Atherosclerosis 203 (2009) 533–537

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Influence of symptomatic status on the prevalence of obstructive coronary artery disease in patients with zero calcium score

Kamran Akram[a,b], Robert E. O'Donnell[b], Spencer King[b], H. Robert Superko[b], Arthur Agatston[c], Szilard Voros[b,*]

[a] Department of Internal Medicine-Graduate Medical Education, Atlanta Medical Center, Atlanta, GA, United States
[b] Fuqua Heart Center of Atlanta, Piedmont Hospital, 1968 Peachtree Rd NW, Atlanta, GA 30309, United States
[c] University of Miami, Miller School of Medicine, Miami, FL, United States

ARTICLE INFO

Article history:
Received 4 March 2008
Received in revised form 15 June 2008
Accepted 10 July 2008
Available online 19 July 2008

Keywords:
Multi-detector computed tomography
Coronary artery calcium
Atherosclerosis
Chest pain
Obstructive coronary artery disease

ABSTRACT

Background: CAC has been used to predict obstructive CAD on invasive coronary angiography. However, it is unknown how the prevalence of obstructive CAD in patients with zero CAC is influenced by the presence or absence of chest pain.
Methods: 210 consecutive patients referred for CAC and CorCTA were included in this analysis. Chest pain was defined based on the Diamond-Forrester classification.
Results: 134 patients (64%) were symptomatic and 76 (36%) were asymptomatic. Seventy patients had negative (33%); 140 had positive CAC (67%). In the symptomatic group with zero CAC, 8.2% (4/49) had an obstructive, non-calcified plaque; of these, 3 were <45 years. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CAC in the symptomatic population for detection of obstructive CAD were 0.86 (0.66–0.95), 0.42 (0.33–0.52), 0.28 (0.19–0.39) and 0.92 (0.8–0.97), respectively ($p = 0.007$). No asymptomatic subject with zero CAC had obstructive CAD. Sensitivity, specificity, PPV and NPV of CAC in the asymptomatic population for detection of obstructive CAD were 1.00 (0.66–1.00), 0.32 (0.21–0.45), 0.18 (0.10–0.31) and 1.00 (0.80–1.00), respectively ($p = 0.05$). Optimal cut-points to predict obstructive CAD and AUC were significantly different in symptomatic versus asymptomatic subjects (91 and 0.78 vs. 296 and 0.89, respectively) ($p = 0.005$). CAC performed much better in symptomatic patients >45 years compared to younger patients to exclude obstructive CAD (AUC: 0.83 vs. 0.5, $p < 0.001$; NPV = 0.98).
Conclusions: CAC is better in asymptomatic compared to symptomatic subjects, especially in patients <age 45, to exclude obstructive CAD. Symptoms and age should be considered when interpreting CAC.

1. Introduction

Coronary artery calcium (CAC) scoring has been introduced to evaluate the extent of coronary atherosclerosis in asymptomatic subjects and has been shown to have prognostic value in predicting future cardiovascular events [1–3]. The incremental value of a positive CAC exceeds that of the traditional risk factors by up to 7 times [4]. In asymptomatic subjects, a negative CAC is associated with very low annual event rates (0.11–0.62% per year) [5–7] and with a low likelihood of an abnormal myocardial perfusion study [8].

CAC has been correlated with angiographic coronary artery disease (CAD), mostly in symptomatic patients or in those with a positive functional test. CAC has been validated to predict obstructive CAD in symptomatic patients using invasive coronary angiography as reference standard [1,9–15]. Also, CAC has been used in patients who present to the emergency department with chest pain. A negative CAC was used to exclude obstructive (CAD) and it has been proposed that such patients can be safely discharged from the emergency department [16]. However, the influence of symptomatic status on the prevalence and the distribution of the severity of CAD in patients with or without CAC are unknown.

Coronary artery computed tomography angiography (CorCTA) has been recently introduced for the diagnosis of CAD. Coronary CTA can evaluate luminal stenosis and offers the advantage of identifying calcified and non-calcified components within plaques non-invasively. In this context, non-calcified plaque has been reported in up to 10% of individuals with zero and low CAC, questioning the predictive value of a zero CAC in certain patient populations [17–20].

* Corresponding author. Tel.: +1 404 605 4905; fax: +1 404 355 9107.
E-mail address: szilard.voros@piedmont.org (S. Voros).

0021-9150/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2008.07.008

In this study we sought to investigate the prevalence and the distribution of the severity of CAD based on symptomatic status and based on the presence or absence of CAC. Additionally, we examined the influence of symptoms on the diagnostic performance of CAC as a predictor of obstructive CAD. Accordingly, we hypothesized that symptomatic status influences the prevalence of obstructive CAD in CAC negative and CAC positive individuals.

