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Chapter 5

Coronary CT Angiography and the Napkin-ring Sign Indicates High-Risk Atherosclerotic Lesions

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61393

Abstract

Coronary computed tomography angiography (CCTA) is used extensively nowadays as a non-invasive imaging method for the evaluation of patients suspected of coronary artery disease, providing data on calcium burden, the presence of coronary artery stenoses, but also, more recently, on coronary atherosclerotic plaque morphology and composition. Plaque morphology analysis by CCTA aims to accurately identify vulnerable plaques, in an attempt to reduce the number of ischemic events triggered by high-risk atherosclerotic lesions. Recent research provides CCTA descriptions of vulnerable plaques and a particular radiological sign shows promising perspectives. The napkin-ring sign refers to a rupture-prone plaque in a coronary artery, comprising a necrotic core covered by a thin cap fibro-atheroma. The napkin-ring sign is described on CCTA in cross-sectional images of coronary arteries as a central low-attenuation area surrounded by an open ring area of high attenuation, having a high specificity and positive predictive value for the presence of advanced lesions. These lesions have been designated as vulnerable plaques, indicating an increased probability of rupture, and were shown to correlate with a higher incidence of cardiovascular events. In acute coronary syndromes, the location of the napkin-ring sign was shown to correspond to the culprit lesions. The aim of the current paper is to provide an overview of the current literature on available methods for quantitative measurement of atherosclerotic plaque features from CCTA and to discuss the clinical implications of the napkin-ring sign as detected by CCTA.

Keywords: Coronary computed tomography angiography, Coronary artery plaque, Napkin-ring sign, Plaque quantification, Plaque characterization

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1. Introduction

The development of atherosclerosis by lipoprotein storage, inflammation, muscle cell proliferation, necrosis, apoptosis, calcification, and fibrosis in the arterial wall triggers important changes in the coronary vessels, leading to coronary artery disease (CAD). In fact, atherosclerosis is the main etiology of CAD, and plaque rupture followed by intraluminal thrombosis is the most common cause of acute coronary events, including sudden coronary death [1, 2]. For that reason, the early and accurate characterization and quantification of atherosclerotic plaques is valuable for preventing and managing acute coronary syndrome (ACS) [3]. In everyday clinical practice, major acute ischemic cardiac events involve plaque rupture in thin-cap fibroatheromas, which are considered vulnerable plaques; these rupture-prone atherosclerotic lesions usually contain a high level of lipids and have a large necrotic core, numerous inflammatory cells, and a thin, vulnerable fibrotic cap [4]. Vulnerable atherosclerotic plaques can be characterized by several invasive and non-invasive methods that are either fully validated, pending validation, or still under scrutiny for clinical practice. Among non-invasive methods, coronary computed tomography angiography (CCTA) by multi-detector computed tomography (MDCT) is currently the preferred modality for evaluating the extent of CAD, providing the advantage of accurate assessment of coronary atherosclerotic plaque morphology and composition. In two recent multicenter trials [5, 6], CCTA was shown to have excellent sensitivity (95–99%) and negative predictive value (97–99%), although rather low specificity (64–83%) for identifying patients with at least one coronary artery stenosis among individuals at low to intermediate risk for CAD. Moreover, CCTA imaging of atherosclerotic plaques was found to correlate well with invasive assessment by intravascular ultrasound (IVUS) [7, 8, 9].

2. Role of MDCT in the detection of plaque morphology and composition

2.1. Plaque characteristics

2.1.1. Plaque morphology and composition

Pathophysiologically, a subendothelial accumulation of lipoproteins generates inflammatory responses involving macrophages and T-cells, leading to the further development of atherosclerotic lesions [10]. Initially, atherosclerotic lesions were classified as fatty streaks, fibroatheromas [11], and advanced plaques, complicated with hemorrhage, calcification, ulceration, and thrombosis [12]. Over the years, this classification became more complex and six types of atherosclerotic lesions have been defined by the American Heart Association (AHA) Consensus Group: type I - characterized by adaptive intimal thickening; type II - fatty streak; type III - transitional or intermediate lesions; type IV - advanced plaques (atheromas); type V - fibroatheroma or atheroma with thick fibrous cap; and type VI - complicated plaques with denudated surface, and/or hematoma/hemorrhage, and/or thrombosis [13]. The earliest lesions are represented by adaptive intimal thickening (AHA type I) and fatty streaks or intimal xanthoma, which are basically foam cell collections (AHA type II) [13]. AHA type III transi-

http://dx.doi.org/10.5772/61393

tional lesions, described as pathological intimal thickening, represent the earliest stage of the progressive plaques and are considered precursor lesions of more advanced fibroatheroma. This type of lesions consists of multiple layers of proliferating smooth muscle cells near the lumen, with an increased quantity of lipids on the intimal medial border. Intimal xanthomas are lesions containing a large amount of foamy macrophages but without lipid acumulation outside the cell [14]. Type IV AHA, also called fibrous cap atheromas, are the first of the advanced lesions of coronary atherosclerosis [15] and are characterized by the presence of a necrotic core with a high amount of lipids surrounded by a fibrous cap containing smooth muscle cells, collagen, and proteoglicans, as well as inflammatory cells such as macrophages and lymphocytes. This type of lesion can cause significant artery stenosis and may be submitted to complications, namely surface disruption, thrombosis, and calcification. Fibrous cap plaques may be more or less prone to complications depending on the thickness of the cap: fibroatheromas are more stable due to the rather thick fibrous cap, while thin-cap fibroatheromas characterize the typycal "vulnerable plaques" [15].

