease. However, some limitations of coronary angiography such as the inability to provide information on the evaluation of both the volume and the morphological characteristics and the composition of plaques; the need for spatial resolution for the identification of subtypes of lesions and better understanding of the hemodynamic significance of these lesions, as well as the evaluation of plaques with less than 50% of stenosis that may have complications leading to acute coronary syndromes, have led to the design and development of new technologies to better assess not only the luminal disease, but for a better quantitative and qualitative analysis of the atherosclerotic plaque.1-4

Atherosclerosis is a complex disease characterized by a chronic systemic inflammatory process that affects the inner layer of the arteries, such as the coronary arteries, the aorta, the carotid arteries and the peripheral arteries of the lower limbs.5-9

In the pathophysiology of atherosclerosis, there is an interaction between environmental risk factors, genetic and psychological components, immune and endocannabinoid system, hematological and endothelial cells, clotting factors and inflammatory mediators.10-13

The characteristics of atherosclerotic plaques are responsible for the form of presentation of clinical events. Therefore, it is necessary to better understand its histology and morphology, as well as its evolutionary lesions, as described below:14-16

- Type I lesions (initial): these are characterized by the presence of the first detectable lipid deposits in the intima and the cellular reactions associated with them. The initial histological changes at this stage are minimal, with small groups of macrophages containing lipid droplets known as foam cells;
- Type II lesions include fatty streaks. Microscopically, they consist of laminated layers of foam cells attached to smooth muscle cells with fat deposits. T lymphocytes can also be found in this type of lesion, but to a lesser extent than the macrophages;

Keywords
Atherosclerosis; Coronary artery disease; Diagnostic imaging.

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• Type III lesions: those with chemical and morphological composition intermediate to type II and to atheroma. They are also known as transitional or pre-atherosclerotic lesions. They are histologically characterized by the presence of lipid accumulation in the extracellular medium;

• Type IV lesions or atheroma: dense and extracellular content of lipids uniformly located in the intima, known as lipid cores. These lesions have arterial wall thickening characteristics without causing luminal narrowing, considering its eccentric growth characteristic;

• Type V lesions: these are characterized by the formation of fibrous connective tissue which, associated with the lipid core, comprises the fibroatheroma type Va lesion. If the lesion calcifies, it is known as type Vb lesion and in cases where the lipid core is absent or scarce, it is then type Vc. Such lesions can cause clinically relevant luminal narrowing;

• Type IV or type V lesions that undergo disruption, hematoma or hemorrhage and thrombosis are called complicated lesions and are classified as type VIa, VIb, VIc, respectively.

Vascular remodeling in atherosclerosis

Vascular remodeling of the coronary artery implies geometric changes in vessel dimensions and evolves with the progression and regression of the atherosclerotic process. This includes a broad spectrum of presentations that may vary from expansive remodeling, in which the dimensions of the coronary artery increase as plaque accumulates, and constricting remodeling in which there is a relative contraction of the vessel wall, which affects the lumen. 17-22

Alternatively, the vascular remodeling can be classified as adaptive (compensatory, suitable for hemodynamic stimulus), or maladaptive (inadequate dysfunctional). The direction and scale of remodeling are coordinated by the production of endothelial growth factors, proteases and cell adhesion molecules in response to the changes detected in blood flow. Degradation of the matrix involved in this process enables the rupture of atherosclerotic plaques, thereby increasing the risk of acute coronary syndromes. 23-25

Imaging modalities of coronary atherosclerosis

There is great advancement in imaging modalities of coronary arteries. This study provides a more accurate assessment of coronary atherosclerosis, as well as scientific advances in the pathophysiology, prevention and treatment.26

The intimal layer of the arterial wall is between the endothelium and internal elastic lamina and has, in its borders, a subendothelium formed by smooth muscle cells and fibroblasts arranged in a matrix of connective tissue. The middle layer is composed of smooth muscle cells arranged in a matrix with a small amount of elastic and collagen fibers with an average thickness of 200 μm and separated from the adventitia by the external elastic lamina. The thickness of the adventitia, the outermost layer of the arterial wall, ranges from 300-500 μm and is composed of fibrous tissue (collagen and elastin) and incorporates the vasa vasorum, nerves and lymph vessels.

This manuscript describes the main types of intravascular imaging of coronary atherosclerosis, as well as the comparison between intravascular ultrasound (IVUS) and optical coherence tomography (OCT) and their applications27 (Chart 1).

