ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

Pathogenesis and Morphology of Coronary Atheromatous Plaque as an Inlet for Interpretation of Diagnostic Imaging

Mustafa Abdelmonem Hegazy[1]; Kamal Saad Mansour[1]; Ahmed Mohamed Alzyat[1]; Mohammad Abdelhady Mohammad[1]; Abdelmonem Awad Hegazy[2,3*]

[1]Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig City 44519, Egypt

[2]Anatomy and Embryology Department, Faculty of Medicine, Zagazig University, Zagazig City 44519, Egypt

[3]College of Biotechnology, Misr University for Science and Technology, Six of October City 12566, Egypt

Corresponding author: Email: ahegazy@zu.edu.eg; ORCID: 0000-0002-5993-6618

Abstract

Atheromatous plaques represent the most common cause of acute coronary syndrome (ACS) and sudden death. Despite significant advances in methods of managing atherosclerotic coronary plaque, it remains the leading cause of non-communicable disease-causing death in developed countries. Accurate awareness of plaque formation and pathogenesis is essential for correct interpretation of diagnostic imaging. This can be reflected in drawing appropriate management lines to save patients with ACD or reduce mortality or morbidity. In this review, we have attempted to clarify the formation and pathogenesis of plaques as well as the available visualization methods regarding their use and limitations.

Keywords: Thin-cap fibroatheroma; Intravascular ultrasound; Coronary angiography; Coronary thrombosis; Atherosclerosis; Low-density lipoprotein.

Abbreviations

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CAG: Coronary angiography; CTCA: Computed to mographic coronary angiography; EPP: Erosion-prone plaques; FLIM: Fluorescence lifetime imaging microscopy; IVPA: Intravascular photo acoustic imaging; IVUS: Intravascular ultrasound; LAD: Left anterior descending; LCX: Left circumflex artery; LDL: low-density lipoprotein; LDL-c: low-density lipoprotein cholesterol; MRI: Magnetic resonance imaging; NIRF: Near-infrared fluorescence imaging; NIRS: Near-infrared spectroscopy; OCT: Optical coherence tomography; PET: Positive emission tomography; RPAP: Ruptured-prone a theromatous plaque; SMCs: smooth muscle cells; STEMI: ST-elevation myocardial infarction; TCFA: Thin-cap fibroatheroma.

Introduction

The catastrophic events of acute myocardial infarction (AMI), stroke, and death may account for up to 20% of patients with chronic stable angina. This necessitates the appropriate identification of risks and the application of aggressive therapy in order to reduce such events. One of most important factors for understanding risks of patients with ACS is a theromatous plaque with respect to its composition, pathogenesis, and vulnerability [(1)].The myocardium has an extensive arterial blood supply represented by the "right and left" main coronary arteries and their branches. The two main branches of the left coronary artery are the left circumflex artery (LCX)

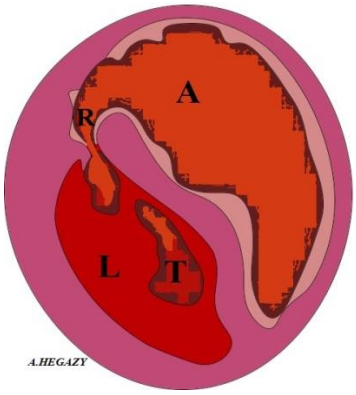
ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

and left anterior descending (LAD) or also called anterior interventricular artery. The terminal branches of these arteries are an astomosed, but unfortunately this is not enough to compensate for blood flow if one of them becomes clogged[(2)]. Therefore, any blockage in one of these arteries due to a theromatous plaque could lead to ischemic heart disease. Furthermore, a thermo atousplaquerupture represents the commonest cause for ACS and sudden death. Despite the great advance in methods of management of atherosclerotic coronary plaque, it remains the main noninfectious disease-causing death in developed countries[(3)].Therefore, an understanding of the pathophysiology of atherosclerotic plaque is essential for interpretation and selection of appropriate diagnostic imaging in order to help manage it properly and limit its potentially devastating effects. We aimed to shed light on the pathogenesis of a theromatous plaque and to clarify the imaging technologies used.

Atheromatous plaquecomposition

Atherosclerosis is a slowly progressive inflammatory disease caused by a lipoprotein that leads to the formation of atherosclerotic plaques within the arterial tree. It is silent in progress. However, the formed atheromatous plaques may rupture leading to thrombosis and possible ACS(Figure 1)[(4)]. Atherosclerosis mainly occurs at the branching sites of the blood vessel where low and oscillating shear stress mostly affects the endothelium[(5)].

Most episodes of ACS are complications of coronary artery thrombosis caused by disorder of a large, fat-rich atheromatous plaque. Such atheromatous plaque is formed of a large core of necrotic tissues infiltrated with macrophages and covered with a thin fibrous cap[(1)]. The thickness of the cap is ≤65µm and infiltrated by T lymphocytes and macrophages as well. Hemorrhage occurring inside the core and its enlargement together with the thin fibrous cap contribute to plaque rupture and subsequent consequences[(3)]. Such hemorrhage can occur as a result of the rupture of new fragile vessels invading the lining intima. Other factors may add to destabilization of the atheromatous plaques including hemodynamic, biomechanical and physical elements[(6)].



Figure(1): Diagram showing a large, lipid-rich atheromatous plaque (A)with rupture (R) and thrombosis (T) into coronary artery lumen (L).

On the other hand, fibrous lesions do not rupture with no subsequent thrombus formation as occurs in thrombotic lesions that may lead to ACS. However, fibrous lesions can lead to coronary artery stenosis leading to ischemic manifestations such as angina pectoris. Therefore, it is important to differentiate between the two types; fibrotic and thin-capped fibro a theromatic

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

lesions. Testing including angiography, and more invasive techniques such as fractional flow reserve (FFR) cannot differentiate between the two types. However, intracoronary imaging can show the composition of the plaques that distinguish their types. Moreover, intracoronary imaging perhaps gives a novel method to improve risk stratification over coronary angiography and/or FFR[1].

Thrombus-prone lesions in case of a theromatous plaques include plaque rupture, erosion or calcifying nodule. The mechanism underlying sudden death varies by type of lesions. It is mostly caused by plaque rupture (73%), followed by erosion of the plaque (30-35%) and rarely by calcified nodules (2-7%)[7,8]. The plaque erosion occurs more in females than in males[7].A thrombus develops from a ruptured plaque when the necrotic area is large (more than 30% of the plaque area) and is covered by a thin necrotic fibrous cap less than 65 microns thick. On the other hand, erosions causing coronary thrombi are characterized by a thrombus superimposed on a matrix rich in proteoglycans with many smooth muscle cells as well as very few inflammatory cells. With regard the calcified nodules, the resulting thrombus most often does not clog the vessel. These nodules are characterized by presence of calcified plates that extend into the lumen and disturb the overlying collagens and endothelium[3,9,10].

