Angiology: Open Access
ISSN: 2329-9495

Youssef and Budoff, Angiol 2013, 1:2
DOI: 10.4172/2329-9495.1000111

Review Article Open Access

Role of Computed Tomography Coronary Angiography in the Detection of Vulnerable Plaque, Where Does it Stand Among Others?

George Youssef* **and Matthew Budoff**

Los Angeles Biomedical Research Institute, Harbor UCLA Medical Center, California, USA

Abstract

Recently, there has been a growing interest in identification of coronary "vulnerable plaques" that are prone to rupture; this potentially would help identify patients with higher risk of development of cardiac events. Recent advances in cardiac imaging modalities have been successful in studying various plaque vulnerability features to variable degrees, strengths and limitations. Computed Tomography Coronary Angiography (CTCA) has gained an increasing popularity in studying plaque anatomy, morphology and composition by the virtue of its widespread availability and non-invasiveness. CTCA has been validated against histology and IVUS with reasonable correlation; moreover, some follow-up studies have shown a significant association to the development of acute coronary syndromes. Nevertheless, attention should be paid to the whole patient big picture that includes other factors operating on other extra-coronary axes that involve inflammation, immunity, coagulation and neuroendocrine systems.

Introduction

Atherosclerotic cardiovascular diseases are still the leading cause of deaths in industrialized Countries and Coronary Artery Disease (CAD) accounts for the majority of this toll [1]. Cardiac events are typically caused by disruption of coronary plaques where plaque rupture occurs in about two thirds of cases, while the remaining third of cases are caused by plaque erosion with subsequent formation of occluding thrombus [2]. Thus, a clinically relevant definition of a rupture-prone (or what has been termed the "vulnerable") plaque, is a lesion that places a patient at risk for future major adverse cardiac events, including death, myocardial infarction, or progressive angina.

On the other hand, the histopathological features that have been associated with vulnerable plaques and defined them, include: 1) A large eccentric necrotic lipid core, occupying approximately one-quarter of the plaque area [3], 2) A thin fibrous cap (<65 μm thick) [4], 3) Heavy infiltration by large number of inflammatory cells (macrophages and T cells) particularly at the shoulder region of the plaque [5], 4) Spotty calcification, 5) Neovascularization due to proliferation of the vasa vasora and formation of immature and leaky microvessels, with subsequent rupture and intra-plaque hemorrhage [6], finally, 6) In contrast to eroded plaques, rupture-prone plaquesusually are non- or mildly obstructive, yet the size of the plaque may be substantial due to the phenomenon of positive remodeling [7]. Yet, some of these aforementioned features, namely calcification and positive remodeling are still controversial about their actual role in plaque stability.

Invasive coronary angiography, though presumably considered as the gold standard for the diagnosis of CAD, is a mere luminogram that focuses mainly on the stenosis severity rather than plaque characteristics. Moreover, other traditional non-invasive stress tests as stress echocardiography or myocardial perfusion imaging only help detect hemodynamically significant lesions rather than non-obstructive potentially vulnerable plaques.

Obstacles in detection of vulnerable plaques include their small size and being localized within the rapidly moving coronary arteries. In addition, plaque vulnerability is a dynamic process, a plaque that appears rupture-prone today could rather be stable tomorrow, even ruptured plaques do not always lead to coronary events as many ruptures occur and heal silently. Therefore, there has been a growing interest for detection and characterization of coronary atherosclerotic plaques. The aim of the present review paper is to shed some light on different diagnostic modalities used for the assessment of plaque vulnerability, with specific focus on the Multi-Detector Computed Tomography (MDCT) as an evolving tool in that field with all its strengths and limitations.

Imaging Modalities used for Assessment of Vulnerable Plaques

Direct visualization of atherosclerotic plaques in vivo is the only way forward for studying the natural history of atherosclerotic disease. The imaging techniques currently used are generally able to provide adequate information on the lumen diameter reduction or its functional significance. So, different imaging techniques; both invasive and non-invasive, have been developed to reliably evaluate plaque composition and identify its vulnerable features, thereby allow implementation of treatment strategies to prevent adverse coronary events. Table 1 lists different invasive and non-invasive imaging modalities with main strengths and limitations.

In addition to being expensive and in need for specially trained personnel, invasive techniques by their very nature, have a lower level of patient acceptability than non-invasive modalities which may provide a good alternative. Collectively, factors that characterize an ideal non-invasive technique would include; patient-related factors: 1) wide range of clinical indications, 2) absence of ionizing radiation, 3) unnecessary administration of contrast media and 4) not precluded by metallic devices or leads, and technical factors: 1) Rapid image acquisition, 2) high temporal, spatial and contrast resolution, 3) ability to provide both anatomic and metabolic information, and 4) accurate and reproducible [26].

