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Plaque Burden and Characterization by Multislice Coronary CT Angiography in Patients with Coronary Artery Disease

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Abstract

Background: Although degree of coronary luminal narrowing continued to guide therapeutic intervention in clinical cardiology, CT coronary angiography provides additional information about atherosclerotic plaque characteristics such as plaque morphology which recently showed good correlation with acute coronary syndrome as an independent factors.

Aim of Study: The purpose of the study is to characterize atherosclerotic plaques as regard plaque burden and morphological features to avoid acute coronary syndrome later on.

Patients and Methods: 60 patients; 36 patients were with stable coronary artery disease and 22 patients were with unstable coronary artery disease. All patients were scanned first with coronary artery calcium scoring then, contrast enhanced coronary angiography. Coronary CT angiography was evaluated for morphologic features.

Results: High risk plaque criteria were identified as NRS, LAP <60, plaque burden >0.7 and R.I >1.1. Characterization of the calcified lesions had the advantage of assessment of post contrast calcium which showed high correlation with pre contrast calcium volume of traditional calcium score as reference (r_s=0.97) Hence, accurate detection of the degree of stenosis (p=<0.001).

Conclusion: Characterization of coronary plaques by quantitative coronary plaque analysis improved image quality for calcified plaques and correlate well with high risk plaque criteria.

Key Words: *CAD= Coronary Artery Disease – CCS= Calcium Score – CCTA=Coronary Computed Tomography Angiography – CTA=CT Angiography – SC= Spotty Calcification – LAP=Low Attenuation Plaque, RI=Remodeling Index – NR=Napkin Ring, HRP=High-Risk Plaque – HU=Housenfield Unit – ROI=Region of Interest – PCI=Percutaneous Coronary Intervention – CABG=Coronary Artery Bypass Graft.*

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Introduction

CORONARY Computed Tomography Angiography (CCTA) recently emerged as a promising non-invasive screening valuable tool for early diagnosis of Coronary Artery Disease (CAD). The strength of CTA encompasses a high sensitivity and negative predictive value of 90-99% for coronary stenosis detection **[1]**.

Although, coronary artery stenosis detection has some drawbacks in diagnosis of CAD; acute coronary thrombosis has been identified as the main cause of myocardial infarction and increased lipid content and positive remodeling are typical pathology features of vulnerable atherosclerotic plaques. In several instances, atheromatous plaques with these characteristics are not flow limiting, but they are prone to rupture and to produce ACS nevertheless **[2]**.

Additionally, coronary calcification is an important diagnostic concern affecting diagnostic accuracy of CCTA. When coronary artery calcification develops, CTA imaging can enlarge the calcified plaque and subsequently influence the visibility of the coronary artery lumen; resulting in measurement errors of Coronary artery stenosis **[3]**.

The advantage of plaque burden estimation and coronary plaque characterization are recently valuable prognostic parameters. Currently, emerging research is focusing on improving quality and coronary risk stratification tools by using CTA parameters, which recently showed a higher accuracy **[4]**.

The importance of plaque composition determined by MDCT in patients presenting with stable

and unstable coronary artery disease remains unknown, as does the development of plaque composition, which may determine the clinical outcome in both disease entities later on [5].

The concept of High-Risk Plaque (HRP) criteria has recently emerged as specific indicators for 'vulnerable plaque' which may allow an early identification of patients at risk for future major adverse cardiac event. Thus, they could further sharpen risk calculators. However, little prospective outcome data are available to date for enrolling small sample size or collecting short-or mid-term outcomes [6].

Besides, a variety of different HRP criteria have been proposed: The Napkin-Ring (NR) sign, a pathohistological correlate for advanced/vulnerable atherosclerotic lesions, positive remodeling and Spotty Calcification (SC), and Low-Attenuation Plaque (LAP) with <30 Hounsfield Units (HU) measured by plaque 'area ROI' (region of interest) or by 'pixel lens' screening techniques. In contrast, ex vivo studies identified LAP <60 and <90 HU as optimal cut-offs for lipid-core plaque [7,8].

Patients and Methods

Study design and population:

This study was conducted at Tanta University Hospital after approval from our local committee; consecutive patients referred for CTA were recruited from March 2018 to March 2019. We enrolled 60 patients in this study: 38 were males and 22 were females in which 24 patients were with unstable coronary artery disease and 36 patients with stable coronary artery disease.

Inclusion criteria:

The enrolled patients with stable coronary artery disease met these criteria; patients with atypical chest pain and class I and II angial pain were included as candidates for stable coronary artery disease. The enrolled patients with unstable coronary artery disease met these criteria; class III and IV angina as well as patients who had experienced major cardiac event that relieved medically were included as candidates for unstable patient group.

Exclusion criteria:

Exclusion criteria were heart rate greater than 70 beats per minute, orthopnea, renal impairment, contrast allergy, pregnancy, patients with unstable angina that needs urgent revascularization and patients with known coronary artery disease; previous (Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG).

Computed tomography angiography:

Non contrast ECG gated Calcium Score (CCS) computed tomography (with standardized scan parameters (1.5mm, 120KV), then coronary CTA was performed using 320 row CT scanner (Aquilion one system, Toshiba Medical Systems, Tokyo, Japan) with 0.35 second gantry rotation time, variable mA according to patient body habitus (range: 100-135Kv). Prospective ECG gating was used, single heart beat acquisition was routinely performed with heart rate below 65bpm and the scan window was set at 70-80% of RR interval while 2 heart beat acquisition was performed in patient with heart rate above 70bpm. When heart rate between 65 and 70bpm, the scanning window was set to 30-80% of RR interval to include end systolic phase.

An iodine contrast agent (Ultravist 370) was injected intravenously 60-90mL bolus at an infusion rate of 5mL/sec, followed by 50mL of saline solution. The scan was performed according to the bolus-tracking technique (230HU, at descending aorta mid heart level).

Image analysis:

Curved Multiplanar Reformations (cMPR) and 3D post-processing software (Vitrea Fx, vital images, USA):

A- Degree of stenosis= Referential diameter-luminal diameter/referential diameter. In turn, referential diameter was defined as the diameter located in the proximal normal vessel or distal normal vessel if the lesion is ostial. The stenosis severity is graded as minimal <10%, Mild <49%, Moderate 50-69%, severe ›_70%, subtotal >90% and total occlusion per coronary segment (AHA-modified-17 segment classification).

