ORIGINAL RESEARCH PAPER

Cardiology

Independent predictors of coronary artery disease through computed tomography coronary angiography

KEY WORDS: Multidetector computed tomography; Coronary artery disease; Risk factors.

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ABSTRACT

Objective: To investigate the presence coronary artery lesions, atherosclerotic plaque characteristics, coronary artery disease (CAD) extension and coronary artery calcium score in normotensive and hypertensive patients, using computed tomography coronary angiography (CTCA).

Methods and Results: Patients with low and intermediate risk CAD were recruited at the Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil. Hypertensive (HT, n = 305) and normotensive (NT, n = 137) patients, 233 men (52.7%), 30 to 90 years old. CTCA-detected CAD was more prevalent in HT (63.6%) than in NT patients (48.9%, p=0.004). Coronary artery lesions (≥ 3 vessels), significant stenosis (≥ 50%), atherosclerotic significant segments (≥ 50%), calcified plaques were more frequent in HT when compared to NT group (p<0.05). Frequency of low CACS (0) was higher in NT (51.8%) than in HT (32.0%) patients (p=0.02), but no differences were observed in high CACS (≥ 100) between these two groups (p>0.05). Age, male gender and dyslipidemia were independent predictors for coronary significant stenosis, atherosclerotic significant segments, multi vessel involvement, high CACS and calcified plaque (p<0.05). Moreover, these variables and diabetes mellitus are predictors of calcified plaques (p<0.05).

Conclusion: CTCA variables and calcium score are useful tools to evaluate the extent and magnitude of coronary artery lesions, independently of risk factors for CAD.

Introduction

Cardiovascular diseases are major burden to Global health, thus, demanding many economic and technological investments from governments around the world. The joint efforts of different countries have the goal of reducing 25% of the worldwide mortality due to cardiovascular diseases by 2025. In most current programs, special attention is given to patients with risk factors for coronary artery disease (CAD), particularly those with diabetes mellitus, dyslipidemia and systemic arterial hypertension. Special attention is given to patients with multiple risk factors, as well as controling systemic arterial hypertension is indicated as an attempt to improve prognosis in the middle and long term onset of major cardiac events. However, nearly one third of patients included in CAD clinical trials have normal blood pressure, suggesting that systemic artery hypertension is not a crucial factor regarding CAD.[1-2].

The computed tomography coronary angiography (CTCA) is a noninvasive technique that allows the identification of CAD and of subclinical lesions in the coronary arteries, thus improving the diagnosis and risk stratification of patients with suspected CAD [4,5,6,7,8] or established disease, with or without SAH[3] assessed by Framingham score[9], independently of hypertension. In this way, it is very useful to evaluate cardiovascular risk for CAD10 in patients with minimal symptoms.

This study aimed to investigate the presence coronary artery lesions, atherosclerotic plaque characteristics, CAD extension and coronary artery calcium score, in hypertensive and normotensive patients, using CTCA.

METHODS

Study subjects

Patients (n = 442) at low and intermediary risk for CAD according Morise score[11], eligible for CTCA evaluation, were selected randomly at the Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil, from September 2011 to January 2013.

Exclusion criteria were age < 30 years, history of previous myocardial ischemia or myocardial infarction, percutaneous coronary intervention or cardiac surgery, malignant arrhythmia, pregnancy, renal insufficiency and contra-indication to the use of beta-blockers or of iodinated contrast media.

The cardiovascular risk factors considered for this study were gathered from the participants' previous clinical history. Individuals with blood pressure on upper limb, at rest, □ 140x90 mmHg or under anti-hypertensive medication were considered hypertensive[12].

All patients provided written informed consent and the study was approved by the Hospital Ethics Committee (CAAE: 0289.0 .107.000-11)

Computed tomography coronary angiography

CTCA was performed using a 64-row scanner (Aquilion 64™, Toshiba Medical Systems Corporation, Otawara, Japan). Patients were evaluated 1 h before the scheduled time and if heart rate was 65 bpm or higher, 25–100 mg of oral beta-blocker (atenolol) was administered. Sublingual nitrate (5 mg Isosorbide dinitrate) was given 10 min before image acquisition.

