Atherosclerosis 238 (2015) 126–131

Contents lists available at ScienceDirect

Atherosclerosis

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

Improving the relationship between coronary artery calcium score and coronary plaque burden: Addition of regional measures of coronary artery calcium distribution

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ARTICLE INFO

Article history:
Received 18 June 2014
Received in revised form
20 October 2014
Accepted 5 November 2014
Available online 24 November 2014

Keywords:
Coronary artery calcium
Coronary artery disease
Coronary computed tomography angiography

ABSTRACT

Background: The Agatston coronary artery calcium (CAC) score predicts cardiovascular events through its association with overall burden of coronary atherosclerosis. It is unclear whether adding regional measures of CAC distribution to the Agatston score improves this association. **Methods**: We studied 920 consecutive patients (mean age 57 ± 12, 53% female), referred for 64-slice Coronary CT angiography (CCTA) who had concomitant CAC scoring. Total atherosclerosis burden was quantified as the segment involvement score (SIS), which describes the number of coronary segments with plaque on CCTA. We studied the heterogeneity between CAC group (0, 1–100, 101–400, >400) and the number of vessels with CAC (0–4), and related this to SIS on CCTA. In patients with multi-vessel disease, we examined the relationship of concentrated vs. diffuse CAC (> or ≤75% total CAC in one vessel) with SIS. **Results**: When CAC was intermediate (1–400), considerable heterogeneity was noted between CAC group and the number of vessels with CAC (CAC 1–100: 53% 1-vessel, 29% 2-vessel, 16% 3-vessel, 2% 4-vessel; CAC 101–400: 9% 1-vessel, 28% 2-vessel, 43% 3-vessel, 20% 4-vessel). Within each CAC group, increase in the number of vessels with CAC was significantly associated with increased SIS. In multi-vessel disease, a higher SIS was associated with diffuse versus concentrated CAC (CAC 1–100: 3.8 vs. 2.8, CAC 101–400: 5.5 vs. 4.3 [both $p < 0.01$]). These associations persisted after adjustment for age, gender, and the absolute Agatston CAC score ($p < 0.01$). **Conclusion**: Addition of measures of regional CAC distribution improves the association of the Agatston CAC score with total plaque burden.

1. Introduction

Coronary artery calcium (CAC) scoring has established utility in refining cardiovascular risk stratification among intermediate-risk patients [1] and in those in whom treatment decisions are uncertain [2]. This is thought to be the result of the strong association between the presence of CAC and the overall burden of coronary atherosclerosis [3], inclusive of non-calcified, mixed calcified and fully calcified coronary plaque.

Agatston et al. [4] developed the most commonly used method for calculating the burden of CAC in the late 1980s. The Agatston score involves multiplying the area of each individual calcified plaque by a factor derived from the maximal plaque density (CT attenuation) in Hounsfield Units, and then adding the values obtained for all coronary plaques identified. The Agatston CAC score is thus an aggregate score and does not account for the regional distribution of CAC. In addition, this method disproportionally weights increased coronary plaque density, meaning that heavily calcified plaque contributes more to the score than less calcified

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.11.008
0021-9150/

"mixed" plaque. Recent research has demonstrated that cardiovascular events may in fact be inversely related to plaque density, and probably more closely linked to total coronary plaque volume [5].

Characterizing the regional distribution of CAC may be important for two reasons. First, patients with more diffuse coronary artery disease (CAD) have worse cardiovascular outcomes when compared to patients with more focal CAD [6]. The PROSPECT study [7] demonstrated the importance of total plaque burden in predicting cardiovascular events, while a sub-study of the COURAGE trial noted the superiority of coronary plaque burden over ischemic burden in predicting the risk of myocardial infarction [8]. Furthermore, while highly dense local plaque may correlate with local coronary artery stenosis severity, focusing on coronary stenosis has the inherent potential to underestimate coronary plaque burden [9], due to the outward remodeling of coronary plaque, as originally described by Glagov et al. [10].

Whether accounting for regional CAC distribution improves the association of the Agatston CAC score with overall coronary atherosclerotic plaque burden has not been rigorously evaluated. We studied whether the addition of measures of increasingly diffuse CAC distribution improves the association of CAC scoring with overall coronary atherosclerotic plaque burden on concomitant coronary CT angiography (CCTA).

