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The Relationship Between Volumetric Plaque Components and Classical Cardiovascular Risk Factors and the Metabolic Syndrome

A 3-Vessel Coronary Artery Virtual Histology–Intravascular Ultrasound Analysis

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Objectives The aim of this study was to analyze volumetric plaque composition of the coronary arterial tree according to the classical cardiovascular risk factors and metabolic syndrome (MS) using virtual histology–intravascular ultrasound (VH-IVUS).

Background It remains unclear how the cardiovascular risk factors correlate with the histological components of coronary plaques.

Methods "Whole vessel" VH-IVUS analysis was performed in 189 vessels of 63 patients. The components of atherosclerotic plaques were classified as fibrous, fibrofatty, necrotic core (NC), and dense calcium. Quantitative assessment of these plaque components and the presence of VH-IVUS–derived thin-cap fibroatheroma in the coronary arterial trees were compared with cardiovascular risk factors.

Results There was a significantly larger mean plaque-plus-media burden in patients with diabetes mellitus (DM) (47 ± 5% vs. 39 ± 7% in non-DM patients, $p < 0.001$) and MS (47 ± 4% vs. 39 ± 7% in non-MS patients, $p < 0.001$). DM patients had a significantly larger %NC (17.8 ± 5.6% vs. 12.5 ± 6.1%, $p = 0.003$) compared with non-DM patients; and MS patients had a significantly larger %NC (17.3 ± 5.8% vs. 12.8 ± 6.2%, $p = 0.016$) as compared to non-MS patients. Finally, VH-IVUS–derived thin-cap fibroatheromas were more frequent in DM patients (3.4 ± 2.0 vs. 2.1 ± 1.7 in non-DM patients, $p = 0.016$) and in MS patients (4.1 ± 2.1 vs. 1.9 ± 1.4 in non-MS patients, $p = 0.001$).

Conclusions Three-vessel VH-IVUS analysis showed that DM and MS patients, compared to patients without DM or MS, had a larger plaque-plus-media burden, larger amount of NC, and more frequent VH-IVUS–derived thin-cap fibroatheromas in coronary arterial trees, implying greater plaque vulnerability in DM and MS patients. (J Am Coll Cardiol Intv 2011;4:503–10) © 2011 by the American College of Cardiology Foundation

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According to autopsy data, the fate of atherosclerosis is related to the composition of the plaque (1,2). Recognizing the histological characteristics of coronary plaques using an in vivo diagnostic modality may be a key to a lesion-specific treatment strategy of patients with coronary artery disease (3). Tomographic images of intravascular ultrasound (IVUS) are widely used for assessing the morphological characteristics of vessels (4,5); however, conventional gray-scale IVUS has significant limitations for identifying specific plaque components (6,7). Spectral analysis of the

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radiofrequency ultrasound backscatter signals known as virtual histology–intravascular ultrasound (VH-IVUS) allows identification of 4 different components of atherosclerotic plaques: fibrous tissue, fibrofatty plaque, dense calcium (DC), and necrotic core (NC) (8,9). Even though the relationship between cardiovascular risk factors and the risk of coronary events is well established, it remains unclear how these risk factors correlate with the histological components of coronary artery plaques in vivo. To the best of our knowledge, no 3-vessel volumetric VH-IVUS study has yet reported the relationship between plaque components and cardiovascular risk factors. The aim of the current study was to evaluate plaque composition in the coronary arterial tree using volumetric 3-vessel VH-IVUS according to classical cardiovascular risk factors, as well as the newly evolving risk factors that are associated with the metabolic syndrome (MS).

Abbreviations and Acronyms

DC = dense calcium
DM = diabetes mellitus
IVUS = intravascular ultrasound
MS = metabolic syndrome
NC = necrotic core
P+M = plaque plus media
VH-IVUS = virtual histology–intravascular ultrasound
VH-TCFA = virtual histology–intravascular ultrasound–derived thin-cap fibroatheroma

Methods

Study population. The primary aim of this prospective study was to determine the clinical correlation of the VH-IVUS parameters in a nonselected population of patients. Between September 2006 and August 2008, at a single medical center, pre-intervention 3-vessel VH-IVUS was successfully performed in 63 patients who were diagnosed with ischemic heart disease for the first time, which was defined as 1 or more native coronary arteries with ≥30% luminal stenosis by visual estimation. Written informed consent was obtained from all patients. Patients with chronic total occlusion, severely tortuous vessel, extensively calcified lesions, severe left main coronary artery disease (diameter stenosis ≥50%), and hemodynamic instability were excluded in this study.