Pathogenesis

A theromatous plaques tend to appear early in life and progress with age. The course of the disease may reach more than 50 years, starting in the teenage years[11].However, this progression is not fully predicted and varies from one person to another. The plaquemight take a long time after its development to appear and be manifested through the first complaint. This often occurs in the later stages of atherosclerosis[12].

Lipid deposition in the vessel intima is the main key in development of atherosclerotic lesions[13]. Lesion affects at first the intima of the arteries then spread to the media and adventitia[11]. Accumulation of lipids in the arterial intima results in formation of local inflammation, formation of foam cells and migration, infiltration and proliferation of several cell types including lymphocytes, neutrophils, macrophages, smooth muscle cells (SMCs) and dendritic cells that play an important role in its progression[4].The mechanism of such progression includes apoptosis of SMCs, matrix formation, angiogenesis, remodeling of the artery, disruption of fibrous cap and formation of thrombosis that might be followed by necrosis and calcification[8].

Reduction of the lipid content with decreased plaque size and increased thickness of fibrous cap induced by resolution of inflammationcould lead to more stable atheromatous plaque and hence reduction of adverse coronary events.This might be achieved through intensivestatins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) therapy[11,14]. In addition to drugs, modification of diet as well as muscular exercises could produce pathological and clinical changes[11].The highest risk lesions showing marked reduction after therapy are that of lipid core burden index >500and plaque burden >70%. However, if the plaque is fibrous at baseline, the therapy doesn't change its lipid core burden[1,15]. Therefore, in non-obstructive plaques, it is important to define the risk stratification by determining the composition of plaque. This might improve the management.

Process of pathogenesis

The basic process of pathogenesis of atheromatous plaque includes the following steps (Figure 2):

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

1- Endothelial injury or dysfunction

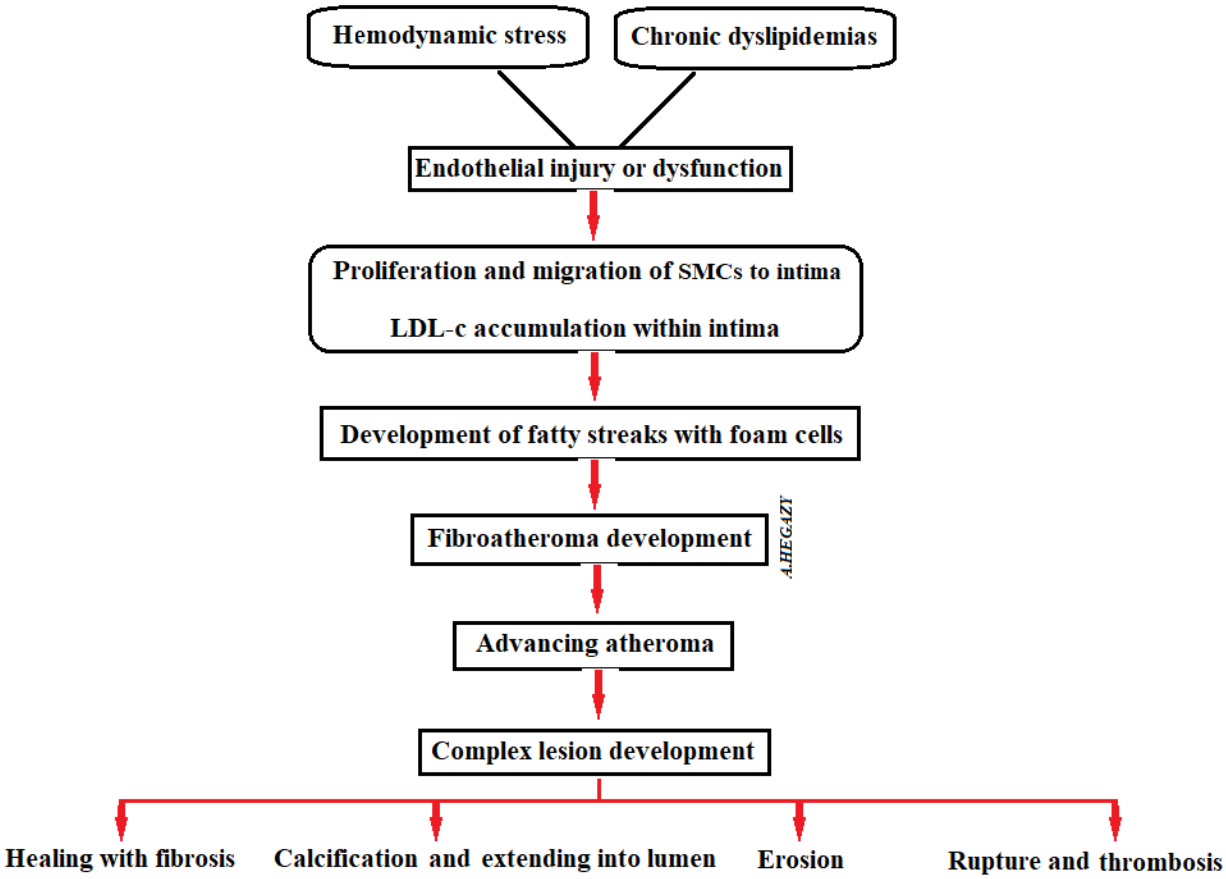
It is the main triggering factor in initiating atheromatous lesions. There are two main elements acting together in initiating vascular endothelial dysfunction in humans. The first is hemodynamic stress caused by hypertension. The second element is chronic dyslipidemias. The role of hemodynamic stress is manifested by the sites of formation of atheromatous plaques at the branching points of blood vessels which are areas subjected to greatest shear stress. On the other hand, chronic dyslipidemia might predispose to endothelial dysfunction through increasing its permeability. Hypercholesterolemia with elevated serum levels of low-density lipoprotein (LDL) promotes macrophages to obtain low-density lipoprotein cholesterol (LDL-c) forming foam cells (Figure3)[16,17].

