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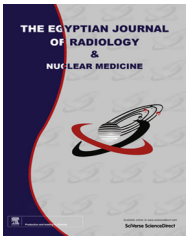

REVIEW

Positive remodeling index by MSCT coronary angiography: A prognostic factor for early detection of plaque rupture and vulnerability

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KEYWORDS

Remodeling index (RI);
Coronary artery disease (CAD);
Left anterior descending (LAD);
Right coronary artery (RCA);
Left circumflex artery (LCX)

Abstract *Purpose:* To emphasis the role of MSCT utilizing the remodeling index in assessment of positive coronary remodeling which was associated with plaque rupture and vulnerability.
Methods and material: Studied group included 35 patients with positive coronary remodeling. One lesion per patient was assessed, either a solitary lesion or the most significant one. All patients were subjected to history taking and radiological evaluation using a contrast-enhanced 64 MSCT then post processed. Assessment of the plaque causing positive remodeling regarding the site, number (single, kissing, or multiple), relative composition and predominant type in H.U. was performed. Specific measurements at the reference and remodeling segment were taken. Calculation of remodeling index was done. Two comparative groups were made between subjects with remodeling index (RI) < 1.5 and RI $\geqslant 1.5$.
Results: A strong correlation was noted between lipid plaque area, plaque cross sectional area and multiplicity of plaques with remodeling index (p value < 0.001). There was no correlation between the RI with either the patient coronary risk factors or symptomatology.
Conclusion: Previous studies had shown that most acute coronary syndromes were initiated by sudden changes of mildly stenotic lesions, commonly found in positively remodeled vessels. Promising comparative results between MSCT and IVUS allowed consideration of MDCT as a useful tool in the noninvasive detection of potentially threatening coronary lesions. In our study, RI $\geqslant 1.5$ showed a strong correlation between the lipid plaque area, multiplicity of the plaques, and cross sectional area which were prognostic factors for plaque rupture and vulnerability, and thus, early detection of coronary artery disease. Modulation and prevention of positive remodeling by statin

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could promote to start medical treatment especially in cases where RI exceeds 1.5 and their follow up non-invasively by MDCT to detect reversal of remodeling and response of treatment.

Contents

1. Introduction

The change of cross-sectional vessel size that occurred during the growth of atherosclerotic lesions was referred to as remodeling (1). Atherosclerosis was a systemic disease with multifocal heterogeneous manifestations. Because multiple plaques at different stages of progression and variable morphology could coexist within the same patient or even artery, characterizing and risk-stratifying each individual plaque in vivo would be invaluable. Increasing attention had been focused on the in vivo identification of high-risk plaques most likely to rupture and cause an acute coronary event (2). Coronary arterial remodeling described changes of vessel size at the site of atherosclerotic lesions. Positive remodeling (expansion) of early lesions maintained lumen size despite plaque accumulation. In contrast, negative remodeling (shrinkage) contributed to luminal stenosis independent of plaque accumulation (3). It was also well established that plaques with high lipid content were more vulnerable to rupture. Coronary artery plaques that underwent positive remodeling had a significantly larger lipid core and a higher macrophage count than did those that underwent vessel shrinkage. Therefore, these findings explained the basis of plaque vulnerability at sites of excessive vessel remodeling and suggested a possible explanation for the apparent paradox of positive remodeling, which might be both beneficial (avoiding luminal stenosis) and harmful (promoting plaque vulnerability) (4). The plaque composition was potentially relevant, provided the histological features known to distinguish high-risk atherosclerotic plaques, such as their large lipid core. Importantly, these lesions did not necessarily present with significant obstruction to flow, but with eccentrically positive remodeling that enlarged the whole diameter of the vessel. This explained why these lesions might pass undetected by conventional angiography, while their adequate invasive assessment required IVUS studies (5).

The aim of this study was to emphasize the role of MSCT in evaluation of coronary artery remodeling being a risk factor for plaque vulnerability and rupture (see Figs. 1,2,3 and 4)

2. Material and methods

2.1. Study population

Over a period of 8 months, from December 2012 till July 2013, MDCT coronary angiography study was performed for 35 patients (20 male and 15 females). Their mean age was 55 ± 8.6 years ranging from 39 to 70 years old while the interquartile range was 49–62 years old. The prevalence of the patients that had cardiovascular symptoms with or without coronary risk factors was 25 cases (71.4%), including chest pain, palpitation or ECG abnormalities, while the asymptomatic subjects came for check up but having identifiable coronary risk factors were 10 cases (28.8%). Cases were analyzed in a specialized private center in Cairo. The study was performed after approval of the Ethics committee of scientific Research, faculty of medicine, Ain Shams University. All patients were requested to do MSCT coronary angiography by their physicians.

2.2. MSCT protocol

The study was performed at 64 multislice CT (Toshiba) for all 35 cases. Reassurance of the patient from the entrance to the scanning room was performed, including an appropriate knowledge of the whole process. A history of hypersensitivity to iodinated contrast media must be ruled out. Previous acute or chronic renal failure had to be considered. A stable venous line should be available, this requiring an 18-to-20 gauge needle placed into an antecubital vein. The preparation for

