Coronary Plaque Type and Burden By Computed Tomography Angiography Without Association to C-Reactive Protein

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Abstract

Background: Contrast-enhanced computed tomography angiography (CTA) of the coronaries allows identification of plaques. Limited data exists on the relationship between C-reactive protein (CRP) and the plaque type or plaque burden detected by CTA. Aims: We studied relationship between CRP and coronary atherosclerosis. Materials and Methods: 92 patients without history of coronary disease underwent coronary CTA for chest pain. Coronary arteries were evaluated with each detected plaque labeled as calcified, noncalcified or mixed. Logarithmic transformation was done on CRP values for statistical analysis. Results: 1380 coronary segments were evaluated. The average age was 57 years (SE 1.0) and basal metabolic index (BMI) 28.9 kg/m² (SE 0.5). Median CRP level was 2.75 mg/L (range 0.17-16.98). No association was found between CRP quartiles and plaque type. In stepwise multivariate analysis, only diabetes was associated with noncalcified plaque (P < 0.001). When calcified and mixed plaques were added to the model, age (P < 0.001), diabetes (P < 0.02), and statin use (P < 0.05) were associated with an increased number of plaques per subject. No association was found between log-CRP for any type of plaque. Conclusion: There was no association between CRP and plaque type by CTA. Lack of association is likely due to limited spatial resolution and underestimation of noncalcified plaque burden by CTA.

Keywords: Atherosclerosis, Computed tomography angiography, Coronary calcium, CRP, CTA, Imaging

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Introduction

High levels of C-reactive protein (CRP) are associated with increased in cardiovascular events, including myocardial infarction, stroke, and cardiovascular death.¹⁻⁷ Despite these epidemiological associations, the mechanism behind this relationship is unclear. The correlation between atherosclerosis burden by Computed Tomography Angiography (CTA) and CRP levels has been studied by using the Coronary Artery Calcium Scores (CAC), but the results have been inconsistent.¹⁻¹² CAC by non-contrast computed tomography can identify the calcified atherosclerotic plaques but does not assess the noncalcified atherosclerotic burden. Contrast enhanced computed tomographic angiography (CTA) of the coronaries is able to detect noncalcified plaque.¹³⁻¹⁷ The dense calcified plaque is thought to represent the stable coronary lesions, whereas the culprit lesions causing the acute coronary syndrome are frequently noncalcified or with minimal amount of calcium.¹⁸ Given the underestimation of noncalcified atherosclerotic plaque in coronary arteries by using CAC, this could explain the inconsistent relationship between coronary atherosclerotic burden and CRP. Thus, we conducted this study to assess the association between CRP and noncalcified atherosclerotic plaque detected by CTA.

Materials and Methods

Study population

We evaluated 142 male patients 30 years of age or older who were referred to CTA with one of these following problems:
1. Presence of chest symptoms (pain, dyspnea) but thought not to be acute coronary syndrome (94 patients),
2. Abnormal stress test (42 patients),
3. Asymptomatic patient with multiple coronary artery risk factors (6 patients).

Patients were excluded from our study if they met one of the following criteria:
1. Previous history of coronary artery disease,
2. Known history of active infection, inflammatory processes, or malignancy
3. Artifacts or image quality that preclude the complete evaluation of epicardial coronary vessels and
4. Rhythm other than sinus.

This left 92 patients for analysis in our study.

Baseline characteristics were collected from a standardized questionnaire and Electronic Medical Records (EMR). The study protocol was approved by our institutional review board and was compliant with the Health Insurance Portability and Accountability Act (HIPAA).

**Laboratory test**
Serum fasting level of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and CRP were collected on the day of CTA. Serum samples were obtained in ethylenediaminetetraacetic acid (EDTA) tubes and were stored at 4°C before processing. The lipid profiles were measured with standard laboratory methods by our laboratory unit. C-reactive protein (CRP) was measured by using a latex immunoturbidimetric on Architect CI 8200 integrated system (Abbott Diagnostics, Abbott Park, Illinois) using Abbott Diagnostics reagents.

**Measurement of atherosclerosis**

**Scan protocol and image reconstruction**
Scanning was performed using the Brilliance 40 multiple detector computed tomography (MDCT) scanner (Philips Medical Systems, Cleveland, Ohio) following slowing of heart rate (HR) with metoprolol or diltiazem. HR during scanning was less than or equal to 65 bpm. Electrocardiogram (ECG)-gated image acquisition was used to reconstruct images retrospectively. The Brilliance 40 is a 40 × 0.625 mm collimation scanner with gantry rotation speed of 0.42 s per rotation, minimal slice thickness 0.67 mm, and temporal resolution 210 ms or less. A volume of 100-120 mL of Ultravist, 370 mgI/ml contrast media, (Berlex, Montville, New Jersey) was injected intravenously at a rate of 5 ml/s. Scanning was triggered automatically when contrast enhancement within the descending aorta reached a threshold level of 150 HU (Hounsfield Units). Scanning was performed at 120 kV and 800-925 mAs with pitch of 0.2. Reconstructions were done with 0.9 mm thick slices at 0.45 mm interval. At least ten phases were reconstructed for each study and coronary analysis was done of diastolic or endsystolic phase. Image analysis was done with dedicated workstations (Philips Extended Brilliance Workspace, Cleveland Ohio and Vitrea, Vital Images, Minnetonka, Minnesota).