Currently, it has been added that COVID-19 virus "SARS-CoV-2" is a new predisposing factor exacerbating endothelial dysfunction[18,19].The coagulation cascade can be caused by the persistent inflammatory state caused by COVID-19 infection primarily through increased circulating cytokines[18,20]. Furthermore, the complement system, a hallmark of severe COVID-19 clinical manifestations, along with plasma levels, showed an elevated local sedimentation associated with thickening of the intima. Deposition of C5b-9 "also called terminal complement complex (TCC)" on endothelial cells enhances the secretion of clotting factors, which leads to the production of inflammatory cytokines[19,21].These inflammatory cytokines play a central role in the development of atherosclerotic plaques. Therefore, it is essential to control inflammation in addition to proper management of other diseases such as such as hypertension, hyperlipidemia and diabetes mellites[22].

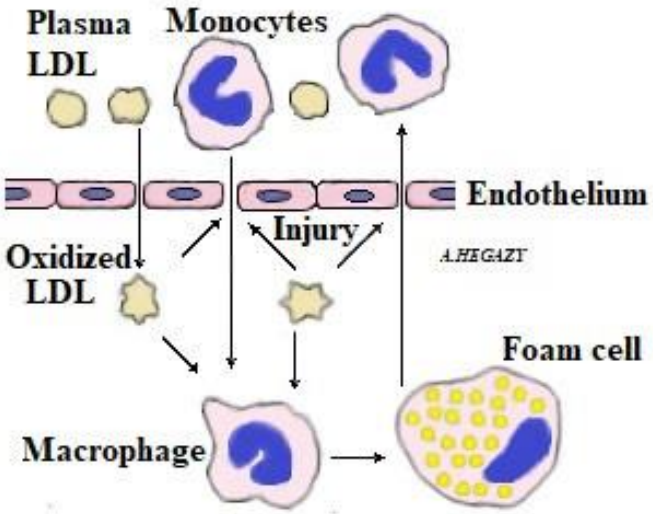
2- Intimal smooth muscle cells (SMCs) proliferation

Endothelial injury promotes platelets' contact with exposed subendothelial tissues. The aggregated platelets induce inflammatory reactions with inflammatory cells' infiltration and proliferation of SMCs. The proliferation and migration of these SMCs from their location in media to reach intima is also promoted by invading monocyte-macrophages[16,17].

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022



Figure(2): Diagram showing steps of process of pathogenesis



Figure(3): Diagram showing mechanism of formation of foam cell.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

3- Early development of fatty streaks

This represents the precursor or the early sign of development of atherosclerotic lesions. The process starts in the childhood and early adolescence. The LDL-c leaves the blood and accumulates within the blood vessel intima. Then, itis modified under the effect of enzymes and oxidation into proinflammatory molecules that provoke inflammatory process in intima.The disrupted endothelium leads to adhesions of platelets and invasion of the intima by inflammatory cells. Also, macrophages acquire LDL-c so that they form foam cellswitha foamy appearance. The degree of lipid within foam cells is an indicatorof the stage of atherosclerosis. However, the mere presence of isolated foam cells or isolated extracellular lipids does not represent atherosclerosis. Fatty streaks' components include foam cells, macrophages, SMCs and possibly aggregated platelets[11,23].

4. Early fibroatheroma

It represents the accumulation of formed and migrated cells at the site of endothelial injury including foam cells, SMCs and inflammatory cells as well as the natural cells of artery. SMCs secrete extracellular proteoglycans that hasten lipid-binding capacity. This promotes cell death of macrophages that control the plaque development with further formation of necrotic debris with the subsequent of development of more inflammation. The enlarging lipid-rich core dominates the affected part of intima and forms about 30-50% of arterial wall thickness. Thereafter, a fibrous tissue collects to form a fibrous cap covering the necrotic lipid-rich core. This forms the fibrous plaque that becomes the dominant lesion[11]. The process begins as early as the adolescence and continues throughout life[24].

5- Advancing atheroma and rupture

Advancing atheroma with thin fibrous cap develops at about 55 years of age or later. Such thin cap is prone to rupture and thrombi formation. The thinning of fibrous cap occurs as a result of increased proteolytic enzymes that dissolve the thick cap. The lesion is then called vulnerable plaque due to its substitutability to rupture with subsequent life-threatening thrombi and myocardial strokes.The rupture of plaques is commonly focal and is often confined to the proximal one third of major coronary arteries[25].

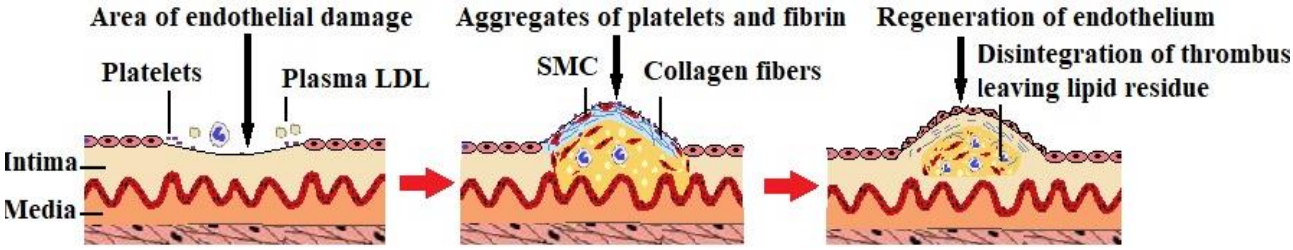
The plaque could extend into the underlying media and adventitia of coronary artery distorting it. Any further enlargement of the plaque can by itself narrow or even block the blood vessel lumen and thus impede or block blood flow. The diseased intima could also be invaded bygrowth of new small blood vessels extending to it from media, a process called angiogenesis. These new vessels called new vasa vasorum are fragile and rupture resulting in intramural hemorrhage which may lead to increased fibrosis in the arterial wall with increased weakness[11].

6- Complex lesion development

Many ruptured atheromatous plaques may pass silent due to development of fibrous tissues that may heal the site of rupture (Figure. 4). However, the healed plaque might rupture again with formation of thrombus. This cycle of rupture, thrombosis, and healing could occur in one location in an individual for up to 4 times; it ismost commonly detected in those who experience sudden death. The cycle is manifested in the arterial wall as multiple healed layers of

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

tissues.Calcific deposition occurs in part of the vessel wall throughout the previous cycle. The plaques may rupture or erode with clot formation, or form calcified plaques that extend into the lumen. The size of atheroma can also be increased somewhat to restrict blood flow[11,26]. The risk factors, including sedentary life, hypertension, hyperlipidemia, diabetes and smoking, can play a pivotal role in the development of these serious consequences[27].



