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Research Article

Predictors for the Detection of Non-Calcified Plaque in Patients with Calcium Score Equal to Zero

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1. Abstract

1.1. Aims: Calcium score (CS) is a reliable test to assess the risk of cardiovascular events, by measuring calcified plaque in coronary arteries. However, Coronary Artery Disease (CAD) also exists in absence of coronary calcifications. There are no clear descriptions of conditions other than symptoms that are associated with the presence of non-calcified plaque (NCP) in patients with calcium score of zero. We sought to determine clinical predictors of NCP and their diagnostic ac-curacy in patients with a CS of zero.

1.2. Methods and results: We analyzed consecutive patients with a CS of 0 Agatston Units for which we had performed a coronary angiography to accurately detect CAD. Three models of mul-tivariate analysis by logistic regression were constructed for the search of predictors. Sensitivity, specificity, NPV, PPV, + LR and - LR were calculated.

1.3. Results: 93 patients were prospectively included. 10% of patients (n=9) presented NCP. Positive exercise ECG testing was an independent predictor of plaques of any severity, including non-severe plaques (OR 6.5; 95% CI 1.3-33, p= 0.02). Predicting power persisted for non-severe plaques when combined with negative gated SPECT (OR 12.4 95% CI 1.5 â€“ 101, p= 0.02). Sensitivity and specificity of ST-segment depression for NCP of any degree of severity was 44.4% and 86%, respectively. NPV was 94% and PPV was 25%, +LR was 3.11 and -LR was 0.65.

1.4. Conclusions: ST-segment depression could be a good predictor of CAD in patients with CS of zero, even in the presence of normal perfusion images (non-obstructive disease).

2. Introduction

Coronary calcium Quantification using non-contrast CT is a study supported by clinical practice guidelines for risk stratification of asymptomatic patients.

The evidence that support its recommendation is based on improving the prediction of coronary events regarding the evaluation of traditional risk factors expressed in the Framingham Score. In individuals with intermediate cardiovascular risk, improvements in the prediction of events have been reported from the net reclassification ranging from 31% to 55% of patients .

Although its systematic indication as screening in asymptomatic patients has not shown reduction of hard endpoints in randomized studies, according to a recent systematic review, its use increases the likelihood of onset or continuation of pharmacological therapies for the prevention of cardiovascular disease.

In the evaluation of patients with suggestive symptoms of coronary artery disease, on the other hand, the use of calcium score is considered a rarely appropriate recommendation in North American imaging guidelines. This is due to the higher prevalence of non-calcified plaque (NCP) in this group of patients [1]. Reported a prevalence of 16.5% NCP in a cohort of symptomatic patients with calcium score of zero, whereas the prevalence of sig-nificant plaques was 3.5% .

Although the limitation of calcium score in symptomatic patients is well established, there are no studies to date that evaluate the

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existence of other conditions that are associated with the presence of NCP in patients with calcium score of zero. To know factors that can predict their presence, would help in the detection of populations of higher cardiovascular risk and in the future design of studies to determine the usefulness of calcium score in reference to hard endpoints.

The objective of our study is to determine clinical predictors of NCP and their eventual diagnostic accuracy in a population of patients without known coronary disease and calcium score equal to 0 UA.

3. Methods

3.1. Study population

The present was a single-center, investigator driven, retrospective study, that involved consecutive patients evaluated in our institu-tion between September 2016 and October 2017 and it was ap-proved by the ethical committee of our institution. We included patients over 18 years of age with calcium Score equal to Zero (0) Agatston units (AU) that were performed coronary angiography in our center. The study was clinically indicated due to the pres-ence of symptoms, abnormal and/or discordant functional tests and cardiac tomography requested for reasons not linked to coro-nary pathology in which the coronary anatomy was viewable by a protocol of Acquisition identical to a coronary CT (Cardiac CT for pulmonary vein evaluation, for example). Additional exclusion criteria: patients with known coronary disease, calcium score more than 0 AU, cardiomyopathy, and patients who presented artifact by respiratory movement or arrhythmia for whom it was not possible to assess at least 1 Coronary segment.