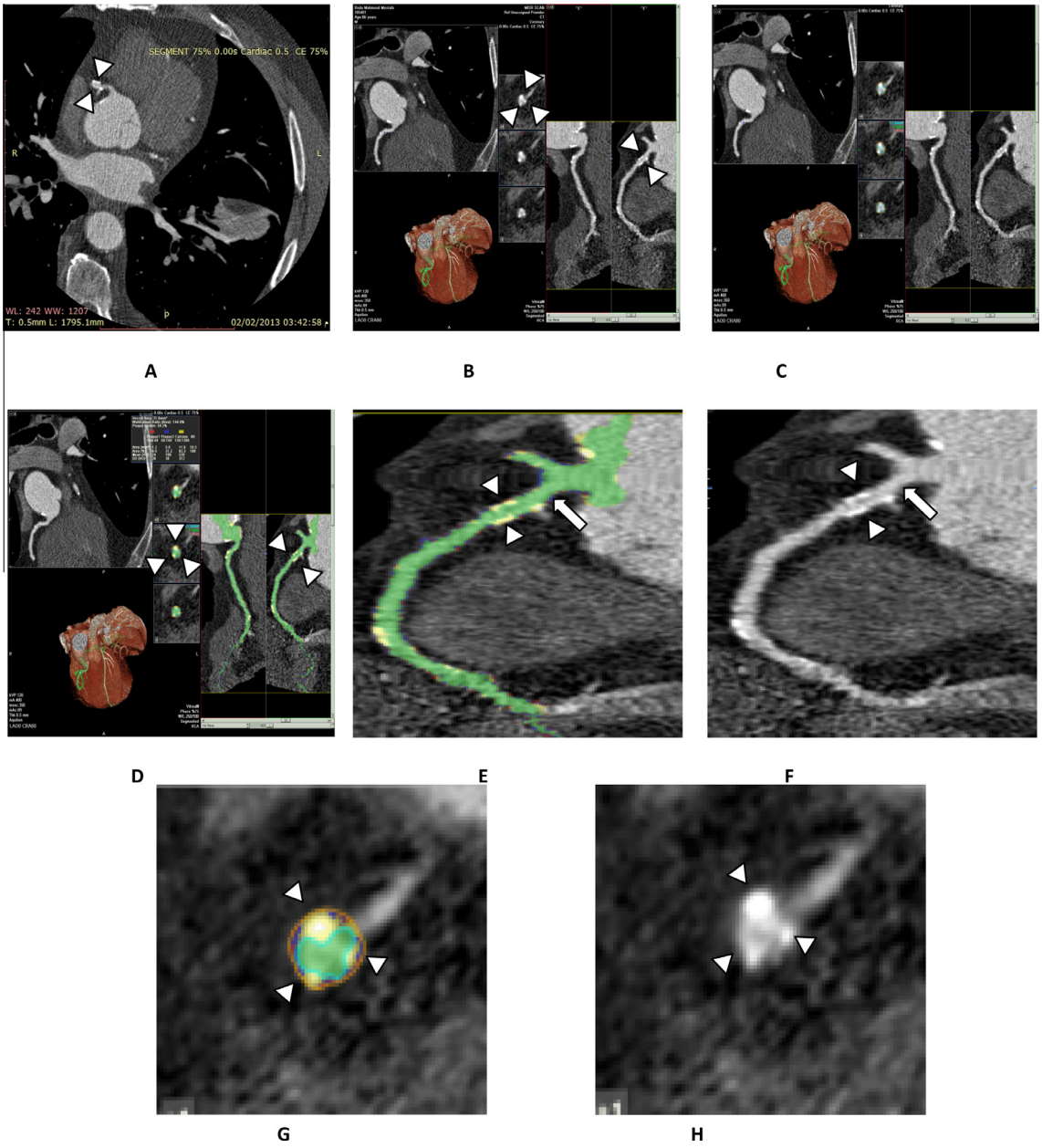

Fig. 1 Female patient, 66 years old, with history of controlled hyperlipidemia, came for evaluation of dyspnea. (A) Contrast-enhanced 64 multi-detector rows cross sectional CT image: average caliber dominant RCA is seen normally arising from right coronary sinus giving PDA and PL branches. There are eccentric multiple small predominantly calcific component plaques (white arrowhead) at proximal portion of RCA causing no significant stenosis, the largest measures 2.9 mm in length and 2.6 mm in width. (B and C) Curved multiplanar reformation images of right coronary artery (RCA) show multiple eccentric predominantly calcific plaques causing positive remodeling (white arrowhead). (D) Colored MPR shows positive remodeling at proximal portion of RCA (white arrowhead) (E and F) magnified colored and gray scaled MPR image shows + ve remodeling (as shown by white arrowhead) while the calcified plaques are yellow colored at E. Note the reference segment is free of plaques (white arrow). (G&H) Colored and grey scaled magnified MPR cross sectional images at the site of positive remodeling show the same findings (white arrowhead). The calculated remodeling index = 1.32.

the study must include a pre-exam testing of the ability of the patient for sustaining a breath-hold long enough for the purposes of the examination. All patients received beta-blocking agents (metoprolol 50–100 mg) to decrease heart rate to about 65–70 beat per minute.

Patients were placed within the gantry of the CT scanner in the supine position. According to the expected location of the coronary arteries obtained from the AP and lateral scout images, a preliminary scan without contrast injection was performed to determine the total calcium burden (calcium score) of the coronary tree; followed by ECG gated acquisition for coronary angiography with contrast material injected via a pump with total volume about 65–75 cc/patient. In all cases, the administration of the contrast was performed at a rate of 4–5 cc/s in order to more reliably enhance the vascular bed.