In fact, thin-cap fibroatheromas are very likely to lead to plaque rupture. Although they are not included as individual entities in the AHA consensus classification, plaque erosion and calcified nodules are also prone to coronary thrombosis. Erosions may occur on intimal thickening or fibroatheroma, whereas the notion of calcified nodules refers to eruptive fragments of calcium that protrude into the lumen, causing a thrombotic event [16]. Also, plaque ruptures may heal by wide accumulation of proteoglycans, having more reduced necrotic cores and more extensive areas of calcification. In their study on early coronary lesion progression near branch points, Nakashima et al. provided evidence endorsing the hypothesis that intimal thickening lesions with macrophages are more advanced [17].

Macrophage infiltration in lipid pools rich in cholesterol and the deterioration of the extracellular matrix believed to be induced by matrix metalloproteinase activity suggest early stages of the necrosis process and should be recognized. This particular feature, combined with macrophage destruction as a consequence of an anomalous phagocytic clearance of apoptotic cells, may contribute to the development of late plaque necrosis. In addition to that, an extended necrotic core is a strong predictor of complications [17, 18].

Thin-cap fibroatheromas are highly prone to plaque rupture due to their rather large necrotic core and thin, inflamed fibrous cap (<65 μm). The accumulation of an increased number of macrophages at the level of the cap is characteristic, although exceptions may occur. However, as a significant number of fatal coronary events are triggered by plaque rupture due to the impairment of the fibrous cap followed by thrombosis, early recognition of thin-cap fibroatheromas is crucial. The fibrous cap mainly contains type I collagen, variable numbers of macrophages and lymphocytes, and rather few alpha-actin positive smooth muscle cells. Fibrous cap disruption exposes the lipid-rich necrotic core, favoring the formation of local thrombi by platelet accumulation. Most plaque ruptures are reported in the proximal segments of the coronary arteries, near branch points, with the left anterior descending coronary artery being the most frequently affected, followed by the right and left circumflex coronary arteries [19]. Although the mechanisms behind plaque rupture are far from being fully understood, the increased activity of matrix metalloproteinases, excessive enzyme secretion by inflamma-

tory cells, high shear stress, macrophage calcification, and iron build-up are recognized as implicated factors. Data are also beginning to pool on different gene expression in stable and unstable atherosclerotic plaques [20]. For instance, in one study, differential expression of 18 genes coding for metalloproteinase ADAMDEC1, retinoic acid receptor responser-1, cysteine protease legumain (a potential activator of matrix metalloproteinases), and cathepsins was shown to contribute to increased lesion vulnerability [20]. As previously mentioned, the extension of the necrotic core is also a main factor in plaque complication development, and intraplaque hemorrhage was shown to favor the accumulation of free cholesterol provided by red blood cells in these lesions [21]. As atherosclerotic lesions expand, more vasa vasorum infiltrate the plaque and become leaky, triggering intraplaque hemorrhage [22]. Morphologic studies have suggested that repeated ruptures are responsible for plaque progression beyond 40–50% cross-sectional luminal stenoses [23]. Three hystological types of lesions have been described in association with acute coronary events: rupture, erosion, and calcified nodule [13]. Ruptured coronary atherosclerotic plaques folowed by intraluminal thrombosis are the most common cause of acute myocardial infarction [24]. In fact, two-thirds of luminal thrombi in acute events result from ruptured atherosclerotic lesions characterized by a necrotic core covered by a thin layer of fibrous cap [4]. Ruptured plaques are characterized by a lipid-rich necrotic core (>40% of the total volume of the plaque), surrounded by a thin, fibrous cap with active inflammation (increased number of monocytes, macrophages, and sometimes even T-cells), endothelial denudation leading to superficial platelet aggregation, and the presence of hemodynamically significant coronary artery stenosis (>90%) [19]. Vulnerable plaques prone to rupture share most of the morphological characteristics with ruptured plaques, showing a large necrotic core, macrophage infiltration, and often an increased number of intraplaque vasa vasorum [4], but an intact, thin fibrous cap [13]. These lesions—called thin-cap fibroatheromas—are considered to be at high risk for rupture and subsequent ischemic events [4].

The destruction of the endothelium exposes the minimally inflammed intima containing smooth muscle cells and proteoglycans to circulating platelets, favoring thrombus formation. In a post-mortem study of 20 patients who died with acute myocardial infarction, plaque ruptures were found in 60% of lesions with thrombi, while the remainder of 40% only revealed superficial erosion [16]. Plaque erosion refers to the lack of endothelial cells on the luminal surface beneath the thrombus. Kramer et al. showed in their study that, when plaque erosion was the incriminated lesion, the thrombus was limited to the luminal portion of the plaque, and no ruptures were identified following serial sectioning of these lesions. In the same study, more than 85% of thrombi in erosions showed evidence of healing, such as acute inflammatory cell lysis, invasion by smooth muscle cells and/or endothelial cells, or organized layers of smooth muscle cells and proteoglycans with varying degrees of platelet/fibrin layering. By contrast, only half of the ruptured plaques showed signs of healing [25].

Beyond histopathological description, a clinically relevant definition of vulnerable plaques refers to the risk of developing future major cardiac events, which may also involve the presence of “vulnerable blood” (prone to hypercoagulability) or “vulnerable myocardium” (susceptible to arrhythmia), either due to acute or pre-existing ischemia and/or non-ischemic electrophysiological anomalies. The presence of one or more of these elements elevates the

http://dx.doi.org/10.5772/61393

individual risk of the patients for cardiovascular events, turning them into "vulnerable patients".