The protocol started with a prospective electrocardiogram gated using a 3 mm non-contrast enhanced slices for evaluation of the coronary artery calcium score [13]. Thereafter a retrospective electrocardiogram gated using 0.5 mm contrast enhanced slices was carried out. ECG modulation (65-80% of the cardiac cycle) was used to minimize radiation exposure and voltage of 100 to 120 kV, according to patient's body mass index. Data acquisition images were transferred to a dedicated workstation for coronary artery calcium score and artery analysis.

Coronary artery calcium score was calculated according to the method described by Agatston *et al* [14-15]. Briefly, in each 3 mm thick slices the operator actively sought for areas with attenuation factor ≥ 130 Housfield units (HU), and an area of at least 1 mm^2 was considered as having calcified lesions. The number of the detected lesions represents the overall coronary artery calcium score, which was adjusted for gender, age and ethnics of the patient, and used to classify the patients in percentiles of risk for CAD. Using multiplanar and curved reformatting, the operator reviewed the coronary artery tree and based on computer aided semi objective analysis, the presence or absence of lesion in each of the 17 arterial segments was reported, according to the American Heart Association classification[16]. Based on the minimal lumen diameter and its relation to the arterial reference diameter (coronary segment without atherosclerosis 10 mm proximal and distal to the lesion), the stenosis was classified as: minimal (≤ 25%), mild (26-50%), moderate (51%-70%) and severe (≥71%). Plaques were considered hemodynamically significant if there was a stenosis □ 50% in any artery.

Plaques were also classified according to their composition as non-calcified, partially calcified and calcified, if it was homogenous and had attenuation coefficient ≤ 70 HU, 71 to 200 HU, and ≥ 201 HU, respectively [14].

In order to evaluate CAD extension we created a CAD index, which corresponds to the ratio of the number of segments with stenosis to the total number of identifiable segments by CTCA. CAD index was classified as low (0-0.9), moderate (1-50) and high (≥51).

Statistical analysis

The quantitative variables with a normal distribution were expressed as mean ± standard deviation and categorical variables were expressed as frequency (percentage). The continuous variables data were compared using t-test or Mann-Whitney or Wilcoxon signed-rank test. Categorical variables are reported as count and percentages and differences were analyzed using chi-square or Fisher test. Multivariate logistic regression analysis was used to study the variables related to significant coronary artery lesions, multivessel involvement, number of atherosclerotic segments, high coronary artery calcium score ≥ 100 and type of atherosclerotic plaque. This analysis use age, gender, hyper tension, diabetes mellitus, dyslipidemia and family history of premature CAD as covariates. For each logistic regression analysis a stepwise backward and a residual analysis was performed. A two tailed P-value of <0.05 was considered as statistically significant. All data were performed using IBM SPSS Version 19.0 (Armonk, NY:IBM. Corp.).

RESULTS

Biodemographic data

Patients were 30 to 90 years old, 233 men (52.7%), and were grouped as hypertensive (HT, n=305) and normotensive (NT, n=137). As shown in table 1, mean age, BMI and waist circumference were higher in HT than in NT ($p<0.05$) (Table 1). Likewise, diabetes mellitus ($p<0.001$), obesity ($p<0.001$), dyslipidemia ($p<0.001$), family history of premature CAD ($p=0.042$) and sedentary lifestyle ($p<0.001$) were also more prevalent in the HT when compared with NT. HT took more medications than NT ($p<0.001$), mainly to control blood pressure in HT and lipid plasma levels. Atypical angina was more prevalent in HT ($p=0.028$), while more cases of asymptomatic CAD were found in NT ($p=0.004$).

As shown in Table 2, total and Low density lipoprotein cholesterol levels were not different between HT and NT. However, HT had higher High density lipoprotein cholesterol, triglycerides and fasting glucose concentrations than NT ($p<0.05$).

Coronary angiography data

All patients were submitted to CTCA in sinus rhythm and the heart rate was 64±9 bpm (range 40-100) for diagnostic quality proposes evaluating all available segments. The mean contrast dose was 82 ± 13 mL, while the effective radiation dose was calculated to 11.1 ± 1.9 (range 7.1-16.2) mSv.