***Corresponding author:** George Youssef, Los Angeles Biomedical Research Institute, Harbor UCLA, 1124 West Carson Street, Torrance CA 90503, USA, Tel: 310-222-4107; Fax: 310-782-9652; E-mail: george.youssef@yahoo.com

Received May 25, 2013; **Accepted** July 26, 2013; **Published** July 28, 2013

Citation: Youssef G, Budoff M (2013) Role of Computed Tomography Coronary Angiography in the Detection of Vulnerable Plaque, Where Does it Stand Among Others? Angiol 1: 111. doi: 10.4172/2329-9495.1000111

Modality	Mechanism	Spatial resolution	Strengths	Limitations	Relevant Studies
Invasive Modalities					
Intravascular ultrasound (IVUS) [8-11]	The intensity of the backscattered signalis processed into gray scale differs among different plaque components	150 μm	Provides information on plaque anatomical features and composition to lesser extent [12]	-Invasiveness -Limited temporal resolution -Limited spatial resolution so cannot recognize thin cap fibrotheroma (TCFA) -Gray scale IVUS cannot accurately differentiate elements of plaque composition	-Features of plaque vulnerability include: eccentric pattern, echolucent core, positive remodeling, presence of thrombi, plaque length, lumen narrowing and spotty calcification [13,14]
IVUS-RF (radiofrequency) analysis e.g. Virtual histology (VH) [8-11]	RF data are more in direct relation to the interaction of ultrasound with tissue	100-200 μm	-Ability to differentiate between 4different tissue types in plaques; dense calcium, fibrous, fibro-fatty and necrotic core [15] -Identification of TCFA	-Invasiveness -Limited spatial resolution	-When compared to histology, sensitivity, specificity and predictive accuracy of VH to detect necrotic core, a vulnerability feature were 67%, 93% and 88% respectively [16] -PROSPECT study showed a correlation between presence of TCFA and future major adverse cardiac events (hazard ratio: 3.35) [17,18]
Palpography (intravascular elastography) [8,10]	Measures the local strain rate of vessel wall and plaque (fibrous plaques are stiffer than lipid-rich ones) high strain regions denote more vulnerable plaques	200-400 μm	Identification of thin fibrous caps	-Invasiveness -Limited spatial resolution -Cardiac motion	Human studies have shown a strong correlation between number of highly deformable plaques and both the clinical presentation (ACS Vs. stable patients) [18]
Intravascular MRI (IV-MRI) [8]	Calculates the water diffusion coefficient: lipid-rich < fibrous plaques	120 μm	Detection of plaque composition	-Invasiveness	There was a good correlation between MRI and histology with sensitivity and specificity of 100% and 89% [19]
Angioscopy [8-11]	Direct visualization of the endothelial surface. The intensity of the yellow color detected is used for plaque characterization	200 μm	Precise visualization of plaque surface detecting disrupted plaques (ulcers, fissures)	-Invasiveness -Limited tissue penetration and spatial resolution	Number of yellow plaques were shown to be a strong predictor of ACS [20]
Optical coherent tomography (OCT) [8-11]	Light-based imaging, measures the amplitude of backscattered light (optical echoes) from a sample as a function of time delay	4-20 μm	-Highest spatial resolution, able to resolve thin fibrous caps <65 μm -Only technique able to detect eroded plaques -Accurate detection of plaque composition	-Invasiveness -Limited tissue penetration (1.25 mm). however, the most relevant morphologic findings are primarily localized within the first 500 μm under lumen surface	Second generation OCT e.g. Optical Frequency Domain Imaging has shown a good potential to define plaque constituents compared to histology [21]
Near Infrared spectroscopy (NIRS) [8,10,11,22]	Different molecules absorb and scatter near-infrared light differently allowing for the chemical characterization of biological tissues	N/A	Detection of plaque composition	-Invasiveness -Limited tissue penetration -Cardiac motion	When compared to histology, sensitivity and specificity of NIRSto detect lipid core, thin cap and inflammatory cellswere 77%-90%, and 89%-93% respectively [23]
Thermography [8,10]	Plaque inflammation and neoangiogenesis produce heat measured at the surface of the plaque	500 μm	Detection of plaque inflammation and neoangiogenesis	-Invasiveness -Limited tissue penetration and spatial resolution -Cooling effect of blood underestimates temperature differences	Thermal heterogeneity has been correlated with features of vulnerable plaque like positive remodeling [24]
Non-invasive modalities					
MDCT [8,10,25,26]	-Detects plaque morphology and composition by measuring local tissue attenuation -Molecular imaging using new contrast agents is under study	500 μm (200-300 μm in dual-source CT)	-Widely available -Detection of lumen narrowing accurately -Detection of plaque morphology and composition (within limits) -High spatial and temporal resolution	-Ionizing Radiation -Contrast agent -Artifacts e.g. blooming -Overlap in the attenuation spectrum of non-calcified plaque components (lipid and fibrous)	See later for details

High resolution MRI [8,10,25,26]	-Uses different contrast weightings (T1, T2, proton-density and time-of-flight) to evaluate the biological features of plaque components -Molecular imagingusing specific agents like paramagnetic nanoparticles targeting: •Fibrin: in plaque disruption and thrombosis •Cellular markers as E-selectin and vascular cellular adhesion molecule (VCAM): in inflammation and •Integrin αvβ3 in angiogenesis	1 mm (improves to 350 μm in carotids)	-Absence of ionizing radiation -High contrast resolution (by nullifying the blood signal from the lumen, by using real time respiratory navigated black blood fast spin echo sequences)	-Contraindicated with many intracardiac devices -Cardiac motion -Poor reproducibility -Contrast agent -Limited spatial Resolution -Time consuming reconstruction techniques	Fayad et al reported positive remodeling and significant coronary wall thickening in patients with CAD compared to control patients [27]
Nuclear imaging (SPECT/PET) [8,10, 25,26]	Molecular imagingtargeting •Macrophages: in inflammation using18F-Flurodeoxyglucose (FDG) •Apoptotic cells: using Annexin V •Vasoconstricting peptides: using 18F-Endothelin-1 (ET-1)	PET: 4-5 mm SPECT: 1-1.6 cm	Holds the potential for superior cellular and molecular imaging compared to MDCT and MRI	-Ionizing Radiation -Cardiac motion -Very limited spatial and temporal resolution renders coronary imaging challenging -Less availability for PET -Myocardial FDG uptake with PET	Tawakol et al showed noticeable correlation between ^{18}F-FDG-PET in vivo signals and macrophage content on histological examination after carotid endarterectomy [28]
Contrast-Enhanced ultrasonography [8,10,25]	-Acoustically active microbubbles (3-4 μm in diameter) that act as pure intravascular tracers, when exposed to ultrasound field, they produce a strong backscatter signal and specific nonlinear signal that differentiates them from surrounding tissues -Molecular imaging; microbubbles labeled monoclonal antibodies targeting endothelial surface molecules e.g VCAM-1	3-4 μm	-Absence of ionizing radiation -High temporal and spatial resolution -Assessment of neovasculature	-Limited spatial resolution and penetration -Limited application to carotid rather than coronary arteries	Enhancement of carotid plaques has been correlated with both histopathology and clinical presentation [29,30]

