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ORIGINAL ARTICLE

Correlation between Acute Coronary Syndrome Classification and Multi-detector CT Characterization of Plaque[△]

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Key words: acute coronary syndrome; coronary plaque; multi-detector CT

Objective To determine if multi-detector CT (MDCT) characterization of plaque is correlated with the classification of acute coronary syndrome (ACS).

Methods Altogether 1900 patients were examined by MDCT from December 2007 to May 2009, of whom 95 patients fulfilled the criteria of ACS. Those patients were divided into the discrete plaque group ($n=61$) and diffuse plaque group ($n=34$) based on the findings in MDCT. The clinical diagnosis of ACS and CT results were analyzed, including segment stenosis score, segment involvement score, 3-vessel plaque score, left main score, calcification score, and remodeling index. The incidences of major adverse cardiac events in follow-up period were also recorded.

Results The patients of the diffuse plaque group were older than those of the discrete plaque group ($P<0.0001$). The diffuse plaque group presented more cases of hypertension, peripheral artery disease, diabetes, and heart failure than discrete plaque group (all $P<0.05$). All the 5 patients with ST-segment elevation myocardial infarction were found in discrete plaque group. The segment stenosis score of the discrete plaque group was lower than that of the diffuse plaque group (5.15 ± 3.55 vs. 14.91 ± 5.37 , $P<0.001$). The other four scores demonstrated significant inter-group difference as well (all $P<0.05$). The remodeling index of the discrete plaque group was higher (1.12 ± 0.16 vs. 0.97 ± 0.20 , $P<0.05$). Follow-up data showed that major adverse cardiac events occurred more frequently in diffuse plaque group than in discrete group (29.41% vs. 11.48%, $P=0.0288$).

Conclusions Characteristics of discrete and diffuse plaques may be significantly different among different classes of ACS. The diffuse plaque may present higher risk, correlated to higher mortality. The diagnosis of discrete and diffuse plaques by MDCT would provide a new insight into the prognosis and treatment of ACS.

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THE acute coronary syndrome (ACS) includes unstable angina pectoris (UAP), ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI). The classification of unstable angina by Braunwald has been widely accepted and correlated to plenty of clinical events.^{1,2} Death and myocardial infarction occur more frequently in those with recent rest pain (class III) and in post-infarction patients (class C). The patients with recent onset or worsening angina have more calcified lesions whereas those with rest angina present more thrombus in angiography.³ It has been reported that higher classes of unstable angina showed more complex lesions in angiography.⁴ The culprit lesions and number of vessels involved vary significantly in the same Braunwald class.⁵ The coronary occlusion or flow limitation detected by coronary angiography (CAG) is more severe in STEMI than in NSTEMI,⁶ yet no difference was observed between STEMI and NSTEMI in terms of prognosis.⁷ Therefore, the clinical diagnosis of unstable angina, STEMI, and NSTEMI do not provide much pathophysiologic information for classification.

CAG is widely applied in the diagnosis of ACS, but it is an invasive procedure. Multi-detector CT (MDCT) is an alternative method to detect the local pathological changes in both the lumen and the arterial wall, thus suitable for the analysis of plaques. It has already been demonstrated that plaques can be divided into three types, namely soft plaque, fibrous plaque, and calcified plaque.⁸ In our clinical practice, we also observed that there are two kinds of plaques, discrete soft plaque and diffuse plaque. We presume that discrete soft plaque and diffuse plaque represent different pathophysiological processes and correlate to the classification of ACS. In this study, we observed the relation between MDCT characterization of plaque and the classification of ACS.

PATIENTS AND METHODS

Patients

From December 2007 to May 2009, altogether 1900 patients were examined with MDCT. The patients presented with UAP, STEMI, and NSTEMI were confirmed as ACS patients, and written informed consent was obtained. The ACS patients were divided into 2 groups based on the plaque types observed in MDCT – the discrete plaque group and diffuse plaque group. Severe plaques (area stenosis > 70%) were observed in all the included patients. Of the severe plaque, the discrete plaque was defined as only one short plaque (length < 20 mm) in each main artery while

the other arteries were normal on MDCT. The diffuse plaque was defined as one long plaque (length ≥ 20 mm) or that most culprit vessels were diseased on MDCT regardless of the number of plaque (Fig. 1).

