

# Characteristics of culprit lesions in young patients with metabolic syndrome and classic cardiovascular risk factors

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**Abstract.** The association between cardiovascular risk factors (CVRFs) and characteristics of coronary plaque in young patients has remained to be fully elucidated. Therefore, the present study sought to determine the association between CVRFs and phenotypes of culprit coronary plaques revealed by optical coherence tomography (OCT) in young patients with stable coronary heart disease (CHD) and acute coronary syndrome (ACS). OCT imaging pullback was performed at corresponding sites on 123 lesions in 123 young patients (age, 36±7 years), including those with stable CHD and ACS. Patients with analyzable OCT images were classified as having thin-cap fibroatheromas (TCFAs), plaque rupture, macrophage accumulation, calcified nodule, vasa vasorum, cholesterol crystal and erosion. TCFAs were more prevalent in patients with metabolic syndrome (MetS) than in those without MetS ( $P=0.020$ ). Plaque rupture was more common in smokers than in non-smokers ( $P=0.002$ ). Multivariate analysis indicated that MetS was independently associated with TCFAs ( $P=0.041$ ) and smoking was independently associated with plaque rupture ( $P=0.006$ ). Young patients with MetS were demonstrated to have more extensive TCFAs and young smokers had a higher prevalence of culprit plaque rupture.

smoking, type 2 diabetes (T2D), hypertension, hypercholesterolemia, family history and metabolic syndrome (MetS) (1,2). Imaging studies have demonstrated an association between plaque phenotypes and CVRFs in middle-aged and elderly patients with CHD (3-5). However, the pathophysiology of atherosclerosis in young patients with CHD differs from that in older patients (6). To date, the association between CVRFs and the characteristics of culprit coronary plaque in young patients has remained to be fully elucidated. Furthermore, the incidence of CHD has increased in young individuals. CHD may have serious consequences, including premature death and long-term disability (7).

Optical coherence tomography (OCT) has emerged as the most accurate imaging modality for intracoronary evaluation, with a resolution of 10-20  $\mu\text{m}$  (8). OCT has been widely used to investigate atherosclerotic plaque microstructure, which may be a key factor in determining plaque stability (9). OCT findings are validated by histologic evaluation (10). In the present study, the association between the phenotype of the culprit atherosclerotic plaque as determined by OCT and CVRFs in young patients were assessed.

## Introduction

Coronary heart disease (CHD) is correlated with well-acknowledged cardiovascular risk factors (CVRFs), including cigarette

## Patients and methods

**Patients.** The present study was a retrospective, single-center study. Consecutive patients (age, 36±7 years; male 87%, female 13%) who underwent OCT between April 2014 and March 2017 in the Cardiology Department of Beijing Anzhen Hospital, including those with stable CHD and acute coronary syndrome (ACS), were selected. The exclusion criteria were a known history of severe hepatic or renal dysfunction, an ongoing inflammatory condition, familial hypercholesterolemia and arthritis. Patients with poor image quality, incomplete pullback, or missing data were also excluded. All of the patients provided informed consent and the study protocol was approved by the Ethics Committee of the Beijing Anzhen Hospital (Beijing, China).

**Definition of CVRFs.** The definition of MetS was based on the criteria established in the Joint Scientific Statement (11). An adult with ≥3 of the following was deemed to have MetS: Waist circumference, ≥90 cm for males or ≥80 cm for females; triglycerides, ≥150 mg/dl; high-density lipoprotein cholesterol,

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$\leq 40$  mg/dl; systolic blood pressure (SBP),  $\geq 130$  mmHg and/or diastolic blood pressure (DBP),  $\geq 85$  mmHg, or treated hypertension; and fasting blood glucose level,  $\geq 100$  mg/dl or treated T2D. Smoking was defined as current cigarette smoking. Hypertension was defined as SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg, or treated hypertension. T2D was defined as fasting blood glucose  $> 126$  mg/dl or treated T2D (a diabetic diet or prescription of oral hypoglycemic agent). Hypercholesterolemia was defined as total cholesterol  $> 200$  mg/dl or treated hypercholesterolemia. A family history of coronary artery disease (CAD) was defined as premature CAD in a first-degree relative (a male aged  $< 55$  years or a female aged  $< 65$  years).