Table 1: Characteristics of different imaging modalities used for detection of vulnerable plaques.

Systematic comparison between invasive and non-invasive modalities for coronary plaque characterization in ex-vivo specimens demonstrated that CTCA and IVUS are reasonably associated with plaque composition and lesion grading according to histopathologic findings, while Optical Frequency Domain Imaging (a second generation of OCT) was strongly associated.

Imaging features that were associated with advanced lesions were, mixed plaque at CTCA, calcification at IVUS and lipid-rich plaque at OFDI). Moreover, OFDI showed a better diagnostic accuracy differentiating early from advanced coronary lesions, with area under the curve (AUC) of 0.8 compared to AUC of 0.63 and 0.68 for IVUS and CTCA respectively [21].

Multi-detector Computed Tomography

First-generation scanners, or "conventional" CT, utilized a single X-ray source and single X-ray detector cell. Over the past two decades with the tremendous advances in technology, MDCT presented a breakthrough in cardiac CT imaging technology by 1) increasing the number of detector rows from 4 to 320 thus increasing the coverage in the Z-axis up to 16 cm in a single heart beat with a single gantry rotation, 2) speeding up the gantry rotation, enough to freeze the cardiac motion by capturing images within the relatively brief period of cardiac diastasis. the use of dual-source MDCT system has markedly improved the temporal resolution to approximately 85 msec, resulting in a shorter scan time and 3) decreasing the thickness of the detectors to 0.5-0.625 mm thus increasing the spatial resolution to image sub-millimeter structures. This has allowed more accurate and detailed imaging of coronary plaques morphology and composition.

MDCT has caught up with coronary angiography, showing an excellent diagnostic accuracy in diagnosis of obstructive CAD when compared to coronary angiography as the gold standard. In a recent meta-analysis of 188 studies (from 2004 to 2011), the mean sensitivity and specificity of MDCT were 97% and 87% respectively [31].

Role of MDCT in Detection of Vulnerable Plaque; Morphology and Composition

The potential for MDCT evaluation of coronary plaques is enormous, given its noninvasive nature and its ability to evaluate the entire coronary arterial tree in contrast to IVUS.MDCT can help detect the suggested triad of the main features associated with plaque vulnerability namely; positive remodeling, low attenuation (<30 HU), and spotty calcifications [32-35]. Other imaging phenomenon, that has been reported to be pathologically related to thin cap fibrotheromais the "napkin ring" sign, defined as the presence of a ring of high attenuation around plaque; with a higher CT attenuation than those of the adjacent plaque but no greater than 130 HU in order to differentiate from calcium depositions [36] (Figures 1 and 2).

Plaque morphology

Assessment of the plaque size rather than the luminal size is a more logical approach especially in plaques that show substantial positive remodeling, potentially indicating a higher risk for events than plaques with lesser extent of remodeling. Motoyama et al. [35] calculated the remodeling index and reported positive remodeling when the diameter at the plaque site was at least 10% larger than reference segment, it was shown that the frequency of positive remodeling among patients with acute coronary syndrome (ACS) was significantly higher than those with stable angina (87% Vs. 12%, P<0.0001)[35]. Similar finding was

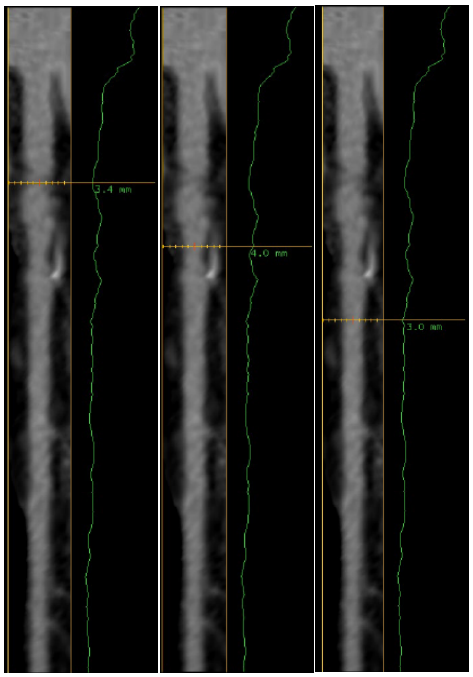

Figure 1: A straight-vessel view for the left anterior descending artery with a proximal plaque. The vessel lumen is measured at the plaque site (B = 4mm) as well as the proximal (A=3.4mm) and distal (C=3mm) reference segments demonstrating positive remodeling.