B- Quantitative CTA lesion analysis was performed on all plaques >25% separating different plaque components by using various attenuation thresholds and provide color map of plaque compositions (–30-60 for lipid plaque, 61-149 for fibrous plaque and 150-1300 for calcium).

C- Plaque types were classified as calcified (calcium >60%), non calcified (Calcium <5%) and mixed (calcium 5-60%) according to the volume of the calcium within. Mixed plaque is further classified as mixed plaque dominantly calcified and mixed plaque dominantly non calcified.

D- All plaques >25% stenosis were analyzed for morphologic features, parameters analyzed include:

• Plaque burden of the whole plaque and at area of maximal narrowing = (Lesion plaque area-lesion lumen area/lesion plaque area), automatically analyzed by quantitative CTA analysis.

• Low Attenuation Plaque (LAP): CT density was recorded with quantitative CTA analysis at area of maximal narrowing. Then, an area of ROI was placed at lowest density plaque area. LAP is defined as hypo-attenuation with CT density <150 HU.

• Napkin Ring Sign (NRS): Was defined as an outer high density rim with inner hypodense area not adjacent to calcification and present on minimum of two adjacent axial 1mm slices.

• Remodeling Index (R.I)= The ratio of maximal cross sectional vessel area including the plaque and the lumen and its closest proximal (or distal in ostial lesion) normal referential vessel area. The lesion with remodeling index >1.10 is considered positively remodeled, less than 0.95 is considered negatively remodeled and 0.95-1.10 is absent.

• Spotty Calcification (SC) was defined as calcification <3mm.

Plaques with image quality limitations (motion artifact, beam hardening and streak artifact) were excluded from quantitative analysis).

The results were validated against coronary angiography as regard localization and degree of stenosis, as standard reference within 20 ± 10 days after coronary CT angiography.

Statistical analysis:

Statistical analysis was performed using SPSS software qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

Chi-square test for categorical variables, to compare between different groups. Student *t*-test for normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

Receiver Operating Characteristic curve (ROC) generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two cutoff values.

Results

Our study included 60 patients, 38 of them were males while 22 of them were females, their ages ranged from 26 to 70 years with a mean of 53.7±8.4 years.

As regard demographic distribution, risk factors, clinical and laboratory characteristics; there was significant difference between two groups as regard gender distribution (p=<0.001), dyslipidemia (p= 0.004) and smoking (p=<0.001) which means strong correlation between these risk factors and unstable coronary artery disease. These findings were listed at (Table 1).

There was no statistical difference between degree of stenosis of both patient groups (p=0.141). However, there was statistical significant difference between plaque burden of both patient groups (p =0.004, Table 1). By ROC curve, plaque burden >70% is identified as optimal cut off value (sensitivity 86.11%, specificity 70.45%) to detect unstable cases (AUC=0.78, p=0.005).

CTA stenosis severity: 116 lesion were studied with perfect significant correlation between degree of stenosis of different plaque types by CT and invasive coronary angiography (p=<0.001), (Table 2).

Plaque types by CTA: There was significant difference between two patient groups as regard plaque type. Non calcified plaques were more prevalent at the unstable group; (p=<0.001). However, calcified plaques were more prevalent at stable group; (p=<0.001). There was no significant difference between the numbers of mixed plaques of between two patient groups (Table 3).

Quantitative coronary plaque analysis:

There was strong perfect correlation between pre contrast calcium volume by calcium score and post contrast calcium volume by quantitative analysis of calcified and mixed plaques (r_s= 0.971, p= <0.001), (Table 4).

There was appreciable difference between CT numbers of non calcified plaques between two patient groups; LAP density was lower in unstable patient group by QA and by ROI; median value

increased from 17 to 60 from <30 to <90 and increased from 24 to 80.50 in stable groups at the same range (p=<0.001). LAP <60 was more prevalent at unstable group (p=<0.001). LAP <60 is identified as optimal cut off value (sensitivity 80.5%, specificity 86.1%) to detect unstable cases (AUC=0.796, p=0.004), (Table 5).

Atherosclerotic plaques in the unstable group displayed specific characteristics including Napkin Ring Sign (NRS), Low Attenuation Plaque (LAP), high plaque burden, Spotty Calcification (SC), and positive remodeling; NRS, LAP, PB >0.7 and SC were more prevalent at unstable patient group than stable one (26 vs. 2 lesions), (58 vs. 6 lesions), (62 vs. 13 lesions) and (12 vs. 0 lesions), p=<0.00 1. There was no significant difference between positively remodeled lesions at both patient group at two cutoff value (>1.1 & >1.4), (p=0.08, 0.3928). Similarly, there was no significant difference between two patient groups (p=0.272). These findings were listed at (Table 6).

Subgrouping positively remodeled lesions according to plaque types; in unstable patient group; non calcified plaque and mixed plaques with predominate non calcified portion (NC>C) exhibited positive remodeling. Controversly, calcified plaques and mixed plaques with predominate calcified portion (C>NC) exhibited positive remodeling. This could explain the insignificant difference between two patient groups.

Comparing non calcified plaques and mixed plaques with predominate non calcified portion (NC>C) as regard R.I, there was significant difference in between two patient groups at cutoff value > 1.1 (p=0.01). R.I >1.10 is identified as optimal cut off value (sensitivity 79.03%, specificity 91%) to detect unstable cases (AUC=0.885, p=<0.001 and 95% C.I 0.74-1.03), (Table 7).

There is strong correlation between plaque characteristics and clinical presentation represented by OR (Odds Ratio) and 95% C.I (Confidence Interval). So, R.I >1.1, plaque burden >0.7, NRS and LAP <60 are considered to be high risk plaque criteria. Napkin Ring Sign (NRS) has the best specificity (95.4%), but lower sensitivity (36.1%) which is due to its low prevalence. Second, Remodeling Index (R.I) >1.1 has specificity (91) and moderate sensitivity (79). Plaque burden >0.7 has moderate degree of sensitivity (86.11) and specificity (70.45), which is due to positively remodeled calcified lesions that were more prevalent at the stable group, Low Attenuation Plaque (LAP <60) has moderate sensitivity (80.5) and specificity (86.3), (Tables 8,9).

Table (1): Comparison between the two studied groups according to demographic distribution, risk factors, degree of stenosis and plaque burden.