Definition of risk factors. Hypercholesterolemia was defined as total cholesterol level ≥220 mg/dl. Smoking was defined as current smoking. A family history of coronary artery disease was defined as premature of coronary artery disease in a first-degree relative (in a man <55 years of age; in a woman <65 years of age). Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of any antihypertensive drug. Diabetes mellitus (DM) was defined as a confirmed diagnosis or using antidiabetic medication (insulin or oral hypoglycemic) at entry into the study. The definition of the MS met the Joint Scientific Statement recently announced (10). The waist circumference criterion was replaced by ≥90 cm for men and ≥80 cm for women.

IVUS imaging and analysis. VH-IVUS studies were performed with a phased-array, 20-MHz, 2.9-F IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California). After intracoronary administration of 100~200 μg nitroglycerin, the transducer was introduced as far distal as possible into each major epicardial artery, paying particular attention to cover any evident atherosclerosis. Using motorized pullback (0.5 mm/s), imaging was performed back to aorto-ostial junction. During pullback, the gray-scale IVUS was recorded; and the raw radiofrequency data were captured at the top of the R waves for the reconstruction of color-coded map by VH data recorder (Volcano Corporation).

Manual contour tracing of the lumen and the media-adventitia interface was performed by an experienced analyst (M.Z.) who was unaware of the patients' cardiac risk factor status. Volumetric VH-IVUS analysis was performed from the most distal point where VH-IVUS plaque components were detected to the respective ostium, and volumetric data were generated with using pcVH software (version 2.1, Volcano Corporation). Total plaque volume was obtained by analyzing 3 vessels in each patient (including all lesions and reference segments), and a volumetric index was calculated as total plaque volume divided by total vessel length. Mean plaque plus media (P+M) burden was calculated as the total plaque volume divided by total vessel volume × 100. VH-IVUS analysis classified the color-coded tissue as green (fibrous), yellow-green (fibrofatty), red (NC), and white (DC). Each plaque component was measured in every recorded frame and expressed as the volume index (absolute measure) and percentages of total plaque volume. Virtual histology–intravascular ultrasound–derived thin-cap fibroatheroma (VH-TCFA) was defined as a lesion that fulfilled the following criteria in at least 3 consecutive frames: 1) NCs ≥10% directly attaching to the lumen; and 2) ≥40% P+M burden (9). Identifying 2 separate lesions in the same artery required a ≥5-mm reference segment between them. If there was a <5-mm reference segment, they were considered part of one long lesion (11). Similarly, identify-

Table 1. Baseline Data for Classical Risk Factors and Metabolic Risk Factors Associated With MS (n = 63)

Classical risk factors	
Age, yrs	59 ± 9
≥65 yrs of age	21 (31.7)
Men	41 (65.1)
DM	17 (27.0)
Hypertension	37 (58.7)
Smoking	28 (44.4)
Hypercholesterolemia	13 (20.6)
Lipid profiles, mg/dl	
Total cholesterol	167 ± 36
Triglycerides	145 ± 103
LDL	96 ± 34
HDL	44 ± 9
Family history of premature coronary artery disease	5 (7.9)
Metabolic risk factors associated with MS	
High triglycerides, ≥150 mg/dl	20 (31.7)
HDL, <40 mg/dl	20 (31.7)
High blood pressure, ≥130/85 mm Hg	41 (65.1)
High fasting glucose, ≥110 mg/dl	25 (39.7)
Abdominal obesity, WC ≥90 cm in men or ≥80 cm in women	23 (36.5)
MS scores	
0	3 (4.8)
1	16 (25.4)
2	28 (44.4)
3	10 (15.9)
4	3 (4.8)
5	3 (4.8)

Values are mean ± SD or n (%).
DM = diabetes mellitus; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MS = metabolic syndrome; WC = waist circumference.

ing 2 separate VH-TCFAs required a non–VH-TCFA–containing reference segment ≥5 mm between them. Two experienced observers (S.C. and M.Z.) who were unaware of the patients' clinical histories evaluated the VH-TCFA in consensus.