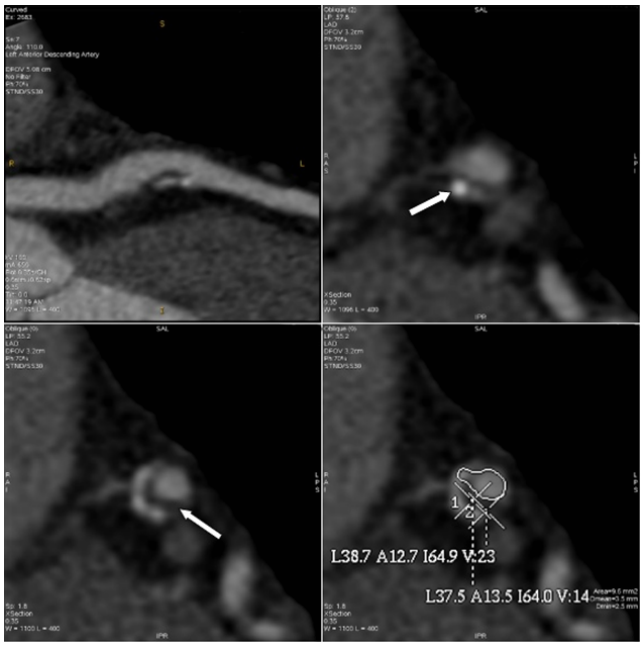

Figure 2: Fig 2A shows a curved multi-planar reformation (MPR) image to the left anterior descending artery with a proximal plaque. Figs 2B, C and D are cross section images of the vessel at the plaque site, the criteria of plaque vulnerability shown are: spotty calcification (arrow 1), low attenuation plaque, ranging between 14-23 HU (arrow 2) and napkin ring sign (arrow 3).

confirmed when Pflederer et al. [37] showed a significantly higher remodeling index in ACS patients when compared to those with stable angina (1.6 ± 0.4 Vs. 0.97 ± 0.17, P<0.001) [37]. When validated against IVUS, The diagnostic accuracy of MDCT in detection of positive remodeling was excellentwhere area under the curve was >0.9with excellent sensitivity and specificity of 100% and 90% respectively [38]. Interestingly, in a recent paper that used coronary artery simulation models, vessel wall stress concentrations were always predicted to be higher in the fibrous cap of plaques with positive remodeling compared to those with negative remodeling independent of the fibrous cap and the degree of stenosis [39].

Invasive coronary imaging is the gold standard for detection of disrupted plaques, the angiographic hallmark of complex lesions was characterized by "Ambrose criteria" including haziness, ulceration, intraplaque dye penetration and intraluminal filling defects, these features correlated with both histology and IVUS [40]. There are only scant data regarding the ability of Computed Tomography Coronary Angiography (CTCA) to identify features of plaque disruption; ulceration and/orintraplaque dye penetration. When compared to IVUS, MDCT was less accurate for the detection of plaque disruption in coronary arteries; sensitivity 57%, specificity 71% [41]. A more recent study that used the invasive angiography as the gold standard, MDCT has shown a good specificity (82-95%) but modest to good sensitivity (53%-58%). The lower sensitivity is likely attributable to the lower spatial resolution of CTCA compared with invasive angiography and presence of plaque calcification [42].

On the other hand, in carotid arteries, the introduction of MDCT did improve the detection of ulceration improving the sensitivity of single slice CT from 60 to 87% and specificity from 74 to 98% [43-46].

Plaque composition

By virtue of MDCT ability to measure local tissue attenuation, MDCT also allows imaging of the vessel wall, potentially providing insights into plaque composition rather than the physiology [47]. Identification of plaque composition is based on measuring the attenuation coefficient which is displayed as a CT number relative to the attenuation of water (0 Hounsfield units HU) and air (–1000 HU) [48]. Calcifications appear as hyperdense, fibrous tissue as isodense and lipid core, intra-plaque hemorrhage and thrombus as hypodense. However, using the absolute CT numbers to define different plaque constituents, especially of soft plaques, is influenced by various factors that could limit its accurate assessment, rendering the exact definition of low attenuation plaque values with the currently available techniques more challenging. These factors include; attenuation of intracoronary contrast medium, tube voltage, degree of stenosis, use of different reconstruction filters [49]. Table 2 shows some studies that reported CT attenuation values of various coronary plaque types in relation to IVUS. Of note, the reported CT numbers showed significant differences in densities of plaque components, yet, with substantial overlap.

Coronary artery calcium (CAC) is defined as a hyper-attenuating lesion >130 HU within an area of ≥ 3 pixels. Agatston score has been widely used to quantify CAC scoreby multiplying the lesion area (mm^2) by a density factor (between 1 and 4) [54]. CAC score with its clinical and prognostic implications will be discussed later.

Different classifications of morphological patterns of calcification have been used in previous reports, one classification was as: speckled (calcified nodules), fragmented (shell-like, linear, or wide, single focus of calcium >2 mm in diameter), or diffuse (≥ 5-mm segment of continuous calcification) [55]. Calcified nodules have been well described on IVUS studies and identified as a less common cause of

plaque disruption (2-7%). On CTCA, Calcified nodules were observed in association with only 6% of obstructive stenotic lesions (>50%), whereas 44% of non-obstructive lesions showed this calcification pattern [55].

Other studies described classification patterns as spotty and dense calcification. Spotty calcification was defined and sub-classified according to their length on curved multiplanar reconstruction into: small spotty (<1 mm), intermediate spotty (1-3 mm), and large spotty calcifications (≥ 3 mm). Dense calcifications were defined as a plaque with high CT density, completely calcified and with calcifications present bilateral on cross-sectional axial slices [33,56,57]. A recent study, used high-resolution micro-computed tomography to identify micro-calcifications in the cap proper of 62 human coronary fibroatheromas, it showed that micro-calcifications were abundant in lipid pools. However, those calcifications observed in the fibrous caps increased the risk of rupture by introducing a stress concentration effect [58]. From the clinical viewpoint, this is highlighting the notion that it is not the micro-calcifications per se that are dangerous but their locations in the cap.