**Coronary CTA analysis**
All scans were analyzed by experienced cardiologist (GS) or radiologist (CS). Calcium scoring was performed according to the Agatston method.[19] Coronary artery segments were divided into 15 separate segments, adapted from modified American College of Cardiology/American Heart Association (ACC/AHA) classification.[20] Proximal portion of the diagonal, obtuse marginal, posterolateral, and posterior descending arteries were evaluated for atherosclerotic plaque. In each coronary artery segment, atherosclerosis was defined as tissue structures more than 1 mm² that existed either within the coronary artery lumen or adjacent to the coronary artery lumen which could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [Figure 1]. Types of atherosclerotic plaque were also defined by the attenuation coefficient of the plaque in Hounsfield Unit (HU). Noncalcified was considered when HU were 50-150 HU and calcified plaque when HU were above arterial lumen contrast attenuation (typically above 300). Mixed plaque was considered when both noncalcified plaque and calcified plaque were noted within the same coronary segment.

![Figure 1: Coronary plaque types (a) Examples of calcified plaque (left picture) (b) Example of mixed plaque (middle picture) (c) Example of noncalcified plaque (right picture) Arrows indicate coronary artery plaque](image-url)
**Statistical analysis**

Statistical analysis was performed with MedCalc version 9.6.3.0 (MedCalc Software, Mariakerke, Belgium). Subjects were divided into quartiles based on the level of CRP. Baseline demographic variables, cardiovascular risk factors, and atherosclerotic plaques were compared across CRP quartiles with chi-square trend test for categorical data and Kruskal Wallis or ANOVA for continuous variables. Cardiovascular (CV) risk factors, demographic variables and natural logarithmic transformation of CRP (ln-CRP) were used as variables to find relationship with the atherosclerotic plaques. Multivariable stepwise regression analysis was used to identify the independent risk factor, including ln-CRP, for total atherosclerotic burden and other type of atherosclerotic plaque. A P value of less than 0.05 was considered statistically significant.

**Results**

The clinical characteristics of ninety two participants are presented in [Table 1] and clinical characteristics according to CRP quartiles are presented in [Table 2]. There was no statistically significant difference across the CRP quartiles in the cardiovascular risk factors, including diabetes, age, body mass index, serum total cholesterol, LDL, and HDL cholesterol. Use of aspirin and statins were equal across quartile of CRP levels. No atherosclerotic plaques was found in 14 (15.2%) subjects. The total number coronary segments evaluated in this study was 1380. There was no statistically significant difference across CRP quartile for total number of plaques, total number of noncalcified plaques, mixed plaques or calcified plaques [Figure 2]. When assessing if subjects with higher total number of plaques, or higher number of any plaque had higher CRP, no association was detected [Figure 3]. Multivariate stepwise analysis of total number of calcified plaques per patient was associated with age (P < 0.0001) and BMI (P < 0.05). Total number of mixed plaques per patient was associated with age (P < 0.05) and diabetes (P < 0.02). Total number of noncalcified plaques was associated only with diabetes (P < 0.01). When we combined three types of plaques in the model, total number of plaques per patient was associated with age (P < 0.01), diabetes (P < 0.02) and statins (P < 0.05). In our cohort, there was no association between CRP and CAC [Figure 4].

**Discussion**

CRP is an acute phase reactant protein primarily produced from hepatocytes. However, recent evidence indicates local CRP production in the inflammatory site modulated by the cytokines, including the atherosclerotic plaque. Study of the relationship between CRP and coronary atherosclerosis by using calcium scores showed inconsistent results. Studies in a certain population including post menopausal women, male military recruits, and hypertensive siblings, found no association between CRP and coronary atherosclerosis using CAC. The St. Francis Heart Study, which showed that CAC predicts CAD events, was unable to

### Table 1: Baseline characteristics including CRP levels and total calcium scores

| Characteristics          | Values       |
|--------------------------|--------------|
| Age years                | 57±1.0       |
| BMI kg/m²                | 28.9±0.5     |
| Total Cholesterol mg/dl  | 175±4.0      |
| CRP mg/L (range)         | 2.75, (0.17–16.98) |
| HDL mg/dl                | 39.2±0.9     |
| LDL mg/dl                | 107±4.5      |
| Diabetes Mellitus%, (n)  | 21.7% (20)   |
| Statin use%, (n)         | 60.9% (56)   |
| Aspirin use%, (n)        | 57.6% (53)   |
| CAC, (range)             | 50.5, (0.3149) |