Characteristics	Total (n=60)		Unstable group (n=24)		Stable group (n=36)		Test of sig.	p
	No.	%	No.	%	No.	%		
Sex:								
Male	38	63.3	22	91.7	16	44.4	χ^2=	<0.001*
Female	22	36.7	2	8.3	20	55.6	13.828*	
Age (years):								
Min.-max.	26.0-70.0		26.0-70.0		45.0-68.0		*t*=	0.110
Mean ± SD.	53.70±8.37		51.58±10.0		55.11±6.86		1.622	
Median	52.50		53.50		52.50			
Diabetic	26	43.3	10	41.7	16	44.4	0.045	0.832
Hypertensive	34	56.7	14	58.3	20	55.6	0.045	0.832
Dyslipidemia	32	53.3	20	83.3	17	47.2	7.94	0.004*
Smoking	20	33.3	16	66.6	4	11	20	<0.001*
Stenosis:								
Min.-max.	32.0-94.0		38.0-93.0		32.0-94.0		1.489	0.141
Mean ± SD.	56.49±15.95		58.48±12.72		53.50±19.63			
Median	54.0		56.0		47.0			
Plaque burden:								
Min.-max.	45.20-100.0 (%)		45.20-100.0 (%)		47.80-99.70 (%)		2.954*	0.004*
Mean ± SD.	79.04±14.87		82.35±12.35		70.62±17.07			

χ^2 : Chi square test.
t : Student *t*-test.
p : *p*-value for comparing between the studied groups.

Table (2): Correlation between degree of stenosis, by computed tomography, of different plaques types and angiographic results.

Invasive coronary angiography	Degree of Stenosis (Coronary CT angiography)											
	Mild		Moderate		Severe		Subtotal		Total occlusion			
	No.	%	No.	%	No.	%	No.	%	No.	%	χ^2	MC$_P$
	Calcified plaques											
	(n=10)		(n=12)		(n=6)		–		–			
Normal	6	21.4	0	0.0	0	0.0					42.584*	<0.001*
Mild	4	14.3	0	0.0	0	0.0	–	–	–	–		
Moderate	0	0.0	12	100.0	0	0.0	–	–	–	–		
Severe	0	0.0	0	0.0	4	66.7	–	–	–	–		
Subtotal	0	0.0	0	0.0	0	0.0	–	–	–	–		
Total occlusion	0	0.0	0	0.0	0	0.0	–	–	–	–		
Non visualized	0	0.0	0	0.0	2	33.3	–	–	–	–		
	Mixed plaques											
	(n=14)		(n=4)		(n=4)				(n=4)			
Normal	0	0.0	0	0.0	0	0.0					28.024*	<0.001*
Mild	14	85.7	0	0.0	0	0.0	–	–	–	–		
Moderate	0	0.0	2	50	0	0.0	–	–	–	–		
Severe	0	0.0	2	50	0	0.0	–	–	–	–		
Subtotal	0	0.0	0	0.0	0	0.0	–	–				
Total occlusion	0	0.0	0	0.0	4	100.0	–	–	4	100.0		
Non visualized	0	0.0	0	0.0	0	0.0	–	–	–	–		
	Soft plaques											
	(n=16)		(n=26)		(n=12)		(n=6)		(n=2)			
Normal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	101.390	<0.001*
Mild	8	50	0	0.0	0	0.0	0	0.0	0	0.0		
Moderate	0	0.0	20	76.9	0	0.0	0	0.0	0	0.0		
Severe	0	0.0	4	15.3	10	91.6	0	0.0	0	0.0		
Subtotal	0	0.0	0	0.0	0	0.0	6	100.0	0	0		
Total occlusion	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0		
Non visualized	8	50	2	7.6	2	8.3	0	0.0	0	0.0		

Table (3): Comparison between the two studied groups according to plaque type.

Plaque type	Total (n=116)		Unstable group (n=72)		Stable group (n=44)		χ^2	p
	No.	%	No.	%	No.	%		
Calcified	28	24.1	6	8.3	22	50.0	25.893*	<0.001*
Mixed (NC>C)	22	18.9	10	16.7	12	27.3	1.872	0.171
Mixed (C>NC)	4	3.4	2	0.0	2	4.5	3.330	0.142
Non calcified	62	53.4	54	75.0	8	18.2	35.435	<0.001*

Table (4): Correlation between pre contrast calcium volume by calcium score and post contrast calcium volume by quantitative analysis.

Calcified & Mixed plaques	Pre contrast Ca volume (Calcium score)	Post contrast Ca volume (QA)	r_s	p
Min.-max.	7.0-294.0	7.0-292.30	0.971	<0.001*
Mean ± SD.	80.17±74.61	81.31±73.58		
Median	53.50	56.0		

r_s : Spearman correlation coefficient. *QA : Quantitative analysis.
p : p-value. * : Statistically significant at $p \leq 0.05$.

LAP <90 (QA):			
N, %	19 (16.3%)	5 (0.05%)	14 (31.8%)	<0.001 *[c]

Table (6): Comparison between two patient groups as regard variable plaque characteristics.

	Total (n=116)		Unstable group (n=72)		Stable group (n=44)		χ^2	*p*
	No.	%	No.	%	No.	%		
NRS	28	25.00	26	36.1	2	4.5	14.860*	<0.001 *[a]
LAP <60	64	55.17	58	80.5	6	13.6	49.44	<0.001 *[a]
PB >0.7	74	63.79	62	86.1	13	29.5	38.238	<0.001 *[a]
SC	12	10.34	12	22.2	0	0.0	11.342*	0.001 *[a]
R.I >1.1	34	29.3	22	30.5	12	35.5	0.2.916	0.08[a]
R.I >1.4	16	22.4	8	11.1	8	18.2	0.7301	0.3928[a]
Calcium score:								
Min.-Max.	6.0-348.0		22.0-348.0		6.0-259.0		U=	0.272[b]
Mean ± SD.	76.36±77.13		90.58±92.76		65.69±62.42		318.0	
Median	52.0		66.0		50.0			

NRS : Napkin Ring Sign.
LAP : Low Attenuation Plaque.
SC : Spotty Calcification.
R.I : Remodeling Index.
a : χ2 test.
b : Mann Whitney test.
p : *p*-value.
* : Statistically significant at $p \leq 0.05$.

Table (7): Comparison between Remodeling Index (R.I) of non-calcified and mixed (NC>C) at both patient groups.