Identifying vulnerable plaques is currently a major challenge, although recent progress in cardiovascular imaging raises new possibilities. As vulnerable plaques are prone to rupture and rapid evolution towards the development of ACS, [26, 27, 28] finding reliable imaging characteristics that could help detect unstable plaques are of the utmost importance. Early identification of such plaques could facilitate timely initiation of adequate primary prevention measures, thus diminishing the incidence of acute coronary events [29]. For this purpose, several imaging methods have been proposed, including IVUS, optical coherence tomography (OCT), magnetic resonance imaging (MRI), or MDCT (Table 1), with variable success [30, 31, 32]. However, the use of many of these methods is mainly confined to experimental studies and has not yet been validated for everyday clinical practice.

Non-invasive imaging methods	Advantages	Limitations
- MDCT	Measures local tissue attenuation to assess plaque morphology and composition Molecular imaging using new contrast agents is under study Identifies lumen narrowing accurately Can help characterize plaque morphology and composition (within limits) Has high spatial and temporal resolution	Patient exposure to ionizing radiation Implies contrast agent use May be hindered by artifacts (e.g., blooming) The attenuation spectrum of non-calcified plaque components (lipid and fibrous) can overlap
- Contrast-enhanced ultrasonography	Uses acoustically active microbubbles acting as pure intravascular tracers; when exposed to ultrasound, they produce a strong backscatter signal and specific nonlinear signal that differentiates them from surrounding tissues Molecular imaging is available There is no exposure to ionizing radiation Has high temporal and spatial resolution Allows neovasculature assessment	Spatial resolution and penetration are limited Good application for coronary arteries
- High-resolution magnetic resonace imaging	Uses different contrast weightings (T1, T2, proton-density, and time-of-flight) to evaluate plaque components Molecular imaging uses specific agents (paramagnetic nanoparticles targeting) Has high temporal and spatial resolution Has high contrast resolution	Contraindicated with many intracardiac devices Cardiac motion Poor reproducibility Contrast agent Limited spatial resolution Time consuming reconstruction techniques
Invasive imaging methods		

Non-invasive imaging methods	Advantages	Limitations
- Coronary angiography	Identifies complex plaques, with irregular surface Quantifies stenoses accurately	Invasive Limited tissue penetration and spatial resolution
- IVUS		
Standard	Quantifies plaque volume, vascular remodeling, and neovascularization Characterizes plaque morphology and composition	Invasive Limited temporal resolution Limited spatial resolution prevents thin cap fibroatheroma quantification Low accuracy for detecting plaque composition by gray scale IVUS
IVUS elastography	Measures the local strain rate of vessel wall and plaque (fibrous plaques are stiffer than lipid-rich ones); high strain regions describe more vulnerable plaques	Invasive Limited spatial resolution Artefacted by cardiac motion
Virtual histology	Identifies the necrotic core, fibro-lipidic plaques, calcified, and non-calcified plaques	Invasive Limited spatial resolution
- Optical methods		
Angioscopy	Identifies lipid plaques, plaque rupture, erosion, and thrombosis	Invasive Limited tissue penetration and spatial resolution
OCT	Provides microscopic characterization of plaque morphology Identifies macrophages presence Allows accurate quantification of the fibrous plaque Highest spatial resolution of all imaging methods Can identify thin fibrous caps <65 μm The only technique for eroded plaques detection Accurate detection of plaque composition	Invasive Limited tissue penetration; however, the most relevant morphologic findings are primarily localized within the first 500 μm under lumen surface
Spectroscopy	Identifies the lipid core and evaluates the chemical structure, temperature and inflammation of the plaque	Invasive Limited tissue penetration Cardiac motion
- Termography	Quantifies plaque temperature Detects plaque inflammation and neoangiogenesis	Invasive Limited tissue penetration and spatial resolution The cooling effect of the blood leads to underestimated temperature differences
- Intravascular cardiac MRI	Quantifies the lipid content of the plaque	Invasive Prolonged duration

Non-invasive imaging methods	Advantages	Limitations
		Implies the use of contrast agents
Plasma markers of plaque vulnerability	Identifies blood hypercoagulability states (augmented platelet activation and aggregation, high levels of coagulation factors, low levels of anticoagulation factors, decreased endogenous fibrinolytic activity, thrombogenic factors)	

Table 1. Methods for the Identification and Characterization of Vulnerable Plaques

A possible imaging method for coronary artery plaque assessment is IVUS, which has been used to measure lumen area, plaque burden, and vascular remodeling [33, 34]; plaque burden and positive remodeling, in particular, can identify high-risk, thin-cap fibroatheromas during follow-up [34, 35, 36]. As suggested by IVUS-based studies, a vulnerable plaque is characterized by the presence of an extensive necrotic core surrounded by a thin-cap fibrous with macrophage infiltration, a large lipid pool, and several more specific traits such as positive remodeling or spotty calcifications [37, 38]. When such characteristics occur, there is an increased risk of fibrous rupture, exposing the thrombogenic lipid core, which leads to thrombus formation and the development of ACS. A more detailed analysis of coronary plaque composition has been provided by virtual histology (VH)-IVUS studies [39, 40, 41].

Another recently developed method for the assessment of coronary artery plaques quantification is intracoronary OCT that provides the advantage of very high resolution (approximately 10 to 20 μm), which is about 10-fold higher than that of IVUS [42, 43]. Unlike some other imaging methods, including CCTA [27, 44, 45], OCT can be used for measuring fibrous cap thickness and for detecting lipid content, which makes it useful for in vivo identification of thin-cap fibroatheromas and for evaluating plaque vulnerability [46]. For the time being, the correspondence between OCT- and IVUS-derived characteristics of thin-cap fibroatheromas, as well as the angiographic stenosis severity, is yet to be established.