Data are presented as percent and mean ± SE. For CRP levels and Calcium scores (CAC) data are presented as median and range, BMI = Body mass index, CAC = Coronary artery calcium scores, CRP = C-reactive protein, HDL = High-density lipoprotein, LDL = Low-density lipoprotein

### Table 2: Baseline characteristics according to CRP levels

| Characteristics          | CRP quartile 1 ≤1.38 mg/L n = 23 | CRP quartile 2 ≤2.68 mg/L n = 23 | CRP quartile 3 ≤6.05 mg/L n = 23 | CRP quartile 4 >6.05 mg/L n = 23 | P value   |
|--------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------|
| Age years                | 57.3 (52.5-62.1)                 | 57 (53.2-61)                     | 54.6 (52.3-56.8)                 | 58.9 (54.1-63.6)                 | 0.48      |
| BMI kg/m²                | 28.2 (25.9-30.4)                 | 29.2 (26.8-32)                   | 29.6 (27.7-31.5)                 | 28.8 (26.7-30.9)                 | 0.80      |
| Diabetes Mellitus, %, (n) | 26.1% (6)                      | 34.8% (8)                       | 13.0% (3)                        | 13.0% (3)                       | 0.11      |
| ASA use, %, (n)          | 60.9% (14)                       | 52.2% (12)                      | 56.5% (13)                       | 60.9% (14)                      | 0.93      |
| Statins use, %, (n)      | 65.2% (15)                       | 60.9% (14)                      | 60.9% (14)                       | 56.5% (13)                      | 0.57      |
| CAC                      | 62 (0-1430)                     | 46 (0-2308)                     | 19 (0-3149)                      | 113 (0-1208)                    | 0.84      |
| Total Cholesterol mg/dl  | 166.6 (153.1-180.1)             | 172.7 (153-193)                 | 181.3 (167.6-195)                | 179 (160.5-197.5)               | 0.58      |
| HDL mg/dl                | 40.5 (37.3-43.8)                 | 40.4 (36.8-44.1)                | 38.3 (35.3-41.4)                 | 37.4 (33.3-41.5)                | 0.48      |
| LDL mg/dl                | 105.5 (94.8-116.1)              | 100.6 (84.2-117)                | 108.8 (97.4-120.1)               | 113 (95.3-130.8)                | 0.63      |

Data are recorded as percent and mean with 95% CI. *Data are presented as median and range, BMI = Body mass index, HDL = High-density lipoprotein, LDL = Low-density lipoprotein
find relationship between coronary calcium scores and CRP in persons between ages 50-70. The Framingham Heart Study, on the other hand, demonstrated a positive correlation between CRP and CAC scores in men and women, but this correlation remained only in men after adjustment for CV risk factors.

Calcified coronary plaques evaluated by using CAC can not represent overall atherosclerotic burden. Dense calcified coronary plaques were found more in patients with chronic stable angina, where as the culprit lesions are less calcified. Kelly et al., found that about 51% of patients with normal coronary calcium scores have noncalcified plaque on coronary CTA and 3.7% of those with normal coronary calcium scores had significant coronary artery stenosis.

Even using the contrast-enhanced CTA which can detect more noncalcified atherosclerotic plaque, this might not reveal a total atherosclerotic burden. Study by Leber et al., comparing between intravascular ultrasonography (IVUS) and CTA, demonstrated that 64-MDCT may underestimate the amount of plaques and overestimate luminal diameter compared to IVUS. Only 78% of sections containing hypoechoic plaque (verified by...
IVUS) were detected by CTA. Even within the proximal segments of coronary artery, CTA was able to identify about 83% of noncalcified plaques. Lack of association between CRP levels and atherosclerosis might be due to inadequate spatial resolution and systematic underestimation of noncalcified plaque volume.

**Study limitations**

Limitations in this study are: small number of participants, male-only population, and single-center study, reducing the external validity of the study. Secondly the CRP level was measured in patients who did not have any history of inflammatory diseases or clinical evidence of active infection/inflammation before coronary computed tomography angiography, but some may have occult or undiagnosed inflammation/infection which resulted in unexpected high CRP levels. Thirdly, interpretation of total atherosclerotic burden is problematic. We didn’t evaluate inter-observer variability in interpretation of CTA. The number of segment with plaque is not a good estimation of atherosclerotic burden and volumetric measurements would be better. Finally, a single measurement of CRP could be affected by medical therapy (statin therapy or aspirin) or non-cardiac disease and therefore not reflecting patients’ prior inflammatory state. Additionally, a snapshot of inflammatory activity at the time of blood collection (CRP levels) may not represent the overall lifelong inflammatory processes.

**Conclusion**

CRP levels are not associated with any specific type of atherosclerotic plaque (calcified, mixed and noncalcified plaque) in patients without history of coronary artery disease. We were unable to identify a relationship between CRP levels and coronary atherosclerosis, which could be due to the underestimation of noncalcified plaque size and volume by CTA. Further development in CTA technology might help in identifying atherosclerosis better and more study in this area is required.

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