When validating MDCT studies, both histology and IVUS have been used as reference standard. Though histology is a better reference standard, IVUS is considered an accepted method for evaluation of the coronary arteries, where histology cannot be obtained.

When compared to histology, MDCT has shown a strong correlation for detection of calcification and fibrous tissue, while correlation was moderate for the detection of the amount of lipid core and fibrous tissue when compared to IVUS (Table 3). Also, MDCT could accurately detect calcified plaques with excellent sensitivity and specificity reaching 100% in a carotid study by Wintermark et al. [46]; however, the detection of calcifications alone is not enough for the assessment of vulnerable plaques. As previously mentioned, due to some technical limitations, the soft tissue contrast of CT is low, resulting in a moderate diagnostic accuracy with a sensitivity range of (62%-94%) and specificity range of (74%-100%) [41,45,46].

Study	Type of plaque and its measured attenuation value
Shroeder et al. 2001 [50]	Soft: 14 ± 26 HU
	Intermediate: 91 ± 21 HU
	Calcified: 419 ± 194 HU
Rasouli 2006 [51]	Soft: 23 ± 71 HU
	Fibrous: 108 ± 79 HU
	Fibro-calcified: 299 ± 112 HU
	Calcified: 404 ± 264 HU
Motoyama et al. 2007 [52]	Soft: 11 ± 12 HU
	Fibrous: 78 ± 21 HU
	Calcified: 516 ± 198 HU
Pohle et al. 2007 [53]	Hypo-echogenic: 58 ± 43 HU
	Hyper-echogenic: 121 ± 34 HU

Table 2: MDCT studies showing attenuation values of different coronary plaques types.

CT parameter	Correlation	P value
Histology		
calcification	r^2=0.74	<0.001
Fibrous tissue	r^2=0.76	<0.001
Lipid core size	r^2=0.24	<0.002
Lipid core size (after excluding calcium)	r^2=0.81	<0.001
IVUS		
Necrotic core %	*r*=- 0.539	<0.001
Fibrous tissue %	*r*=0.571	<0.001
Fibrofatty tissue %	r=- 0.074	=0.512
Calcification %	r=- 0.113	=0.316

Table 3: Summary of studies showing correlation between different CT plaque densities and histology or IVUS [50-53,59-64].

Similar to positive remodeling, low attenuation plaque value (defined as <30 HU) and spotty calcification (defined as <3mm in size) were significantly more frequent in ACS patients than in stable disease (79% Vs. 9%, p<0.0001 and 63% Vs. 21%, p=0.0005 respectively) [35]. The concomitant presence of the 3 high risk features was associated with a high positive predictive value for culprit lesions in ACS (95%) while their absence showed a high negative predictive value (100%) [35]. Of note, in a study where dual source CTCA was used, both spotty calcification and napkin ring signs were exclusive to ACS patients [37].

The role of calcification in determining the stability of individual plaque and its likelihood to rupture causing an event is still controversial. Some authors have assumed calcification to be protective against plaque rupture and a sign of healed plaques, especially that plaques with erosions (a less frequent mechanism of acute coronary syndromes) are often not calcified [65]. On the other hand, others have shown that the presence of small hard-rock calcium adjacent to soft tissues create forces that contribute to plaque instability and coronary events [66-69]. In the majority of patients with acute coronary syndromes, some CAC was detected, with a substantially greater score than in matched control subjects without coronary artery disease [70].

CAC score has been shown to have a high prognostic power being associated with hard cardiac events and total mortality in follow up studies. While the zero calcium score was associated with very low event rate <0.03% per year in metaanalysis studies [71], the hazard ratio for major coronary events went up to 3.89 and 7.1 in patients with CAC score between (1-100) and (101-300), respectively when compared to individuals without calcium [72].

It is worth noting that in spite of the relationship between CAC and plaque burden, there is only a weak correlation between the amount of CAC and the angiographic stenosis severity. Large amounts of CAC are not necessarily associated with the presence of significant stenoses. Even the absence of CAC, though makes the presence of significant stenosis relatively unlikely, 'zero' calcium score cannot be used to rule out coronary stenoses in symptomatic individuals, especially when they present at young age and with acute symptoms [73].

Detection of Vulnerable Plaque in Asymptomatic "Vulnerable" Subjects

The current appropriateness criteria do not recommend using computed angiography as a screening tool in asymptomatic population considering the risk of radiation and contrast media, cost and lack of supporting evidence. Motoyama et al. studied 1059 asymptomatic subjects by MDCT where atherosclerotic plaques were analyzed for the presence of the three vulnerability features; the plaque characteristics of lesions resulting in ACS during the follow-up of 27 ± 10 months were evaluated. It was shown low attenuation and/or positive remodeling independently predicted ACS (hazard ratio=22.8, CI=6.9–75.2, p<0.001) with a significantly higher likelihood of ACS than 2 feature-negative plaques or no plaques (p<0.001) [74].

Since HIV patients show high rates of MI and sudden cardiac deaths, a recent study has assessed the plaque vulnerability in asymptomatic relatively young HIV-infected subjects versus non-HIV-infected controls who were cardiovascular risk matched. The study concluded that the HIV-infected group has higher prevalence of

subjects with one or more vulnerability criterion, Moreover; there was a significantly higher number of low attenuation plaques and positive remodeling per subject [75].