– Intravascular Ultrasound (IVUS)

Intracoronary ultrasound is the intravascular imaging most used today. This modality requires inserting a catheter with a transducer at its tip, which emits an ultrasound signal perpendicular to its axis with a frequency of 20-70 MHz.

Detection of the intimal layer on intravascular ultrasound depends on its thickness. The minimum measurement of 160 μm is required for its definition. The thickness of the intimal layer increases with age, despite the absence of atherosclerotic lesions. Reflections of the signals emitted are received by the transducer and analyzed to generate cross-sectional images, which enables the identification of luminal borders and media and adventitia layer. It is also possible to evaluate the atherosclerotic plaque load and characterize its composition.28,29

The IVUS ability to detect the composition of the plaque surface is moderate according to studies based on the histology of atherosclerotic plaque.30 Recent studies are skeptical about the reliability of evaluating the type of plaque, especially in segments with stent and calcium deposits31,32 as well as significant limitations of IVUS that do not allow the detection of characteristics associated with increased risk of plaque rupture (microcalcifications, neovascularization, plaque erosion, etc.).33
The main indications for the use of intravascular ultrasound are: a) evaluation of moderate coronary lesions; b) evaluation of ambiguous lesions in the left main coronary artery; c) detection of unstable plaques; d) the guide method in the implant of coronary stents (bare-metal and/or drug-eluting stents). Figure 1 shows the image of a normal coronary artery by the IVUS. Chart 2 shows the differences in the IVUS modes of operation.

**IVUS with virtual histology**

The IVUS with radiofrequency, also called virtual histology, allows the evaluation of the plaque dimensions and detailed tissue characterization of the atherosclerotic lesion. The four basic components of the plaque are defined by this method: fibrolipidic tissue (light green), fibrous tissue (dark green), calcium (white) and the areas of inflammatory activity and necrosis (red). The IVUS with virtual histology demonstrates plaque components that can be quantified in relation to their corresponding areas and the percentage occupied by each component of the total plaque volume.

Based on the percentage composition of the plaque and the location of necrotic and calcium contents in relation to the vascular lumen, the following classification of lesions is obtained by virtual histology:

- fibrotic plaque: predominant fibrotic tissue without confluent areas of necrotic or calcium tissue;

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### Chart 1

**IVUS and OCT and their applications**

<table>
<thead>
<tr>
<th>Specifications</th>
<th>IVUS</th>
<th>TCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial resolution (μm)</td>
<td>100-150</td>
<td>10-20</td>
</tr>
<tr>
<td>Lateral resolution (μm)</td>
<td>150-300</td>
<td>25-40</td>
</tr>
<tr>
<td>Recoil velocity (mm/s)</td>
<td>0.5-2.0</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Scanning diameter (CV) (mm)</td>
<td>8-10</td>
<td>6.8</td>
</tr>
<tr>
<td>Tissue penetration (mm)</td>
<td>4-8</td>
<td>1-2</td>
</tr>
<tr>
<td>Frame rate per second</td>
<td>30</td>
<td>15-20</td>
</tr>
</tbody>
</table>

**Applications**

- Evaluation of stenosis severity
- Evaluation of atherosclerotic plaque
- Evaluation of stent coverage and position
- PCI guide
- Allows better understanding the various stages of atherosclerotic disease and vascular response to treatment.
- Detects arterial structures and helps determining different histological constituents.
- Distinguishes different degrees of atherosclerotic changes and various types of plaques.
- Allows extraordinary evaluation of the characteristics and thickness of the fibrous cap.
- Evaluates the neointimal coverage, tissue patterns for stent strut and apposition.
- Invasive test.
- Invasive test.
- Its low axial penetration (1.5-2.0 mm) does not provide optimal view of the arterial wall, especially in large vessels, in which the outer layers of the artery cannot be identified.

**Advantages**

- Pre-intervention:
  - accurate evaluation of the lesion length;
  - accurate evaluation of the vessel size;
  - better evaluation for direct stent implant.
- Post-intervention:
  - accurate evaluation of the apposition of stent struts;
  - avoid gaps (implanting > 2 stents).

**Disadvantages**

- Invasive test.
- Limits the study of the microstructure, resulting in a sensitivity of only 37% for the detection of plaque rupture.