As advanced coronary artery plaques have a high level of complexity, basic classifications that include non-calcified plaques, calcified plaques, and mixed plaques are rather crude and of limited use for establishing the potential risk for acute ischemic clinical events of individual lesions [4, 26, 47]. For that reason, some authors have attempted to provide more detailed descriptions of vulnerable plaques and to establish correlations between CCTA imaging characteristics (Figure 1) of the lesions and the risk for acute events. Motoyama et al. suggested that vulnerable plaques are characterized by positive remodeling, low attenuation plaque and spotty, limited calcification [44]. In later research, non-calcified plaques were more extensively characterized by modern MDCT and several authors described a ring-like attenuation of the non-calcified portion of the coronary atherosclerotic lesion, which is now called the napkin-ring sign [48, 49, 50]. The description of the napkin-ring sign has changed current classifications of non-calcified plaques, which are now classified in three categories: homogenous plaques, non-napkin-ring sign heterogeneous plaques, and napkin-ring sign heterogeneous plaques [49]. The napkin-ring sign corresponds to a morphological type of vulnerable plaque described

on coronary CCTA (thin-cap fibroatheromas) comprising a necrotic, low attenuation core surrounded by a thin area of higher attenuation, which some believe may represent the thin peripheral fibrous cap (Figure 2) [26, 47]. However, in vulnerable plaques, the fibrous cap has extremely reduced thickness [48, 51], which makes it indistinguishable by non-invasive imaging methods; by contrast, the necrotic core may be visualized and quantified on thin sections (<0.6 mm) on modern CCTA [52, 53]. As the presence of the napkin-ring sign was shown to have a high predictive value for future cardiac events and is considered a valuable correlate of unstable plaques [49, 27, 20, 54, 55], its detection could add specificity to the CCTA assessment of vulnerable plaques.

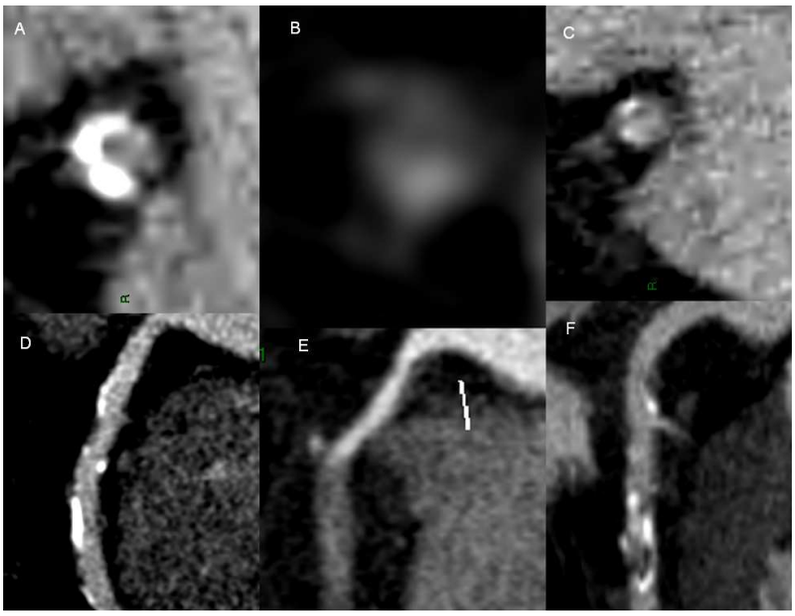


Figure 1. Different Types of Coronary Plaques by CCTA. The 3 main types of coronary plaques are shown: calcified plaques (A, D), non-calcified plaques (B, E) and partially calcified plaques (C, F), illustrated in curved planar reformatted and cross-sectional views.

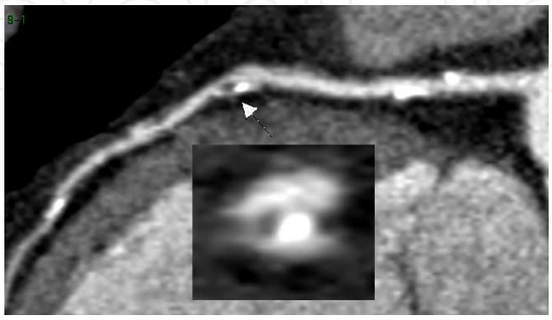


Figure 2. Representative CCTA Images with Napkin-ring Signs. An atherosclerotic plaque with positive remodeling, low attenuation plaque, and a napkin-ring sign in the proximal left anterior descending artery on computed tomography angiography. The boxed area indicates cross-sectional images of atherosclerotic plaque showing a napkin-ring sign.

http://dx.doi.org/10.5772/61393

However, in studies conducted over the last decade, CCTA was also shown to have excellent sensitivity for detecting, and particularly, for excluding coronary atherosclerosis in patients with symptoms suggesting either stable or acute CAD [56]. In addition to that, data from large prospective registries support the use of CAD absence/presence and extension evaluation by CCTA for prognostic purposes [53, 57, 58, 59, 60]. Recent studies conducted with more advanced scanners having 64 to 320 detector rows, and higher spatial (230 to 625 μm) and temporal (75 to 175 ms) resolution focused on identifying vulnerable coronary artery plaques and on establishing correlation between plaque characteristics and ischemic events [61]. Currently available spatial resolution of CCTA scanners approach the spatial resolution provided by invasive methods such as IVUS (100 μm) and invasive coronary angiography (200 μm). Moreover, spatial resolution reaching 0.3 mm in-plane in modern CCTA scanners allows a more accurate discrimination of the non-calcified portion of the plaques [62].

