Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 9731 - 9738
Received 25 April 2021; Accepted 08 May 2021.

Role of Non-Invasive Coronary Computed Tomogram Angiography in Improving Risk Stratification for Patients with Coronary Artery Disease in IbnAl-Nafees Cardiac Center

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Abstract

Background

From a worldwide perspective, the rate of change in the global burden of CVD is accelerating, reflecting the changes in the low- and middle-income economies, which represent 85% of the world's population [(1,3)]. This fact triggered a great demand for improving risk stratification for CVD (IHD on top of the list), PCI angiography being the golden standard in IHD, nevertheless, non-invasive imaging fell in trail at this target as a very attractive non-invasive alternative tool [(1.2.)]. This has yielded the rapidly growing field of Non-Invasive Cardiac Imaging using different techniques such as CCTA and MRCA among many others[(1.4)].

Methods:

We have retrieved previous CCTA studies, of which we have excluded evidence-lacking or ambiguous results, and chose the best results in 40 patients who had conventional PCI angiography within 4-10 days after CCTA. We traced the hospital records for these patients, according to which, 27 patients were diagnosed to have ACS (UA or NSTMI) and the remaining 13 had SA [(2.1)].

Results:

We re-evaluated 40 lesions (one lesion from each patient-the most significant and most assessable) with high image quality (obtained by Toshiba Aquilione 64-slice CT machine at Ibn Al-Nafees Cardiac Center), in 27 patients with ACS and 13 patients with SA. Culprit lesions in patients with ACS (n=14) had greater plaque area and a higher remodeling index (RI) - on cross section vessel analysis – than both stable culprit lesions in patients with ACS (n=13) and in patients with SA (n=13), showing Plaque Area (PA) as follows; (15.2 ± 2.2 mm^2 VS. 7.8 ± 1.3 mm^2 VS. 13.7 ± 4.8 mm^2, $p = 0.01$; and RI (1.5 ± 0.2, 0.9 ± 0.1, 1.2 ± 0.08) $p = 0.01$, respectively. The prevalence of non-calcified plaque was 100%, 62%, and 77%, respectively, and the prevalence of calcified plaque was 71%, 92%, and 85%, respectively, in culprit lesions in patients with ACS and in stable lesions in patients with ACS or stable angina.

Conclusion:

In this study, we introduce the concept of noninvasive detection and characterization of atherosclerotic lesion and plaque characteristics (morphology and composition) in patients with CAD, so both qualitative and quantitave analysis is achieved. We demonstrate (comparing to standard IVUS methodology, i.e., cross-sectional measurements of stenosis degree, lumen and plaque area) that CCTA can noninvasively detect differences in lesion composition and morphology between culprit lesions in patients with ACS, stable lesions in patients with ACS, and stable lesions in patients with stable angina. These data suggest that noninvasive visualization of coronary atherosclerotic plaque by CCTA might improve risk stratification of patients with suspected CAD.

Coronary Computed Tomogram Angiography (CCTA) now permits nearly motion-free visualization of the coronary arteries and accurate detection of significant stenosis as compared

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with selective X-ray coronary angiography at low heart rates. Initial data on the detection and characterization of coronary atherosclerotic plaque indicate that CCTA can measure plaque area, remodeling index (RI), and the degree of stenosis with good correlation to intravascular ultrasound (IVUS) [5.1] and coronary angiography [5.2], respectively, in selected patients with high image quality.

Introduction and Aims

From a worldwide perspective, the rate of change in the global burden of CVD is accelerating, reflecting the changes in the low- and middle-income economies, which represent 85% of the world's population [1.1,1.3]. This fact triggered a great demand for improving risk stratification for CVD (IHD on top of the list), PCI angiography being the golden standard in IHD, nevertheless, non-invasive imaging fell in trail at this target as a very attractive non-invasive alternative tool [1.2.]. This has yielded the rapidly growing field of Non-Invasive Cardiac Imaging using different techniques such as CCTA and MRCA among many others[1.4].