2. Methods

2.1. Study population

A total of 920 consecutive patients (93% symptomatic) who underwent multi-detector CT coronary angiography (CCTA) between January 2006 and December 2009 were included in this study. This is a cross-sectional study, the details of which have been previously published [11]. The institutional review board at the study institution approved the study, and patients' informed consent requirement was waived. Exclusion criteria were known CAD, iodine allergy, and chronic kidney disease (creatinine >1.5 mg/deciliter).

2.2. CT data acquisition

Using a 64-slice CT scanner (Lightspeed VCT, GE Healthcare, Milwaukee, WI, USA), patients underwent non-enhanced prospective electrocardiographic (ECG) gated sequential scanning to measure the Agatston CAC score.

A total of 60–80 ml of iodinated contrast medium was used at a high flow rate (5 ml/s) followed by saline flush for CCTA acquisition. Patients with heart rates >65 beats per minute received intravenous beta-blockers (5–10 mg metoprolol). Before 2008, CCTA was performed using retrospective ECG gating. After June 2008, prospective gating became available and nearly 70% of patients underwent prospective gating. The collimation was 64 × 0.625 mm; gantry rotation time was 350 ms, tube current was 500–600 mA, and voltage was 100–120 kV, depending on patient size. Synchronization of the scan with contrast medium was achieved by using the timing bolus technique [12]. Mean radiation exposure was 1051 mGy/cm.

2.3. Image analysis

CAC was defined as the presence of at least 3 contiguous pixels with a density >130 Hounsfield Units. CAC scoring was quantified based on the scoring algorithm proposed by Agatston [4]. Two experienced readers assessed images by a consensus decision in a joint reading session.

For CCTA, each lesion was identified using a multi-planar reconstruction technique of axial, sagittal, coronal and oblique views. Plaques were identified as lesions larger than 1 mm^2 within or adjacent to the vessel lumen, which were clearly distinct from epicardial fat and vessel lumen. The total coronary artery plaque burden was described as the total number of coronary segments with any plaque on CCTA (segment involvement score [SIS]), using the modified 16-segment Society of Cardiovascular CT coronary model [13]. Coronary plaque on CCTA was scored on a per-segment basis for plaque composition based on the presence of calcified tissue as calcified (plaques without a non-calcified portion), non-calcified (no calcified component) or mixed plaques (combination of both calcified and non calcified portions).

2.4. Definitions

The regional dispersion of CAC was described as an ordinal variable (0–4), accounting for the number of vessels with CAC including the left main, left anterior descending, left circumflex, and right coronary arteries. In patients with CAC in more than one vessel, "concentrated CAC" was defined as the presence of >75% of the overall Agatston CAC score in the single most affected vessel, whereas diffuse CAC was defined as ≤75% overall Agatston CAC score in one vessel. For each patient, the maximal percentage of CAC in one vessel was also determined, in order to express the dispersion of CAC as a continuous variable (higher percentage translates to more concentrated CAC pattern).

2.5. Statistical analysis

Continuous variables were expressed as means ± standard deviations and categorical variables as percentages. Chi-square testing was employed to determine the statistical significance of heterogeneity between CAC groups and the number of coronary arteries with CAC. Differences in the SIS (total coronary artery disease burden measured by number of coronary segments with plaque) were compared using linear regression, adjusting for age and gender, as well as the Agatston CAC score to adjust for residual differences in absolute CAC score within each CAC group. Given prior studies which have suggested SIS >4 as a cutoff for more extensive CAD [6], a similar analysis was also conducted using SIS >4 as a dichotomous variable. A p value <0.05 was considered

Table 1
Baseline characteristics of the study sample.

Baseline characteristics ($n = 920$)		Frequency
Age (years)		57 ± 12
Gender (male)		432 (47%)
Ethnicity	White	538 (58%)
	African American	309 (34%)
BMI kg/m^2 ($n = 878$)		31 ± 7
Smoking status ($n = 915$)	Current	154 (17%)
	Former	252 (28%)
	Never	509 (56%)
Hypertension		669 (73%)
Diabetes mellitus		181 (20%)
Hyperlipidemia		606 (66%)
Family History of Premature CAD		300 (33%)
Symptoms		852 (93%)
	Typical chest pain	94 (10%)
	Atypical chest pain	569 (62%)
	Non-cardiac chest pain	77 (8%)
	Dyspnea	327 (36%)
Number of stress tests performed		421 (46%)
Abnormal/Equivocal stress test		291 (32%)

BMI, Body mass index; CAD, coronary artery disease.