Figure(4): Diagrams showing development and healing of atheromatous plaque

High-risk plaque morphology

Ruptured-prone atheromatous plaque (RPAP)

RPAP is characterized by thin-cap fibroatheroma (TCFA) morphology that posses some features including thin overlying fibrous cap of less than 65 µm and infiltration with inflammatory cells and macrophages[7]. While inflammation has a role in progression of plaque through promoting calcification as a healing process, the macrophages play the pivotal role in development of plaque vulnerability. This is evidenced through the role of macrophages in lipoprotein uptake and metabolism, secretion of growth factors and production of toxic metabolites and enzymes that aid in weakness and rupture of fibrous cap[28]. The role of calcification can be either progression or regression of the pathogenesis of the plaque. Progression might occur through formation of spotty pattern of microcalcifications about 1-3 mm in diameter. The impact of microcalcifications in destabilization of plaque is carried out by the mechanical stress generated within the atheroma at local sites of the vessel[29]. Co-localization of microcalcifications with macrophages in atheromatous plaque is an important indicator of plaque vulnerability, along with other features such as increased thickness of blood vessel media[30]. On the other hand, regression could occur through macrocalcification process which promotes plaque stability and thus limits the inflammation[29].

Preceding factors for plaque rupture encompass the followings:

- Increased thinning and weakness of overlying fibrous cap can lead to its rupture[8].
- Presence of cholesterol microcrystals within TCFA might promote inflammation[31].
- Other features that might be involved in plaque rupture process includelarge plaque size, neovascularization, intraplaque hemorrhage and adventitial inflammation[8].

Rupture of plaques expose its deep necrotic tissue to the vessel lumen with the possibility of clot formation.

Erosion-prone plaques (EPP)

EPP differs from RPAP in that it is more or less heterogenous in morphology where it lacks the distinctive features. There may also be minor calcifications in eroded plaques compared to plaque rupture. The media in the deficient part of endothelium is intact and thickened indicating that vasospasm may be involved in causing pathogenesis of plaque erosion. In EPP type, there is immediate contact between the vessel lumen and underlying fibroatheroma in an area with

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

deficient endothelium; therefore, it is sometimes called acute thrombus. Furthermore, there is little or no inflammation with matrix enrichment with proteoglycans and SMCs[32].

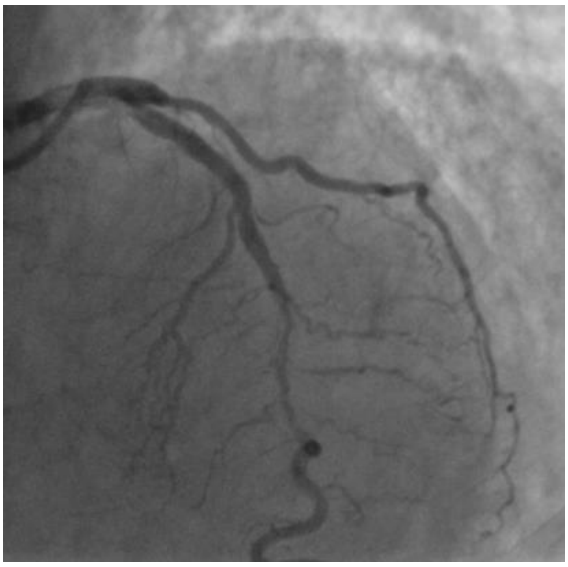
Imaging technologies for detection of a theromatous plaques

Imaging techniques could detect RPAP; however, challenges remain with regard to detecting EPP and distinguishing it from stable plaques through imaging[4]. The imaging could be categorized into invasive and non-invasive methods.

I- Invasive imaging

1- Coronary angiography (CAG)

CAG is the first choice for diagnosing ACD and investigation of the vessels' lumen[33]. Furthermore, it remains the gold standard for diagnosis of coronary a theromatous plaque and obstructive lesions. CAG depicts the general branching of the coronary arteries, their stenosis, occlusion and their an astomosis, if any (Figure5). It has an auxiliary role in the early detection of vulnerable plaques. However, it is limited in characterizing the morphology of plaque and blood vessel wall and lumen that are factors playing an important role in pathogenesis of vulnerability. Despite these limitations, it still plays an important role in determining status of coronary artery movements, stenosis, and plaque rupture as well as possible thrombosis and calcification. The initial CAG enables us to explore the relationship between culprit lesion and the severity of underlying coronary stenosis[34].



Figure(5): Photograph of CAG showing left anterior descending (LAD) and left circumflex (LCX) coronary arteries and their branching.

2- Intravascular ultrasound (IVUS)

IVUS is an in-vivo catheter-based imaging method for assessing the vessel wall dimensions as well as phenotypic characters, distribution and severity of atherosclerotic plaques. It also helps classify the plaques; soft, fibrous, calcified or mixed plaque[35].Further advances in this technique have been developed by adding radiofrequency (RF) analysis to IVUS. The IVUS- RF, also

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

called virtual histology of IVUS (VH- IVUS), has improved the visualization of the mechanical characters and structure of vulnerable plaque[36]. However, concerns have been raised about the IVUS accuracy and its being independent diagnostic modality for predicting acute coronary disease (ACD). It is unable to elucidate the entire coronary tree assessing only up to 53% of lesions[37].

3- Near-infrared spectroscopy (NIRS)

NIRS is another in vivo catheter-based modality. It scans the vessel wall in both longitudinal and circumferential views; therefore, it could investigate the lipid core components of plaques distinguishing cholesterol from collagen[38].Moreover, it might enable prediction of the long-term outcome of cases of non-culprit coronary lesions[39]. However, this method has many limitations including failure to support the complete evaluation of plaque and its burden as well as its inability to visualize the blood vessel lumen[4].

4- Optical coherence tomography (OCT)

OCT is also an invasive intravascular modality. It has the advantage of providing evaluation of atherosclerosis microstructure. Therefore, more information about plaque formation can be obtained through the use of OCT. This allows us to identify not only the ruptured plaque but also the vulnerable plaques and provides more reliable information about cap disruption, subsequent erosion and intracoronary thrombus[40]. Furthermore, OCT can also enable us to visualize spontaneous coronary artery dissection which is challenging to diagnose using coronary angiography. This is because angiography detects the lumen of the vessel, not the wall. Acute artery dissection that means tear of the vessel intima or medial hemorrhage may mimic a theromatous plaque and thrombus formation in the pathogenesis of ACD[33].