Statistical analysis. Statistical analysis was performed with SPSS software (version 13.0, Chicago, Illinois). Categorical data were expressed as numbers or frequencies of occurrence with comparisons using chi-square statistics or Fisher exact probability test. All continuous variables were tested by Kolmogorov-Smirnov Z test for normality analysis. Continuous data were reported as mean ± SD with comparisons using unpaired Student t test analysis. If normality tests failed, the continuous values were presented as median and interquartile range and were compared by Mann-Whitney U test between patients with risk and without. Comparisons of VH-IVUS parameters among MS scores were performed using Spearman correlation. Multiple stepwise logistic regression analysis was performed to assess independent predictors for mean P+M burden, mean %NC, and number of VH-TCFA. Multivariate regression analysis included variables with a $p < 0.15$ on univariate analysis. For multivariate analysis, old age (≥65 years), DM (yes/no) and MS (yes/no) were considered as binary values. Bonferroni correction was performed to address the problem of multiple comparisons. A p value <0.05 was considered statistically significant in this study.

Results

Baseline clinical and VH-IVUS characteristics. Baseline clinical characteristics are listed in Table 1. The study subjects had a mean age of 59 years; 31.7% of the patients were ≥65 years of age; 65.1% were men; 27.0% had a history of DM; 58.7% had a history of hypertension; 44.4% had a history of smoking; 20.6% had a history of hypercholesterolemia; 7.9% had a family history of coronary artery disease; and 25.4% had MS. Forty-nine patients (77.8%) were diagnosed with acute coronary syndrome in this population. The analyzed vessel length was 56.1 ± 17.4 mm for the left anterior descending coronary artery, 51.9 ± 19.0 mm for the left circumflex coronary artery, and 74.2 ± 18.8 mm for the right coronary artery (Table 2). The number of VH-TCFAs was 1.0 ± 0.8 for the left anterior descending, 0.6 ± 0.7 for the left circumflex, and 0.8 ± 1.0 for the right coronary arteries.

IVUS and VH-IVUS findings according to classical risk factors and risk factors associated to the metabolic syndrome. The quantitative volumetric VH-IVUS findings with regard to the presence or absence of each cardiovascular risk factor are shown in Table 3. Total analyzed vessel length was not different regardless of any risk factor (data not shown). Patients with DM had larger absolute measures

Table 2. Baseline Lesion Characteristics in the VH-IVUS Analysis (n = 63)

No. of vessels with >60% plaque burden*	
0	15 (23.8)
1	16 (25.4)
2	18 (28.6)
3	14 (22.6)
Mean analyzed vessel length, mm	
Total length per patient	182.6 ± 45.4
LAD	56.1 ± 17.4
LCX	51.9 ± 19.0
RCA	74.2 ± 18.8
VH-TCFA, n	
Total number per patient	2.5 ± 1.9
LAD	1.0 ± 0.8
LCX	0.6 ± 0.7
RCA	0.8 ± 1.0

Values are n (%) or mean ± SD. *Number of vessels with >60% plaque burden was defined based on maximum plaque burden in each vessel.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; VH-IVUS = virtual histology–intravascular ultrasound; VH-TCFA = virtual histology–intravascular ultrasound–derived thin-cap fibroatheroma.