**Coronary angiography (CAG) and OCT procedures.** Diagnostic angiograms were recorded via radial access using a 5.24-mm French (5-Fr) catheter and after administering a 5,000-IU bolus of heparin. Culprit lesions were identified via CAG and electrocardiographic ST-segment alterations. The decision of whether to perform OCT was at the discretion of the operator. A 0.014-inch guidewire was placed distally in the target vessel and an intracoronary injection of 200 mg nitroglycerin was administered via a 6-Fr guiding catheter. Frequency domain OCT images were acquired using a C7-XR OCT Intravascular Imaging System (St. Jude Medical), which was advanced to the culprit lesion. During image acquisition, the coronary blood flow was replaced by continuously flushing contrast media directly from the guiding catheter at a rate of 3–4 ml/sec with a power injector, thus creating a virtually blood-free environment with the integrated automated pull-back device at 20 mm/sec. In the OCT investigations, 5–10 ml of contrast media was used, the fluoro time was 2–4 sec and the radiation dose was 30.6–61.2 mGray.

**OCT image analysis.** The operator who performed the pull-back and an independent investigator who was blinded to the clinical presentation analyzed the OCT images offline. Any disagreements were resolved by consensus. A thin-cap fibro-atheroma (TCFA) was defined as an OCT-delineated necrotic core subtending a  $> 90^\circ$  arc and covered by a fibrous cap with a thickness of  $< 65 \mu\text{m}$  (5). Plaque erosion was defined by the presence of preserved vascular integrity (intact fibrous cap), a larger residual lumen and a platelet-rich thrombus (12). A vasa vasorum was defined as a small black hole within a plaque, 50–300  $\mu\text{m}$  in diameter, that was present on at least 3 consecutive frames in pullback images (13). Cholesterol crystals were defined as thin linear structures with high backscatter and without attenuation within the plaque (14). Plaque rupture, macrophage accumulation, calcified nodules and percent area stenosis (AS%) were defined as per the International Working Group for Intravascular Optical Coherence Tomography consensus standards (15).

**Statistical analysis.** Categorical data are presented as counts and proportions and were compared using a  $\chi^2$  test. The distributions of the continuous variables across the study groups were tested with the Shapiro-Wilks test. Normally distributed data are presented as the mean  $\pm$  standard deviation and were compared using an independent-samples t-test. Non-normally distributed data are presented as the median (interquartile range)

Table I. Baseline characteristics of the patients (n=123).

Item	Value
Age (years)	36 $\pm$ 7 (20–45)
Male sex	107 (87.0)
Family history of CHD	10 (8.1)
Smoking	67 (54.5)
Hypertension	63 (51.2)
Diabetes mellitus	22 (17.9)
Hypercholesterolemia	15 (12.2)
Metabolic syndrome	82 (66.7)
ACS	77 (62.6)
Smoking	49 (63.6)
Stable CHD	46 (37.4)
Smoking	18 (39.1)
Pharmacological therapy	
Aspirin	28 (22.8)
Statins	25 (20.3)
Beta blockers	31 (25.2)
ACEI or ARB	34 (27.6)
Insulin	5 (4.1)
EF (%)	63 (60–68)
Culprit vessel	
Left main	4 (3.3)
Left anterior descending	83 (67.5)
Left circumflex	10 (8.1)
Right coronary artery	26 (21.1)
CTNI (ng/ml)	0.10 (0.02–7.33)
BNP (pg/ml)	57 (35–340)

Values are expressed as the mean  $\pm$  standard deviation, median (interquartile range) or n (%). ACS, acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; EF, ejection fraction; CHD, coronary heart disease; CTNI, cardiac troponin I; BNP, b-type natriuretic peptide. Normal ranges: CTNI (0–0.04 ng/ml); BNP (0–125 pg/ml).

and were compared using a non-parametric test. Univariate and multivariate logistic regression analyses were performed to assess independent predictors. All of the statistical calculations were performed using SPSS software version 22 (IBM Corp.).  $P < 0.05$  was considered to indicate statistical significance.