Technical Limitations of CTCA

As previously highlighted in table 1, some technical factors might affect the role of CTCA in characterization of coronary plaques. These limitations include: 1) Radiation exposure; typical effective dose of radiation for retrospectively gated reconstruction is about 15 mSv, radiation doses delivered have markedly reduced to less than 2 mSv with the advent of newer prospective gating and ultra-low-dose protocols, these advances in technology are expected to further expand the CTCA applications and would permit follow-up studies to evaluate the progression of atherosclerotic plaques over time and with the use of interventional drugs like statins. 2) contrast agents; currently used contrast media in CTCA are considerably safe, however, there is a minimal risk that should be anticipated and dealt with in patients with contrast allergy or those with advanced renal insufficiency. 3) artifacts; various CT artifacts could limit the accuracy of CTCA in studying the plaque composition. Of note, dense calcification is a major limiting factor that could result in the blooming artifact phenomenon where calcium looks bigger than it actually is and 4) the significant overlap between tissue densities as previously discussed, rendering the accurate definition of plaque constituents more challenging [76].

Future Perspectives and Conclusions

The concept of "vulnerable plaque" has been introduced with the intention of detection of those high risk plaques that are potentially capable of causing acute cardiac events. Further risk stratification of asymptomatic or previously assumed low risk population is a complex process that goes far and beyond the mere use of risk score calculators or blood biomarkers. This process has been recently supported by the rapidly advancing imaging modalities that have shown some capabilities in visualizing various physical, chemical and biological aspects of atherosclerotic plaques that could define their vulnerability.

Among non-invasive modalities, MDCT seems to have the highest possibility of fulfilling the expectations of researchers and clinicians. In addition to its role in assessment of significant coronary obstruction with excellent diagnostic accuracy, it is getting popular as a promising non-invasive tool in detection of vulnerable features. This has been supported by studies that showed MDCT to have a good diagnostic accuracy and correlation when compared to histology and IVUS.A bigger role is expected from MDCT with the development of higher resolution scanners with lower radiation dose and the use of novel contrast media that could be targeted towards specific plaque constituents.

A major question after the identification of a vulnerable coronary plaque, should it be treated and how? At present there are no data to prove that interventional treatment strategies for those high risk but asymptomatic plaques are superior to conventional medical treatment. Data from large prospective studies will be needed to determine which approach will be beneficial.

Finally, we always should remember looking at the big picture accepting the idea that the pathogenesis of ACS does not involve only factors operating at the plaque level, but rather there is a concurrence of local and extra-coronary factors that involve coagulation, neuroendocrine, inflammatory and immune response of the vascular tissue.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, et al. (2010) Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 121: 948-954.
2. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, et al. (2008) Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 5 Suppl 2: S2-S10.
3. Virmani R, Burke AP, Farb A, Kolodgie FD (2006) Pathology of the vulnerable plaque. J Am Coll Cardiol 47: C13-C18.
4. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, et al. (1997) Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 336: 1276-1282.
5. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 20: 1262-1275.
6. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, et al. (2003) Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med 349: 2316-2325.
7. Fishbein MC, Siegel RJ (1996) How big are coronary atherosclerotic plaques that rupture? Circulation 94: 2662-2666.
8. Vancraeynest D, Pasquet A, Roelants V, Gerber BL, Vanoverschelde JL (2011) Imaging the vulnerable plaque. J Am Coll Cardiol 57: 1961-1979.
9. Kato K, Yasutake M, Yonetsu T, Kim SJ, Xing L, et al. (2011) Intracoronary imaging modalities for vulnerable plaques. J Nippon Med Sch 78: 340-351.
10. Toutouzas K, Stathogiannis K, Synetos A, Karanasos A, Stefanadis C (2012) Vulnerable atherosclerotic plaque: from the basic research laboratory to the clinic. Cardiology 123: 248-253.
11. Uemura S (2013) Invasive imaging of vulnerable atherosclerotic plaques in coronary artery disease. Circ J 77: 869-875.
12. DeMaria AN, Narula J, Mahmud E, Tsimikas S (2006) Imaging vulnerable plaque by ultrasound. J Am Coll Cardiol 47: C32-C39.
13. Fujii K (2003) intravascular ultrasound assessment of ulcerated ruptured plaques: a comparison of culprit and non-culprit lesions of patients with acute coronary syndromes and lesions in patients without acute coronary syndromes. Circulation 108(20): p. 2473-2478.
14. Ehara S, Kobayashi Y, Yoshiyama M, Shimada K, Shimada Y, et al. (2004) Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. Circulation 110: 3424-3429.
15. Konig A (2008) Technology insight: in vivo coronary plaque classification by intravascular ultrasonography radiofrequency analysis. Nat Clin Pract Cardiovasc Med 5: p. 219-29.
16. Nasu K, Tsuchikane E, Katoh O, Vince DG, Virmani R, et al. (2006) Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. J Am Coll Cardiol 47: 2405-2412.
17. Maehara A, Cristea E, Mintz GS, Lansky AJ, Dressler O, et al. (2012) Definitions and methodology for the grayscale and radiofrequency intravascular ultrasound and coronary angiographic analyses. JACC Cardiovasc Imaging 5: S1-S9.
18. Schaar JA, Regar E, Mastik F, McFadden EP, Saia F, et al. (2004) Incidence of high-strain patterns in human coronary arteries: assessment with three-dimensional intravascular palpography and correlation with clinical presentation. Circulation 109: 2716-2719.
19. Schneiderman J, Wilensky RL, Weiss A, Samouha E, Muchnik L, et al. (2005) Diagnosis of thin-cap fibroatheromas by a self-contained intravascular magnetic resonance imaging probe in ex vivo human aortas and in situ coronary arteries. J Am Coll Cardiol 45: 1961-1969.
20. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, et al. (2008) Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. JACC Cardiovasc Interv 1: 74-80.
21. Maurovich-Horvat P, Schlett CL, Alkadhi H, Nakano M, Stolzmann P, et al. (2012) Differentiation of early from advanced coronary atherosclerotic lesions: systematic comparison of CT, intravascular US, and optical frequency domain

imaging with histopathologic examination in ex vivo human hearts. Radiology 265: 393-401.