The evaluation of vulnerable plaque could be achieved by OCT through quantification of its content of macrophages that represents the main feature of inflammation detected in vulnerable lesions[41]. Among the advantages of OCT is the higher resolution of 10-20 µm versus 150-200 µm in case of IVUS[42]. However, OCT also has some limitations which include low penetration depth of about 2-3 mm impeding determination of plaque burden as well as attenuation of its optical beam by blood within the artery. Therefore, a 2nd generation of OCT such as Fourier-domain OCT has been developed to allow visualization of a long segment of coronary artery[43]. Despite the apparent importance of these new modalities, studies investigating their efficacy in predicting plaque progression are often missed[4].

5- Near-infrared fluorescence imaging (NIRF)

NIRF is proposed to improve the visualization of atheromatous plaques at cellular and molecular levels. It could be useful for detecting the inflammatory process activity in a theroma by evaluating cysteine protease activity as well as identifying stent-induced coronary artery injury[44]. Its limitations include the weakening of light caused by the presence of intravascular blood; there is a need for a vessel surface free of blood[4].

6- Intravascular photoacoustic imaging (IVPA)

IVPA provides chemical analysis of the plaque composition especially lipid components including cholesterol and cholesterol esters so this method can be called analytical chemistry

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

imaging[45]. Its limitations are like that in the case of NIRF. It also fails to fully determine the lipid content in case of plaque with large lipid core[4].

7- Fluorescence lifetime imaging microscopy (FLIM)

FLIM is a promising optical modality for biochemical characterization of the atheromatous plaques. However, it doesn't visualize the morphological characters of plaque needed to interpret the biochemical structure[46]. Unlike the previous two modalities, its efficacy is not affected by presence of blood[4].

8- Multimodality imaging

Multimodality imaging is an alternative method to overcome the limitations of the single modality. This depends on the objective of investigation. For example, combined IVUS-NIRS is used to demonstrate in-vivo histopathological characters of plaque. NIRS can detect lipid even in presence of calcification whichmay mask visualization by IVUS alone. This combination might be able to distinguish ST-elevation myocardial infarction (STEMI) culprit from non-culprit lesions[47]. Table (1) shows examples of combinations of intravascular imaging modalities and their performance in diagnosis of venerable plaques[4].

Table (1): Performance of multimodality imaging in venerable plaques' characterization.

Combined modality	Vessel lumen dimensions	Positive vessel remodeling	Plaque burden	Plaque fibrous cap thickness	Plaque neo-angiogenesis	Plaque inflammation	Plaque lipid pool	Total score (21)
IVUS-OCT	**3**	**3**	**3**	**3**	**2**	**1**	**2**	**17**
IVUS-NIRS	**3**	**3**	**3**	**2**	**0**	**0**	**3**	**14**
OCT-NIRS	**3**	**1**	**1**	**3**	**2**	**1**	**3**	**14**
IVUS-NIRF	**3**	**3**	**3**	**1**	**0**	**3**	**1**	**14**
OCT-NIRF	**3**	**1**	**1**	**3**	**2**	**3**	**2**	**15**
IVUS-IVPA	**3**	**3**	**3**	**1**	**1**	**2**	**2**	**15**
IVUS-FLIM	**3**	**3**	**3**	**3**	**1**	**2**	**2**	**17**

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

3: High performance;**2**: Moderate performance;**1**: Modest performance;**0**: No performance (no information)

II- Non-invasive imaging

1- Positive emission tomography (PET)

PET isa non-invasive imaging based on intravenous injection of a radio-labelled molecular tracer such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG) to detect cellular activity and biological processes related to atherosclerosis such as vasculitis, neo-angiogenesis, hypoxia and microcalcification. The ^{18}F-FDG detects plaque density of macrophages and thus reflects the extent of inflammation through its direct deposition into the vessel wall parallel to degree of the cellular glycolysis[(48)]. Advantages of PET include its high sensitivity and excellent quantitative efficacy. However, it also has limitations including that PET resolution of 6 mmlimits its use to small vessels such as coronary arteries. Furthermore, PET signal degradation caused by respiratory and cardiac motions during imaging, makes assessment of mid- and distal coronary tree to be difficult[(49)].

2- Computed tomographic coronary angiography (CTCA)

CTCA is a non-invasive alternative method that allows assessment of the dimensions of both the lumen and the outer wall of the blood vessels. Furthermore, it detects high-risk plaque burden as well as morphology and remodeling. However, it has limitationsdistinguishing between lipid components and fibrotic tissue[(50)]. Moreover, exposure to radiation and use of an iodinated contrast agent are major disadvantages of CTCA[(51)].

3- Magnetic resonance imaging (MRI)

The MRI gives a good information about the artery morphology such as its wall thickness and volume. Moreover, it identifies the plaque constituents that indicate plaque instability. It can also detect arterial remodeling in cases of subclinical atherosclerosis in asymptomatic patients[(52,53)]. The main advantages of MRI include lack of radiation exposure, high evaluation quality of soft tissues and absence of blooming artefacts noticed in calcified plaques[(54)]. The disadvantages include a relatively long MRI scan time burdensome cross-sectional image and its limitation to a single plaque or blood vessel segment. Table (2) summarizes the advantages and disadvantages of non-invasive imaging techniques[(4)].

Table (2): Summary of non-invasive modalities

Imaging	Advantages	Disadvantages
PET	High sensitivity High reproducibility over short-term Identification and evaluation of plaque inflammation Detection of atherosclerosis course and major acute coronary events' risk. Monitoring effectiveness of therapeutics.	Expensive. Not available for wide use. Limitations for imaging of coronary arteries. Requiring radiotracer.
CTCA	High specificity High predictive value	Low sensitivity Low spatial resolution causing difficulty in differentiation lipid

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

		and fibrous components. Radiation exposure. Use of iodinated contrast agent.
MRI	Providing details about vessel wall and plaque morphology and composition. No ionizing radiation (safe). Suitable for molecular imaging and serial studies.	Consuming long time. Not suitable in case of patients with metal devices.

.

4- Nanotechnology and molecular imaging

Molecular imaging is designed through development of molecular probe for visualization of in-vivo cellular functions and measurement of molecular processes. Nanoparticles ranging from one to 100 nm are typically used in such molecular imaging. Nanoparticles include several types such as gold, iron oxide, dendrimers and biodegradable polymers. In this context, they represent a broad platform aimed at molecular imaging of different molecules of atherosclerotic plaques. Therefore, molecular imaging provides visualization of venerable plaquesat both the cellular and molecular levels[(55)]. Like all other modalities, there are also some limitations and drawbacks to the use of molecular imaging. They includenanotoxicity and nanoparticles surface opsonization.Nanoparticles might interact with elements of immune system including macrophages and cause undesirable side effects such as immunosuppression or immunostimulation[(56,57)].