Despite improvement in medical therapy and use of novel interventional techniques, acute coronary syndromes (ACS) continue to be one of the leading causes of morbidity and mortality in developed countries. In the occurrence of coronary events, atherosclerotic plaque characteristics (including degree of stenosis as well as composition and morphology) have been demonstrated to play a crucially important role. Based on pathological studies of the victims of sudden cardiac death, lesions containing a large amount of necrotic core with an overlying thin fibrous cap (referred to as thin cap fibroatheroma, TCFA) have been linked to plaque rupture. With regard to the degree of stenosis, ACS may frequently arise from lesions with only mild to moderate stenosis since these lesions may be more common than severe obstructive lesions [1.5].

Accordingly, in vivo detection of potentially vulnerable plaques may improve prevention of cardiovascular events. Both invasive and non-invasive techniques are currently under development. Recently, virtual histology intravascular ultrasound (VH IVUS) has been introduced. This invasive imaging modality allows in vivo quantitative evaluation of four coronary plaque components, namely fibrotic tissue, fibro-fatty tissue, necrotic core and dense calcium[1.6]. Non-invasively, plaque extent and composition may be evaluated by multi-slice computed tomography (MSCT) coronary angiography. Previous studies have suggested that MSCT can recognize differences in coronary plaque composition with different clinical presentations, although comparison with invasive imaging is lacking [1.7].

The purpose of the present study was to evaluate plaque characteristics in patients presenting with ACS and stable coronary artery disease (CAD) using both non-invasive MSCT and invasive VH IVUS.

Sudden vessel occlusion as a consequence of atherosclerotic plaque rupture with subsequent coronary artery thrombosis is the most common cause of acute myocardial infarction (AMI) and sudden cardiac death in the industrialized world. Conventional X-ray coronary angiography still remains the gold standard for detection of coronary artery disease (CAD). However, this technique is invasive and provides limited information on the composition of atherosclerotic plaque. Coronary computed tomography angiography (CCTA) on the other hand, is a very fast evolving and in the meanwhile well-established non-invasive technique for the visualization of both coronary artery lumen narrowing and coronary calcification. In addition, CCTA with the help of commercially available software tools provides objective and quantitative assessment of atherosclerotic plaque composition.

Based on recent developments with CCTA hardware and software technologies, including iterative reconstruction algorithms, a substantial reduction in radiation exposure and improvement of image quality could be achieved. In addition, dedicated post-processing tools

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constituted major steps towards the reliable and quantitative assessment of atherosclerotic plaque composition.

The growing body of evidence for the prognostic value of CCTA-based plaque characterization underscores its potential for implementation in the clinical realm. In this regard, features indicating plaque vulnerability include a large necrotic core, thin fibrous cap and positive vessel remodeling. The early and non-invasive detection of such vulnerable rupture-prone atherosclerotic lesions remains a major challenge in patient care [(1.8)].

The introduction of multi-slice-computed tomography coronary angiography (CTA) has changed the field of non-invasive imaging. In addition to existing functional imaging techniques assessing myocardial perfusion and wall motion, CTA currently provides direct non-invasive anatomic assessment of the coronary arteries. This allows for detection of coronary artery disease (CAD) at an earlier stage compared to functional imaging, which may have important implications for the diagnosis as well as prognosis of CAD. For diagnosis, numerous studies support the use of CTA for rule out of the presence of CAD with a high accuracy. As a result the technique is increasingly used as a gatekeeper for further diagnostic testing. In addition, data are emerging that early identification of CAD with CTA may be useful for risk stratification. Since the first publications on the prognostic value of CTA in 2007 a number of studies have been published providing further insight into the potential value of non-invasive anatomic imaging for risk stratification. The purpose of this review is to provide an overview of the literature on the prognostic value of CTA and to discuss how the prognostic information obtained with CTA can be used to further integrate the technique into clinical practice [(1.9)].