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Table 3. Volume Indexes of VH-IVUS Quantitative Findings in Regard to Being With or Without Cardiovascular Risk Factors (n = 63)

	P+M Volume Index (mm^3/mm)	FI Volume Index (mm^3/mm)	FF Volume Index (mm^3/mm)	NC Volume Index (mm^3/mm)	DC Volume Index (mm^3/mm)
≥65 yrs of age	6.4 [5.5–7.2]	1.9 [1.3–2.3]	0.4 [0.2–0.6]	0.4 [0.3–0.6]	0.2 [0.1–0.3]
<65 yrs of age	5.6 [4.7–7.2]	1.6 [0.9–2.7]	0.3 [0.2–0.4]	0.3 [0.2–0.5]	0.2 [0.1–0.3]
p value	0.205	0.937	0.773	0.261	0.504
p_c value	1.000	1.000	1.000	1.000	1.000
Men	6.1 [5.1–7.2]	1.7 [1.1–2.4]	0.3 [0.2–0.5]	0.4 [0.2–0.5]	0.2 [0.1–0.3]
Women	6.3 [4.8–7.1]	1.8 [0.7–2.6]	0.3 [0.3–0.5]	0.3 [0.2–0.4]	0.1 [0.1–0.3]
p value	0.858	0.476	0.519	0.542	0.819
p_c value	1.000	1.000	1.000	1.000	1.000
Diabetes	6.7 [5.6–8.1]	1.9 [1.5–2.6]	0.3 [0.2–0.5]	0.5 [0.4–0.9]	0.3 [0.2–0.4]
No diabetes	5.7 [4.8–7.0]	1.7 [1.0–2.5]	0.3 [0.2–0.5]	0.3 [0.2–0.4]	0.1 [0.1–0.2]
p value	0.037	0.736	0.565	0.004	0.024
p_c value	0.296	1.000	1.000	0.032	0.192
Hypertension	6.7 [5.1–7.8]	1.9 [1.0–2.7]	0.3 [0.2–0.6]	0.4 [0.2–0.6]	0.2 [0.1–0.4]
No hypertension	5.6 [4.9–6.7]	1.6 [1.0–2.1]	0.2 [0.1–0.5]	0.3 [0.2–0.4]	0.1 [0.1–0.2]
p value	0.064	0.757	0.334	0.169	0.054
p_c value	0.512	1.000	1.000	1.000	0.432
Smoker	5.7 [4.9–7.4]	1.6 [1.1–2.7]	0.3 [0.2–0.5]	0.4 [0.2–0.5]	0.2 [0.1–0.3]
Nonsmoker	6.4 [5.2–7.1]	1.9 [1.0–2.4]	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.2 [0.1–0.4]
p value	0.833	0.427	0.721	0.791	0.236
p_c value	1.000	1.000	1.000	1.000	1.000
Hypercholesterolemia	6.7 [4.9–7.9]	2.1 [1.1–2.9]	0.4 [0.2–0.5]	0.4 [0.2–0.5]	0.2 [0.1–0.2]
Normal cholesterol	6.1 [4.99–7.10]	1.8 [1.0–2.4]	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.2 [0.1–0.3]
p value	0.374	0.724	0.749	0.436	0.519
p_c value	1.000	1.000	1.000	1.000	1.000
Familial CAD	7.0 [7.0–7.1]	2.2 [1.7–2.9]	0.6 [0.5–1.3]	0.3 [0.2–0.5]	0.2 [0.1–0.2]
No family history of CAD	5.9 [4.9–7.2]	1.8 [1.0–2.5]	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.2 [0.1–0.3]
p value	0.170	0.633	0.115	0.750	0.932
p_c value	1.000	1.000	0.920	1.000	1.000
Metabolic syndrome*	7.5 [6.9–8.3]	2.6 [1.9–2.9]	0.4 [0.3–0.5]	0.7 [0.4–0.9]	0.4 [0.2–0.6]
No metabolic syndrome	5.5 [4.8–6.7]	1.5 [0.9–2.1]	0.3 [0.2–0.5]	0.3 [0.2–0.4]	0.1 [0.1–0.2]
p value	<0.001	0.120	0.605	0.001	0.004
p_c value	<0.001	0.960	1.000	0.008	0.032

Values are median [lowest and highest quartile]. The p_c.value is a p value corrected by Bonferroni correction. *Including 8 patients with both diabetes and metabolic syndrome.
CAD = coronary artery disease; DC = dense calcium; FF = fibrofatty; FI = fibrous; NC = necrotic core; P+M = plaque plus media; VH-IVUS = virtual histology–intravascular ultrasound.

of NC (p = 0.032) than those without DM; and patients with MS had larger normalized plaque mass (p < 0.001) and larger absolute measures of NC (p = 0.008) and DC (p = 0.032) than patients without MS.