2. Methods

2.1. Patient enrollment

This was a retrospective, single-center, observational study. The investigational protocol was approved by the institutional review board of Piedmont Hospital. Consecutive patients referred to our institution between January 2005 and June 2006 for simultaneous coronary artery calcium scoring and coronary artery CTA were included. Patients with a history of revascularization (30 patients) and inadequate study quality (15 patients) were excluded. Enrollment criteria were met by 210 patients. Demographic and clinical information was collected from medical records. Patients were divided into two groups on the basis of symptomatic status using the Diamond-Forrester classification [21]. Chest pain was evaluated for three different characteristics: 1. Substernal chest pain of typical quality, 2. Exacerbation by physical or emotional stress and 3. Relieved by nitrates and/or rest in less than 10 min. Typical angina, atypical chest pain and non-cardiac chest pain were characterized by the presence of all three, two or one of the three features, respectively. Patients with typical angina and atypical chest pain were classified as symptomatic and those with non-cardiac chest pain or without any symptoms were classified as asymptomatic.

2.2. MDCT

All CT examinations were performed on a 32 × 2 MDCT system (Siemens Somatom 64; Erlangen, Germany). CAC was obtained with non-contrast enhanced scans and images were acquired using 3 mm collimation with 2 mm interslice gap. Acquisition parameters included a gantry rotation of 330–375 ms, pitch 0.24, tube voltage 120 kV and tube current of 250 mAs.

Coronary CTA was performed during end-respiratory breath-hold with retrospective ECG-gating. Oral and intravenous metoprolol was administered as needed to keep the heart rate below 60 beats/min. After non-contrast localization image acquisition, a test bolus of 20 ml iodinated contrast (Visipaque, Amersham Health, USA) was administered intravenously at a rate of 3–5 ml/s to determine the delay until the arrival of contrast in the ascending aorta. Contrast-enhanced coronary CT angiography was performed using 80–100 ml of intravenous contrast followed by 30 ml normal saline flush. Acquisition parameters included 32 × 2 detector rows, 0.6 mm collimation, gantry rotation 330–375 ms, pitch 0.24, tube voltage 120 kV and tube current 800–950 mAs. Images were reconstructed in 0.6 mm axial slices.

2.3. Image interpretation

Image postprocessing and data analysis was performed on an off-line workstation (Siemens WIZARD). CAC scores were expressed as Agatston score.We measured the minimal luminal diameter (MLD) on curved MPR images in the lesion. Percent diameter stenosis then was calculated by dividing the lesion MLD by the mean of the proximal and distal reference segment diameters. The proximal and distal reference segments were placed in visually normal coronary segments proximal and distal to the lesion. Coronary artery stenoses were then converted to a graded semi-quantitative scale: no luminal stenosis, mild (<30%), intermediate (30–70%) and obstructive (>70%) luminal stenosis. One experienced reader performed all clinical interpretation (SV). A study was classified as inadequate if the vessel borders were not sharply delineated in any vessel or segment >2 mm in diameter.

2.4. Invasive angiography

Coronary angiography was performed by the Judkins technique with a minimum of five views of the left coronary system and two views of the right coronary system. The absence or presence of discrete coronary artery stenoses was examined in two orthogonal views and obstructive disease (>70%) was confirmed by visual assessment.

2.5. Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using contingency tables (MedCalc Vesion 9.2.0.1). The predictive variable was determined by CAC and the presence or absence of obstructive CAD by CorCTA. The relationship between categorical variables (i.e. age, gender and modifiable cardiac risk factors) and obstructive CAD was determined using either the Fisher's exact or χ^2-test. Statistical significance was determined by a p-value ≤ 0.05. Receiver operating characteristics (ROC) curve analysis was used to assess the performance of CAC to predict obstructive CAD. ROC cut-points were compared by determining the proportion of positive results predicted by different cut-points using commercial software (Meta-analysis v.2).

3. Results

3.1. Demographics

The study group consisted of 210 patients. Clinical characteristics are shown in Table 1. Median CAC was significantly higher in males than in females (mean CAC 318 ± 565, median 42.7, range 0–3689 in males and mean CAC 132 ± 251, median 1.8, range 0–1234 in females; $p = 0.0014$). Since CAC scores did not follow normal distribution, median values were used for statistical comparison.

3.2. Prevalence and distribution of the severity of CAD in the overall group

Mean CAC in the overall group of 210 patients was 220 ± 438 (median 18.3, range 0–3689). Of these, 70 patients (33%) had a

Table 1
Baseline demographic data and prevalence of CV risk factors for the entire group, symptomatic and asymptomatic patients

	n (%)		
	Total	Symptomatic	Asymptomatic
Total	210 (100)	134 (64)	76 (36)
Mean age ± SD (yrs)	57.4 ± 11.8	58.5 ± 12.5	55.5 ± 10.3
Male	99 (47)	63 (47)	36 (47)
Female	111 (53)	71 (53)	40 (53)
Hypertension	140 (67)	97 (72)	43 (57)
Diabetes Mellitus	37 (18)	27 (20)	10 (13)
Smoker	50 (24)	36 (27)	14 (18)
Hypercholesterolemia	144 (69)	92 (69)	52 (68)

CV, cardiovascular; SD, standard deviation; yrs, years.