Presence and severity of noncalcified coronary plaque in asymptomatic patients

Poster No.: C-0539
Congress: ECR 2011
Type: Scientific Paper
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Keywords: Cardiovascular system, CT-Angiography, Contrast agent-intravenous
DOI: 10.1594/ecr2011/C-0539

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Pathologic and angioscopic studies have demonstrated that disruption or erosion of vulnerable plaques and subsequent thromboses are the most frequent cause of acute coronary syndromes (ACS). It has long been recognized that ACS is associated with lipid-rich, vulnerable plaques. Timely and anatomically precise imaging of vulnerable plaques is a medical necessity.

Although invasive coronary angiography (ICA) offers a direct visualization of the plaque surface and intra-luminal structures, ICA could not distinguish the component of plaques. Intravascular ultrasound (US) has been proved as an effective approach to distinguish the composition of plaques. However, the complexity, expense, and invasiveness limit its widespread clinical application. American Heart Association classification showed that a large number of vulnerable plaques are predominantly non-calcified plaques. Coronary CT angiography (CTA) is an emerging non-invasive technique that can evaluate both calcified and non-calcified plaque. Previous studies of non-calcified plaque in CT angiography has confirmed the correlation between non-calcified plaques and vulnerable plaques. What's more, some studies have also observed the high risk of non-calcified plaques on the ACS.

Pathological studies demonstrate that ACS is more likely to be associated with plaques without flow limiting stenosis. It is important to detect the anatomic localization and vulnerability of plaques at an early stage without symptom. Therefore, our purpose was to prospectively study the prevalence, severity of non-calcified coronary plaques in asymptomatic patients and investigate the relative risks.
Methods and Materials

Study Population

The study protocol and radiation dose information was approved by the local Ethics Committee. All patients were given written informed consent, having received information about the risk of radiation and iodine allergic reactions.

Between September 2009 and April 2010, 573 patients were prospectively enrolled. Patients were excluded from the study cohort because of: refusal or withdrawal of consent (n=2); allergy to iodinated contrast agents (n=3); renal insufficiency (creatinine >120 µmol/L, n=2); history of coronary artery bypass graft surgery and myocardial infarction (n = 63); non-anginal chest pain (n=69); atypical angina (n=77); and typical angina (n=65).

After the exclusion of the 281 patients with the criteria listed above, the study included the remaining 292 patients (134 women, 158 men; mean age, 58.3±10.7 years; age range, 35-94 years).

For these asymptomatic patients, reasons for referral for CT angiography were classified as follows:

1. Screening (presence of one risk factor or more risk factors);
2. Evaluation prior to high-risk cardiac surgery;
3. Regional wall motion abnormalities on echocardiography;
4. Electrocardiographic evidence of ischemic ST-segment, or T-wave changes;
5. Clinical suspicion of valvular heart disease.

Risk factors were identified through a structured interview and existing medical record data. Data collected included the patient’s age, gender, estrogen status, and the presence or absence of diabetes mellitus, hypercholesterolemia, current or prior cigarette smoking, hypertension, and a positive family history (age<60) coronary disease in a first-degree relative. Patients were also assessed for body mass index (BMI): (weight /height²). Obesity was defined as a BMI > 27. Hypertension was defined as a documented history of high blood pressure>140/90 mmHg or the use of antihypertensive medication. Hypercholesterolemia was defined as a total cholesterol level #5 mmol/L or treatment with medication.[13] Estrogen status was considered positive if women were premenopausal or had missing or nonfunctioning ovaries with oral estrogen replacement therapy and negative if they were postmenopausal (ovaries missing or nonfunctioning) and were not on estrogen replacement therapy.[14]
According to classification methods presented by Morise,[15] patients were classified as having a low, intermediate or high pre-test likelihood for coronary artery disease (CAD) based on age, gender, estrogen status, diabetes mellitus, hypertension, smoking, hypercholesterolemia, family history, and obesity. Classification of risk was carried out by a blinded observer who had no knowledge of the outcome of CT angiography.

**CT Protocol**

All CT examinations were performed using a 320-raw detector CT (Aquilion ONE, Toshiba, Nasu, Japan). The Agatston score was assessed on unenhanced images with a detection threshold of 130 HU by using semi-automated software (Vitrea II FX#Vital Images, Corp, USA). Next, in absence of contraindications (hypotension, current use of nitrate medications, migraine sensitive to nitrates), 0.4 mg nitroglycerin was administered two minutes prior to scanning. The scanning range was set from the level of the tracheal bifurcation to the diaphragm to ensure entire heart coverage (Scanning range coverage was 12-14cm).

All scanning was carried out using detector collimation, 320 × 0.5 mm. Other scanning parameters were varied according to BMI. For BMI <18, tube voltage was 100kV and tube current 350 mA; for BMI 19 - 24#tube voltage was 100kV and tube current 400 mA; for BMI >24, tube voltage was 120kV and tube current 450 - 500 mA.