Conclusions

Atherosclerosis is a slowly progressive inflammatory disease caused by a lipoprotein that leads to the formation of atherosclerotic plaques within the arterial tree. It mainly occurs at the branching sites of the blood vessel where low and oscillating shear stress mostly affects the endothelium. Coronary atheromatous plaque is formed of a large core of necrotic tissues infiltrated with macrophages and covered with a thin fibrous cap. Hemorrhage occurring inside the core and its enlargement together with the thin fibrous cap contribute to plaque rupture and subsequent consequences. Accumulation of lipids in the arterial intima results in formation of local inflammation, formation of foam cells and migration, infiltration and proliferation of several cell types including lymphocytes, neutrophils, macrophages, SMCs and dendritic cells that play an important role in its progression. Imaging techniques could detect RPAP; however, challenges remain with regard to detecting EPP and distinguishing it from stable plaques through imaging. The imaging could be categorized into invasive and non-invasive methods. Invasive methods include CAG, IVUS, NIRS, OCT, NIRF, IVPA and FLIM; while, PET, CTCA and MRI. All modalities have some limitations and drawbacks. None of them could detect all characters of atheroma. Therefore, some authors reverted to use of multimodalities. However, CAG remains the gold standard method for diagnosis of coronary atheromatous plaque particularly in acute phases of ischemic diseases.

Conflicts of interest

There are no conflicts of interest.

Funding: None.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

Authors' contributions: All authors share in all steps of the article.

Acknowledgements: All figures are original & diagrams are drawn bythe last author "AAH".

References

1. Moreno PR, Kini AS. Impact of Coronary Plaque Morphology on Prognosis of Patients with Chronic CAD. American College of Cardiology; 2016. https://www.acc.org/latest-in-cardiology/articles/2016/04/14/09/58/impact-of-coronary-plaque-morphology-on-prognosis-of-patients-with-chronic-cad?wt.mc_id=twitter
2. Hegazy A. Clinical anatomy of thorax for medical students and doctors. LAP, Lambert Academic Publishing; 2018
3. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. Pathophysiology of atherosclerosis plaque progression. Heart Lung Circ. 2013 Jun;22(6):399-411. DOI: 10.1016/j.hlc.2013.03.001. Epub 2013 Mar 29. Erratum in: Heart Lung Circ. 2014 Apr;23(4):387. PMID: 23541627.
4. Mushenkova NV, Summerhill VI, Zhang D, Romanenko EB, Grechko AV, Orekhov AN. Current Advances in the Diagnostic Imaging of Atherosclerosis: Insights into the Pathophysiology of Vulnerable Plaque. Int J Mol Sci. 2020 Apr 23;21(8):2992. DOI: 10.3390/ijms21082992. PMID: 32340284; PMCID: PMC7216001.
5. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol. 2007 Jun 26;49(25):2379-93. DOI: 10.1016/j.jacc.2007.02.059. Epub 2007 Jun 8. PMID: 17599600.
6. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014 Dec;276(6):618-32. DOI: 10.1111/joim.12296. Epub 2014 Sep 25. PMID: 25156650.
7. 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;20:1262–75.
8. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013 Mar;34(10):719-28. DOI: 10.1093/eurheartj/ehs411. Epub 2012 Dec 13. PMID: 23242196.
9. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93:1354–63.
10. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999;82:269–72.
11. Insull W Jr. The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. Am J Med. 2009 Jan;122(1 Suppl):S3-S14. DOI: 10.1016/j.amjmed.2008.10.013. PMID: 19110086.
12. Eikendal AL, Groenewegen KA, Bots ML, Peters SA, Uiterwaal CS, den Ruijter HM. Relation Between Adolescent Cardiovascular Risk Factors and Carotid Intima-Media

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

Echogenicity in Healthy Young Adults: The Atherosclerosis Risk in Young Adults (ARYA) Study. J Am Heart Assoc. 2016 May 12;5(5):e002941. DOI: 10.1161/JAHA.115.002941. PMID: 27172911; PMCID: PMC4889174.

13. Venugopal SK, Anoruo MD, Jialal I. Biochemistry, Low Density Lipoprotein. [Updated 2021 Apr 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500010/
14. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz GS, Fuster V, Narula J, Sharma SK, Moreno PR. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol. 2013 Jul 2;62(1):21-9. DOI: 10.1016/j.jacc.2013.03.058. Epub 2013 May 1. PMID: 23644090.
15. Dohi T, Maehara A, Moreno PR, Baber U, Kovacic JC, Limaye AM, Ali ZA, Sweeny JM, Mehran R, Dangas GD, Xu K, Sharma SK, Mintz GS, Kini AS. The relationship among extent of lipid-rich plaque, lesion characteristics, and plaque progression/regression in patients with coronary artery disease: a serial near-infrared spectroscopy and intravascular ultrasound study. Eur Heart J Cardiovasc Imaging. 2015 Jan;16(1):81-7. DOI: 10.1093/ehjci/jeu169. Epub 2014 Sep 4. PMID: 25190072; PMCID: PMC4357809.
16. Mohan H. Textbook of pathology. Jaypee Brothers Medical Publishers (P) Ltd. Sixth Edition: 2010
17. Saçlı H, Kara İ, Kırali MK. Focus on Coronary Atherosclerosis. InAtherosclerosis-Yesterday, Today and Tomorrow 2018 Aug 1. IntechOpen. DOI: 10.5772/intechopen.77301
18. Hegazy AA, Hegazy RA. COVID-19: Virology, pathogenesis and potential therapeutics. Afro-Egypt J Infect Endem Dis. 2020 Jun 1;10(2):93-9.
19. Vinciguerra M, Romiti S, Sangiorgi GM, Rose D, Miraldi F, Greco E. SARS-CoV-2 and Atherosclerosis: Should COVID-19 Be Recognized as a New Predisposing Cardiovascular Risk Factor? J Cardiovasc Dev Dis. 2021 Oct 10;8(10):130. DOI: 10.3390/jcdd8100130. PMID: 34677199; PMCID: PMC8539652.
20. Paar V, Wernly B, Zhou Z, Motloch LJ, Hoppe UC, Egle A, Lichtenauer M. Anti-coagulation for COVID-19 treatment: both anti-thrombotic and anti-inflammatory? J Thromb Thrombolysis. 2021 Jan;51(1):226-231. DOI: 10.1007/s11239-020-02212-6. PMID: 32632558; PMCID: PMC7338133.
21. Speidl WS, Kastl SP, Huber K, Wojta J. Complement in atherosclerosis: friend or foe? J Thromb Haemost. 2011 Mar;9(3):428-40. DOI: 10.1111/j.1538-7836.2010.04172.x. PMID: 21155967.
22. Sterpetti AV. Inflammatory Cytokines and Atherosclerotic Plaque Progression. Therapeutic Implications. CurrAtheroscler Rep. 2020 Oct 6;22(12):75. DOI: 10.1007/s11883-020-00891-3. PMID: 33025148; PMCID: PMC7538409.
23. Alfarisi HAH, Mohamed ZBH, Ibrahim MB. Basic pathogenic mechanisms of atherosclerosis. Egyptian Journal of Basic and Applied Sciences. 2020;7(1):116-125. DOI: https://doi.org/10.1080/2314808X.2020.1769913
24. Eggen DA, Solberg LA. Variation of atherosclerosis with age. Lab Invest. 1968;18:571-579