22. Sanon S, Dao T, Sanon VP, Chilton R (2013) Imaging of vulnerable plaques using near-infrared spectroscopy for risk stratification of atherosclerosis. Curr Atheroscler Rep 15: 304.

23. Moreno PR, Lodder RA, Purushothaman KR, Charash WE, O'Connor WN, et al. (2002) Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. Circulation 105: 923-927.

24. Wainstein M (2007) Vulnerable plaque detection by temperature heterogeneity measured with a guidewire system: clinical, intravascular ultrasound and histopathologic correlates. J Invasive Cardiol 19: p. 49-54.

25. Leong-Poi H (2009) Molecular imaging using contrast-enhanced ultrasound: evaluation of angiogenesis and cell therapy. Cardiovasc Res 84: 190-200.

26. Sharif F, Lohan DG, Wijns W (2011) Non-invasive detection of vulnerable coronary plaque. World J Cardiol 3: 219-229.

27. Fayad ZA, Fuster V, Fallon JT, Jayasundera T, Worthley SG, et al. (2000) Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. Circulation 102: 506-510.

28. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, et al. (2006) *In vivo* 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol 48: 1818-1824.

29. Coli S, Magnoni M, Sangiorgi G, Marrocco-Trischitta MM, Melisurgo G, et al. (2008) Contrast-enhanced ultrasound imaging of intraplaque neovascularization in carotid arteries: correlation with histology and plaque echogenicity. J Am Coll Cardiol 52: 223-230.

30. Xiong L, Deng YB, Zhu Y, Liu YN, Bi XJ (2009) Correlation of carotid plaque neovascularization detected by using contrast-enhanced US with clinical symptoms. Radiology 251: 583-589.

31. Schueler S, Walther S, Schuetz GM, Schlattmann P, Dewey M (2013) Methodological quality of diagnostic accuracy studies on non-invasive coronary CT angiography: influence of QUADAS (Quality Assessment of Diagnostic Accuracy Studies included in systematic reviews) items on sensitivity and specificity. Eur Radiol 23: 1603-1622.

32. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, et al. (2006) Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol 47: 1655-1662.

33. Kitagawa T, Yamamoto H, Horiguchi J, Ohhashi N, Tadehara F, et al. (2009) Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography. JACC Cardiovasc Imaging 2: 153-160.

34. Leber AW, Knez A, Becker A, Becker C, von Ziegler F, et al. (2004) Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol 43: 1241-1247.

35. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, et al. (2007) Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 50: 319-326.

36. Kashiwagi M, Tanaka A, Shimada K, Kitabata H, Komukai K, et al. (2013) Distribution, frequency and clinical implications of napkin-ring sign assessed by multidetector computed tomography. J Cardiol 61: 399-403.

37. Pflederer T, Marwan M, Schepis T, Ropers D, Seltmann M, et al. (2010) Characterization of culprit lesions in acute coronary syndromes using coronary dual-source CT angiography. Atherosclerosis 211: 437-444.

38. Schoenhagen P, Tuzcu EM, Stillman AE, Moliterno DJ, Halliburton SS, et al. (2003) Non-invasive assessment of plaque morphology and remodeling in mildly stenotic coronary segments: comparison of 16-slice computed tomography and intravascular ultrasound. Coron Artery Dis 14: 459-462.

39. Cilla M, Peña E, Martínez MA, Kelly DJ (2013) Comparison of the vulnerability risk for positive versus negative atheroma plaque morphology. J Biomech 46: 1248-1254.

40. Ambrose JA (1991) Prognostic implications of lesion irregularity on coronary angiography. J Am Coll Cardiol 18: 675-676.

41. Caussin C, Ohanessian A, Ghostine S, Jacq L, Lancelin B, et al. (2004) Characterization of vulnerable nonstenotic plaque with 16-slice computed tomography compared with intravascular ultrasound. Am J Cardiol 94: 99-104.

42. Madder RD, Chinnaiyan KM, Marandici AM, Goldstein JA (2011) Features of disrupted plaques by coronary computed tomographic angiography: correlates with invasively proven complex lesions. Circ Cardiovasc Imaging 4: 105-113.

43. Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, et al. (2002) Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. Stroke 33: 977-981.

44. Kagawa R, Moritake K, Shima T, Okada Y (1996) Validity of B-mode ultrasonographic findings in patients undergoing carotid endarterectomy in comparison with angiographic and clinicopathologic features. Stroke 27: 700-705.

45. Oliver TB, Lammie GA, Wright AR, Wardlaw J, Patel SG, et al. (1999) Atherosclerotic plaque at the carotid bifurcation: CT angiographic appearance with histopathologic correlation. AJNR Am J Neuroradiol 20: 897-901.

46. Wintermark M, Jawadi SS, Rapp JH, Tihan T, Tong E, et al. (2008) High-resolution CT imaging of carotid artery atherosclerotic plaques. AJNR Am J Neuroradiol 29: 875-882.