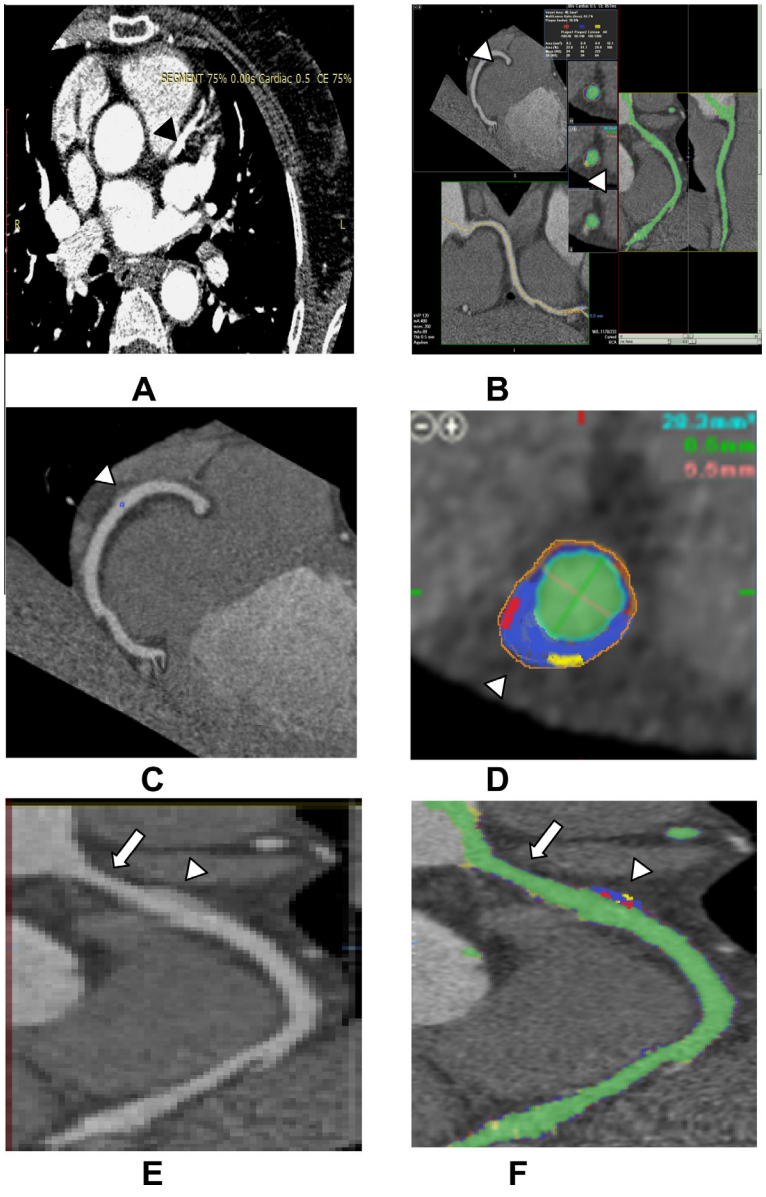

Fig. 2 A male patient, 40 years old, with history of controlled hypertension, came for check up examination with no cardiac symptoms. (A) Contrast-enhanced 64 multi-detector row cross sectional CT image: average caliber of LAD is seen arising from LM demonstrating an eccentric mixed plaque, predominantly of soft tissue component at its mid portion causing no significant stenosis. The plaque measures 5.7 mm in length and 1.4 mm in width (black arrowhead). (B) Curved multiplanar reformation images of left anterior descending artery (LAD) show a single eccentric predominantly soft tissue plaque having foci of calcification causing positive remodeling (as shown by white arrowhead). Note the lumen is patent with no plaque encroachment upon the lumen. (C) Magnified MPR image shows the +ve remodeling as shown by white arrowhead. (D) A colored cross-sectional image at site of positive remodeling (white arrowhead) showing the medium attenuation plaque (blue colored), and foci of calcium (yellow colored) and scanty lipid (red colored). (E&F) colored and grey scaled magnified MPR showing the same findings. Note the reference segment is free of plaques (white arrow). The calculated remodeling index = 1.22.

3. Data processing for MSCT

3.1. Post processing

The acquired images were transferred to off-line workstations (extended work space "EWS"); (Toshiba Vitrea Medical Systems and Philips Medical Systems). The most expansive atherosclerotic lesion in the original MDCT data sets was identified; serial multiplanar reconstructions (slice thickness 1 mm) were rendered in an orientation perpendicular to the longitudinal axis of the respective coronary artery segment. The cross-sectional vessel area was determined in a reference segment without detectable plaque proximal to and as close as possible to the respective coronary lesion (in absence of a segment