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

25. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. J Am Coll Cardiol. 2007 Sep 4;50(10):940-9. DOI: 10.1016/j.jacc.2007.04.086. Epub 2007 Aug 20. PMID: 17765120.
26. Ibañez B, Badimon JJ, Garcia MJ. Diagnosis of atherosclerosis by imaging. Am J Med. 2008;122[suppl]:S15-S25.
27. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. DOI: 10.1016/S0140-6736(04)17018-9. PMID: 15364185.
28. Abdelbaky A, Corsini E, Figueroa AL, Subramanian S, Fontanez S, Emami H, Hoffmann U, Narula J, Tawakol A. Early aortic valve inflammation precedes calcification: a longitudinal FDG-PET/CT study. Atherosclerosis. 2015 Feb;238(2):165-72. DOI: 10.1016/j.atherosclerosis.2014.11.026. Epub 2014 Dec 2. PMID: 25525744.
29. Shioi A, Ikari Y. Plaque calcification during atherosclerosis progression and regression. J. Atheroscler Thromb. 2018, 25, 294–303.
30. Burgmaier M, Milzi A, Dettori R, Burgmaier K, Marx N, Reith S. Co-localization of plaque macrophages with calcification is associated with a more vulnerable plaque phenotype and a greater calcification burden in coronary target segments as determined by OCT. PLoS One. 2018 Oct 24;13(10):e0205984. DOI: 10.1371/journal.pone.0205984. PMID: 30356326; PMCID: PMC6200236.
31. Janoudi A, Shamoun FE, Kalavakunta JK, Abela GS. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. Eur. Heart J. 2016, 37, 1959–1967.
32. Hao H, Gabbiani G, Camenzind E, Bacchetta M, Virmani R, Bochaton-Piallat ML. Phenotypic modulation of intima and media smooth muscle cells in fatal cases of coronary artery lesion. Arterioscler Thromb Vasc Biol. 2006 Feb;26(2):326-32. DOI: 10.1161/01.ATV.0000199393.74656.4c. Epub 2005 Dec 8. PMID: 16339500.
33. Leopoulou M, Mistakidi VC, Oikonomou E, Latsios G, Papaioannou S, Deftereos S, Siasos G, Antonopoulos A, Charalambous G, Tousoulis D. Acute coronary syndrome with non-ruptured plaques (NONRUPLA): Novel ideas and perspectives. CurrAtheroscler Rep. 2020 May 28;22(6):21. DOI: 10.1007/s11883-020-00839-7. PMID: 32468244.
34. Chan KH, Ng MK. Is there a role for coronary angiography in the early detection of the vulnerable plaque? Int J Cardiol. 2013 Apr 15;164(3):262-6. DOI: 10.1016/j.ijcard.2012.01.027. Epub 2012 Jan 30. PMID: 22289298.
35. Mintz G.American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents developed in collaboration with the European Society of Cardiology endorsed by the Society of Cardiac Angiography and Interventions. Eur J Echocardiogr. 2001 Dec;2(4):299-313. PMID: 11908481.
36. Mehta SK, McCrary JR, Frutkin AD, Dolla WJ, Marso SP. Intravascular ultrasound radiofrequency analysis of coronary atherosclerosis: an emerging technology for the

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

assessment of vulnerable plaque. Eur Heart J. 2007 Jun;28(11):1283-8. DOI: 10.1093/eurheartj/ehm112. Epub 2007 May 5. PMID: 17483541.

37. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35. DOI: 10.1056/NEJMoa1002358. Erratum in: N Engl J Med. 2011 Nov 24;365(21):2040. PMID: 21247313.
38. Waxman S, Dixon SR, L'Allier P, Moses JW, Petersen JL, Cutlip D, Tardif JC, Nesto RW, Muller JE, Hendricks MJ, Sum ST, Gardner CM, Goldstein JA, Stone GW, Krucoff MW. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results of the SPECTACL study. JACC Cardiovasc Imaging. 2009 Jul;2(7):858-68. DOI: 10.1016/j.jcmg.2009.05.001. PMID: 19608137.
39. Oemrawsingh RM, Cheng JM, García-García HM, van Geuns RJ, de Boer SP, Simsek C, Kardys I, Lenzen MJ, van Domburg RT, Regar E, Serruys PW, Akkerhuis KM, Boersma E; ATHEROREMO-NIRS Investigators. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol. 2014 Dec 16;64(23):2510-8. DOI: 10.1016/j.jacc.2014.07.998. PMID: 25500237.
40. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, Tanimoto T, Matsuo Y, Masho T, Kitabata H, Tsuda K, Tomobuchi Y, Akasaka T. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol. 2007 Sep 4;50(10):933-9. DOI: 10.1016/j.jacc.2007.04.082. Epub 2007 Aug 20. PMID: 17765119.
41. Phipps JE, Vela D, Hoyt T, Halaney DL, Mancuso JJ, Buja LM, Asmis R, Milner TE, Feldman MD. Macrophages and intravascular OCT bright spots: a quantitative study. JACC Cardiovasc Imaging. 2015 Jan;8(1):63-72. DOI: 10.1016/j.jcmg.2014.07.027. Epub 2014 Nov 5. PMID: 25499133; PMCID: PMC4297553.
42. Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, Seung KB, Choi KB, Shishkov M, Schlendorf K, Pomerantsev E, Houser SL, Aretz HT, Tearney GJ. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. J Am Coll Cardiol. 2002 Feb 20;39(4):604-9. DOI: 10.1016/s0735-1097(01)01799-5. PMID: 11849858.
43. Tearney GJ, Waxman S, Shishkov M, Vakoc BJ, Suter MJ, Freilich MI, Desjardins AE, Oh WY, Bartlett LA, Rosenberg M, Bouma BE. Three-dimensional coronary artery microscopy by intracoronary optical frequency domain imaging. JACC Cardiovasc Imaging. 2008 Nov;1(6):752-61. DOI: 10.1016/j.jcmg.2008.06.007. PMID: 19356512; PMCID: PMC2852244.
44. Jaffer FA, Calfon MA, Rosenthal A, Mallas G, Razansky RN, Mauskapf A, Weissleder R, Libby P, Ntziachristos V. Two-dimensional intravascular near-infrared fluorescence molecular imaging of inflammation in atherosclerosis and stent-induced vascular injury. J Am Coll Cardiol. 2011 Jun 21;57(25):2516-26. DOI: 10.1016/j.jacc.2011.02.036. PMID: 21679853; PMCID: PMC3123768.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