MDCT scan protocol

Dual-source CT (DSCT) scanning was performed on a SOMATOM Definition (Siemens Medical Solutions, Forchheim, Germany). For contrast enhanced scanning, vessel opacification was achieved with automated injection of 80 mL iohexol injection (Ominpaque®, GE Healthcare, Shanghai) at a flow rate of 5 mL/s by a power injector. Individual circulation time was estimated based on the test-bolus technique, using a 20 mL bolus and dynamic evaluation software (Dyn EvaTM, Syngo®, Siemens). The scanning parameters were as follows: collimation 2×32×0.6 mm, slice acquisition 64×0.6 mm using the z-flying focal spot technique, gantry rotation time 330 ms, pitch 0.20-0.43 adjusted to heart rate, tube voltage 120 kV, and maximum tube current 400 mAs per rotation. Beta-blockers (oral metoprolol, 25-50 mg according to heart rate) were applied to the patients whose heart rate was over 65 beat/min to ensure the temporal resolution.

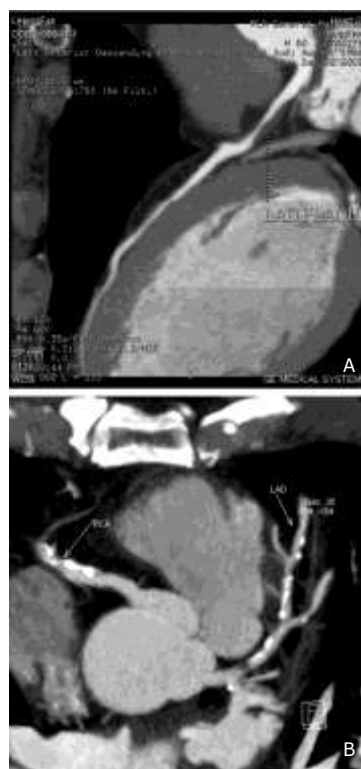


Figure 1. CT images of discrete plaque and diffuse plaque.
A. A low density, discrete, and positively remodeled plaque at left anterior descending (LAD) coronary artery.
B. Stenotic and calcified diffuse LAD lesions and areas of low density.

Cardiac scanning was performed on a 64-slice MDCT scanner (LightSpeed VCT, GE Healthcare) with rotation time of 350 ms and pitch of 0.2. Helical scan data were obtained with retrospective electrocardiographic gating. Images were reconstructed immediately after scanning to identify motion-free coronary artery images. The optimal reconstruction phase was determined as the one with the least amount of coronary artery motion after comparison of different phases. Five MDCT postprocessing techniques – maximum intensity projection, multiplanar reformation, cross-sectional area, and diameter and area derived from semi-quantitative coronary software – were relied upon to grade plaques.

Plaque score

The plaque score was calculated according to the method developed by Min et al⁹ combining segment stenosis score, segment involvement score, 3-vessel plaque score, and left main score. The segment stenosis score was adopted as a measure of the overall extent of coronary artery plaque. Each individual coronary segment was graded from 0 (having no plaque) to 3 (having severe plaque) based on the extent of coronary area stenosis, and the scores of all 16 individual segments were summed to yield a total score ranging from 0 to 48. The segment involvement score was calculated as the total number of coronary artery segments presenting with plaque, irrespective of the degree of area stenosis in each segment. The 3-vessel plaque score was determined at 0 or 1 based on the simultaneous presence of plaque in the left anterior descending, left circumflex, and right coronary arteries, irrespective of severity. Left main score was measured according to the presence of any plaque within the left main artery. The calcification score represented the calcification degree of each segment, which ranged from 0 (having no calcification) to 3 (having severe calcification). Images of poor quality were excluded. Two independent observers blind to the clinical data interpreted the CT images.

Plaque remodeling

The coronary arterial remodeling was defined as a change in the vessel diameter at the plaque site in comparison with the normal-appearing vessel segment proximal to the plaque (reference segment). The remodeling index (diameter at plaque site/reference diameter) was determined by manual inspection in longitudinal reconstruction. The remodeling index on MDCT was calculated and positive remodeling reported when the diameter at plaque site was at least 10% larger than the reference diameter.¹⁰

Follow-up

The primary point of this study was the incidence of major adverse cardiac events (MACE), defined as re-hospitalization for angina pectoris, revascularization, acute myocardial infarction, and cardiac death.