CTCA showed that 59.0% of the patients that some degree of CAD, which was more frequent in HT (63.6%) than in NT (48.9%, p=0.004) (Table 3). Moreover, multi vessel coronary artery lesions (≥ 3 vessels) and significant stenosis (≥50%) were more prevalent in HT than in NT ($p<0.05$) (Table 3). Significant atherosclerotic segment (□50%) and CAD extension index were higher in HT than NT ($p<0.05$) (Table 3).

Results from coronary artery calcium score and Agatston score equivalent in HT an NT are shown in table 3. Frequencies of intermediate (□ 75) and high (□ 100) coronary artery calcium score were similar between HT and NT ($p>0.05$). However, coronary artery calcium score low as well as Agatston score equivalent very low were found more prevalent in NT than in HT ($p<0.05$).

Analysis of plaque characteristics showed that all types of plaques were present in both HT and NT patients (Figure 1), however calcified plaques were more frequent in HT (55.7%) than in NT (42.3%, p=0.009).

Multivariate logistic regression models were used to investigate independent predictors of CTCA critical variables. It was possible to show that age, male gender and dyslipidemia are independent predictors ($p<0.05$) for significant coronary stenosis, multi vessel involvement, atherosclerotic significant segments and high coronary artery calcium score (□ 100) (Table 4).

Logistic regression analysis was also performed to identify predictors of plaque types. Age, male gender, dyslipidemia and diabetes mellitus independently predicted the presence of calcified plaques ($p<0.05$). Moreover, male gender was also related to non-calcified plaque (OR=2.02, 95%CI=1.08-3.77; p=0.026) and older patients were at higher risk to present partially calcified plaques (OR=1.05, 95%CI=1.01-1.08; p=0.005).

DISCUSSION

It is well known that hypertension is an important risk factor for CAD and it is present in a large proportion of patients selected for clinical trials. Search for new markers of CAD risk along with attempts to improve non-diagnostic accuracy rank among the leading goals in current clinical practice. CTCA has emerged as a promising procedure to improve non-invasive evaluation of the coronary arteries and to allow the identification of individuals at higher risk of significant CAD and major cardiac events[17-18].

In this study, only atypical angina was associated with hyper tension, however CAD normotensive subjects were mainly asymptomatic (48.2%, p = 0.004), which is suggestive that hypertension is an important risk factor for CAD clinical manifestations. Descalzo M. *et al* studied the coronary artery calcium score in 232 Spanish asymptomatic individuals (64.4% normotensive) and showed that the calcium score is an effective method to determine the extent and magnitude of CAD19. Therefore, the analysis of coronary artery calcium score and other CTCA-related variables provide relevant elements to evaluate the risk for CAD in asymptomatic normotensive subjects.

This study revealed high prevalence of CTCA-detected CAD, in HT (63.6%) and NT patients (48.9%). Moreover, HT had more coronary lesions (≥ 3 vessels), significant stenosis (≥ 50%), significant atherosclerotic segments (≥ 50%), calcified plaques and CAD extension index. The coronary artery calcium score low was more prevalent in NT group than in HT group suggesting that normotensive have less probability to have intermediate and high coronary artery calcium score values, even though increased coronary artery calcium score (≥ 100) was not related directly with hypertension. These findings demonstrate the importance of implementing strategies for CAD risk stratification also in normotensive individuals, although emphasize the importance of hypertension as a traditional risk factor.

CTCA data showed that the frequency of CAD was higher in HT patients but was not negligible in NT. The relationship between hypertension and angiographically detectable CAD has been discussed and still a matter of controversy. The data describing the relationship of hypertension and cerebral vascular disease or CAD compared to others risk factors as age, gender, obesity, diabetes and metabolic syndrome is relatively consistent20. Millar *et al* 21 showed an association between increased systolic blood pressure (≥ 165 mmHg) with high occurrence (>70%) lesions in coronary arteries, in a sample of men. In that study, the relationship between coronary artery stenosis and hypertension was not influenced by gender.

Most studies have described age, male gender and the presence of DM as independent risk factors related to CAD[3]. Diabetes mellitus, in particular, showed a very high correlation to the presence of atherosclerotic lesions[20]. Our results contributed with these data, and interestingly, showed age, gender masculine e dyslipidemia was independent predictor of multi vessel involvement, number of segments atherosclerotic, significant stenosis and high coronary artery calcium score.