Some researchers [63, 64, 65] attempted to distinguish lipid-rich from fibrous plaque by CCTA based on attenuation criteria, as expressed by Hounsfield Units (HU), but conflicting results have been obtained. In addition to that, HU values cannot accurately discriminate between the types of plaques, mostly due to the small dimensions of the plaque, insufficient spatial resolution of CCTA, and reduced contrast difference between lipid-rich and fibrous plaques. In these studies, certified methods of coronary artery plaque quantification (such as IVUS and histology) were used for comparison to CCTA [63, 64, 65].

Despite current technical limitations, progress has been made in the non-invasive imaging assessment of coronary artery lesions by CCTA. Data from recent studies suggest that low attenuation (<30 HU) is more common to culprit lesions in acute coronary events, as well as to high-risk, vulnerable plaques [26, 27, 47, 66]. Currently, there is not enough data to support a valid assumption on the accuracy of CCTA for detecting non-calcified coronary plaques at high risk. Small studies comparing CCTA to IVUS reported sensitivities and specificities between 80 and 90% for the detection of coronary artery segments with plaque [8, 9, 67, 68]. Other studies demonstrated significant correlations between measurements of plaque cross-sectional area, volume of single plaques, and plaque volume per coronary segment on CCTA and IVUS [8, 69, 70, 71]. However, despite significant and quite high correlation coefficients, the limits of agreement were typically large in most studies, which betrays the limitations of CCTA, mainly imposed by the spatial resolution of the method. Plaque quantification is particularly challenging when plaques have low thickness. Reported interobserver variability is also unusually high (30% variability for plaque volume quantification) [9, 72, 73] and is very much influenced by image quality. In a research on 41 patients, the interobserver variability was 17±10% for the left anterior descending coronary artery, which was best, visualized with fewer artifacts, but escaladed to 29±13% for the left circumflex and 32±10% for the right coronary artery [73].

2.1.2. Low CT attenuation plaques

In CCTA studies investigating patients with ACS, several features of high-risk plaques have been described, such as low attenuation plaque, positive remodeling, and spotty calcification [74, 54]. Recent studies have also described a specific CCTA aspect of coronary artery lesions

called the napkin-ring sign consisting of a low attenuation area surrounded by a rim-like area of higher CCTA attenuation [22, 47]. Speculations were made on the histological substrate of this aspect, as it was believed to be given by either a central lipid core within a fibrous cap, deep micro-calcifications, neo-vascularization, or the presence of intramural thrombus [22, 27]. Current criteria for the definition of the napkin-ring sign include the presence of a high attenuation ring around a certain coronary artery plaque and higher CCTA attenuation of the ring by comparison to the adjacent plaque, but no greater than 130 HU, in order to differentiate from calcium deposits [27, 47]. Plaques with rich necrotic core have been described as plaques of low attenuation; low attenuation areas were shown to correlate strongly with echolucent areas in IVUS [75]. In a large prospective study on more than 1000 patients, low attenuation plaques and positive remodeling were shown to correlate with the development of acute coronary events. In this group, 45 patients had both CCTA characteristics and 10 of them (22%) experienced an acute coronary event vs. only 4 (0.5%) of the patients who did not exhibit neither positive remodeling nor low attenuation plaques. Patients with normal CCTA did not have any coronary events at all ($p<0.001$). In this study, positive remodeling and/or low attenuation plaques were independent predictors of acute coronary events (hazard ratio: 23, 95% confidence interval: 7 to 75, $p<0.001$) [74].

A limitation of CCTA in quantifying atherosclerotic plaques may have its origin in the fact that intravascular attenuation significantly influences the attenuation of the plaques. Cademartiri et al. performed a phantom test that supports this hypothesis [76, 77] and Schroeder et al. also obtained similar results in their study [78]. Comparative studies between CCTA density and IVUS or histopathology suggest that lipid-rich plaques have lower CCTA density than fibrous plaques. However, low CCTA attenuation is not a constant finding in lipid-rich plaques, raising controversy over its ability to discriminate between lipid-rich and fibrous plaques. As mentioned above, some studies have reported that luminal density influences neighboring structures CCTA attenuation. Some authors reported that, when contrast medium is not used for examination, significant overlaps can occur between CCTA attenuation values of lipid-rich and fibrous plaques.

CCTA resolution is defined in terms of spatial, contrast and temporal resolution. Although significant technological progress has been made in CCTA, the spatial resolution of CCTA (0.5 mm) is still inferior to that of cardiac catheterization or IVUS. The 0.5 resolution is suboptimal, considering the fact that the average diameter of a coronary artery is 3–4 mm. CCTA density is influenced by the partial volume effect and contrast resolution has not improved despite other technological advances in MDCT [27]. CCTA attenuation values, measured in HU, are given by the amount of radiation absorbed by tissue in the voxel and density is directly proportional to the attenuation coefficient. A CCTA value of –1,000 HU corresponds to air, while 0 HU corresponds to water. Most soft tissues CCTA averages have values of 50 HU. Some tissues, such as bone, calcified tissues, or the iodine-rich tissue of the thyroid gland are >100 HU, whereas fat or fatty mixed tissue and lung tissue are <0 HU. If the value for a tissue type, with the exception of calcified or fatty tissues, deviates from the soft tissue attenuation, artifacts should be considered, particularly if contrast is used and the beam hardening effect is suspected; another element of confusion may be the presence of a near-by area of calcification

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or fat that may induce a partial volume effect. MIn addition to that, motion artifacts should be considered. CCTA values can also be influenced by tube voltage [27].