Statistical analysis

Data were presented as means±SD. Statistical analysis was performed using SPSS13.0. The comparison between the discrete plaque group and the diffuse plaque group was conducted using the Student's *t*-test and chi-square test. A *P* value lower than 0.05 was considered statistically significant.

RESULTS

General information of the patients

Of the 1900 patients examined, 95 patients satisfied the entry criteria of STEMI, NSTEMI, and UAP. Sixty-one patients (64.2%) were classified into the discrete plaque group and 34 (35.8%) the diffuse plaque group. The patients in the diffuse plaque group were older ($P<0.0001$), with higher incidences of hypertension ($P=0.0012$), diabetes ($P=0.0033$), peripheral artery disease ($P=0.0024$), and heart failure ($P=0.0184$). No difference in gender was observed between the two groups (Table 1).

Comparison between discrete and diffuse plaque groups in ACS

There was no significant difference between the two groups in terms of the case number of STEMI, NSTEMI, and UAP. However, the percentages showed that there were more diffuse plaque cases than discrete plaque ones in the NSTEMI patients. All the 5 patients with STEMI were in discrete plaque group (Table 2).

Plaque score and remodeling index

The segment stenosis score, segment involvement score, and 3-vessel plaque score showed that the average score in the discrete plaque group was significantly lower than in the diffuse plaque group ($P<0.0001$). There were significantly more left main lesions in the diffuse plaque group ($P=0.0217$) (Table 3).

Most of the discrete plaques showed positive remodeling (23 in the 28 discrete plaques suitable for remodeling measurement, 82.1%) and most of the diffuse plaques negative remodeling (8 in the 12 diffuse plaques suitable for remodeling measurement, 66.7%). The remodeling index was higher in the discrete plaque group than that in the diffuse plaque group (1.12 ± 0.16 vs. 0.97 ± 0.20 , $P<0.05$).

Table 1. Clinical information of the 95 enrolled ACS patients

Group	Age (yr)	Male [n (%)]	Smoking [n (%)]	Family history [n (%)]	Hypertension [n (%)]	Diabetes [n (%)]	PAD [n (%)]	Hyperlipidemia [n (%)]	Heart failure [n (%)]
Discrete plaque (n=61)	54.0±10.5	46 (75.4)	28 (45.9)	11 (18.0)	22 (36.1)	10 (16.4)	3 (4.9)	7 (11.5)	0 (0.0)
Diffuse plaque (n=34)	66.4±11.2	28 (82.4)	16 (47.1)	7 (20.6)	24 (70.6)	15 (44.1)	9 (26.5)	3 (8.8)	3 (8.8)
<i>P</i>	0.0000	0.4343	0.9137	0.7606	0.0012	0.0033	0.0024	0.6864	0.0184

ACS: acute coronary syndrome; PAD: peripheral artery disease.

Table 2. STEMI, NSTEMI, and UAP in the discrete plaque and diffuse plaque groups

Group	Clinical diagnosis		
	STEMI [n (%)]	NSTEMI [n (%)]	UAP [n (%)]
Discrete plaque (n=61)	5 (8.2)	3 (4.9)	53 (86.9)
Diffuse plaque (n=34)	0 (0.0)	4 (11.8)	30 (88.2)
<i>P</i>	0.2280	0.4151	0.8948

STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UAP: unstable angina pectoris.

Table 3. Severity of ACS represented by plaque score

Group	Segment stenosis score	Segment involvement score	3-vessel plaque score	Left main score	Calcification score
Discrete plaque (n=61)	5.15±3.55	2.46±1.89	0.20±0.40	0.15±0.36	1.51±2.90
Diffuse plaque (n=34)	14.91±5.37	6.15±2.00	0.68±0.47	0.38±0.49	8.88±7.91
<i>P</i>	0.0000	0.0000	0.0000	0.0217	0.0000

Table 4. Major adverse cardiac events (MACE) at follow-up

Group	MACE [n (%)]	Re-hospitalization [n (%)]	Revascularization [n (%)]	AMI [n (%)]	Cardiac death [n (%)]
Discrete plaque (n=61)	7 (11.48)	4 (6.56)	3 (4.92)	0 (0.00)	0 (0.00)
Diffuse plaque (n=34)	10 (29.41)	5(14.71)	3 (8.82)	0 (0.00)	2 (5.88)
<i>P</i>	0.0288	0.3500	0.7564	-	0.6018

AMI: acute myocardial infarction.