	Total (n=84)		Unstable group (n=62)		Stable group (n=20)		χ^2	*p*
	No.	%	No.	%	No.	%		
>1.1	28	33.3	26	40.6	2	10	6.4312	0.01 *
>1.4	8	9	8	12.5	0	0.0	1.356	^{FE}p= 0.568

N : Number of non calcified and mixed (NC>C).
χ^2 : Chi square test.
p : *p*-value for comparing between the studied groups.

Table (8): Correlation between plaque characteristics and clinical presentation.

	Unstable group (n=72)		Stable group (n=44)		OR	95% CI
	No.	%	No.	%		
• RI >1.1 [a]	26	47.2	2	4.5	58.5*	9.66-354.31
•Plaque burden >0.7	62	86.1	13	50.0	14.78 *	5.83-37.48
• NRS	26	36.1	2	4.5	11.870*	2.65-53.08
• LAP <60	58	80.5	6	13.6	6.015*	2.56-14.12
• SC	12	22.2	0	2.3	–	–

OR: Odds Ratio. CI: Confidence Interval.
OR for R.I is calculated for non calcified plaques and mixed (NC>C).

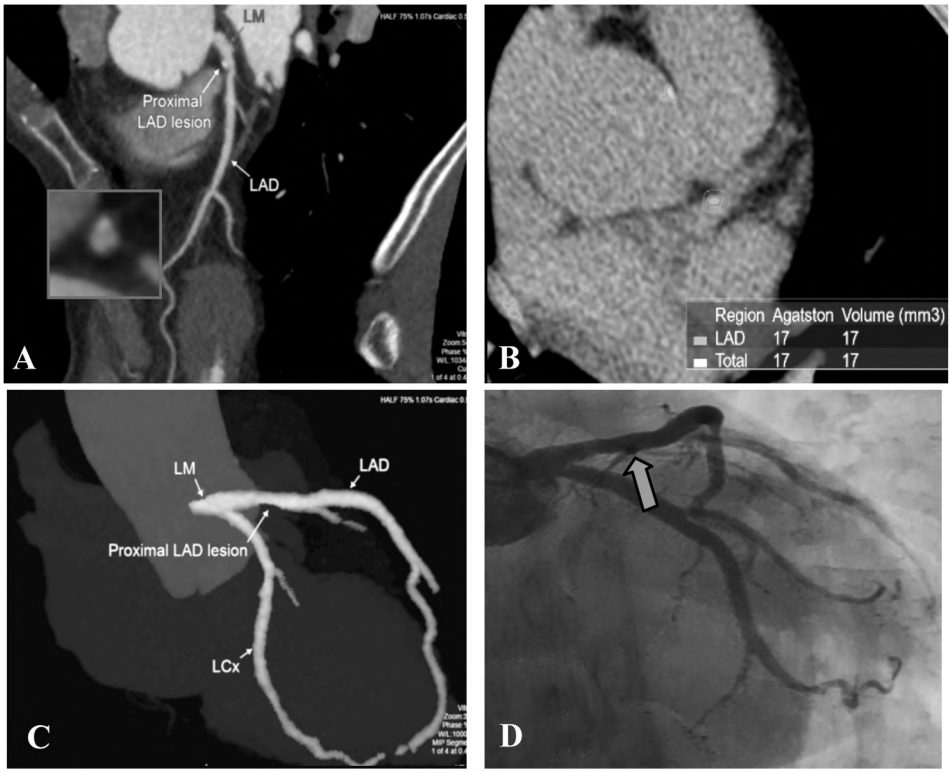

Fig. (1): 65-year-old female patient, diabetic, hypertensive complaining of typical chest pain on exertion relieved by rest (Class I). (A) Curved multiplanar reformatted image showed mild proximal LAD lesion exerted by mixed plaque with the corresponding cross sectional analysis at the site of maximal narrowing. (B) The corresponding pre-contrast volume of the calcified component (17mm ^{3}) by calcium score. (C) MIP reconstruction of coronary tree in the RAO CAU view showing mild proximal LAD lesion. (D) Invasive coronary angiography RAO CAU view showed mild proximal LM lesion (blue arrow).

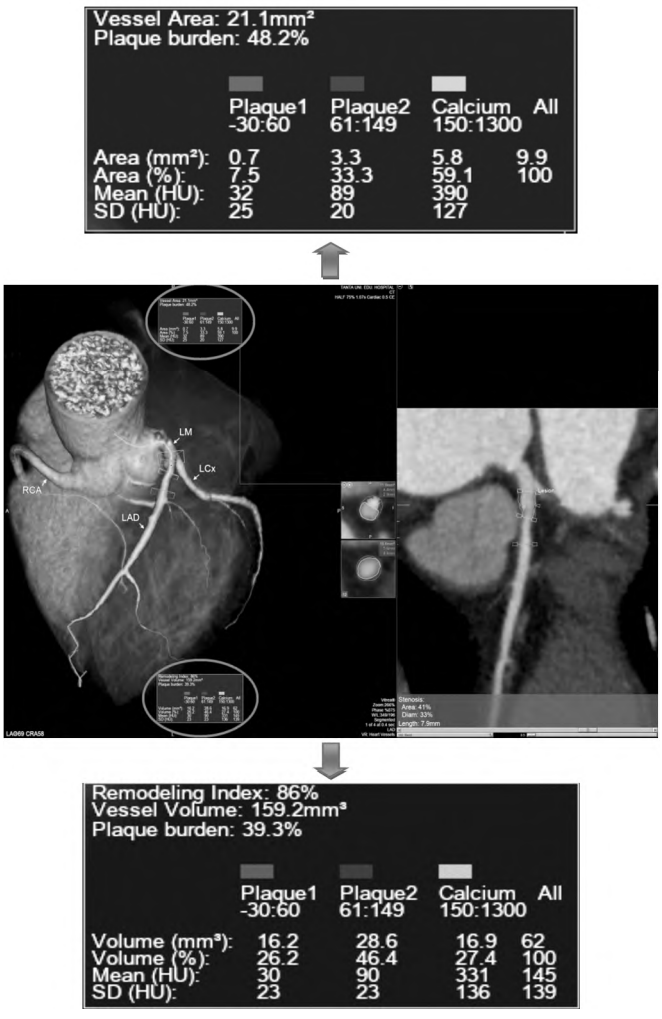

Fig. (2): Semi-automated quantitative coronary plaque analysis revealed negatively remodeled fibrocalcified lesion (Calcium represented 27.4% of total plaque volume) with predominant non calcified portion, graded as mild stenosis (33%) in relation to distal referential diameter. Post-contrast calcium volume 16.9mm ^{3} which showed good correlation with pre-contrast calcium volume. Plaque characterization at the site of maximal plaque burden revealed non high risk plaque characteristics (plaque components; calcified component 59.1%, fibrous component 33.3% of high CT number 89±20HU and low percentage of lipid component 7.5%).