Mean P+M burden was significantly correlated with increasing patient age (r = 0.292, p < 0.05). In addition, patients with DM had significantly larger mean P+M burden (47 ± 5% vs. 39 ± 7%, p < 0.001) compared with non-DM patients, and MS patients had significantly larger mean P+M burden (47 ± 4% vs. 39 ± 7%, p < 0.001) compared with the non-MS patients. Mean P+M burden did not correlate with any other risk factors (data not shown).

Patients with DM had significantly larger values of mean %NC (17.8 ± 5.6% vs. 12.5 ± 6.1%, p = 0.003) and mean %DC (10.7 ± 5.4% vs. 7.7 ± 5.3%, p = 0.032). MS patients also had significantly larger mean %NC (17.3 ± 5.8% vs. 12.8 ± 6.2%, p = 0.016) and mean %DC (10.6 ± 4.6% vs. 7.4 ± 5.5%, p = 0.052) as compared to non-MS patients.

The higher triglyceride and higher glucose levels were related to a larger mean plaque burden, and the lower HDL level was related to a larger mean %NC. The presence of a VH-TCFA was more frequent in patients with a higher triglyceride level or a higher blood sugar level (Table 4).

VH-TCFAs were significantly more frequent in DM patients than in non-DM patients (3.4 ± 2.0 vs. 2.1 ± 1.7, p = 0.016) and in MS patients than in non-MS patients (4.1 ± 2.1 vs. 1.9 ± 1.4, p = 0.001) (Fig. 1).

The mean P+M burden, %NC, and the number of VH-TCFAs were significantly correlated with increasing MS scores (Fig. 2).

Table 4. The Mean Percentages of Plaque Burden and VH-IVUS Components and the VH-TCFAs According to Each Risk Factor Associated With Metabolic Syndrome (n = 63)

	Mean P+M Burden (%)	Mean %FI	Mean %FF	Mean %NC	Mean %DC	VH-TCFAs (n)
Triglyceride <150 mg/dl	39.7 ± 7.6	63.1 ± 7.2	15.5 ± 8.2	13.0 ± 6.4	7.8 ± 5.6	1.9 ± 1.4
Triglyceride ≥150 mg/dl	46.1 ± 6.3	62.0 ± 7.1	13.2 ± 6.8	15.4 ± 6.3	9.2 ± 5.0	3.7 ± 2.1
p value	0.002	0.593	0.273	0.242	0.327	0.002
p_c value	0.010	1.000	1.000	1.000	1.000	0.010
BP <130/80 mm Hg	40.8 ± 8.5	65.1 ± 7.7	15.5 ± 7.1	12.6 ± 6.3	6.5 ± 4.5	2.0 ± 1.5
BP ≥130/80 mm Hg	42.2 ± 7.4	61.5 ± 6.6	14.4 ± 8.2	14.7 ± 6.4	9.1 ± 5.8	2.7 ± 2.0
p value	0.506	0.060	0.613	0.216	0.074	0.266
p_c value	1.000	0.300	1.000	1.000	0.370	1.000
Fasting blood sugar <110 mg/dl	39.5 ± 7.7	63.6 ± 7.5	16.5 ± 8.4	12.4 ± 6.1	7.4 ± 5.3	1.8 ± 1.5
Fasting blood sugar ≥110 mg dl	45.0 ± 6.7	61.5 ± 6.6	12.3 ± 6.1	16.3 ± 6.3	9.6 ± 5.4	3.4 ± 2.0
p value	0.006	0.274	0.026	0.017	0.118	0.002
p_c value	0.030	1.000	0.130	0.085	0.590	0.010
HDL >40 mg/dl	40.9 ± 7.4	64.3 ± 6.4	16.4 ± 7.8	12.1 ± 5.4	7.0 ± 4.6	2.3 ± 1.7
HDL ≤40 mg/dl	43.4 ± 8.5	59.3 ± 7.7	11.4 ± 6.9	18.0 ± 6.6	11.0 ± 6.3	2.9 ± 2.1
p value	0.252	0.009	0.017	0.000	0.006	0.330
p_c value	1.000	0.045	0.085	<0.001	0.030	1.000
Absence of abdominal obesity	40.9 ± 7.0	61.7 ± 7.8	13.8 ± 8.0	15.3 ± 6.6	9.0 ± 5.8	2.6 ± 2.2
Abdominal obesity	43.1 ± 9.0	64.5 ± 5.5	16.6 ± 7.3	11.6 ± 5.4	7.0 ± 4.5	2.4 ± 1.7
p value	0.282	0.147	0.170	0.027	0.167	0.960
p_c value	1.000	0.735	0.850	0.135	0.835	1.000