In this study, hypertension was associated with increased atherosclerotic coronary segments and CAD extension index. These results are suggestive that hypertension contributes to the progression of atherosclerosis in the coronary arteries. We can assume that the more widespread the atherosclerosis in the patient, the higher the risk of the individual to present major cardiac events at mid and long term follow-up. It is noteworthy that CAD extension index proposed in this study is a useful tool to evaluate the overall atherosclerotic burden of patients at low risk for CAD. This index may be also a valuable marker to evaluate plaque instability, to be validated in multicentric studies.

Interestingly normotension was associated with low (zero) CAC and Agatston score equivalent. However, intermediate and high coronary artery calcium score and Agatston score equivalent scores were present in both HT and NT. These findings are interesting and this is the study to evaluate the influence of hypertension on coronary artery calcium score and other CTCA findings in patients with low and intermediate pre-test probability of CAD. Prospective and retrospective studies demonstrate the ability of coronary artery calcium score to predict mortality and major cardiac events, adding information to traditional risk scores[17-18]. According to Graham G. et al, the increase of coronary artery calcium score contributes significantly to traditional risk factors in order to predict mortality in patients with or without systemic artery hypertension[22].

In this sample, increased coronary artery calcium score was not associated with hypertension, which is suggestive that normo tensive patients have similar risk for CAD than hypert ensives. In this way, it is relevant to monitor this population in order to detect cardiovascular events and mortality.

Our findings are suggestive that CTCA could bring equally useful benefits in hypertensive and normotensive patients, for even though the first group had more extensive CAD; the presence of coronary lesions in normotensive patients could have been underestimated by traditional forms of evaluation[23], particularly in older men with dyslipidemia and normal blood pressure. The most clinically relevant current use of CTCA is the screening of symptomatic patients at intermediate risk, providing information on coronary anatomy lesions, which added to the clinical history, functional tests, might lead to better therapeutic decisions [4,5,17].

In our study the presence of arterial hypertension in individuals with low CAD risk was associated with calcified plaque. However, multivariate regression analysis did not indicate hypertension as a relevant predictor for calcified plaque. Instead, dyslipidemia, diabetes, age and male gender were associated with the presence of calcified plaques, whereas age and male gender were related to the presence of partially and non-calcified plaques, respectively. Lim *et al* [24] evaluated effect of metabolic syndrome on coronary stenosis and plaque characteristics as assessed with CTCA and revealed that partially calcified plaques were more frequent in patients with MS. Similar results were found for non-calcified and partially calcified plaques in diabetes mellitus compared to normoglycemic patients. They reported that hyperlipidemia and family history of CAD were significantly associated with the presence of non-calcified plaques.

In a recent study, Hadamitzky M et al reported in a 29 months follow-up no significant difference in major cardiac events between normotensive and hypertensive patients (p = 0.38) undergoing CTCA, even though hypertensive patients had an increased prevalence of obstructive CAD and more extensive atherosclerotic changes[25].

Our results suggest that prevention of major cardiac events should not be overlooked in normotensive individuals with other risk factors for CAD, especially dyslipidemia and older male patients. Many governmental policies in different countries aiming prop hylaxis and treatment of CAD are most valued in hypertensive individuals. We suggest that genomic studies can be used to make predictive occurrence based in data that CAD is a multifactorial disease reflecting a multigenic involvement[26].

The limitations of this study should be mentioned. Patients were enrolled from the clinical practice of a public institution, and that might have introduced a selection bias and attenuated the relationship between arterial hypertension and atherosclerosis. However, we have minimized the biases by excluding all patients with confirmed CAD diagnosis. Additionally, CTCA findings in this study were not compared with intravascular ultrasonography study for confirmation of plaque type, but plaque characterization was similar to that of other CTCA studies[27].

CONCLUSION

CTCA variables, including calcium score, are a useful tools to evaluate the extent and magnitude of coronary artery lesions, independently of the risk factors for CAD.