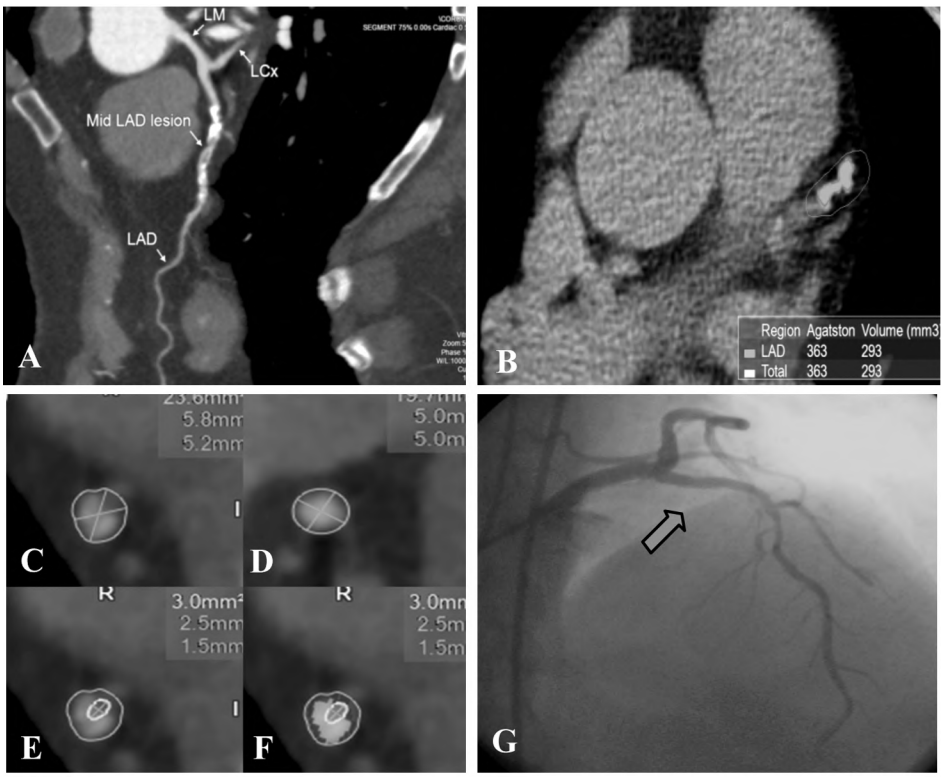

Fig. (3): 53-years old female patient, diabetic, hypertensive complaining of recurrent attacks of atypical chest pain (chest discomfort), and dypnea on exertion. Echocardiography revealed no regional wall motion abnormalities. (A) Curved multiplanar reformatted image showed moderate mid-LAD lesion exerted by mixed calcified and non calcified plaques. (B) Pre-contrast calcium volume was 293mm^3 (by Calcium score). Remodeling index was obtained from the ratio of lesion plaque area (23.6 mm^2) at (C) To referential area (19.7mm^2) at (D), In the case represented=1.20. (E) Cross sectional area at the site of maximal narrowing; inner circle represented luminal cross sectional area. (F) Application of color map at the site of maximal narrowing; yellow color represented calcium, blue color represented fibrous component and red color represented lipid component. (G) Invasive coronary angiography RAO CRA view showed moderate mid-LAD lesion.

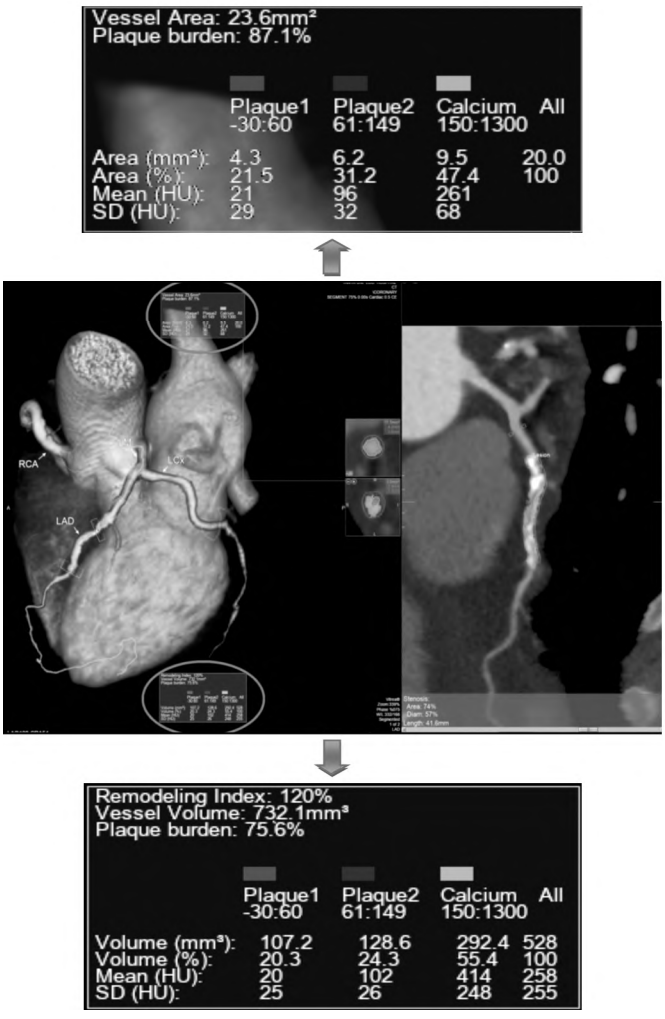

Fig. (4): Semi-automated quantitative coronary plaque analysis with 3D volume rendered and cMPR images revealed positively remodeled mixed plaque with predominant calcified portion (Calcium represented 55.4% of total plaque volume) graded as moderate stenosis (57%) in relation to proximal referential diameter. Post-contrast calcium volume 292.4mm ^{3} which showed good correlation with pre-contrast calcium volume (293mm ^{3}). Plaque characterization at the site of maximal plaque burden revealed non high risk plaque characteristics (plaque components; calcified component 47.4%, fibrous component 31.2% of high CT number 96±32HU and low percentage of lipid component 21.5%).