Aims:

This study is a trial to assess coronary artery lesions in patients who has CAD, both in a qualitative and quantitative way, using non-invasive MDCT, for the purpose of identifying both "culprit" (be it unstable or stable) and "stable" coronary lesions, aiming to improve risk stratification in patients presenting with chest pain and/or other IHD symptoms [(1.10)].

Image quality and lesion classification

After data retrieval, Seventy-four coronary segments with a >50% stenosis were detected in 52 patients by invasive coronary angiography. In 12 patients, at least one coronary segment with a lesion of >50% luminal narrowing was not assessable by CCTA for the following reasons;

1- Accurate assessment of the degree of stenosis or coronary remodeling was not possible due to the presence of severe motion artifacts that most often affected the mid RCA segment (n = 4).
2- Previous intracoronary stent placement precluded assessment of the degree of stenosis and measurement of CT attenuation of non-calcified plaque (n = 3).
3- Insufficient contrast-to-noise ratio in distal coronary segments (obtuse marginal branches [n = 3] and diagonal branches [n = 2]) with a small vessel caliber precluded the accurate delineation of non-calcified plaque.

All those 12 patients were excluded from the analysis, 40 patients were analysed and the results collected. One lesion from each patient was chosen to be both the most significant and most assessable lesion, so 40 lesions with >50% luminal narrowing in 40 patients were re-evaluated and analyzed.

Fourteen unstable culprit lesions were identified in 3 patients with NSTEMI and in 11 patients with unstable angina. Thirteen stable lesions with >50% diameter luminal narrowing (most significant) were identified in 13 patients with stable angina, and 13 non-culprit lesions were identified in patients with unstable angina or NSTEMI.

The distribution of the lesions among the three groups was not significantly different with respect to the four major epicardial coronary vessels (left main [LM], left anterior descending [LAD], left circumflex [LCX], and RCA) or the location in proximal, mid, or distal coronary

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segments (p = 0.4). Most frequently, lesions were located in the proximal LAD (n = 10), mid LAD (n = 8), proximal RCA (n = 6), mid LCX (n = 6), and mid RCA (n = 4). In contrast, relatively few lesions were located in the proximal LCX (n = 3) and the first obtuse marginal branch (n = 2) or LM (n = 1). No lesions were located in the distal segments.

Table 1. There were no statistically significant differences with respect to age, gender, cardiovascular risk profile, and heart rate between patients with ACS and stable angina.

	ACS (n = 14)	SA (n = 26)	p Value
Age (yrs)	60 ± 6	63 ± 7	NS
Men (%)	87.5%	91	NS
Hypertension	9/14	18/26	NS
Hypercholesterolemia	13/14	22/26	NS
Diabetes mellitus	5/14	7/26	NS
Smoking	4/14	9/26	NS
Family history of premature CAD	5/14	12/26	NS
HR (beats/min)	60 ± 11	65 ± 12	NS

Demographics and risk factors in patients with acute coronary syndrome (ACS) and stable angina (SA). Data are given as mean ± SD. CAD = coronary artery disease; HR = heart rate during multidetector computed tomography scanning.

CT lesion characteristics

Plaque composition:

The prevalence of non-calcified plaque was 100% in culprit lesions (14 of 14) compared with 62% of stable lesions in patients with ACS (8 of 13) and in 77% stable lesions in patients with stable angina (10 of 13), and the prevalence of calcified plaque was 10 of 14 (71%), 12 of 13 (92%), and 11 of 13 (85%), respectively. Both calcified and non-calcified plaques were present in 71% of culprit lesions in patients with ACS (10 of 14), in 54% of stable lesions in patients with ACS (7 of 13), and in 62% stable lesions in patients with stable angina (8 of 13). Exclusively non-calcified plaque was demonstrated in 29% of culprit lesions in patients with ACS (4 of 14), in 8% of stable lesions in patients with ACS (1 of 13), and in 15% of stable lesions in patients with stable angina (2 of 13). In contrast, exclusively calcified plaque was demonstrated in none of the culprit lesions in patients with ACS (0 of 14), in 38% of stable lesions in patients with ACS (5 of 13), and in 23% of stable lesions in patients with stable angina (3 of 13). This was calculated using SPSS/one-way ANOVA.