3.2. Coronary CT and Calcium Score acquisition

The acquisition of images was performed using 64-row scanners (Brilliance 40, Philips, the Netherlands) with a slice thickness of 0.5 mm, a rotation time of 0.4 seconds, pitch of 0.20-0,24, tube voltage adjusted to the BMI of the patient (120 kV if BMI greater than or equal to 30 kg/m2 and 100 kV if BMI less than 30 kg/m2) and tube current between 700 mA and 1.000 mA. Prospective or retrospective modulated gating was used according to the heart rate (HR) and the presence of arrhythmia at the time of acquisi-tion. Beta-blockers with HR greater than 65 BPM were indicated at the time of acquisition and sublingual nitrites between 2 and 3 minutes prior to acquisition in the absence of contraindications. 90-125 ml of iodine contrast was administered (Optiray®, Iover-sol 350 mg/ml, Mallinckrodt, St. Louis, USA) intravenously at a flow rate of 4 to 6 ml/sec using the Bolus tracking technique to synchronize the arrival of contrast to the coronary artery with the onset of Acquisition. Calcium scoring was performed with the use of prospective electrocardiographic (ECG) gating, a rotation time of 0.4 seconds, 120 kV voltage, 300 mA current and a slice thickness of 3 mm.

3.3. CT images analysis and Calcium Score quantification

Multi-planar curves, three-dimensional reconstructions and maximum intensity projections (MIP) were used to evaluate the coronary segments. The images were initially reconstructed in diastole (75% of the R-R interval) and the quality of the images was evaluated. In case of insufficient quality, successive recon-structions were obtained at 70% and 80% (prospective protocol) and 30% and 40% in case of retrospective protocol. Two indepen-dent observers reported the presence of plaques according to the classification suggested by the Society of Cardiovascular Com-puted Tomography (0% absence of injury, 1% to 24% minimum lesion, 25 to 49% mild stenosis, 50 to 69% moderate stenosis, 70 to 99% severe stenosis, 100% occlusion). The segments with at least a visible stenosis of 25% were manually quantified with the use of commercially available software (Philips IntelliSpace Portal 8.0). An average of the measurements of both observers was obtained. Visual and quantitative inter-observer differences exceeding 50% were resolved by a third observer. The quantifica-tion of coronary calcium was performed with Philips IntelliSpace Portal 8.0, taking all pixels with a density greater than 130 HU. A calcification was defined as a minimum of 2 adjacent pixels with a density higher than 130 HU. The calcium score was calculated according to the method described by Agatston.

3.4. NCP definition

Non-calcified plaque was defined as a lesion that would gener-ate a stenosis at least minimal and not present any focus of calcification. This definition was considered as Gold Standard when evaluating the diagnostic accuracy of the predictors found. Due to the exclusion of patients with at least one coronary calcification focus (Agatston Score more than 0 AU), all plaques found in our cohort were non-calcified.

Statistical analysis

Three models of multivariate analysis by logistic regression were constructed for the search of predictors. The dependent variables were NCP of any severity in the first model, and NCP less than 70% severity in the second and third models. In the first two mod-els the following variables were included: 1) Age greater than 50 years 2) Hypertension 3) Dyslipidemia 4) Smoking or ex-smok-ing 5) presence of symptoms (chest pain or shortness of breath that motivates the study) 6) Exercise testing reported as positive for presenting 2 mm ST-segment depression assessed at 0.06 sec-onds after the J point. In the third model were included the same variables of the other two, modifying the sixth independent vari-able (positive exercise testing), by functional mismatch, also defined from a positive exercise ECG but in context of SPECT myo-cardial perfusion or Stress echocardiography without evidence of ischemia. In order to evaluate diagnostic accuracy of a predic-tor, double entry tables were performed. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio (+ LR) and negative likelihood ratio (-LR) were calculated. Those who presented at least a non-calcified plaque as it was defined in the preceding section were consid-ered carriers of disease (true positives or false negatives of the predictor analyzed). Discrete variables were presented as counts and percentages and compared using Fisher's exact test. Continu-ous variables with normal distribution were presented as means ± SD and compared using independent sample t-test, whereas variables with skewed distribution were presented as median and compared using non-parametric tests (Mann-Whitney U test). All statistical analyses were performed using Epi InfoTM soft-ware, version 7.2.2.2. (CDC Atlanta, US). A two-sided p value of less than 0.05 indicated statistical significance.

4. Results

93 patients with coronary calcium score equal to 0 AU were pro-spectively included in the study protocol. 10% of patients (n= 9) presented NCP and 2% severe grade plaques (n= 2). 7% of pa-tients presented symptoms and 26% at least one abnormal func-tional test that motivated the study clinical indication. Indica-tions of the tomography other than suspected coronary artery disease accounted for 28% of the population (see **Table 1**).