2.1.3. Spotty calcium in plaques

Besides plaque density (Figure 3), other CCTA features such as positive remodeling and spotty calcification can suggest plaque vulnerability. Positive remodeling is appreciated by referral to the remodeling index; obviously, expanded plaques have higher remodeling index, above the cut-off values, but borderline values can hamper interpretation, considering the narrow lumen of the coronary arteries, which barely averages 4 mm; a difference of 10% is less than 1 pixel on the CCTA image. Consequently, when the set cut-off value is near one, plaque expansion may be erroneously measured as positive. Also, the presence of spotty calcification can lead to overestimation of plaque expansion. As the presence of more calcium is considered to be an element of increased atherosclerotic plaque stability, low calcification plaques are regarded as more vulnerable [27].

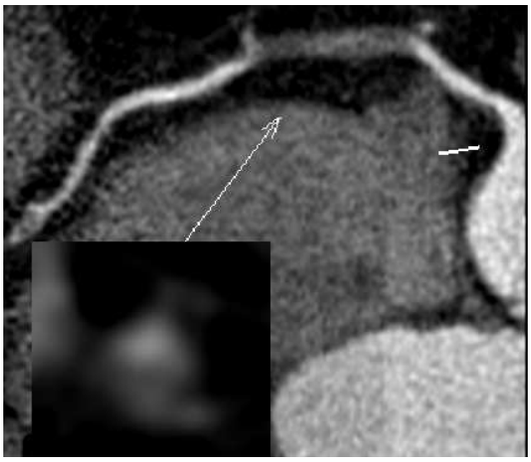


Figure 3. Curved Planar Reformation of the Coronary Artery in CCTA. The curved planar reformatted computed tomography angiography image of the right coronary artery demonstrates two large, predominantly non-calcified atherosclerotic plaques with spotty calcification (arrowheads) in the proximal segment and mild of the right coronary artery.

However, pathological studies concluded that calcium is commonly encountered in ruptured plaques causing sudden cardiac death and that a few scattered small calcium deposits are often present in the fibrous cap of fibroatheromas [79]. The development of scattered small calcium around the necrotic core is believed to be triggered by osteogenic changes under the influence of inflammatory factors and oxidized lipids [80, 81]. The presence of spotty calcifications seems to induce mechanical instability at the interface with non-calcified plaque components [82]. Clinical studies have shown that: spotty calcification has been associated with an increased incidence of ischemic cardiovascular events [83] and, more accurately, that patients with ACSs have a different pattern of calcification when compared to those with stable angina [84]; spotty calcifications are more likely to be found in culprit lesions in patients with myocardial infarction than in patients with stable angina [38]; spotty calcification are more commonly

encountered in patients with accelerated disease progression [85]; ruptured coronary plaques are associated with spotty calcification, particularly in deep locations and the number of deep calcium deposits is an independent predictor of culprit plaque ruptures in patients who had ACSs [84]; and superficial spotty calcifications in IVUS are associated with very late stent thrombosis after bare-metal stent implantation [86]. A possible caveat in CCTA imaging may be the fact that microcalcifications under the detection level of CCTA seem to induce very high plaque instability. However, the presence of calcification increases CCTA values, which seems to contradict the finding that low attenuation plaques are unstable.

2.2. Plaque quantification

Currently, MDCT with at least 64 detectors allows nearly motion-free visualization of the coronary arteries and accurate detection of significant stenosis, comparing well to coronary angiography at low heart rates [8, 87]. Contrast-enhanced scans are performed by injecting intravenously 80–100 ml of contrast agent at a flow rate of 6 ml/s followed by 70 ml of saline. The delay time is previously established using the bolus tracking technique with a region of interest positioned in the ascending aorta; a manually triggered threshold of 100 HU is specified for the main scanning. All scans are performed during a single breath-hold.

Non-contrast CCTA is also useful for atherosclerotic plaque description, allowing the calculation of the coronary artery calcium (CAC) score. The CAC is validated as a good marker of atherosclerotic burden and high values are associated with increased cardiovascular risk [88], However, despite relatively easy quantification, the CAC is hindered by several disadvantages, including the inability to identify small, scattered calcifications in non-calcified plaques, which may lead to the underestimation of disease severity and cardiovascular risk. Also, plaque morphology cannot be described on native calcium scans.

Quantitative measurements of coronary plaques aim to assess global atherosclerotic burden and provide detailed and specific descriptions of plaque morphology that could accurately evaluate the risk for cardiovascular events [70, 89, 90]. However, volumetric measurements of coronary artery plaques with manual tracing contours is strenuous and time-consuming; current software, such as AUTOPLAQ (APQ; Cedars-Sinai Medical Center, Los Angeles, CA), allow semi-automated quantification of both calcified and non-calcified plaques that has reduced the examination time and was shown to correlate very well to the IVUS assessment of the coronary plaque volume

[91]. Dey et al. [92] evaluated the accuracy of APQ and compared semi-automated quantification on CCTA using APQ to IVUS with manual tracing of the coronary artery plaque. Average examination time was significantly reduced by automated quantification. Manual IVUS required the longest processing time (15 to 35 minutes), followed by manual CCTA (5 to 15 minutes), while automated plaque segmentation and quantification took less than 20 seconds. There were no significant differences in plaque volumes calculation between IVUS compared with APQ, or between manual CCTA quantification and APQ. Interestingly, APQ quantification revealed smaller absolute differences from IVUS results than CT manual quantification. APQ has also been shown to have reliable interscan reproducibility of quantitative plaque measurements. Schuhbaeck et al. evaluated total plaque volume, volume of calcified and non-calcified plaque, and maximal remodeling index by performing CCTAs

twice in consecutive patients; using APQ there were no significant differences in any of the measurements between scans [93].