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Table 1. Biodemographic and clinical data of CAD patients

Variable	Total	Hypertensive	Normotensive	P -value
Number of patients	442	305 (69.0)	137 (31.0)	
Age, years	59 ± 11	60 ± 10.4	57 ±12.4	.015
Male	233 (52.7)	159 (52.1)	74 (54.0)	.714
Heart rate, beats/min	64 ± 9	64 ± 8	63 ± 10	.109
Diabetes mellitus	96 (21.7)	82 (26.9)	14 (10.2)	<.001
Obesity	128 (30.3)	108 (35.4)	20(14.5)	<.001
BMI, kg/m^2	27.7 ± 4.8	28.7 ± 5.0	25.7 ± 3.7	<.001
Waist Circumference, cm	95.7 ± 12	98 ± 11.5	90.6 ± 11.8	<.001
Dyslipidemia	243 (55.0)	195 (63.9)	48 (35)	<.001
Symptoms (*)				
Typical angina	94 (21.3)	69 (22.6)	25 (18.2)	.299
Atypical angina	128 (29.0)	98 (32.1)	30 (21.9)	.028
No cardiac chest pain	48 (10.9)	37 (12.1)	11 (8.0)	.200
Asymptomatic	169 (38.2)	98 (32.1)	66 (48.2)	.004
Family history of premature CAD	219 (49.5)	161 (52.8)	58(42.3)	.042
Current smoker	29 (6.6)	21 (6.9)	8 (5.9)	.885
Current drinker	106 (30.5)	63 (20.6)	43 (31.3)	.019
Sedentary lifestyle	294 (74.4)	214 (70.1)	80(58.3)	.001
Medications				
Beta-blocker	237 (45)	204 (66.8)	33 (24.1)	<.001
Aspirin	272 (41.6)	233 (76.3)	39 (28.4)	<.001
Statin	204 (53.8)	157 (51.4)	47 (34.3)	<.001
Calcium channel blocker	160 (14.1)	156 (51.1)	4 (2.9)	<.001
Angiotensin-converting enzyme inhibitor	108 (35.5)	94 (30.8)	14 (10.2)	<.001
Angiotensin II receptor blockers	185(23.2)	180 (59.0)	5 (3.6)	<.001

Data are presented as mean ± SD and n (%) and compared by t-test and chi-square test, respectively. BMI, body mass index; CAD, coronary artery disease.

Table 2. Laboratory data of CAD patients

Variable, mg/dL	Total (442)	Hypertensive (305)	Normotensive (137)	P
Fasting glucose	103.8 ± 36	107.8 ± 36.	93.2 ± 19.1	<.001
Total cholesterol	183.4 ± 49.6	181.6 ± 48.	188.3 ± 52.7	.350
HDL cholesterol	52.7 ± 19.3	51 ± 16	57.2 ± 25.6	.027
LDL cholesterol	107.2 ± 37.3	104.6 ± 33.	113.5 ± 44.8	.102
Triglycerides	137.7 ± 92.6	148.8 ± 101.4	108.5 ± 55.4	<.001
Creatinine	.92 ± .44	.90 ± .25	1.0 ± .79	.101

Data are presented as mean ± SD and compared by t-test. CAD, coronary artery disease; HDL, High-density lipoprotein; LDL, Low-density lipoprotein.

Table 3. Coronary artery calcium score and artery lesions in CAD patients

Variable	Value (CAD risk)	Total (442)	Hypertensive (305)	Normotensive (137)	P
CTCA-detected CAD		261 (59.0	194 (63.6	67 (48.9	.004
Coronary artery lesions	≥ 3 vessels	33 (7.5)	28 (9.1)	5 (3.6)	.030
	≥ 2 vessels	89 (20.1)	64 (20.9)	25 (18.2	.365
Significant atherosclerotic segment	≥50%	92 (20.8)	72 (23.6)	20 (14.6	.031
Significant stenosis	≥50%	0 (0 - 6)	0 (0 - 6)	0 (0 - 3)	.028
CAD extension index	0-0.9 (low	235 (53.2	153 (50.3	84 (60.8	.036
	1-50 (moderate	199 (45.0	145 (47.5	54 (39,1	.073
	≥ 51 (high	8 (1.8)	7 (2.2)	1 (0.1)	.254
CACS	0 (low)	168 (38.0	97 (32.0)	71 (51.8	.020
	≥ 75 (intermediate)	132 (29.9	99 (32.5)	33(24.1)	.075
	≥ 100 (high)	116 (26.2	85 (27.9)	31 (22.6	.247
ASE	0 (very low)	184 (41.6	113 (37.0	71(51.8)	.019
	1-99 (low	142 (32.1	107 (35.0	35(25.5)	.055
	100-399 (intermediate)	64 (14.5)	44 (14.4)	20(14.6)	.100
	≥ 400 (high)	52 (11.8)	41 (13.4)	11 (8.0)	.090
Plaque type	Calcified	228 (51.5)	170 (55.7)	58 (42.3)	.009
	Partially calcified	51 (11.5)	38 (12.5)	13 (9.5)	.366
	Non-calcified	61 (13.8)	45 (14.8)	16 (11.7)	.386