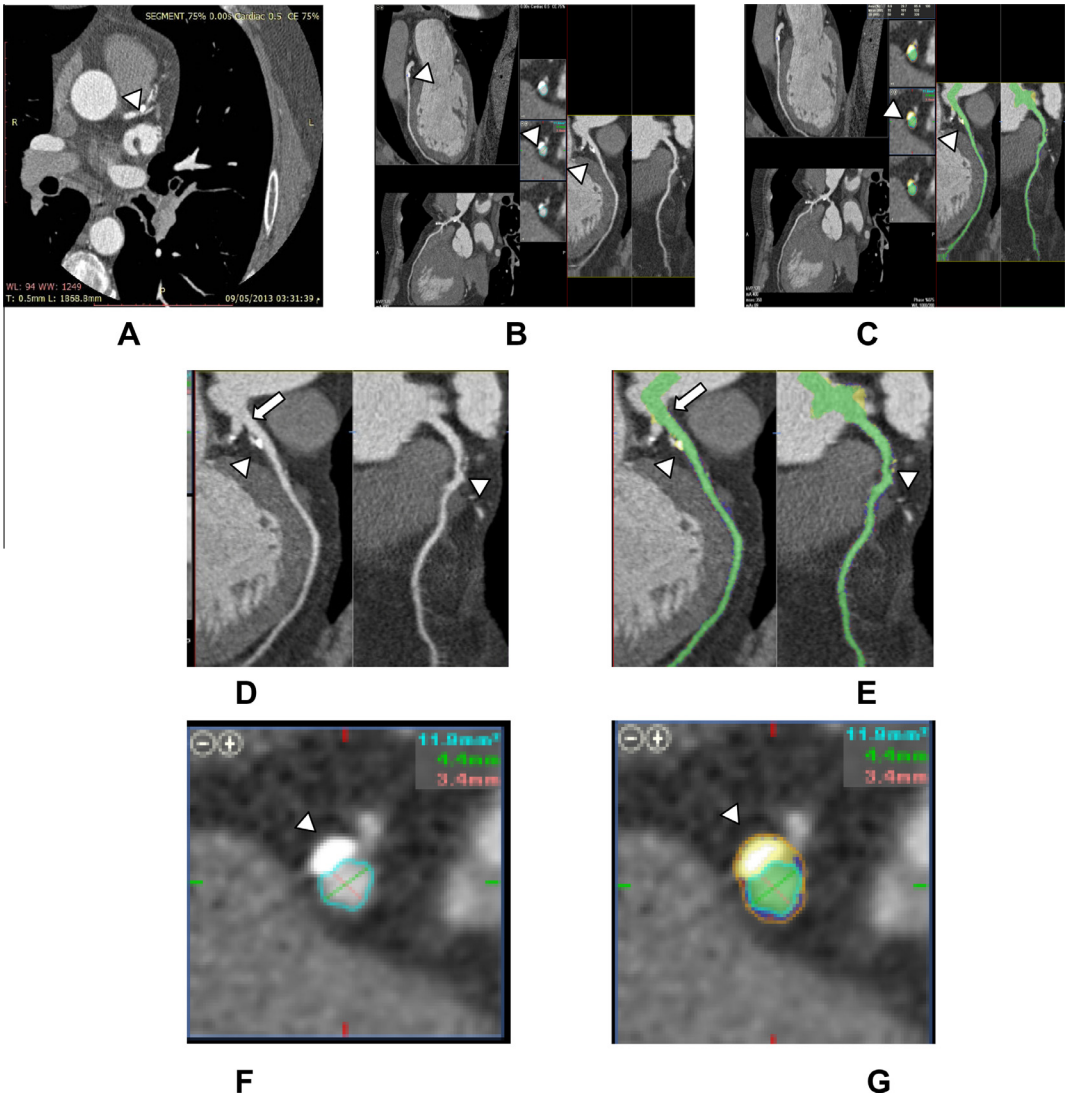

Fig. 3 A male patient, 58 years old, with controlled diabetes, came for check up for atypical chest pain. (A) Contrast-enhanced 64 multi-detector row cross sectional CT image: average caliber LAD is seen arising from LM demonstrating an eccentric mixed plaque, predominantly of calcific component at its mid portion causing no significant stenosis. The plaque measures 5.7 mm in length and 1.4 mm in width (white arrowhead). (B&C) Grey scale and colored curved MPR images respectively of left anterior descending artery (LAD) show a single eccentric predominantly calcific plaque causing positive remodeling (as shown by white arrowhead). Note the lumen is patent with no plaque encroachment upon the lumen. (D&E) Magnified MPR image grey scale and colored images respectively shows the +ve remodeling as shown by white arrowhead. The calcified component is yellow colored while the scanty soft tissue component is blue colored. Note the reference segment is free of plaques (white arrow). (F and G) A colored cross-sectional image at site of positive remodeling (white arrowhead) showing the calcified component of the plaque (yellow colored). The calculated remodeling index = 1.72.

without plaque, the least diseased segment between the lesion and the coronary ostium or major bifurcations), and several measurements were acquired including the lumen area, vessel wall surface area, wall thickness, as well as wall percent area (wall thickness/vessel surface area) and wall/lumen percentage. Also, these measurements were repeated at the site of maximum arterial remodeling and compared with the reference segment measurements. Each plaque was analyzed separately and the relative component (low attenuation, medium attenuation, calcific components), was measured by both surface area and area percentage. The average mean density of the plaque was measured.

3.2. Statistical methods

Data were analyzed on a personal computer using the IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 12.5 (MedCalc© Software bvba, Ostend, Belgium). The Shapiro–Wilk test was used to test the normality of numerical data distribution. Numerical data were presented as median and interquartile range, and the Mann–Whitney test is used to compare between-group differences. Nominal data were presented as number and percentage, and differences between groups were compared using Fisher's exact test.

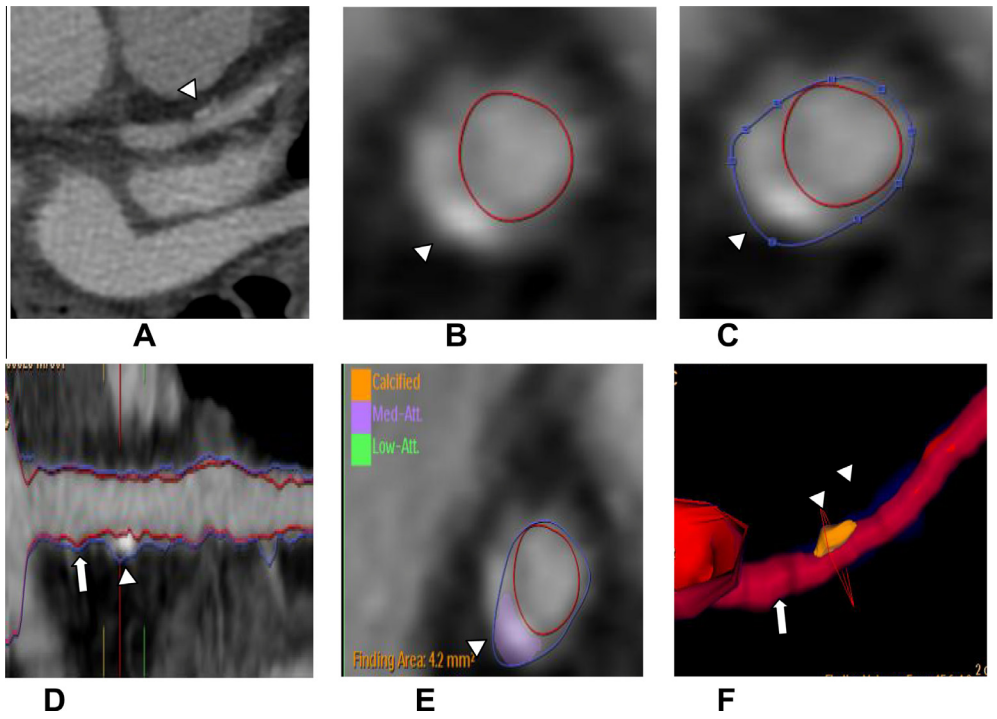

Fig. 4 Male patient, 62 years old, has history of controlled hyperlipidemia, with past history of primary stent of RCA, came for check up, the stent was patent. (A) Contrast-enhanced 64 multi-detector row CT cross sectional image: show site of positive remodeling with a mixed plaque of predominantly soft tissue component at mid portion of LAD measuring 5.7 × 2.6 mm, there was no luminal narrowing or stenosis as shown by white arrowhead. (B and C) Cross-sectional image at site of positive remodeling showing a predominantly soft tissue plaque at mid portion of LAD. Note the delineation of the lumen area in (B) in red line and delineation of the lumen (red line) and the whole vessel surface area (blue line) in (C) making the plaque causing positive remodeling more obvious (white arrowhead). (D) Curved MPR shows the eccentric predominantly soft tissue plaque with a small calcific component causing positive remodeling (white arrowhead) with no luminal narrowing. Note the reference segment is free of plaques (white arrow). (E) A colored cross sectional image at the site of remodeling shows the main plaque component which was soft tissue as violet colored (white arrowhead). (F) Colored volume rendered image shows the plaque causing positive remodeling with tagging the main soft tissue component as blue colored and the small calcific component as orange colored (white arrowhead). Note the reference segment is free of plaques (white arrow). The calculated remodeling index in this case = 1.86.