## Results

**Patient information.** In the present study, 123 patients (age, 36 $\pm$ 7 years; male 87.0%, female 13%) who underwent CAG and OCT were analyzed. Their baseline clinical characteristics and CAG data are presented in Table I. Cigarette smoking, hypertension, T2D, hypercholesterolemia and MetS were present in 54.5, 51.2, 17.9, 12.2 and 66.7% of the study population, respectively. The percentages of patients using aspirin, statins, beta-blockers, ACEIs or ARBs, and insulin were 22.8, 20.3, 25.2, 27.6 and 4.1%, respectively. The percentages of smokers in the stable angina cohort vs. the ACS cohort

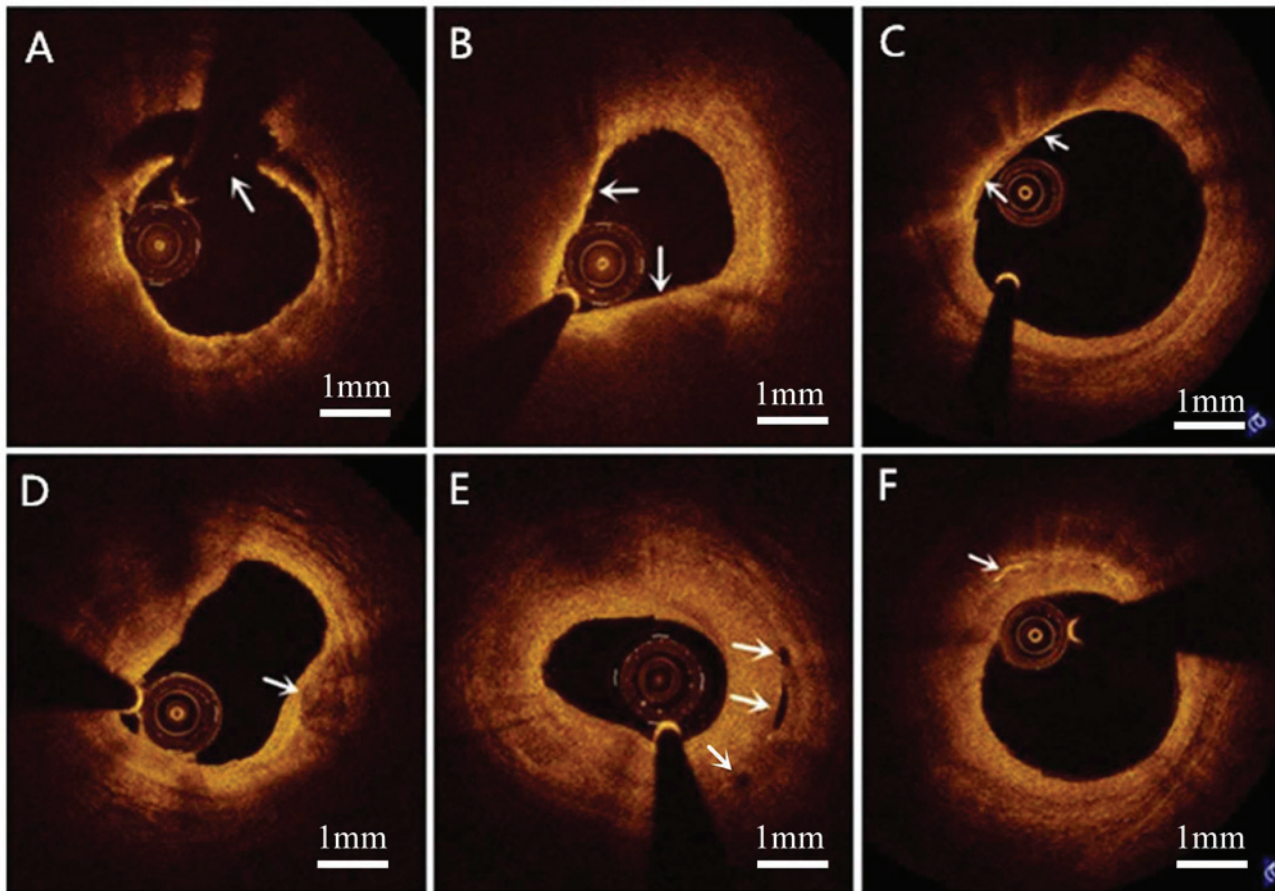


Figure 1. Representative optical coherence tomography images of different coronary plaque phenotypes (arrows). (A) Plaque rupture: The fibrous cap is broken and the plaque content is partially washed away, leaving a cavity (11 to 3 o'clock). (B) Thin-cap fibroatheroma: A large ( $>90^\circ$ ) lipidic core and a thin ( $<65\ \mu\text{m}$ ) fibrous cap (5 to 11 o'clock). (C) Macrophage accumulation: Signal-rich, distinct or confluent punctate regions that exceed the intensity of the background (9 to 12 o'clock). (D) Calcified nodule: A single region of calcium (signal-poor or heterogeneous, with a sharply delineated border) protruding into the lumen (3 to 4 o'clock). (E) Vasa vasorum: Small black holes within a plaque, 50–300  $\mu\text{m}$  in diameter, present on at least 3 consecutive frames. (F) Cholesterol crystal: A thin linear structure with high backward scatter and without attenuation.

were 39.1% vs. 63.6%, respectively ( $P=0.013$ ). Left-anterior descending lesions accounted for 67.5% of all culprit lesions.

**Characteristics of OCT-derived plaques and CVRFs.** Distinct phenotypes of OCT-derived plaques and their associations with CVRFs are presented in Table II. TCFAs and macrophage accumulation were more prevalent in patients with than without MetS ( $P=0.020$ ) and hypertension ( $P<0.001$ ), respectively. Cholesterol crystals presented more frequently in patients with than without a family history of CHD ( $P=0.004$ ) and