Table 1: Demographical characteristics of patients.

	(n=93)
Age (years ± SD)	45 +/- 15
Hypertension (%)	50(54)
Hypercholesterolemia (%)	11 (12)
Diabetes (%)	2 (2)
Smoking (%)	9 (10)
Presence of symptoms (%)	6(7)
Positive exercise ECG (%)	16(17)
Positive myocardial perfusion or Stress echo*	8(9)
CT indicated due to aortic pathology evaluation (%)	13(14)
CT indicated due to pulmonary veins anatomical evaluation (%)	13(14)

*****Positive myocardial perfusion or Stress echorefers to patients with myocardial perfusion SPECT or stress echocardiography with evidence of ischemia.

Patients with plaques were older and had more positive exercise ECG testing in relation to patients without plaques (see **Table 2**). In multivariate analyses adjusted for age over 50 years, gender and risk factors, positive exercise ECG testing was independent predictor of plaques of any severity (adjusted OR 6.5; 95% CI 1.3-33, p= 0.02) and non-severe plaques (adjusted OR 14.9 95% CI 2-106, p= 0.007) (see **Tables 3** and **4**).

When evaluating positive exercise ECG combined with negative gated SPECT or stress echocardiography (functional test mis-match) persisted its independent predictor value for non-severe plaques (adjusted OR 12.4 95% CI 1.5 – 101, p= 0.02) (see **Table 5**).

The sensitivity and specificity of exercise ECG for non-calcified plaques of any degree of severity was 44.4% (95% CI 13.7%-78.8%) and 86% (95% CI 76.38%-92.39%), respectively. The NPV was 94% (95% CI 88.86%-96.30%) and the PPV was 25% (95% CI 11.95% to 45.02%); The + LR was 3.11 (95% CI 1.27-7.64) and - LR was 0.65 (95% CI 0.36-1.17) (see **Table 6** and **7**).

Table 2: Demographic characteristics according to presence or absence of NCP.

	NCP		
	with (n = 9)	without (n=84)	p
Age (years ± SD)	55 +/- 7	45+/-16	0,02
Male (%)	4 (44)	46 (55)	0,7
Diabetes (%)	0	2 (2,4)	1
Hypertension (%)	2 (22)	7 (8,3)	0,2
Smoking (%)	2 (22)	7 (8,3)	0,2
Hypercholesterolemia (%)	1 (11)	10 (11,9)	1
Presence of symptoms (%)	1 (11)	5 (6)	0,46
Positive exercise ECG (%)	4 (44)	12 (14,3)	0,04
Functional mismatch* (%)	2 (22)	4 (4,8)	0,1

*****Functional mismatchrefers to patients with positive exercise ECG testing and myocardial perfusion SPECT/Stress echo without evidence of ischemia.

Table 3: Predictors of NCP of any degree of severity in multivariate analysis (model 1).

Variable	OR	CI 95%	p
Age greater than 50 years	0,84	0,05- 15	0,9
Hypertension	4	0,5-33,7	0,2
Hypercholesterolemia	0,86	0,08-8,7	0,9
Smoking	3,8	0,46-31,8	0,2
Positive exercise ECG	6,5	1,3 -32,6	0,02
Presence of symptoms	1,85	1,11 – 30,6	0,66

Table 4: Predictors of NCP less than 70% in multivariate analysis (Model 2).

Variable	OR	CI 95%	p
Age greater than 50 years	3,9	0,2- 80	0,4
Hypertension	1,2	0,07 - 21	0,13
Hypercholesterolemia	1,1	0,1-12	0,9
Smoking	1,1	0,07-17,5	0,9
Positive exercise ECG	14,9	2 -106	0,007
Presence of symptoms	5,9	0,33-107	0,23

Table 5: Predictors of NCP less than 70% in multivariate analysis (Model 3).

Variable	OR	CI 95%	p
Age greater than 50 years	1,8	0,12- 28	0,6
Hypertension	1,83	0,11-28	0,65
Hypercholesterolemia	1,67	0,14-19	0,62
Smoking	1,4	0,1-19	1
Functional mismatch	12,46	1,5 -101	0,02
Presence of symptoms	2,8	0,2-37	0,43

Functional mismatchrefers to patients with positive exercise ECG testing and myocardial perfusion SPECT/Stress echo without evidence of ischemia.

Table 6: Diagnostic accuracy of *exercise ECG testing*forNCP detection.