Correlations among normally distributed numerical variables were examined parametrically using the Pearson product moment correlation. For non-normally distributed variables, correlations were examined non-parametrically using the Spearman rank correlation. The value of numerical variables for discrimination between binary attributes was tested with receiver-operating (ROC) curve analysis and estimation of the area under the ROC curve (AUC). Two-sided p values < 0.05 were considered statistically significant.

4. Results

The study was performed on thirty-five patients, their mean age was 55 ± 8.6 years ranging from 39 to 70 years while the interquartile range was 49–62 years, twenty were male and fifteen patients were female, 14 patients (40%) were hypertensive, 15 patients (42.9%) were diabetic, 25 patients (71.4%) were smokers, 3 patients (8.6%) had obesity, 8 patients (22.9%) had hyperlipidemia, 11 patients (11.4%) had previous PCI, 9 patients (25.7%) had positive family history of CAD (Table 1). 18 patients had two or more coronary risk factors. 10 patients had a single coronary risk factor. 7 patients had no coronary risk factors.

The prevalence of the patients having cardiovascular symptoms with or without coronary risk factors was 25 cases (71.4%), including chest pain, palpitation or ECG abnormalities, while the asymptomatic subjects came for check up but had identifiable coronary risk factors were 10 cases (28.8%).

The resultant remodeling index was ranging from 1.07 to 1.98 with mean 1.36 + 0.22 while the interquartile range was 1.24–1.49. As 50% of the patients were in the interquartile range, the value of 1.5 represents the 75th percentile. So, two comparative groups were made, depending on the remodeling index value dividing all cases into who were below 1.5 (25 cases) and who were above 1.5.

In our study, there were 4 plaques (11.4%) in LM artery, 17 plaques (48.6%) in LAD, 3 plaques (8.6%) in LCX, 11 plaques (31.4%) in RCA. The distribution of the study cases regarding the site of predilection was 2 plaques at the ostium, 15 plaques at the proximal region, 13 plaques at mid region, and 5 plaques at distal region (Table 2). There was no correlation between the RI ⩾ 1.5 and predilection for certain blood vessels or a specific area of the blood vessel.

Table 1 Comparison between subjects with remodeling index < 1.5 (< 75th percentile) and those with remodeling index ⩾ 1.5 (⩾75th percentile): patient characteristics and risk factors.

Variable		Remodeling index < 1.5 (< 75th percentile, n = 27)	Remodeling index ⩾ 1.5 (⩾75th percentile, n = 8)	p value
Gender				
Female	N	11	4	0.700
	%	40.7%	50.0%	
Male	N	16	4	
	%	59.3%	50.0%	
Smoking status				
Non-smoker	N	20	5	0.626
	%	74.1%	62.5%	
Ex-smoker	N	2	0	
	%	7.4%	0.0%	
Current smoker	N	5	3	
	%	18.5%	37.5%	
Risk factors for CAD				
Obesity	N	3	0	1.0
	%	11.1%	0.0%	
Hypertension	N	11	3	1.0
	%	40.7%	37.5%	
Hyperlipidemia	N	6	2	1.0
	%	22.2%	25.0%	
Diabetes	N	10	5	0.246
	%	37.0%	62.5%	
Family history of CAD	N	6	3	0.396
	%	22.2%	37.5%	

The mean plaque density was calculated with mean density of 352.6 + 210.4 while the range was from 34H.U. up to 848H.U. The predominant type of the plaques were 2 plaques of low attenuation, 4 plaques of medium attenuation, 16 calcific plaques, 13 mixed plaques. As regards the number of the plaques at the focused lesion, it was found the plaque was a single component in 29 cases, kissing (2 components) in 4 cases, and multiple components in 2 cases. There was a strong correlation between the multiplicity of the plaque and the RI ⩾ 1.5 with p value = 0.016 (Table 3). However, no correlation was found between RI ⩾ 1.5 and the predominant type of the plaque.

The median of lipid plaque area in the patients with RI < 1.5 was 0.3 with the interquartile range 0.2–0.9 mm^2 when compared to those patients with RI ⩾ 1.5, the median was 1.5 with the interquartile range 0.6–2.8 mm^2, there was a strong correlation between RI and Lipid plaque area (mm^2) with p value = 0.004.

The median of cross sectional area of the plaque in the patients with RI < 1.5 was 5.7 with the interquartile range 4–7.8 mm^2 when compared to those patients with RI ⩾ 1.5, the median was 9.1 with the interquartile range 7.7–17 mm^2, there was a strong correlation between RI and the cross sectional area (mm^2) with p value = 0.001 (Tables 3 and 4).

There was a significant correlation between the high remodeling index ⩾ 1.5 and the increased any of the plaque compositions of either lipid plaque area, soft plaque area, or calcium plaque area with p value < 0.001 (Table 5).

There was no significant correlation between the coronary risk factors, the patient gender and the RI ⩾ 1.5 as shown in Table 1. Also, no correlation was found between the patient symptomatology and remodeling index (Table 2).

It was found by using Receiver-operating characteristic (ROC) curve analysis for the value of the remodeling index that the remodeling index could not be used as tool for discrimination between symptomatic and asymptomatic subjects.