hypercholesterolemia ( $P=0.031$ ). The extent of plaque rupture was greater in smokers than in non-smokers ( $P=0.002$ ). Vasa vasorum was more common in the culprit lesions of non-smokers than in those of smokers ( $P=0.003$ ). By contrast, no significant association was observed between erosions and CVRFs or between calcified nodules and CVRFs in the present study. Representative OCT images are provided in Fig. 1.

**Multivariate analysis.** To assess the association between TCFAs and CVRFs or between plaque rupture and CVRFs, multivariate regression analyses were performed. Risk factors with  $P<0.100$  from the univariate analysis were included in the multivariate analyses. As presented in Table III, after adjusting for traditional confounding factors, MetS was independently

associated with TCFAs [risk ratio (RR), 2.421; 95% CI, 1.038–5.649;  $P=0.041$ ]. Of the CVRFs, smoking retained an independent association with plaque rupture (RR, 8.301; 95% CI, 1.813–38.015;  $P=0.006$ ).

## Discussion

The major results of the present study were as follows: i) MetS was independently associated with TCFAs; and ii) smoking was independently associated with plaque rupture. To the best of our knowledge, the present study was the first OCT study investigating the association between culprit plaque phenotype and CVRFs in young patients.

Young individuals with premature CHD may have fewer risk factors of CHD, but MetS is frequently present in this group of patients and puts them at a high risk of early-onset clinical CHD (16). In the present study, 66.7% of the patients had MetS. Kalantzi *et al* (7) reported that MetS is highly associated with ACS in patients  $<45$  years of age and is more predictive than other cardiovascular risk factors. TCFAs are known as important predictors of cardiovascular events (CVEs) (17). Using virtual-histology intravascular ultrasound (VH-IVUS), Zheng *et al* (3) analyzed the volumetric plaque composition of the coronary arterial tree and its association

Table II. Optical coherence tomography-derived plaque characteristics according to cardiovascular risk factors.