	NCP		
exercise ECG	present	absent	total
Positive	4	12	16
Negative	5	72	77
Total	9	84	93

Table 7: Sensitivity, specificity and Likelihood ratios of *exercise ECG testing*for NCP detection.

Sensitivity	44,4% (13,7 - 78,8)
Specificity	86% (76,38 - 92,39)
+LR	3,11 (1,27- 7,64)
-LR	0,65 (0,36 - 1,17)

5. Discussion

In this cohort of patients with calcium score equal to zero the prevalence of non-calcified plaque was 10% and the positive exercise ECG proved to be independent predictor of plaques of any severity and not- severe. In the context of gated SPECT or negative stress echocardiogram, positive exercise ECG retained its predictor power for not-severe plaques. The specificity and + LR of ST-segment depression for diagnosis of non-calcified plaque of any severity was 86% and 3.11 respectively.

The prevalence of non-calcified in our cohort is consistent with that described in the CONFIRM registry for patients with symptoms7. This may demonstrate a limitation of the calcium score in the risk stratification of patients who have ST-segment depression perhaps attributable to the loss of negative predictive value in this population. In other words, regardless of the symptoms, the pres-ence of ST-segment depression in patients without coronary cal-cifications could alert us to a population of higher cardiovascular risk. The specificity and + LR of exercise ECG test for no-calcified plaque detection (value that depends on the precision of the test and not on the prevalence) found in this cohort would support this hypothesis.

The second relevant finding in our cohort refers to the persistence of the predictive power of exercise ECG test for non-significant plaques in the context of normal myocardial perfusion. Myocardial perfusion (as well as stress echocardiogram) is not an appropriate method to differentiate between plaque absence and non-obstructive coronary artery disease (mild or moderate plaques). This is why the absence of ischemia is a frequent finding in the history of patients suffering from cardiovascular events. There is evidence of improvement in the predictive value of myocardial perfusion in the long term with the addition of calcium score to perfusion images (hybrid SPECT/CT equipment).

The implications of these findings can be summarized as follows: Alterations in the exercise ECG test associated with detection of mild to moderate non-calcified plaques in patients without ischemia would demonstrate the validity of the ST-segment depression as a prognostic marker. This is consistent with previous publication by our group regarding changes in ventricular-arte-rial coupling in patients with ST segment depression and normal perfusion. Several publications show that the combination of ST-segment depression and normal myocardial perfusion would reflect global alterations of subendocardium underestimated by the SPECT due to the phenomenon of balanced ischemia. Therefore, we interpreted that the presence of non-significant plaques associated with abnormal exercise ECG test in patients with calcium score equal to zero could represent a subrogate point of microvascular disease, being this overlooked by gated SPECT due to its global and non-segmental involvement .

6. Limitations

A number of limitations should be acknowledged. The relatively small sample size and the low prevalence of symptoms (7 per cent of our population) due to the inclusion of patients with indications of CT not linked to the assessment of coronary ar-teries (assessment of pulmonary veins, for example) might lead to selection bias. Taking into account the high prevalence of non-calcified plaque in symptomatic patients described in other publications, the realization of a study that includes a greater number of patients with symptoms could give consistency to our findings. On the other hand, the low prevalence of severe plaques in our cohort (2%) does not allow us to have certainty about the predictor power of ST-segment depression regard-ing the presence of severe plaques in patients with calcium score equal to zero. If prospective clinically driven studies show that ST-segment depression lacks of predictive value for severe plaques detection in the absence of both coronary calcifications and ischemia on stress perfusion imaging (being only a predic-tor of non-obstructive coronary artery disease in this setting) strategies of coronary CT angiogrphy versus Calcium Score in a randomized design study could be analyzed. This could alter the current recommendation in clinical practice guidelines for performing coronary CT angiography in patients with function-al mismatch (ST-segment depression without ischemia on stress perfusion imaging), leaving the use of coronary CT angiography (and therefore of contrast and more radiation doses) for cases with both functional mismatch and evidence of calcifications on calcium scan.

7. Conclusions

The absence of coronary calcifications in the evaluation by to-mography is not synonymous with the absence of plaques, due to the existence of non-calcified components in the atherosclerotic process. The presence of coronary artery disease in this context could be suspected from abnormal results in exercise ECG test, even in the presence of normal perfusion images (non-obstruc-tive disease). These affirmations and their implications must be confirmed in studies of diagnostic precision with greater number of patients and in randomized studies of usefulness where rel-evant clinical outcomes are evaluated.

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