47. Goldstein JA (2009) Coronary plaque characterization by computed tomographic angiography: present promise and future hope. JACC Cardiovasc Imaging 2: 161-163.

48. Kalender (2006) Fundamentals, system technology, image quality, applications, in Fundamentals, system technology, image quality, applications. 29.

49. Morsbach F, Berger N, Desbiolles L, Poropat T, Leschka S, et al. (2013) Systematic analysis on the relationship between luminal enhancement, convolution kernel, plaque density, and luminal diameter of coronary artery stenosis: a CT phantom study. Int J Cardiovasc Imaging 29: 1129-1135.

50. Schroeder S, Kopp AF, Baumbach A, Meisner C, Kuettner A, et al. (2001) Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. J Am Coll Cardiol 37: 1430-1435.

51. Rasouli ML, Shavelle DM, French WJ, McKay CR, Budoff MJ (2006) Assessment of coronary plaque morphology by contrast-enhanced computed tomographic angiography: comparison with intravascular ultrasound. Coron Artery Dis 17: 359-364.

52. Motoyama S, Kondo T, Anno H, Sugiura A, Ito Y, et al. (2007) Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. Circ J 71: 363-366.

53. Pohle K, Achenbach S, Macneill B, Ropers D, Ferencik M, et al. (2007) Characterization of non-calcified coronary atherosclerotic plaque by multi-detector row CT: comparison to IVUS. Atherosclerosis 190: 174-180.

54. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, et al. (1990) Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 15: 827-832.

55. Friedrich GJ, Moes NY, Mühlberger VA, Gabl C, Mikuz G, et al. (1994) Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern. Am Heart J 128: 435-441.

56. van der Hoeven BL, Liem SS, Oemrawsingh PV, Dijkstra J, Jukema JW, et al. (2006) Role of calcified spots detected by intravascular ultrasound in patients with ST-segment elevation acute myocardial infarction. Am J Cardiol 98: 309-313.

57. Van Velzen JE (2011) Comprehensive assessment of spotty calcifications on computed tomography angiography: comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis. J Nucl Cardiol. 18: 893-903.

58. Maldonado N, Kelly-Arnold A, Vengrenyuk Y, Laudier D, Fallon JT, et al. (2012) A mechanistic analysis of the role of microcalcifications in atherosclerotic plaque stability: potential implications for plaque rupture. Am J Physiol Heart Circ Physiol 303: H619-628.

59. Moselewski F (2004) Comparison of measurement of cross-sectional coronary atherosclerotic plaque and vessel areas by 16-slice multidetector computed tomography versus intravascular ultrasound. Am J Cardiol, 94: 1294-1297.

60. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, et al. (2004) Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. J Am Coll Cardiol 43: 842-847.

61. Achenbach S, Moselewski F, Ropers D, Ferencik M, Hoffmann U, et al. (2004) Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. Circulation 109: 14-17.

62. Imazeki T, Sato Y, Inoue F, Anazawa T, Tani S, et al. (2004) Evaluation of coronary artery remodeling in patients with acute coronary syndrome and stable angina by multislice computed tomography. Circ J 68: 1045-1050.

63. Iriart X, Brunot S, Coste P, Montaudon M, Dos-Santos P, et al. (2007) Early characterization of atherosclerotic coronary plaques with multidetector computed tomography in patients with acute coronary syndrome: a comparative study with intravascular ultrasound. Eur Radiol 17: 2581-2588.

64. Choi BJ (2008) Comparison of 64-slice multidetector computed tomography with spectral analysis of intravascular ultrasound backscatter signals for characterizations of noncalcified coronary arterial plaques. Am J Cardiol 102: 988-93.

65. Taylor AJ, Burke AP, O'Malley PG, Farb A, Malcom GT, et al. (2000) A comparison of the Framingham risk index, coronary artery calcification, and culprit plaque morphology in sudden cardiac death. Circulation 101: 1243-1248.

66. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, et al. (2003) From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 108: 1772-1778.

67. Schaar JA, Muller JE, Falk E, Virmani R, Fuster V, et al. (2004) Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. Eur Heart J 25: 1077-1082.

68. Youssef G, Kalia N, Darabian S, Budoff MJ (2013) Coronary calcium: new insights, recent data, and clinical role. Curr Cardiol Rep 15: 325.

69. Youssef G (2012) Coronary artery calcium scoring, what is answered and what questions remain. Cardiovascular Diagnosis and Therapy.

70. Pohle K, Ropers D, Mäffert R, Geitner P, Moshage W, et al. (2003) Coronary calcifications in young patients with first, unheralded myocardial infarction: a risk factor matched analysis by electron beam tomography. Heart 89: 625-628.

71. Shareghi S, Ahmadi N, Young E, Gopal A, Liu ST, et al. (2007) Prognostic significance of zero coronary calcium scores on cardiac computed tomography. J Cardiovasc Comput Tomogr 1: 155-159.

72. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, et al. (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 358: 1336-1345.

73. Gottlieb I, Miller JM, Arbab-Zadeh A, Dewey M, Clouse ME, et al. (2010) The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. J Am Coll Cardiol 55: 627-634.

74. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, et al. (2009) Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 54: 49-57.

75. Zanni MV, Abbara S, Lo J, Wai B, Hark D, et al. (2013) Increased Coronary Atherosclerotic Plaque Vulnerability by Coronary Computed Tomography Angiography in HIV-Infected Men. AIDS .

76. Marano R, Savino G, Merlino B, Verrillo G, Silvestri V, et al. (2013) MDCT coronary angiography -- postprocessing, reading, and reporting: last but not least. Acta Radiol 54: 249-258.