Another CCTA automated software for plaque quantification, QAngio (Medis, Netherland), has been developed and compared with IVUS. In their study, Boogers et al. [90] evaluated the accuracy of CCTA automated plaque quantification using a single algorithm to co-register CT and IVUS after having previously established anatomical markers; slice-by-slice comparisons of each location along the transverse axis of the coronary arteries have been made. The compared parameters included the percent lumen area stenosis, plaque burden, the degree of remodeling at the level of minimal lumen area, and the mean plaque burden for the whole coronary plaque. The study revealed significant correlations between the two methods regarding the quantification of lumen area stenosis, plaque burden at the level of the minimal lumen area, as well as mean plaque burden. However, CCTA failed to quantify all parameters as accurately as IVUS, underestimating minimal lesion area and overestimating lumen area stenosis. Moderate correlations were established between the two methods regarding coronary plaque remodeling. Automated plaque quantification methods are expected to reduce interobserver variability by comparison with manual quantification techniques. Several studies were conducted in order to assess the reproducibility of the results. Papadopoulou et al. [94] reported little inter- and intraobserver variability for lumen and vessel areas. Also, in an additional study inter- and intraobserver relative differences for lumen, vessel, plaque area, and plaque burden did not reach statistical significance. Automated plaque quantification proved, however, less reliable for compositional measurements of plaque attenuation values, demonstrating high inter-observer variability (12%), which is an important limiting factor. Despite this drawback, automated softwares can be used for evaluating coronary artery sclerosis progression, as demonstrated by Papadopoulou et al [95]. In another study, Blackmon et al. [96] tested the accuracy and interobserver variability for volumetric measurement of non-calcified lesions of another automated postprocessing software algorithm. Very strong correlations were found between manual measurements performed by highly experienced examiners and automated plaque volumetry, and interobserver variability was reduced when using the plaque analysis algorithm. As demonstrated by the aforementioned studies, automated softwares provide the major advantage of higher reproducibility, while also allowing faster quantifications, which make them elligible for more widespread use. CCTA is very accurate for stenosis detection [97] and for the measurement of calcified plaque burden [98, 99]. The amount of coronary calcification quantified by CCTA is a strong predictor of CAD [100, 101], but fails to accurately identify the site of stenosis. Moreover, even in modern CT scanners, spatial resolution is not sufficient to provide an accurate analysis of the fibrous cap by CCTA [102]. Also, histopathologically-based studies suggest that vulnerable plaques are enlarged in all three spatial dimensions [103] and that average measurements of the necrotic core, such as length and area [104] are beyond the plaque detection threshold for CCTA [105].

2.3. Functional plaque characteristics

Recently, some techniques have been developed for the purpose of analyzing functional parameters, as well as anatomical structures. CT-based fractional flow reserve (FFR-CT) and

CT perfusion allow the non-invasive hemodynamic assessment of coronary stenoses and increase the specificity of CCTA, which may greatly influence the management of CAD patients in the future [106].

2.3.1. Endothelial Shear Stress (ESS)

ESS refers to the tangential stress that is applied on the endothelial surface of the arterial wall by flowing blood friction and is expressed in units of force/unit area [107]. ESS is influenced by blood viscosity and the spatial gradient of blood velocity at the wall. When a fluid passes through a tube, its flow is influenced by the characteristics of the tube walls such as surface irregularities or obstructions. Fluid flow may be laminar or turbulent. Laminar flows are streamlined and may be either completely smooth ("undisturbed flows") or "disturbed", with areas of reversed flow. In turbulent flow, velocities vary continuously in a certain point in space [108]. The presence of low ESS favors the formation and development of coronary artery plaques, as well as their progression to high-risk, vulnerable plaques. Local blood hemodynamics can influence atherosclerosis development for better or for worse. Therefore, an accurate in vivo quantification of plaque characteristics, local ESS, and vascular remodeling response would facilitate a better understanding of the mechanisms behind CAD progression, as well as clinical decision making regarding possible pre-emptive local interventions [109]. The evolution of each coronary artery plaque is individual and considerably influenced not only by the progression of atherosclerosis, but also by vascular remodeling. Extensive remodeling leads to the development of vulnerable plaques and is triggered by ESS. Persistent ESS favors local lipid build-up, inflammation, oxidative stress, and matrix breakdown, with subsequent plaque progression and further remodeling [109]. Advanced plaques in areas of severe stenosis are submitted to considerable shear stress that promotes plaque destabilization [110].