Item	Family history of CHD			Smoking			Hypertension			Diabetes mellitus			Hypercholesterolemia			Metabolic syndrome		
	Yes (n=10)	No (n=113)	P-value	Yes (n=67)	No (n=56)	P-value	Yes (n=63)	No (n=60)	P-value	Yes (n=22)	No (n=101)	P-value	Yes (n=21)	No (n=102)	P-value	Yes (n=82)	No (n=41)	P-value
TCFA	5 (50.0)	82 (72.6)	0.155	51 (76.1)	36 (64.3)	0.168	49 (77.8)	38 (63.3)	0.112	14 (63.6)	73 (72.3)	0.444	15 (71.4)	72 (70.6)	1.000	64 (78.0)	23 (56.1)	0.020
Macrophage accumulation	7 (70.0)	68 (60.2)	0.739	45 (67.2)	30 (53.6)	0.141	49 (77.8)	26 (43.3)	<0.001	16 (72.7)	59 (58.4)	0.238	15 (71.4)	60 (58.5)	0.333	51 (62.2)	24 (58.5)	0.700
Calcified nodule	2 (20.0)	10 (8.8)	0.252	6 (9.0)	6 (10.7)	0.769	6 (9.5)	6 (10.0)	1.000	0 (0.0)	12 (11.9)	0.122	2 (9.5)	10 (9.8)	1.000	6 (7.3)	6 (14.6)	0.212
Vasa vasorum	3 (30.0)	29 (25.7)	0.719	10 (14.9)	22 (39.3)	0.003	18 (28.6)	14 (23.3)	0.543	5 (22.7)	27 (26.7)	0.794	8 (38.1)	24 (23.5)	0.180	22 (26.8)	10 (24.4)	0.830
Cholesterol crystals	6 (60.0)	18 (15.9)	0.004	12 (17.9)	12 (21.4)	0.654	16 (25.4)	8 (13.3)	0.113	7 (31.8)	17 (16.8)	0.137	8 (38.1)	16 (15.7)	0.031	16 (19.5)	8 (19.5)	1.000
Erosion	0 (0.0)	6 (5.3)	0.455	4 (6.0)	2 (3.6)	0.688	2 (3.2)	4 (6.7)	0.432	2 (9.1)	4 (4.0)	0.292	0 (0.0)	6 (5.9)	0.588	6 (7.3)	0 (0.0)	0.177
Plaque rupture	0 (0.0)	18 (15.9)	0.355	16 (23.9)	2 (3.6)	0.002	10 (15.9)	8 (13.3)	0.801	2 (9.1)	16 (15.8)	0.525	2 (9.5)	16 (15.7)	0.736	14 (17.1)	4 (9.8)	0.418
%AS	84.5± 14.8	82.4± 12.9	0.624	81.2± 14.0	84.2± 11.7	0.196	80.7± 14.5	84.5± 11.1	0.111	85.8± 9.2	81.8± 13.6	0.104	78.8± 16.4	83.3± 12.2	0.237	83.6± 13.9	80.4± 10.9	0.205

Values are expressed as the mean ± standard deviation, or n (%). %AS, percent area stenosis; TCFA, thin-cap fibroatheroma.



Table III. Univariate and multivariate analysis for TCFA and plaque rupture predictors.

A, Predictors of TCFA

Factor	Univariate analysis			Multivariate analysis		
	RR	95% CI	P-value	RR	95% CI	P-value
Gender	1.54	0.514-4.610	0.440			
Smoking	1.771	0.809-3.877	0.153			
Hypertension	2.026	0.917-4.477	0.081	1.574	0.679-3.650	0.291
Diabetes mellitus	0.671	0.254-1.774	0.421			
Hypercholesterolemia	1.042	0.369-2.942	0.939			
Metabolic syndrome	2.783	1.240-6.246	0.013	2.421	1.038-5.649	0.041
Aspirin	0.678	0.277-1.660	0.395			
Statins	0.542	0.216-1.355	0.190			
Beta blocker	0.827	0.343-1.993	0.673			
ACEI or ARB	1.210	0.499-2.934	0.674			
Insulin	0.607	0.097-3.796	0.594			

B, Predictors of plaque rupture

Factor	Univariate analysis			Multivariate analysis		
	RR	95% CI	P-value	RR	95% CI	P-value
Smoking	8.471	1.855-38.690	0.006	8.301	1.813-38.015	0.006
Hypertension	1.226	0.449-3.352	0.691			
Diabetes mellitus	0.531	0.113-2.499	0.423			
Hypercholesterolemia	0.566	0.120-2.670	0.472			
Metabolic syndrome	1.904	0.585-6.205	0.285			
Aspirin	0.380	0.082-1.763	0.217			
Statins	0.446	0.095-2.081	0.304	2.064	0.422-10.093	0.371
Beta blocker	0.328	0.071-1.514	0.153			
ACEI or ARB	0.285	0.062-1.314	0.107			
Insulin	4.250	0.658-27.443	0.128			