Follow-up

65 patients underwent percutaneous coronary intervention (PCI), in whom 39 were in the discrete plaque group and 26 in the diffuse plaque group. Two patients with NSTEMI died after emergent PCI, both in the diffuse plaque group. Coronary artery bypass grafting was performed in 4 cases, 1 in the discrete plaque group and the other 3 in the diffuse plaque group. The median follow-up period was 500 (range, 247-760) days. The total incidence of MACE was higher in the diffuse plaque group than in the discrete plaque group [10 (29.41%) vs. 7 (11.48%), $P<0.05$, Table 4].

DISCUSSION

Researchers used to consider that the atherosclerosis is a continuous process.¹¹ The vulnerable plaque theory is the most popular in explaining ACS. The plaques prone to instability and rupture have a large lipid core, a low density of smooth muscle cells, a high concentration of inflammatory cells, and a thin fibrous cap covering the lipid core compared with stable plaques.¹² ACS is a cluster of clinical syndrome consisting of STEMI, NSTEMI, and UAP. Although

the diagnosis conveys some information, there is an enormous overlap in terms of prognostic assessment among these three classes of ACS. What makes the classification even less accurate is the varying mortality, from 5% to as high as 25%-35%. Based on CAG, which could pinpoint the location and extent of the coronary lesions, the Appropriateness Criteria for Coronary Revascularization and SYNTAX Score are the two most comprehensive guidelines for coronary revascularization,^{11,13} yet none of them could avoid the invasive procedure.

Although CT angiography may be more accurate and provides more information on the nature of ACS, MDCT could image both the lumen and arterial wall noninvasively. The quantitative measurement of CT profile developed by James K. Min et al greatly facilitates the understanding of the nature of plaque.¹⁴ Therefore, the plaque characteristics measured by MDCT could combine with clinical data to produce a better ACS stratification.

The clinical diagnosis of ACS does not differentiate plaque characteristics. In this study, no significant difference was found between the discrete plaque group and the diffuse plaque group in the number of cases of UAP, STEMI,

and USTEMI. Resulting from an acute imbalance between myocardial oxygen demand and supply, mostly from a reduction in myocardial perfusion, NSTEMI has seen an increasing incidence, and a mortality surpassing that of STEMI. According to the data of the National Registry of Myocardial Infarction in America, the proportion of NSTEMI in ACS increased from 14.2% to 59.1% from 1990 to 2006, whereas the proportion of STEMI decreased.¹⁵

The patients with STEMI are exclusively of large soft plaque. It has long been understood that the acute occlusion is mainly caused by a soft vulnerable plaque, possibly a thrombus. A single large soft plaque is the most dangerous.¹⁶ In the study by Huang et al,¹⁷ culprit lesions in the occlusive group had significantly longer length and higher MDCT lesion attenuation compared with the lesions in the stenotic group.

The score system by Min et al⁹ is an efficient indicator of the extensiveness of atherosclerosis. The higher the score is, the severer the coronary disease is, and the poorer the prognosis. By dividing the patients with ACS into the discrete plaque and the diffuse plaque groups, we observed huge inter-group difference without much overlap. The patients in the discrete plaque group were much younger and had lower percentage in some risk factors including hypertension, diabetes, peripheral artery disease, and heart failure. The plaques in the discrete plaque group showed a low to very low density, a zigzag shape, and positive remodeling. These plaque characteristics deserve great attention. In a large proportion of previously asymptomatic individuals, sudden coronary death or acute myocardial infarction occurs as the first manifestation of coronary atherosclerosis.

The patients in the diffuse plaque group showed a different picture. The MDCT showed diffuse, extensively calcified, fibrotic, and negatively remodeled plaques. The patients usually had a protracted course and rarely developed sudden coronary events. The pathological basis of ACS with diffuse lesion is usually considered to be that atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS.

MACE rate at the follow-up would be the best way to test the hypothesis of discrete and diffuse plaque theory. The total incidence of MACE was significantly higher in the diffuse plaque group than in the discrete plaque group. Two deaths occurred, and both in the diffuse plaque group. The rest of the events were due to revascularization and re-hospitalization, which were not hard endpoint. The follow-up result reconfirms the important issue that the

diffuse lesions produce more ischemic events and worse prognosis.

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