**Notes**

IVUS: intravascular ultrasound; OCT: optical coherence tomography; VF: vision field; PCI: percutaneous coronary intervention.
• calcified fibroatheroma: presence of calcium confluent areas (> 10% of the plaque area percentage) in three or more consecutive sections;
• fibroatheroma: presence of confluent areas of necrotic tissue (> 10% of the percentage of plaque area) in three or more consecutive sections;
• thin cap fibroatheroma (TCFA): presence of confluent areas of necrotic tissue (> 10% of the percentage of plaque area) in three or more consecutive sections and in direct contact with the lumen.

Figure 2 represents the morphology of the atheroma plaque.40 Figure 3 shows the types of images that can be viewed from the atherosclerotic plaque41 and Figure 4 shows the types of plaques.42

– Optical coherence tomography (OCT)

Optical coherence tomography (OCT) has an axial resolution (12-18 μm) that delivers a detailed intravascular view, including all layers of the vessel wall (provided that there is no disease in the intima) and, in the presence of macrophages, neovascularization, microcalcifications and thrombi, it allows estimating the fibrous cap thickness.42-45

Histology-based studies have shown that this is a reliable technique to detect the plaque type, although some studies have been concerned with their ability to discriminate calcified plaques and plaques rich in lipids.44-46 Its imaging limitations are: incapacity to penetrate the lipid-rich cores and tissue penetration (interval: 2-3 mm), which repeatedly inhibits the image of the entire atheroma plaque; limitations in portraying the longitudinal 3D morphology of the plaque on the artery. Figure 4 shows coronary OCT image. Chart 3 describes the particularities of the OCT in different types of plaque.

– Magnetic resonance intravascular spectroscopy

Magnetic resonance intravascular spectroscopy involves advancing the catheter with a magnetic resonance probe at its tip, which creates a field of vision with a 60° radial sector, which allows the identification of the lipid component into two zones: superficial (0-100 μm) and deep (100-250 μm). This technique does not show the lumen, the vessel wall and the plaque morphology.44-48

– Intravascular magnetic resonance imaging

Intravascular magnetic resonance imaging shows the plaque behind the calcified tissue. Its limitations include the noise introduced by the movements, the heat generated during the imaging and increased time required to acquire the images, which would limit its application in humans. Recent advances in intravascular magnetic resonance imaging enabled high-resolution (80 μm) real-time study of the in vivo image.49

– Intravascular photoacoustics (IP)

Intravascular photoacoustic imaging allows identifying many plaque components and is able to differentiate plaques rich in fibrous tissue lipids and detect the presence of neoangiogenesis.50,51 In addition,
## Chart 2
### IVUS: operating modes

<table>
<thead>
<tr>
<th>Modes</th>
<th>Mechanic (rotation)</th>
<th>Electronic (solid state)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A single piezoelectric transducer at the catheter tip, which rotates at 1800 rpm to create the tomographic image</td>
<td>64 transducer elements in an annular array is sequentially activated to generate the cross-sectional image</td>
</tr>
<tr>
<td>Frequency of the ultrasound beam</td>
<td>30 – 45 MHz</td>
<td>~ 20 MHz</td>
</tr>
<tr>
<td>Catheter size</td>
<td>3.2 F (Atlantis SR, BSC)</td>
<td>3.5 F (Eagle Eye, Volcano)</td>
</tr>
<tr>
<td>Positive points</td>
<td>– Best image quality and easier to interpret.</td>
<td>– Slightly easier to set up.</td>
</tr>
<tr>
<td></td>
<td>– Requires saline washing to provide a pathway for the ultrasound beam fluid (air bubbles may degrade image quality).</td>
<td>– Simultaneous display of blood flow in color, which facilitates the distinction between lumen and wall limits.</td>
</tr>
<tr>
<td>Traps</td>
<td>– Requires saline washing to provide a pathway for the ultrasound beam fluid (air bubbles may degrade image quality).</td>
<td>– Artifacts and image can be problematic, immediately adjacent to the transducer.</td>
</tr>
<tr>
<td></td>
<td>– It is necessary to use the closer field ring down the subtraction.</td>
<td></td>
</tr>
</tbody>
</table>

**IVUS: intravascular ultrasound.**

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### Figure 2

**Morphology of atheroma on IVUS.** Soft (left), fibrous and calcified atheromas (center) and highly calcified mixed atheromas. **Source:** adapted from Nissen et al. 40 **IVUS: intravascular ultrasound.**

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markers can be used to detect cells or molecules that are involved in atherosclerosis and inflammation process (macrophages, metalloproteinases, selectins). 35,33

The significant advantages of IP imaging are the ability to view the stent morphology and its high penetration and lateral and axial resolution which allow a more detailed and thorough assessment of the vessel wall. 54 Figure 5 shows a coronary IP image. 55

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### Infrared fluorescence (IRF)

Infrared fluorescence imaging is a modality that is rapidly evolving in the study of atherosclerosis. This method is based on the injection of agents that have the ability to attach molecules and cause fluorescence when viewed with infrared light.