TCFA, thin-cap fibroatheroma; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; RR, risk ratio.

with other CVRFs and MetS in patients diagnosed with ischemic heart disease (age, 59±9 years) and indicated that MetS patients had more frequent VH-IVUS-derived TCFA within the tree than non-MetS patients. Similarly, the present study suggested that patients with MetS had more frequent TCFA than patients without MetS. Zheng *et al* (3) also demonstrated that T2D is independently associated with TCFA.

Previous studies investigating features of coronary plaques in patients with MetS have provided conflicting results. Specifically, a previous IVUS study demonstrated no significant association between the presence of TCFA and MetS in patients with stable angina pectoris (age, 64.7±9.5 years) (18). Another study using OCT indicated that coronary plaques in patients with MetS (age, 60±11 years) and T2D (age, 59±11 years) contain larger amounts of lipids, but neither MetS nor T2D was significantly associated with TCFA (19). These conflicting results may have several reasons. First, the population of the present study was significantly younger than that in

the aforementioned studies. The pathophysiology underlying atherosclerosis and plaque characteristics differ between young and old patients with CHD (20). Furthermore, in the study by Yonetsu *et al* (19), selected 198 patients who had nonculprit or nontarget coronary plaques with area stenosis >50% as measured by OCT; however, whether they are culprit or non-culprit may affect the characteristics of plaques (21).

The present study indicated that cigarette smoking is independently associated with plaque rupture. Cigarette smoking is associated with a high incidence of CVEs, including ACS (22). It is also associated with a higher burden of necrotic cores in coronary atherosclerotic plaques, which may be one of the mechanisms underlying the increased risk it poses for plaque rupture and CVEs (23,24). By far, the most common risk factor for early-onset CHD is cigarette smoking (6), which increases the risk of plaque rupture. Cigarette smokers accounted for 54.5% (n=67) of the patients of the present study. Cigarette smoking is thought to increase the burden of cardiovascular

disease by inducing endothelial dysfunction, increasing the burden of coronary atherosclerosis and increasing the risk of plaque rupture and CVEs (25). T2D was not significantly associated with TCFAs or rupture in the present study. This may be due to the larger number of patients with T2D than without (63.6% vs. 10.9%) using statins, which may reduce TCFAs and plaque rupture (26).

The universally acknowledged features of vulnerable plaques currently include TCFAs, macrophage accumulation, calcified nodules, vasa vasorum and cholesterol crystals (27-31). The association between TCFAs and CVRFS was described above. In the present study, macrophage accumulation was more common in patients with hypertension and cholesterol crystals were present more often in patients with a family history of CHD and hypercholesterolemia. By contrast, no significant correlation was observed between calcified nodules or vasa vasorum and CVRFS in the patients of the present study. The sample examined was not extracted from the general population but was rather composed of relatively young patients. Thus, the results may not be extrapolatable to the general population. In addition, the results may be affected by lifestyle factors, including diet and physical exercise.

In conclusion, by using OCT evaluation, the present study demonstrated that young patients with MetS had more extensive TCFAs and that young cigarette smokers were at increased risk for culprit plaque rupture. Young patients with CHD should therefore actively control their body weight, blood lipids, blood pressure and blood sugar levels, as well as quit smoking, so as to reduce the occurrence/risk of TCFAs and ruptures.

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### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

### Authors' contributions

YZ and JG conceived the study. FH, WL, YD and YL collected and analyzed the patients' general information. FH and WL wrote the manuscript. SY, XM and ZW analyzed the OCT images. All of the authors read and approved the final manuscript.

### Ethics approval and consent to participate

The Ethics Committee of the Beijing Anzhen Hospital (Beijing, China) approved the study protocol and all of the participants provided written informed consent.

### Patient consent for publication

All of the participants provided written informed consent for publication.

### Competing interests

The authors declare that they have no competing interests.

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