* Total plaque burden by Adapted leaman score (CT-LeSC)=3.75.

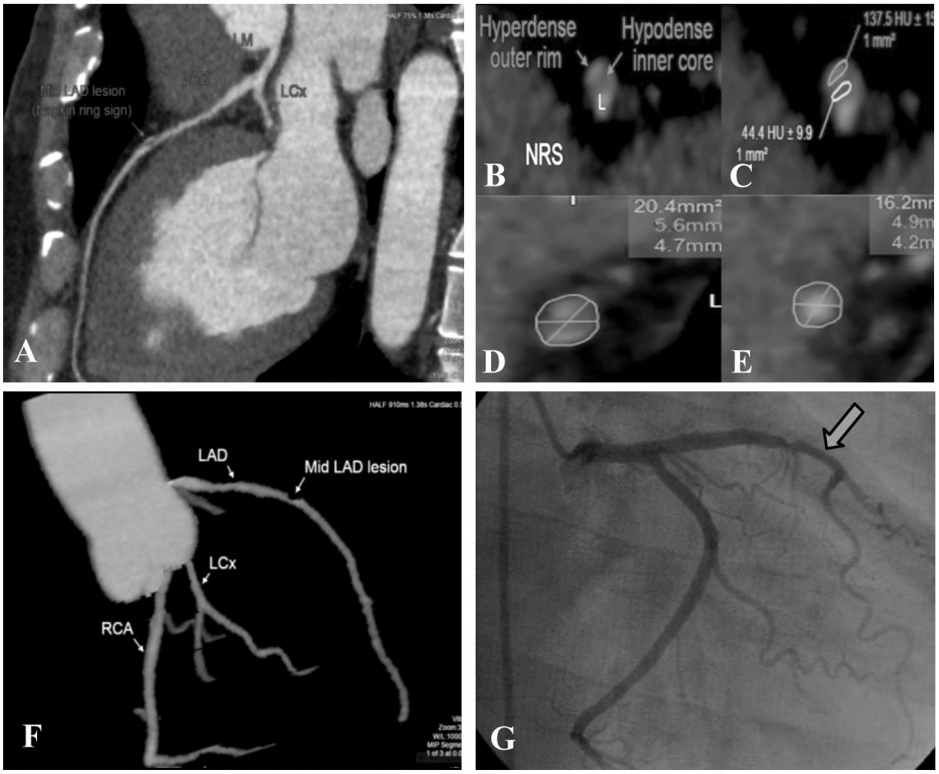

Fig. (5): 52-year-old male patient, smoker with hypercholesterolemia complaining of recurrent attacks of typical chest pain on moderate exertion (class III); with history of NSTEMI and ICU admission 10 days before coronary CT examination. (A) Curved multiplanar reconstructed image showed moderate mid-LAD lesion exerted by non calcified plaque, cross sectional analysis of showed NRS with hypodense core and hyper dense outer rim (B) ROI was applied at hyper dense outer rim and CT number was obtained 137.5 ±15.9HU (C): ROI was applied at hypodense core and CT number was 44.4±9.9HU. Positive remodeling was obtained from the ratio of lesion plaque area (20.4mm^2) at (D) To referential area (16.2mm^2) at (E), In the case represented=1.25. (F): CTA reconstruction of left coronary arteries in the RAO CAU view showing mid LAD lesion. (G) Invasive coronary angiography RAO CAU view confirmed moderate mid-LAD lesion (blue arrow).

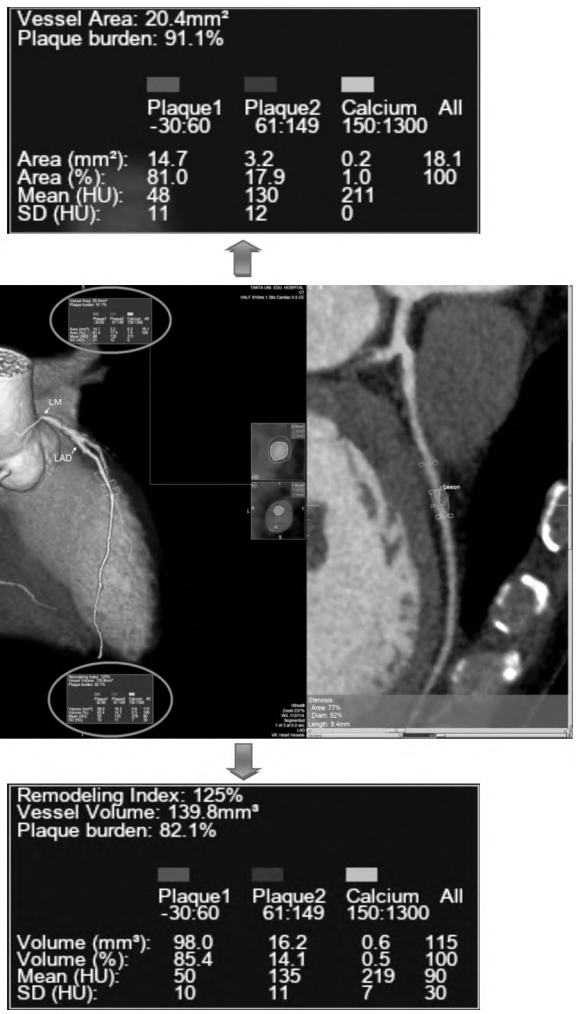

Fig. (6): Semi-automated quantitative coronary plaque analysis revealed fibrofatty plaque with predominate lipid component (calcium=0.5 %). Plaque characterization at area of maximal plaque burden revealed high risk plaque characteristics; positively remodeled non calcified lesion (1.25) with Plaque burden >0.7 (91.1.1%), NRS (inner hypodense lipid core representing 8 1. 0 % of plaque area, CT number 48±11 and hyper dense fibrotic outer rim with spotty calcification seen within its outer rim, CT number 130±12).

Table (9): Comparison between high risk plaque criteria as regard sensitivity, specificity and OR.