CT measurements of luminal area at stenosis, luminal reference area, degree of stenosis:

The CT measurements in culprit lesions in patients with ACS, stable lesions in patients with ACS, and stable lesions in patients with stable angina are summarized in Table 2. The outer vessel area (corresponds to the external elastic membrane-EEM- area in IVUS) at the site of greatest luminal narrowing was significantly different among the groups (p = 0.01). Culprit lesions in patients with ACS had much larger outer vessel area than both stable lesions in patients with ACS and stable lesions in patients with stable angina.

Table 2: CCTA Measurements of Coronary Vessel Lumen and Atherosclerotic Plaque

	Culprit Lesions in AC (n = 14)	Stable Lesions in AC (n = 13)	Stable Lesions i SA (n = 13)	p Valu
Outer vessel area at	18.9 ± 3.6	11.8 ± 5.7	15.6 ± 10.5	0.01

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	Culprit Lesions in AC (n = 14)	Stable Lesions in AC (n = 13)	Stable Lesions i SA (n = 13)	p Valu
stenosis (mm^2)				
Luminal area at stenosis (mm^2)	3.7 ± 1.6	2.7 ± 3.3	2.1 ± 1.4	0.18*
Plaque area (mm^2)	15.2 ± 2.2	9.1 ± 4.8	13.5 ± 10.7	0.02*
RI	1.4 ± 0.2	1.0 ± 0.4	1.2 ± 0.3	0.04

Differences between groups were determined with analysis of variance test Non-invasive characterization of the morphology of 40 lesions with >50% luminal narrowing as derived from contrast enhanced 64-slice multidetector computed tomography (CCTA). The measurements were performed on cross-sectional images. Outer vessel area at stenosis includes both luminal and plaque area.

Discussion:

In this study, we introduce the concept of noninvasive detection and characterization of atherosclerotic lesion and plaque characteristics (morphology and composition) in patients with CAD, so both qualitative and quantitave analysis is achieved. We demonstrate (comparing to standard IVUS methodology, i.e., cross-sectional measurements of stenosis degree, lumen and plaque area) that CCTA can noninvasively detect differences in lesion composition and morphology between culprit lesions in patients with ACS, stable lesions in patients with ACS, and stable lesions in patients with stable angina. These data suggest that noninvasive visualization of coronary atherosclerotic plaque by CCTA might improve risk stratification of patients with suspected CAD.

There is evidence that CCTA can measure plaque area, RI, and the degree of stenosis with good correlation to IVUS [11.12] and coronary angiography[13.14], respectively, in selected patients with good and assessable CT image quality. We included, similar to studies for the detection of significant and assessable variables [13.14], only 30% (40 of 135) of patients for the analysis, the excluded patients had at least one segment with stenosis with impaired image quality. This is mainly owing to the fact that all coronary segments were included in the evaluation and reflects some limitations of the current CT technique; however, initial data on 64-slice CCTA[15.16] demonstrate that further improvement of image quality can be expected, especially that now CT machines of 320- and 640-slice and even more, are available, and the developing cardiac imaging technologies, especially CCTA, are on full run, and should be able to give much higher accurate imaging quality. Distinctly, improved temporal and spatial resolution will lead to a decrease of the number of unassessable segments, making CCTA technique potentially useful in a clinical environment.

Our study adds further evidence to the presumption that morphology and composition of coronary atherosclerotic plaque are different between patients with ACS and stable angina. Earlier, an angiographic study reported a high prevalence of complex plaques in patients with ACS [4.6], and several IVUS studies suggest that positive remodeling of plaque and presence of thrombus are independent predictors of ACS [17.18-19]. Our study confirms these observations with the noninvasive CCTA imaging technique.