Values are mean ± SD. The p_c value is a p value corrected by Bonferroni correction.
BP = blood pressure; TG = triglycerides; other abbreviations as in Tables 1, 2, and 3.

Multivariate analysis of the risk factors for plaque burden, the %NC, and the VH-TCFAs. In the multivariate analysis, age ≥65 years, DM, and MS were independent predictors of the mean P+M burden; and DM was also the independent predictor of %NC. MS was the only independent predictor for the presence of VH-TCFA (Table 5).

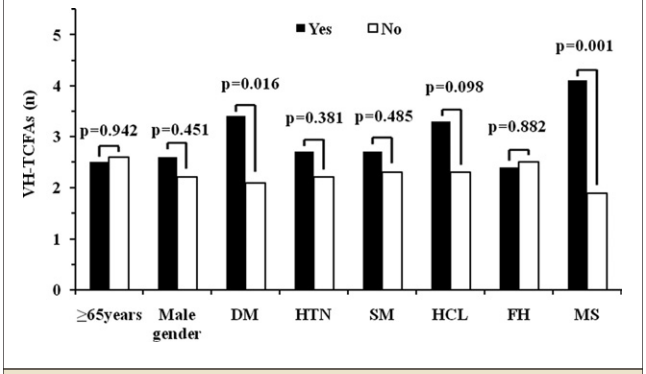

Figure 1. VH-TCFAs in Regard to Being With or Without Risk Factors

The virtual histology–intravascular ultrasound–derived thin-cap fibroatheroma (VH-TCFA) was significantly more frequent in diabetes mellitus (DM) patients or metabolic syndrome (MS) patients than in the patients without DM or MS. FH = family history of coronary artery disease; HCL = high cholesterol level; HTN = hypertension; SM = smoking.

Discussion

To the best of our knowledge, this is the first clinical study to analyze the relationship between cardiovascular risk factors and 3-vessel plaque components using volumetric VH-IVUS. The major findings of this study were that: 1) DM or the metabolic syndrome was associated with a larger P+M burden and a higher %NC than the absence of DM or the metabolic syndrome; 2) VH-TCFAs were significantly more frequent in DM or metabolic syndrome patients as compared to patients without DM or metabolic syndrome; and 3) among the metabolic syndrome components, a high blood sugar level was related to larger P+M burden and NC and more frequent VH-TCFA. In addition, the mean P+M burden, %NC, and the number of VH-TCFAs were well correlated with increasing metabolic syndrome scores.

Previous pathological studies have shown the relationship between lesion instability and the size of the NCs or the presence of TCFAs. One study showed that ruptured plaques had the largest NCs, followed by TCFA, plaque erosion, and fibrocalcific plaques (12). Atheromatous plaques may be rendered unstable by increases in their size, increases in intra- and extracellular lipid accumulation, and development of intraplaque hemorrhage (13). As the size of an NC within a TCFA enlarges, the TCFA may become more likely to rupture (14).