5. Discussion

Coronary artery wall remodeling (CAR) had recently been recognized as an important feature of atherosclerosis development (6). Coronary artery disease (CAD) was currently defined as clinically significant when luminal narrowing was present, typically at the 50% diameter reduction threshold. However in early atherosclerosis, the first arterial changes consisted of compensatory enlargement of both the outer wall of the vessel as well as the lumen, termed compensatory enlargement or positive remodeling. Evidence from histopathologic and clinical studies suggested that positive remodeling was associated with plaque vulnerability and plaque rupture. As coronary artery wall thickness increased, the overall vessel size (outer contour area) increased at a greater rate than the change in the lumen area. This indicated the coronary vessel size enlarged to compensate for atherosclerotic change, i.e., positive remodeling (7).

Surmely et al. (8), confirmed that positive coronary arterial remodeling predominantly occurred in plaques of patients with acute coronary syndromes, the observation was made in a larger series of patients by using virtual histology – intravascular ultrasound. In a series of 85 patients, 25% of patients with negative remodeling by IVUS presented with acute coronary syndrome compared with 52% of patients whose plaque had evidence of positive remodeling.

Table 2 Comparison between subjects with remodeling index < 1.5 (< 75th percentile) and those with remodeling index ⩾ 1.5 (⩾ 75th percentile): principal findings on MSCT.

Variable			Remodeling index < 1.5 (< 75th percentile, $n = 27$)	Remodeling index ⩾ 1.5 (⩾ 75th percentile, $n = 8$)	p value
Principal vessel involved by remodeling	LMA	N	4	0	0.223
		%	14.8%	0.0%	
	LAD	N	13	4	
		%	48.1%	50.0%	
	LCX	N	1	2	
		%	3.7%	25.0%	
	RCA	N	9	2	
		%	33.3%	25.0%	
Site of principal plaque	Osteal	N	2	0	0.218
		%	7.4%	0.0%	
	Proximal	N	9	6	
		%	33.3%	75.0%	
	Mid-lesion	N	11	2	
		%	40.7%	25.0%	
	Distal	N	5	0	
		%	18.5%	0.0%	
Multiplicity of plaques	Single	N	25	4	0.016
		%	92.6%	50.0%	
	Kissing	N	1	3	
		%	3.7%	37.5%	
	Multiple	N	1	1	
		%	3.7%	12.5%	
Predominant type of plaque	Low-attenuation	N	1	1	0.389
		%	3.7%	12.5%	
	Medium-attenuation	N	3	1	
		%	11.1%	12.5%	
	Calcific	N	14	2	
		%	51.9%	25.0%	
	Mixed	N	9	4	
		%	33.3%	50.0%	

Table 3 Comparison between subjects with remodeling index < 1.5 and those with remodeling index ⩾ 1.5: numerical variables.

	Remodeling index < 1.5 (< 75th percentile, $n = 27$)			Remodeling index ⩾ 1.5 (⩾ 75th percentile, $n = 8$)			
Variable	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile	p value
Age (y)	55.0	49.0	62.0	57.0	47.0	58.8	0.937
Lipid plaque area (mm^2)	0.3	0.2	0.9	1.5	0.6	2.8	0.004
Lipid plaque area percentage (%)	6.7	3.5	12.6	13.5	5.7	22.1	0.080
Soft plaque area (mm^2)	2.0	1.0	3.6	3.9	2.2	7.5	0.052
Soft plaque area percentage (%)	34.0	24.0	50.7	41.4	24.9	43.6	0.860
Calcium plaque area (mm^2)	2.6	1.5	4.1	6.3	1.4	8.4	0.121
Calcium plaque area percentage (%)	56.5	43.7	67.1	45.7	20.0	54.5	0.195
Plaque cross-sectional area (mm^2)	5.7	4.0	7.8	9.1	7.7	17.0	0.001
Mean plaque density (HU)	340.0	187.0	478.0	227.0	146.5	673.3	0.504

Miao et al. (7), studied noninvasively the positive coronary wall remodeling in asymptomatic individuals with no history of CAD as well as the relationship between coronary calcification and arterial wall thickness by black-blood coronary MRI. Positive remodeling was present in the coronary arteries of both men and women. Mean coronary wall thickness was assessed by MRI as a measure of atherosclerosis, and the lumen area on average showed a slight increase as wall thickness increased. However the predominant change in the vessel size was a more substantial increase in the outer contour area of the vessel wall, these relationships persisted after adjusting for body size or heart size.

In an interesting article by Burke et al. (9), coronary segments ($n = 2885$) were harvested from the hearts of 36 patients who died of severe coronary artery disease and remodeling was determined by morphometric analysis of 657 sections selected as reference segments and 1318 segments with atheromatous plaques. There was no significant difference in remodeling in age > 65 or < 65, although in men there was more remodeling in the older group. In the present study, the two comparative

Table 4 Comparison between subjects with remodeling index < 1.5 (< 75th percentile) and those with remodeling index ⩾ 1.5 (⩾75th percentile): indication for MSCT and symptomatology.

Variable		Remodeling index < 1.5 (< 75th percentile, $n = 27$)	Remodeling index ⩾ 1.5 (⩾75th percentile, $n = 8$)	p value
Indication for MSCT				
Typical chest pain	N	9	4	0.433
	%	33.3%	50.0%	
Atypical chest pain	N	5	3	0.346
	%	18.5%	37.5%	
Dyspnea	N	4	0	0.553
	%	14.8%	0.0%	
Palpitations	N	1	0	1.0
	%	3.7%	0.0%	
Abnormal ECG	N	1	0	1.0
	%	3.7%	0.0%	
Follow-up for Previous PCI	N	2	2	0.218
	%	7.4%	25.0%	
Dilated cardiomyopathy	N	1	0	1.0
	%	3.7%	0.0%	
Patient's request for check-up	N	10	1	0.387
	%	37.0%	12.5%	
Symptomatology				
Chest pain, dyspnea, and/or palpitation	N	18	7	0.390
	%	66.7%	87.5%	
Asymptomatic		9	1	
		33.3%	12.5%	

Table 5 Correlation between the remodeling index and other numerical variables.