The RI of culprit lesions in patients with ACS was significantly larger than in stable lesions in patients with ACS and in stable lesions in patients with stable angina; we observed, as in IVUS studies, a relatively wide overlap between the three groups. In stratified analysis, 12 of 14 culprit lesions, and 6 of 13 stable lesions in patients with ACS (had an RI above or below 1.05, creating the hypothesis that the detection of positively remodeled coronary lesions by

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CCTA might be helpful to noninvasively identify the culprit lesion in patients with ACS. Larger prospective studies, even clinical trials, will be required, however, to prove that positive remodeling as determined by CCTA has sufficient specificity to detect culprit lesions on an individual basis, especially in patients with a known history of coronary artery disease or multi-vessel disease. We recognize that the assessment of remodeling in diffuse disease is problematic, because LAD and LCX taper, whereas the RCA does not; however, the distribution of lesions was similar among the three groups with respect to the four major epicardial coronary vessels (LM, LAD, LCX, and RCA) or the location in proximal, mid, or distal coronary segments.As expected from lesion pathology studies [20.21], CCTA detected some differences in plaque composition between culprit and stable lesions: 1) non-calcified plaque as detected by CCTA is always present in culprit lesions (none of the culprit lesions consisted of calcified plaque only), although absence of non-calcified plaque is highly prevalent in stable lesions; and 2) absence of calcified plaque is very rare in stable lesions but frequent in culprit lesions. The majority of both stable and culprit lesions, however, contain both calcified and non-calcified plaque. Especially the absence of calcified plaque in 34% of culprit lesions suggests that the absence of calcified plaque alone might not be safe to exclude ACS, as suggested by some non-contrast electron beam computed tomography studies [20.21]. Leber et al. made similar observations in regard to prevalence frequency of non-calcified and calcified plaque while assessing the difference of overall plaque burden between patients with ACS and stable angina on a per-patient basis [22.23].

There is controversy, however, as to whether the presence of calcification in atherosclerotic lesions is an indicator of lesion stability. According to the AHA classification of atherosclerotic plaque [24.25], calcified plaque is present in the advanced stages of atherosclerosis, but histopathology studies have demonstrated that calcification is present in more than 50% of stable and vulnerable plaques as well as in acute ruptured plaques and plaque with healed rupture [26.27]. One of the most intriguing new theories on the role of calcium in culprit lesions is that calcification creates a region of mechanical instability at the interface between calcified and non-calcified plaque [26.27]. Thus the role of calcification needs to be further studied specifically with respect to its localization within a plaque and relation to plaque rupture sites.

Conclusions

We introduce the concept of noninvasive detection and characterization of coronary atherosclerotic lesions in patients with ACS by sub-millimeter 64-slice, CCTA, as a tool for risk stratification for both, High-, and Medium- risk groups of patients with CAD presenting to ED or CCU.

We identified differences in lesion morphology and plaque composition between culprit lesions in patients with ACS and stable lesions in patients with ACS or stable angina, consistent with previous studies conducted with IVUS, emphasizing the potential of CCTA to improve noninvasive risk stratification in patients with acute chest pain.

This diagnostic tool has a very high potential to modify the overall process of management of patients with CAD, both symptomatic and asymptomatic, and on all risk levels. This may lead to a breakthrough in the field of IHD diagnosis, management, and prognosis, which in turn would elevate the cost-effectivity and lower the huge burden on the health care system (HCS), and make a better standards of referral systems for family physicians when dealing with the usual daily patient seen at the primary health care center (PHC), and by those we mean all risk groups of patients such as those with hypertension, diabetes, obesity and hyperlipidemia and other risk factors for IHD, encountered almost on daily basis by the family physician. This might imply better risk stratification, more efficient referral practice, less burden on Cardiac

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Received 25 April 2021; Accepted 08 May 2021.

Centers (Tertiary Level), and more organized and efficient follow up for diagnosis confirmation, management, prognosis and for research purposes.

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