HRP criteria	Sensitivity	Specificity	OR	*p*-value
R.I >1.1	79	91	58.5*	<0.001
Plaque burden >0.7	86.11	70.45	14.78*	0.005
NRS	36.1	95.4	11.870*	<0.001
LAP <60	80.5	86.3	6.015*	<0.001

Discussion

Coronary Computed Tomography (CCTA) recently emerged as promising non invasive tool not only able to identify coronary artery stenoses, but also to assess the characteristics of atherosclerotic plaques itself. This unique property of the coronary CTA holds many advantages for patient risk stratification than other invasive tests **[9,10]**.

Different authors underwent different study designs and proposed variety of HRP criteria, however many studies were limited more importantly by homogenousity of the selected sample.

We investigated the semi automated quantitative analysis to characterize coronary plaques as regard geometric and volumetric properties and its additive value in improving image quality and risk stratification tools.

Firstly, 116 lesions were studied with significant correlation between degree of stenosis by coronary CT angiography and invasive coronary angiography as regard different plaque types (p=<0.001 for calcified, mixed and non calcified plaques). Concerning mixed and calcified plaques which is in line with study conducted by Dodd et al., **[11]**, they assumed that there was moderate to strong correlation between degree of stenosis by coronary CT angiography and invasive coronary angiography in quantifying degree of stenosis (p=>0.001). Concerning calcified plaque, the current study finding is disagreed by the aforementioned study stating that there was poor correlation for calcified plaque.

Secondly, we followed a distinct novel for plaque assessment proposed by Feuchtner et al., **[12]** based on semi-automated quantitative assessment of atherosclerotic plaques graded as calcified plaque, mixed plaque with predominant calcified portion (mixed C>NC), mixed plaque with predominant non calcified portion (mixed NC>C) and non-calcified plaque. The current study showed that non calcified lesions were more prevalent at the unstable patient group compared to the stable group (p=<0.001). Controversly, calcified lesions were more prevalent at the stable plaque compared to unstable plaque (p=<0.001). These findings are matched with aforementioned study reporting that increasing non calcified component in patients who had experienced Major Adverse Cardiac Event (MACE).

Thirdly, characterization of the calcified lesions had the advantage of assessment of post contrast calcium volume (after manual adjusted contour editing) which showed strong good correlation with pre contrast calcium volume of traditional calcium score as reference (r_s=0.97). These findings are disagreed by Muhlenbruch et al., **[13]** stating failed attempt to separate intracoronary contrast from intramural calcium on using 16 row multislice computed tomography with detection threshold of 130HU.

Later on, study done by Glondy et al., **[14]** revealed very high correlation with agatston and volume score. However, unablility to adequately measure lower density coronary calcium that is often present in person with lower coronary calcium score on using 64 multidetector CT with detection threshold 160HU.

On the other hand, our study revealed strong perfect correlation between pre contrast calcium volume by agatston score and post contrast calcium volume by quantitative analysis on using 320 multidetector CT with detection threshold 150 which is closely matched with study done by Otten et al., **[15]**, reporting that calcium score estimation of enhanced CT compared with coronary artery calcium quantification that used agatston method performed well with high accuracy and reliability (R^2=0.99). Furthermore, Saremi et al., **[16]** suggested good agreement of 150HU threshold for calcium detection as compared to intravascular ultrasound.

So, characterization of calcified lesions by post contrast semi automated quantitative coronary plaque analysis allowed accurate delineation of the remaining patent lumen. Hence, accurate detection of degree of stenosis (p=<0.001).

At the same time, characterization of non-calcified lesions by semi-automated quantitative coronary plaque analysis provided the chance to assess association between quantitative analysis and qualitative high risk plaque features which is concordant with recently published study encountered by Liu et al. **[17]**, they assumed that quantitative analysis could predict high risk plaque features.

We identified high risk plaque criteria as R.I >1.1 (OR 14.78 and 95% C.I 9.66-354.31) and Plaque burden >0.7 (OR 14.78 and 95% C.I 5.83-

37.48) NRS (OR 11.870 and 95% C.I 2.65-53.08) and LAP <60 (OR 6.015 and 95% C.I 2.56-14.12).

As regard plaque burden, there was significant difference between two patient groups which is superior to degree of stenosis (p=0.004) which is matched with study encountered by Nakazato et al. [18], they assumed that aggregate plaque volume which represent plaque burden improve identification of ischemic lesion.

Controversly, the degree of stenosis was insignificant between two patient groups (p=0.141) which is agreed with Yang et al. [19], they stated that there was no significant difference between stable and unstable groups concerning degree of stenosis.

The current study revealed higher plaque burden for unstable patient group with proposed cutoff value >0.7 to detect unstable cases (AUC=0.78 and p=0.005) this cutoff value is in line with study established by Conte et al., [20] reporting that positively remodeled non calcified lesion with plaque burden >0.7 was significantly associated with occurrence of all cardiac events (HR 2.40, p =0.03).

As regard Low Attenuation Plaque (LAP), we observed an increasing cumulative number of plaques with increasing CT density indicating more stable fibrous plaque in stable patient group. As well, the relative percentage of LAP frequency was low in stable patient group. Differently, the cumulative CT number is significantly lower than that of the stable one (by quantitative analysis 23.8 ±22.7 and by area ROI (region of interest) 35.12 ±22.7). Those findings are matched with study established by Feuchtner et al., [12] assuming that low attenuation plaques were usually associated with major adverse cardiac event.

We proposed cutoff value for LAP <60 as optimal threshold to detect unstable cases, AUC was 0.796, (p=0.004) and 60 HU (sensitivity 80.5%, specificity 86.3%) which is closely in line with the aforementioned same study. They proposed cutoff 63HU as optimal threshold, AUC was 0.89 (p=<0.001) and 63HU (sensitivity 89.2%, specificity 82.3%).

In different circumstances, a prospective midterm outcome study done by Motoyama et al., [21]. The study was encountered on larger sample size and defined high risk plaque based on LAP <30 as an independent predictor of major adverse cardiac event. The criterion LAP <30 had very low prevalence in unstable patient group. Additionally, the criterion LAP <30 is based on only culprit lesion analysis that caused acute coronary syndrome, thus thrombotic apposition on the studied lesion that is characterized by lower CT densities. This may explain why LAP <60 performed better in our study where all lesions are studied.

In vivo studies utilizing optical coherence tomography as standard reference demonstrated that high risk plaques have lower CT numbers as compared to stable lesions (35-45 vs. 62-79HU; p= <0.001) [21].