	Remodeling index	
	Correlation coefficient	p value
Age	−0.078	0.656
Lipid plaque area	0.644	< 0.0001
Lipid plaque area percentage	0.283	0.100
Soft plaque area	0.655	< 0.0001
Soft plaque area percentage	0.146	0.403
Calcium plaque area	0.652	< 0.0001
Calcium plaque area percentage	−0.252	0.145
Plaque cross sectional area	0.880	< 0.0001
Mean plaque density	−0.078	0.655

groups were between those had remodeling index below 1.5 and those had remodeling index more than 1.5, no correlation was noted between either age or sex with high remodeling index ⩾ 1.5.

Two recent studies had shown an association between positive arterial remodeling and both unstable angina pectoris and acute myocardial infarction. However, what was unclear was by what mechanism the positive arterial remodeling led to unstable syndromes. Cardiovascular risk factors had been suggested as predictive of the degree of arterial remodeling, but with some conflicting results. In one study in patients undergoing percutaneous coronary intervention, there were no plaque characteristics as identified by IVUS that predicted arterial remodeling, nor were any risk factors predictive of negative remodeling apart from smoking, which was associated with negative remodeling. Lipoproteins had been described in relation to arterial remodeling, and HDL level was correlated with positive arterial remodeling in the aforementioned histopathological study. One small IVUS-based study found an association between total cholesterol levels and positive arterial remodeling, although this had not been confirmed by another larger study. Thus, there was no clear association between any cardiovascular risk factors and the degree of arterial remodeling in the literature, patients with stable angina pectoris undergoing percutaneous coronary intervention, were identified to have a positive relationship between arterial remodeling at the culprit site and systemic markers of inflammation (10). In our present study, there was no association between any coronary risk factors and arterial remodeling.

Cardiovascular risk factors like hypertension and hypercholesterolemia were associated with reduced positive or even negative remodeling. Moreover, the total number of classical cardiovascular risk factors was a strong predictor for reduced positive remodeling. In contrast, coronary flow reserve, a measure of shear stress imposed on the vessel wall, positively correlated with compensatory enlargement. Cardiovascular risk factors impaired compensatory arterial enlargement and even predispose to shrinkage of epicardial arteries during the initial stage of atherosclerosis. Reduced positive vascular remodeling might contribute to the clinical manifestation of CAD by facilitating the development of flow-limiting stenosis in patients at risk (11).

Lee et al. (16), had reported that HDL-cholesterol level was negatively correlated with coronary remodeling index, implying that coronary arteries tend to develop a positive remodeling pattern as serum level of HDL-cholesterol decreases. When stratified according to diabetic status of the patients, the negative correlation between HDL-cholesterol and the remodeling index was only observed in nondiabetic patients. It was found

that the diabetic status of the patients might have an impact on the correlation between HDL-cholesterol level and remodeling index, with significant correlation demonstrated only in non-diabetic patients. The remodeling index was not significantly associated with any of the demographic and coronary risk factors named age, gender, ethnicity, hypertension, mean body mass index, diabetes, hyperlipidemia, smoking, family history of coronary artery disease, and previous infarction.

In another study performed by Schmid et al. (12), it was noted that positive remodeling of coronary atherosclerotic lesions correlated to lower CT attenuation of plaque, which had been demonstrated to be associated with lipid-rich plaque. Both characteristics indicated increased risk for plaque rupture and subsequent events and could thus prove useful when the use of CT imaging for the detection of vulnerable plaque. Achenbach et al. (1), reported that The CT information from their study was also similar to the descriptions available from an IVUS study, where in the plaques leading to an acute coronary event subsequently exhibited a large eccentric plaque containing an echolucent zone by IVUS.

In an intravascular ultrasound study on 41 consecutive patients retrospectively selected after screening a 54 patient database having angiographically non-obstructive ($<50\%$) lesions with positive remodeling, it was found that significantly larger lipid core percentages were correlated more with positive remodeling than lesions with no remodeling or negative remodeling(13).

Varnava et al. (4), studied 88 male subjects who died suddenly with coronary artery disease, 108 plaques were studied. The percent remodeling was calculated. Lesions with remodeling $\geqslant 0\%$ were considered to have positive remodeling, and those in which remodeling was $<0\%$ were considered to have negative remodeling. Percent lipid core and macrophage count at the plaque were assessed. Of 108 plaque sites, 64 (59.2%) had undergone no remodeling or positive remodeling, and 44 (40.7%) had negative remodeling (vessel shrinkage). Lesions with positive remodeling, compared with lesions with vessel shrinkage, had a larger lipid core (percent mean lipid core was $39.0 \pm 21.0\%$ versus $22.3 \pm 23.1\%$, respectively; $p < 0.0001$) and a higher macrophage count (mean macrophage count was 15.6 ± 12.3 versus 8.9 ± 11.6, respectively; $p = 0.005$).

Clarkson et al. (1994) studied the left anterior descending coronary artery from 100 humans and 416 monkeys with a histomorphometric study on human right, left anterior descending, and left circumflex arteries. This study showed that, in distal segments, lumen size decreased with plaque area, suggesting that remodeling had occured much less in distal segments than in proximal segments, and the plaque size itself was an important component of luminal compromise in these vessels. In addition, the degree of remodeling, as compared with reference segments, was lesser in distal segments based on plaque area than proximal segments. These data differed from those of Sabate et al. (1999), who, in an ultrasound study, showed that the location of plaque at distal segments was an independent predictor of compensatory enlargement (8). In the present study, no specific predilection could be made between the RI $\geqslant 1.5$ and a certain coronary vessel or a specific location.

The assessment of remodeling by MDCT in coronary atherosclerotic lesions might add additional information about the propensity of a plaque to rupture and cause coronary events. Thus, if MDCT imaging for risk assessment were considered, the ability of MDCT to determine the extent of remodeling in coronary atherosclerotic lesions could be useful. In a subset of 13 patients, IVUS was performed to verify the accuracy of MDCT measurements, and cross-sectional vessel areas measured in MDCT correlated closely to the external elastic membrane area measured in IVUS (1).