With the gantry rotation of 350 ms, DVCT provided a temporal resolution of 175 ms. Beta-blockade was used to achieve a target heart rate of 65 bpm. There were no patients with a contraindication to beta-blockade, and no observed or reported side effects from the beta blockers. A target heart rate <65 bpm during scanning was used to allow a sufficiently long coronary artery rest period to allow scanning during a single heart beat.

**Reconstruction Method**

Image reconstruction was performed with a section thickness of 0.5mm and an increment of 0.25mm. The reconstructed field of view was adjusted to exactly encompass the heart (180-240 mm). Images were reconstructed at 75% of the R-R interval. In case of insufficient image quality, additional reconstructions were performed in 2% steps of the R-R interval within the scanning window. Multi-planar reconstruction (MPR), curve planar reconstruction (CPR) and volume rendering (VR) were applied on workstation to assess the extent of vessel stenosis and image quality of coronary artery.

**CT Data Analysis**

All CT data were interactively assessed by two readers (S. G. and L. G.), with 7 and 6 years of experience in cardiovascular radiology) who were blinded to clinical information. Decisions were reached by consensus.
The presence of non-calcified atherosclerotic plaque tissue was defined as any structure in the coronary artery wall with a CT density less than the contrast enhanced coronary lumen but greater than the surrounding connective tissue. Standard display settings were used for the evaluation of the contrast-enhanced CT scans (window width 800 Hounsfield units [HU]; window center 250 HU).

The degree of stenosis was measured using the narrowest dimension of the lumen at the level of stenosis compared with a more normal lumen diameter distally. Segments were graded as normal appearance (grade 1 stenosis, 0% to 24%); slightly narrowed, (grade 2 stenosis, 25% to 49%); moderately narrowed, (grade 3 stenosis, 50% to 74%) and severely narrowed#(grade 4 stenosis, >75%)(Fig. 1). In patients with a technically limited coronary CTA examination, vessel segments that could not be evaluated were assumed to be normal.
Results

The average heart rate of patients during scanning was 65.6 ± 6.2 bpm (range, 53-78 bpm). In total, 102 patients (34.9 %) had a low pre-test likelihood of CAD, 150 patients (51.4%) had an intermediate pre-test likelihood of CAD and 40 patients (13.7%) presented with a high pre-test likelihood of CAD.

A total of 135 patients (46.2%) had a normal calcium score, in whom subsequent contrast enhanced coronary CT angiography revealed the presence of non-calcified plaques in 24 patients (17.8%, 24/135). In 157 patients (53.8%) with coronary calcifications, additional non-calcified plaques in other segments were detected in 88 patients (56.1%, 88/157) (Fig.1 on page 7). In summary, non-calcified plaques, alone or in combination with calcifications in other segments, were detected in a total of 112 in 281 patients (38.4%).

In patients with non-calcified plaques, mild disease was present in 83 of 112 patients (74.1%), and moderate disease without stenosis was present in 13 of 112 (11.6%). Ten patients (8.9%) had at least moderate (# 50%) stenosis, and 6 (5.4%) had severe stenosis (> 75%). There was significantly difference of stenosis among patients with low, intermediate and high pre-test likelihood (P=0.001) (Fig. 2 on page 7).

The prevalence of non-calcified plaques did not differ among low, intermediate and high pre-test likelihood (P=0.08). Logistic regression demonstrated that patients with non-calcified plaques were characterized by significantly higher total cholesterol (P=0.008) and presence of diabetes mellitus (P<0.001). Age, gender, estrogen status, smoking, hypertension, and family history did not differ between patients with and without non-calcified plaques.

In 149 patients without diabetes mellitus, there were 41 (27.5%, 41/149) patients with non-calcified plaques, whereas non-calcified plaques were more common in patients with diabetes mellitus (49.7%, 71/143). There were 129 patients without hypercholesterolemia, including 91 patients without non-calcified plaques (70.5%, 91/129). In patients with hypercholesterolemia, a higher proportion had non-calcified plaques (54.6%, 89/163).
Fig. 0: Distribution of coronary CT angiography findings.

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**Fig. 0:** Distribution of lumen narrowing classified by different pre-test likelihood.

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Conclusion

1. The results show that the prevalence of non-calcified plaques is higher when there is coronary calcification in other segments. A recent study of intravascular US also confirms that patients with high calcium score have more vulnerable plaque components compared with those with low calcium score. Therefore, calcium scoring is in fact an indirect reference index to classify the risk of ACS. In the future, studies about risk stratification classified by non-calcified plaques may have more accuracy and practicability.

2. Our study also confirms that Morise scores were associated with severity of non-calcified plaques. However, it is ineffective to classify the risk of incidence of non-calcified plaques. For ACS, the composition of these plaques, rather than the degree of the stenosis, is the major cause of ACS. Thus, the prevalence of non-calcified plaque is an important for risk classification of ACS. Among the CAD risk factors, the prevalence of non-calcified plaques is only characterized by hypercholesterolaemia and diabetes mellitus.

In conclusion, for asymptomatic patients, hypercholesterolaemia and diabetes mellitus are high risk factors of the prevalence of non-calcified plaques, while Morise score is associated with severity of non-calcified plaques.
References


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