As regard Remodeling Index (R.I), R.I was higher in unstable patient group but not significant (p=0.08 and 0.39 at R.I >1.1 and 1.4 respectively) due to high prevalence of calcified and mixed plaques with predominate calcified portion that were usually associated with positive remodeling. Those findings are agreed with what was suggested by Feuchtner et al., [12], they stated that Remodeling Index (R.I) was higher in patients who had experienced major adverse cardiac events but no significant predictive due to inclusion of calcified nodules which appear larger on CTA (positively remodeled).

Subgrouping positively remodeled lesions based on plaque types revealed that positive remodeling was more prevalent at the calcified lesions and mixed plaque with predominant calcified portion at the stable patient group. On the other way, it was more prevalent not only at non calcified and mixed plaques with predominant non calcified portion but also at low attenuation plaque. So, we found significance on measuring R.I in non-calcified lesions. We suggested cutoff value >1.1 to detect unstable patient group, AUC was 0.885 (p=>0.001) and R.I >1.1 (sensitivity 79.03, specificity 91). These findings are nearly in line with study done by Motoyama et al., [22], they identified R.I as high risk plaque feature (sensitivity=87, specificity=88).

As regard Napkin Ring Sign (NRS), our study revealed that NRS has excellent specificity to detect unstable cases (95.4%) which is matched with Liu et al., [18], they stated that NRS had the best specificity to identify advanced lesions (98.9%, C.I 97.6-100%). Notably, its low prevalence limits its sensitivity which is in line with study done by Feuchtner et al., [12], they stated low prevalence of napkin ring sign in patient with major adverse cardiac event.

Napkin ring sign is caused by difference in CT attenuation between its lipid rich core corresponding to central low attenuation area and fibrous

plaque corresponding to rim of high CT attenuation which is matched with study done by Horvat et al., [23], they stated that the average CT number of the hypo dense core approximately 50-60HU and higher CT number of the outer rim representing significant amount of fibrous tissue. We set higher threshold for the outer rim (<150) while lower CT number for inner core (<60); the outer rim may contain dense fibrous tissue and micro calcification which may lead higher HU than 130 [24].

Seifarth et al., [24] investigated the histological correlate of the napkin ring sign and concluded the detection of this specific plaque attenuation linked to lipid core, the size of the plaque and the vessel area as measured in histology.

As regard Spotty Calcification (SC) criterion, it was prevalent only at the unstable patient group which hinders assessment of its risk despite being statistically significant (p=0.001).

Up till now, high risk plaques criteria are still point of research with no standardization or verification. However, intensification of preventive measures is recommended in patients with high risk criteria. Statins have proven beneficial effect in reducing mortality even in reducing mortality even in patients with non-obstructive CAD on CTA, related to stabilizing effect on lipid rich fibroatheroma by increasing dense fibro calcified Plaque component [25,26]. On the other hand, stenting of non emptive lesion due to high risk plaque features haven't been studied yet.

Study limitations:

- The Lack of intravascular ultrasound as reference to assess plaque morphology could be considered a limitation, although previous studies have shown strong correlation between mulislice CT and Intravascular Ultrasound (IVUS) measurements of the composition of coronary atherosclerotic plaques.
- Another drawback of this study is the fact that the patient population of both patient groups was still rather small.
- Previous studies have assessed association between both quantitative and qualitative features of coronary plaques as detected by coronary CTA in comparison with Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT) and histology. The direct comparison between qualitative and quantitative assessment and added value of quantitative assessment of coronary atherosclerotic plaques hasn't been studied. So, larger clinical research trials may be needed to investigate the clinical utility of such quantitative measurements.

Conclusion:

320 slice coronary CT angiography is a reliable tool with high accuracy for detection of stenosis severity. Furthermore, characterization of coronary plaques by quantitative coronary plaque analysis improved image quality for calcified plaques and correlate well with high risk plaque detection which may improve cardiovascular risk stratification. High risk plaque features are NRS, LAP <60, positively remodeld non calcified plaque with R.I >1.1 and P.B >0.7. Among high risk plaque features, NRS and LAP <60 are the most powerful detectors of high risk plaques suggesting their integration into coronary risk stratification, as well as an intensification of individual preventive measures.

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تقييم التكوين الكمى لتصلب الشرايين التاجية وخصائصها بواسطة الآشعة المقطعية متعددة المقاطع للمرضى الذين يعانون من تصلب الشرايين التاجية

فى العقود الآخيرة، أصبحت تصوير الآوعية المقطعية التاجية متعددة الشرائح إحدى النقاط الهامة فى تكنولوجيا تصوير القلب والآوعية الدموية. وقد تم تطبيق هذه الطريقة لتقييم تضيق الشرايين التاجية كإجراء بديل محتمل للقسطرة التشخيصية.

فى الآونة الآخيرة، لا تسمح ماسحات التصوير المقطعى بالآشعة المقطعية الحديثة بالتصوير التجويفى للشرايين التاجية فقط مثل القسطرة التشخيصية، ولكن أيضاً جدار الوعاء الدموى، مما يمنح تحليلاً غير جراحى لتصلب الشرايين نفسه. تتيح جودة الصورة الممتازة للآشعة المقطعية الحديثة تحديداً كمياً لجدار الشريان التاجى وتوصيفها والتى تفتح طرقاً جديدة لتحديد القابلية للإصابة بمتلازمة الشريان التاجى الحاد.

فى هذه الدراسة تم فحص ستين مريضاً: ثمان وثلاثون ذكراً وإثنتى وعشرون أنثى قد تراوحت أعمارهم بين ست وعشرون وسبعون عاماً بمتوسط ثلاث وخمسون عاماً.

تصوير الشرايين التاجية بواسطة الآشعة المقطعية متعددة المقاطع يعد أداة موثوقة مع دقة عالية للكشف عن درجة ضيق الشريان التاجى. علاوة على ذلك، فإن توصيف التكوين المسئول عن تصلب الشريان التاجى بتالتقييم الكمى نصف الآلى أدى إلى تحسين جودة الصورة للتكوبن المتكلس وتحديد المؤشرات عالية الخطورة للتكوين الغير متكلس مما قد يحسن من تقييم مرضى تصلب الشرايين التاجية وتحديد قابليتهم للإصابة بمتلازمة الشريان التاجى الحاد.