Kröner et al. (2011) studied the association between positive remodeling on computed tomography angiogram (CTA) and vulnerable plaque characteristics on virtual histologic intravascular ultrasound (VH IVUS) images. Forty-five patients underwent computed tomographic angiography followed by VH IVUS. On CTA, the remodeling index was determined for each lesion by a blinded observer using quantitative analysis. Positive remodeling was defined based on a remodeling index $\geqslant 1.0$. Percent necrotic core and presence of thin-capped fibroatheroma (TCFA) were used as markers for plaque vulnerability on VH IVUS images. Ninety-nine atherosclerotic plaques were evaluated, of which 37 lesions were identified as having positive remodeling on CTA. Higher levels of plaque vulnerability were identified in lesions with positive remodeling compared to lesions without positive remodeling. Percent necrotic core was significantly higher in lesions with positive remodeling compared to lesions without this characteristic. Furthermore, significantly more TCFA lesions were identified in positively remodeled lesions than in lesions without positive remodeling. In conclusion, lesions with positive remodeling on CTA were associated with increased levels of plaque vulnerability on VH IVUS images including a higher percent necrotic core and a higher prevalence of TCFA. Thus evaluation of remodeling on CTA might provide a valuable marker for plaque vulnerability (14).

Prior studies had indicated that the process of positive remodeling could be prevented and modulated by statin therapy. Schoenhagen et al. (2006), studied the effect of lipid lowering drugs on positive remodeling over 210 patients and their follow up by IVUS. Their results demonstrated that plaque-stabilizing therapy with statin medications was associated with constrictive wall remodeling. In multivariable analyses, the percentage change in plaque area, baseline remodeling ratio, and baseline lesion lumen area, showed a significant, direct relation with the remodeling ratio at follow-up. These findings had important implications for the understanding of plaque stability and remodeling. Together with previous findings describing the association of expansive wall remodeling with lesion inflammation and unstable clinical presentation, their results were consistent with the hypothesis that constrictive remodeling was associated with plaque stabilization. Based on these results, lipid depletion and fibrosis were considered to be related to the concept of plaque regression and stabilization. In clinical IVUS studies, the stabilizing effect of lipid-lowering therapy was primarily reflected in changes of plaque burden. However, standard gray-scale analysis in serial clinical IVUS studies had demonstrated a shift to more fibrotic lesion morphology during lipid-lowering therapy; other studies had suggested that disease regression might in fact be associated with constrictive remodeling. In analogy to the process of vessel wall expansion during plaque progression as described by Glagov et al., vessel constriction during regression has been termed ''reverse remodeling''. There were no significant differences in IVUS measurements between the intensive and moderate treatment group.

The promising results of comparison between MDCT and IVUS allowed consideration of MDCT as a useful tool in the noninvasive detection of potentially threatening coronary artery lesions. The technique still had, however, some limitations in this sense. Although recent equipments offered spatial resolution at the submillimetric level (0.5 mm) which was adequate for a morphological assessment of lesions, it did not permit visualization of important (though very small) structures, such as the fibrous cap of the lesions. The use of Hounsfield unit values as a surrogate method for the identification of plaque components was also limited by the heterogeneous nature of lesions themselves; the attenuation coefficient of thrombotic material into the vessel lumen, for instance, was close to that exhibited by adipose plaques (15).

6. Conclusion

Positive remodeling was associated with plaque vulnerability and plaque rupture. Most acute coronary syndromes were initiated by sudden changes of mildly stenotic lesions, commonly found in positively remodeled arterial regions, rather than from progression of lesions already causing significant luminal narrowing. The identification of mildly stenotic but vulnerable atherosclerotic lesions and the overall plaque burden could provide better markers of coronary risk than measuring of luminal stenosis. There was evolving evidence from basic and clinical research that some of these ubiquitous coronary hotspots are suddenly activated and rupture, causing acute events, whereas others are associated with asymptomatic disease progression. With sufficient image quality, MDCT may permit assessment of remodeling of coronary atherosclerotic lesions.

Manual inspection, in both cross-section and longitudinal reconstruction, was used for defining the remodeling index (lesion diameter/reference diameter). The remodeling index on MSCT was calculated and reported as positive remodeling if more than 1.

The acquisition technique for a proper classification of a lesion had not yet been standardized, and MDCT could only provide a mere indication of the predominant component. The description of an atherosclerotic lesion by MDCT was, in summary, highly informative, as it included its morphological features, degree of remodeling of the vessel wall, RI, presence of calcification, and attenuation properties of the plaque itself, thus constituting an approach to the recognition of its main tissue component.

Although there was no identifiable remodeling index value to discriminate between mildly elevated RI and significant RI in the literature, in our study; the RI value of 1.5 could be suggested as a cut off because it showed a strong correlation between the lipid plaque area, multiplicity of the plaques, and cross sectional area which were prognostic factors of plaque rupture and vulnerability value and thus, could be used as a prognostic indicator of early detection of coronary artery disease and risk stratification.

Modulation and prevention of positive remodeling by statin which was proved by prior studies promotes the physician to start medical treatment in those subjects having positive remodeling, especially $\geqslant 1.5$ and follow up non-invasively by MDCT to detect reversal of remodeling and response of treatment.

In spite of establishing the relationship between the positive remodeling on computed tomography angiogram (CTA) and vulnerable plaque characteristics on virtual histologic intravascular ultrasound (VH-IVUS) images, it would be recommended to perform our study on a large scale to confirm a cut off value of RI as a predictable value of plaque rupture and vulnerability.

7. Study limitations

The small population size was acknowledged as a limitation. Correlation with other modalities such as IVUS + virtual histology and MRI would be beneficial. Also, follow up of the patients to detect acute coronary syndrome was not feasible. Postmortem studies did not have the potential to provide prospective information about the natural history of high risk plaques. Furthermore, it had not yet been clarified which structures of the arterial wall actually contribute to the measurement of cross-sectional vessel areas in MDCT. In spite of the limitations, the results illustrated the method's potential for depicting coronary artery anatomy and pathology and correlations of vessel dimensions and remodeling Indices to IVUS were close. The noninvasive nature of MDCT made it an attractive method for further development, especially when the cost and risk of IVUS were considered.

Conflict of interest

None.

Acknowledgments

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