2.3.2. Fractional Flow Reserve (FFR)

FFR is calculated as the ratio between the maximum blood flow within a diseased coronay artery and the theoretical maximum flow in a normal coronary artery. An FFR of 1.0 is considered normal, while values of less than 0.75–0.80 are acknowledged by most as associated with myocardial ischemia [111]. FFR values >0.8 but <1 are considered indicative of a hemodinamically unsignificant stenosis, while values <0.75 reflect significant stenoses. In earlier works, values between 0.75–0.80 represented a grey area and were interpreted according to the clinical context. Investigators estimated that the cut-off value for FFR could be extended to 0.80, thus improving sensitivity without significantly compromising specificity. The cut-off value of 0.80 was already used in the FAME 1 and FAME 2 trials and proved to be clinically valid [112, 113]. This is now the recommended ischemic reference standard for the invasive assessment of myocardial ischemia [114]. Invasive coronary angiography is the established clinical standard for coronary artery disease assessment, with IVUS providing the advantage of intramural and transmural coronary artery imaging. OCT offers an even more accurate visualization of the coronary arteries [115]. The use of these additional invasive imaging methods can facilitate therapeutical decisions regarding revascularization and help guide percutaneous coronary interven-

http://dx.doi.org/10.5772/61393

tions, leading to better postprocedural results. However, in current clinical practice, the reported rates of use for these techniques in assessing intermediate (40–70%) coronary stenoses are fairly low, 20.3% for IVUS and 6.1% for FFR [116].

In the Percutaneous Coronary Intervention of Functionally Non-significant Stenosis (DEFER) Study [117], investigators evaluated 181 patients with stable ischemic heart disease and FFR > 0.75 across an intermediate stenosis. These patients were randomized to either percutaneous coronary interventions or to deferral of percutaneous coronary interventions with medical treatment. At 5-year follow-up, patients in the deferred group had a significantly decreased (less than half) rate of death or myocardial infarction by comparison with the percutaneous coronary interventions group. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial [113], 1,005 patients with multivessel disease were randomized to either FFR- or angiography-guided percutaneous coronary interventions. In patients with FFR-guided interventions, the composite rate of death, MI, or repeated revascularization at 1 year was significantly lower (13.2% vs. 18.3%, P<0.02). The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial [113] compared the outcomes of FFR-guided percutaneous coronary interventions with optimal medical therapy against optimal medical therapy alone in a group of 888 patients with stable ischemic heart disease. In this trial, unlike in others such as COURAGE, only patients having at least one lesion with FFR <0.80 were enrolled [118].

FFR assessment of lesions with 50% to 70% diameter narrowing revealed that only 35% of the lesions were hemodynamically significant. Interestingly, in severe lesions with 71% to 90% diameter stenoses, 20% were not hemodynamically significant based on FFR and did not require percutaneous coronary interventions. These results endorse the hypothesis that FFR can have essential clinical implications regarding revascularization decisions even in more severe angiographic stenoses and, particularly when noninvasive data is discordant with coronary angiography [119]. In patients with multivessel coronary artery disease, FFR can be performed, allowing an accurate determination of the Functional SYNTAX Score, and subsequently, a better selection of patients that could benefit from percutaneous coronary intervention rather than being submitted to coronary artery by-pass graft [120]. The use of CCTA for non-invasive anatomic assessment has increased considerably and the method is considered an accurate tool for detecting or excluding CAD [6, 5]. FFR-CT is a recently developed method based on computational fluid dynamics to calculate coronary blood flow, pressure, and FFR based on routinely acquired CCTA datasets [121, 122, 123, 124, 125, 126, 127, 128, 129].

3. Clinical implications of napkin-ring sign plaque for prognosis and management

Recent research has shown that the napkin-ring sign is associated with future cardiac events, frequently corresponding to the culprit lesion in ACS [53]. In the study by Otsuka et al., 895 patients were evaluated by CCTA and followed up for 2.3±0.8 years; in this popula-

tion, the presence of the napkin-ring sign on CCTA was strongly associated with ACS events: 24 patients (2.6%) experienced ACS events, of which 41% developed plaques with napkin-ring sign during the follow-up period [53]. Kashiwagi et al. conducted a CCTA-based study on 273 patients with either ACS or stable angina. In their research, the authors described the napkin-ring sign as the presence of a ring of high attenuation and the CT attenuation of a ring presenting higher than those of the adjacent plaque and no greater than 130 HU. The napkin-ring sign was more frequently encountered in culprit lesions (12.7% vs. 2.8%, $p<0.01$). Moreover, napkin-ring sign plaques were associated with a higher remodeling index and lower CT attenuation (1.15 ± 0.12 vs. 1.02 ± 0.12, $p<0.01$ and 39.9 ± 22.8 HU vs.72.7 ± 26.6 HU, $p<0.01$) [50]. Similar results were obtained in another study in which the napkin-ring sign was more common in patients developing ACS than in those with stable angina [28].

Besides the napkin-ring sign, other imaging characteristics such as large plaque volume, low CT attenuation, positive remodeling, and spotty calcification were proved to be correlated with a higher risk of acute events [130]. Motoyama et al. found that positive remodeling and low attenuation correlated best with the development of ACS, [74] which is consistent with results from other studies [131, 132]. Considering the results of the previously mentioned studies, one can conclude that the identification of CCTA aspects suggesting vulnerable lesions may be useful for several reasons. Firstly, although statins are known to reduce the incidence of acute cardiovascular events [133], proving their effect on a certain individual is challenging. CCTA may help identify coronary artery lesions regression, but, as it is not routinely performed, there is not enough data to support this hypothesis. Risk stratification in asymptomatic individuals has also been taken into account as a possible use for CCTA, but the actual ability of MDCT for detecting small non-stenotic plaques is yet to be established [134].

In conclusion CCTA is used extensively nowadays as a non-invasive imaging method for the evaluation of patients suspected of CAD and the napkin-ring sign described on CCTA has been designated as a valid element for identifying vulnerable plaques, indicating an increased probability of rupture, and was shown to correlate with a higher incidence of cardiovascular events.

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