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Data are expressed as number of patients (percentages) and compared by chi-square or Fisher test compared by Mann-Whitney test. ASE, Agatston score equivalent; CACS: coronary artery calcium score; CAD, coronary artery disease; CTCA, computed tomography coronary angiography; HU, attenuation coeficient.

Table 4 Multivariate logistic regression reduced models for variables associated with coronary artery lesions

Variable	Significant Stenosis (≥ 50%)		Coronary artery lesions (≥ 3vessels)		Atherosclerotic significant segments (≥ 50%)		High CACS (≥ 100)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*p*
Age	1.03 (1.01-1.06)	*.002*	1.04 (1.01-1.06)	*.002*	1.05 (1.03-1.07)	*<.001*	1.09 (1.06-1.11)	*<.001*
Gender (male)	2.99 (1.79-5.00)	*<.001*	2.56 (1.47-4.46)	*.001*	2.35 (1.56-3.54)	*<.001*	3.46 (2.09-5.73)	*<.001*
Hypertension	1.49 (.83-2.68)	*.178*	1.31 (.80-1.99)	*.375*	1.12(0.71-1.78)	*.609*	.95 (.54-1.66)	*.868*
Dyslipidemia	1.78 (1.08-2.94)	*.024*	2.47 (1.04-4.35)	*.002*	2.30 (1.52-3.47)	*<.001*	1.99 (1.21-3.27)	*.007*
Diabetes mellitus	1.07 (.60-1.90)	*.809*	1.08 (.62-1.81)	*.786*	1.10(0.67-1.83)	*.685*	1.05(.60-1.82)	*.864*
Family history of premature CAD	1.46 (.89-2.39)	*.126*	1.33 (.81-2.01)	*.229*	1.21(0.70-1.78)	*.352*	1.17(.72-1.90)	*.506*

OR, odds ratio; CI, confidence interval; CACS, coronary artery calcium score; CAD, coronary artery disease.

Table 5 Multivariate logistic regression reduced models for variables associated with plaque types

Variable	Calcified		Partially calcified		Non-calcified	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*p*
Age	1.09 (1.06-1.12)	*<.001*	1.05 (1.01-1.08)	*.005*	1.00 (.97-1.03)	*.703*
Gender (Male)	1.75 (1.09-2.79)	*.018*	1.63 (.82-3.26)	*.161*	2. 02 (1.08-3.77)	*.026*
Hypertension	1.12(.95-2.23)	*.060*	1.45 (.64-3.29)	*.369*	1.26 (.64-2.49)	*.490*
Dyslipidemia	1.87 (1.17-3.00)	*.009*	1.60 (.78-3.26)	*.193*	1.11 (.58-2.10)	*.748*
Diabetes mellitus	1.87 (1.04-3.38)	*.036*	1.09 (.49-2.45)	*.818*	1.37 (.68-2.75)	*.364*

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease

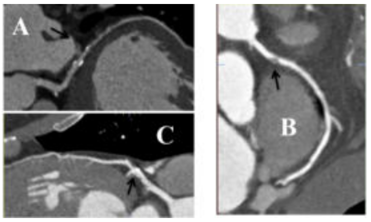

Figure 1 – Type of plaques in normotensive patients. A - Calcified Plaque ; B – Non calcified Plaque; C – Partially calcified Plaque.

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