45. Jansen K, van der Steen AF, Wu M, van Beusekom HM, Springeling G, Li X, Zhou Q, Shung KK, de Kleijn DP, van Soest G. Spectroscopic intravascular photoacoustic imaging of lipids in atherosclerosis. J Biomed Opt. 2014 Feb;19(2):026006. DOI: 10.1117/1.JBO.19.2.026006. PMID: 24522806.
46. Lee MW, Song JW, Kang WJ, Nam HS, Kim TS, Kim S, Oh WY, Kim JW, Yoo H. Comprehensive intravascular imaging of atherosclerotic plaque in vivo using optical coherence tomography and fluorescence lifetime imaging. Sci Rep. 2018 Sep 28;8(1):14561. DOI: 10.1038/s41598-018-32951-9. PMID: 30267024; PMCID: PMC6162321.
47. Madder RD, Puri R, Muller JE, Harnek J, Götberg M, VanOosterhout S, Chi M, Wohns D, McNamara R, Wolski K, Madden S, Sidharta S, Andrews J, Nicholls SJ, Erlinge D. Confirmation of the Intracoronary Near-Infrared Spectroscopy Threshold of Lipid-Rich Plaques That Underlie ST-Segment-Elevation Myocardial Infarction. Arterioscler Thromb Vasc Biol. 2016 May;36(5):1010-5. DOI: 10.1161/ATVBAHA.115.306849. Epub 2016 Mar 3. PMID: 26941016.
48. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, Yates D, LaMuraglia GM, Furie K, Houser S, Gewirtz H, Muller JE, Brady TJ, Fischman AJ. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol. 2006 Nov 7;48(9):1818-24. DOI: 10.1016/j.jacc.2006.05.076. Epub 2006 Oct 17. PMID: 17084256.
49. Polycarpou I, Tsoumpas C, King AP, Marsden PK. Impact of respiratory motion correction and spatial resolution on lesion detection in PET: a simulation study based on real MR dynamic data. Phys Med Biol. 2014 Feb 7;59(3):697-713. DOI: 10.1088/0031-9155/59/3/697. PMID: 24442386.
50. Voros S, Rinehart S, Qian Z, Vazquez G, Anderson H, Murrieta L, Wilmer C, Carlson H, Taylor K, Ballard W, Karmpaliotis D, Kalynych A, Brown C 3rd. Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study. JACC Cardiovasc Interv. 2011 Feb;4(2):198-208. DOI: 10.1016/j.jcin.2010.10.008. PMID: 21349459.
51. Harden SP, Bull RK, Bury RW, Castellano EA, Clayton B, Hamilton MC, Morgan-Hughes GJ, O'Regan D, Padley SP, Roditi GH, Roobottom CA, Stirrup J, Nicol ED; CTCA standards working party of the British Society of Cardiovascular Imaging, the Royal College of Physicians and the Royal College of Radiologists. The safe practice of CT coronary angiography in adult patients in UK imaging departments. Clin Radiol. 2016 Aug;71(8):722-8. DOI: 10.1016/j.crad.2016.04.008. Epub 2016 May 17. PMID: 27207375.
52. Kawasaki T, Koga S, Koga N, Noguchi T, Tanaka H, Koga H, Serikawa T, Orita Y, Ikeda S, Mito T, Goto Y, Shintani Y, Tanaka A, Fukuyama T. Characterization of hyperintense plaque with noncontrastT(1)-weighted cardiac magnetic resonance coronary

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

plaque imaging: comparison with multislice computed tomography and intravascular ultrasound. JACC Cardiovasc Imaging. 2009 Jun;2(6):720-8. DOI: 10.1016/j.jcmg.2009.01.016. PMID: 19520342.

53. Miao C, Chen S, Macedo R, Lai S, Liu K, Li D, Wasserman BA, Vogel-Claussen J, Lima JA, Bluemke DA. Positive remodeling of the coronary arteries detected by magnetic resonance imaging in an asymptomatic population: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2009 May 5;53(18):1708-15. DOI: 10.1016/j.jacc.2008.12.063. Erratum in: J Am Coll Cardiol. 2009 Jun 9;53(23):2230. Vogel-Clausen, Jens [corrected to Vogel-Claussen, Jens]. PMID: 19406347; PMCID: PMC2793325.
54. Kim WY, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, Langerak SE, Weber OM, Pedersen EM, Schmidt M, Botnar RM, Manning WJ. Coronary magnetic resonance angiography for the detection of coronary stenoses. N Engl J Med. 2001 Dec 27;345(26):1863-9. DOI: 10.1056/NEJMoa010866. PMID: 11756576.
55. Nune SK, Gunda P, Thallapally PK, Lin YY, Forrest ML, Berkland CJ. Nanoparticles for biomedical imaging. Expert Opin Drug Deliv. 2009 Nov;6(11):1175-94. DOI: 10.1517/17425240903229031. PMID: 19743894; PMCID: PMC3097035.
56. Karagkiozaki V, Logothetidis S, Pappa AM. Nanomedicine for Atherosclerosis: Molecular Imaging and Treatment. J Biomed Nanotechnol. 2015 Feb;11(2):191-210. DOI: 10.1166/jbn.2015.1943. PMID: 26349296.
57. KaragkiozakiV, Pappa F, Arvaniti D, Moumkas A, Konstantinou D, Logothetidis S. The melding of nanomedicine in thrombosis imaging and treatment: a review. Future Sci OA. 2016 Mar 23;2(2):FSO113. DOI: 10.4155/fso.16.3. PMID: 28031960; PMCID: PMC5138016.