This modality has been implemented to view the accumulation of cathepsin in rat models. 56 Since then,
Intravascular imaging of atherosclerosis

From the radio frequency backscattering data, different types of information can be seen: (1) Virtual histology, (2) retinography, (3) integrated backscattered image with intravascular ultrasound (4) iMAP.

Virtual histology can detect four types of tissues: necrotic core, fibrous tissue, fibrofatty tissue and dense calcium tissue. Plaque strain on retinography is reported in strain values, which are further classified into four categories according to the Rotterdam classification. The tissues characterized by integrated backscattered image with intravascular ultrasound are the lipid, fibrous and calcified tissues; iMAP detects the fibrous, lipid, necrotic and calcified tissues.

Source: adapted from García-García et al.\textsuperscript{41}

**Figure 3**

Intravascular imaging of atherosclerosis

**Figure 4**


Source: adapted from Bezerra et al.\textsuperscript{42}
advances in molecular biology have allowed the development of several markers, such as thrombin, metalloproteinases 2 and 9, cathepsin K, D and S. A number of in vitro and in vivo studies were tested for the feasibility and accuracy of IRF, providing evidence that it can be used to study the plaque biology, inflammation and neovascularization.

– Fluorescence spectroscopy (FS)

Fluorescence spectroscopy is based on the evaluation of the time needed to resolve the fluorescence emitted after the molecules have been excited by light. Several experimental studies have shown that FS is able to discriminate between different degrees of atherosclerotic lesions and detect the presence of macrophages.

A recent study on samples taken from carotid endarterectomy showed that FS can be used to differentiate types of plaque (intimal thickening, fibrous plaques/fibrocalcified plaques, inflamed and necrotic plaques) with high sensitivity and specificity. Among its limitations, FS is not able to provide information on the vessel lumen, wall and plaque morphology, and its field of vision does not study the entire vessel circumference.
– Infrared spectroscopy (IS)

Infrared spectroscopy allows evaluating the chemical composition of the plaque and the lipid component. The IS ability to detect lipid-rich plaques was evaluated and compared to histology. The result was reliable in relation to the lipid component in 83% of the vessels studied.69,70

The IS allows identifying the superficial plaque (cap thickness < 450 μm) and the width of the lipid cores (circumferential measurement > 60°; plaque thickness > 200 μm) and detecting lipid-rich plaques located behind calcified deposits.71,72 Its limitations include the inability to view the lumen and the outer wall of the vessel to quantify the atheroma load and retract plaque characteristics associated with increased vulnerability, such as fibrous cap thickness, integrity, the presence of thrombi and neovascularization.

– Raman spectroscopy (RS)

Raman spectroscopy involves the scattering of light through the molecules.43 A number of experimental studies have shown that this method provides accurate characterization of different types of plates, detailed analysis of its chemical composition and the detection of many constituents such as elastin, collagen, calcium, esterified and non-esterified cholesterol.73-76

RS allows quantifying the effect of treatment on the composition of the plaque surface and identifying vulnerable plaques with high sensitivity and specificity (79% and 85%, respectively).77 Its limitations are the inability to show the morphology of the vessel wall lumen and the plaque and to measure their dimensions.

In summary, advances in intravascular imaging modalities greatly contributes to the evaluation of atherosclerosis, enabling high-resolution evaluation of plaque characteristics with better characterization and quantification of atherosclerosis. Randomized controlled trials with large numbers of patients should be conducted to better understand the real impact of their use in terms of prevention and treatment.

Author contributions

Conception and design of the research: Borges LSR. Acquisition of data: Borges LSR. Analysis and interpretation of the data: Borges LSR. Writing of the manuscript: Borges LSR, Mesquita CT. Critical revision of the manuscript for intellectual content: Borges LSR, Mesquita CT.

Potential Conflicts of Interest

This study has no relevant conflicts of interest.

Sources of Funding

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Academic Association

This study is not associated with any graduate programs.

References