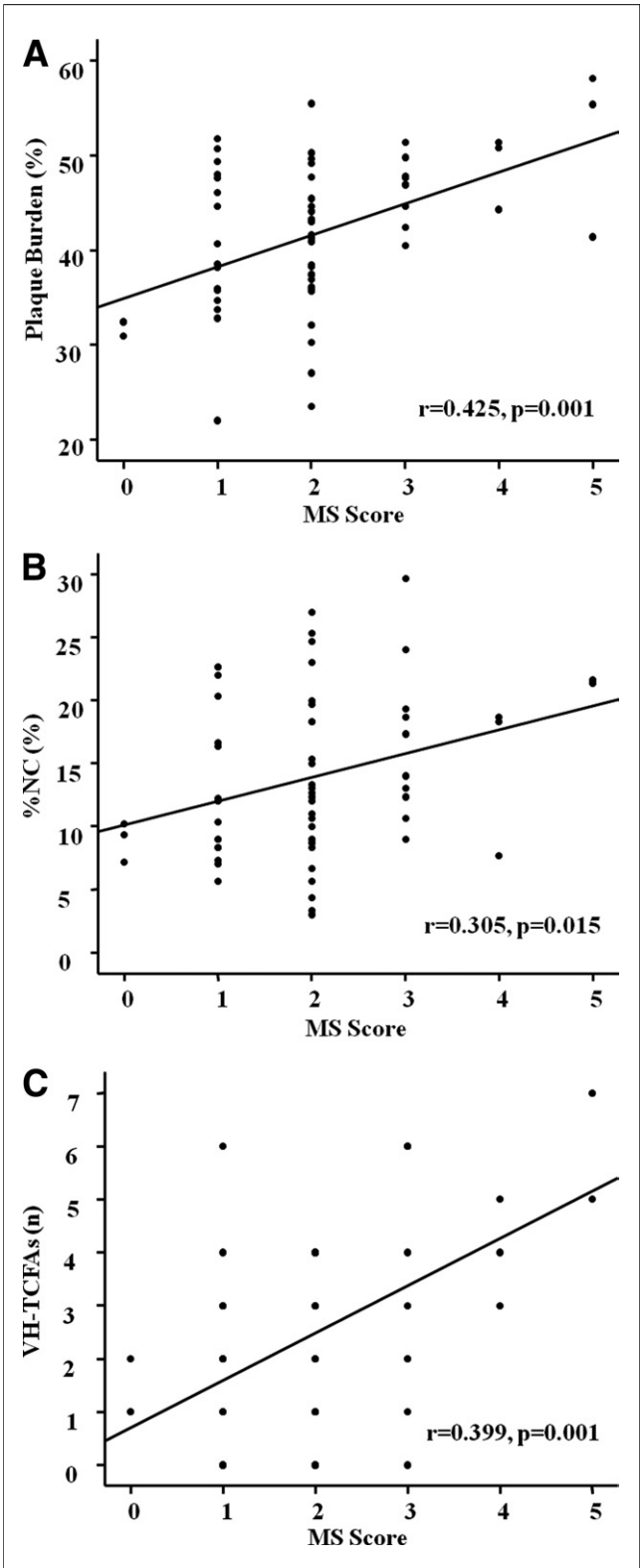

Figure 2. The Correlation Between the Plaque Components and the MS Scores

Results showing the positive correlations between the MS scores and the plaque burden **(A),** the percentage of necrotic core (%NC) **(B),** and VH-TCFA **(C).** Abbreviations as in Figure 1.

Table 5. Multivariate Predictors of the Plaque Burden, the %NC, and the VH-TCFAs (n = 63)

Parameters	B Coefficient	95% CI	p Value
Predictors of mean P+M			
≥65 yrs	3.620	0.069 to 7.171	0.046
Diabetes mellitus	4.981	1.087 to 8.874	0.013
Metabolic syndrome* (Y/N)	7.098	3.144 to 11.052	0.001
Predictors of %NC			
Diabetes mellitus	4.467	0.927 to 8.006	0.014
Metabolic syndrome* (Y/N)	3.069	−0.540 to 6.674	0.094
Predictors of VH-TCFA			
Diabetes mellitus	0.699	−0.282 to 1.680	0.159
Metabolic syndrome* (Y/N)	2.230	1.269 to 3.192	<0.001

*Including 8 patients with both diabetes and metabolic syndrome.
CI = confidence interval; mean P + M = plaque burden; Y/N = yes or no; other abbreviations as in Tables 2 and 3.

The relation between cardiovascular risk factors and coronary artery disease was first suggested by the Framingham study that used an epidemiological approach (15,16). Recently, investigators have used noninvasive modalities—including B-mode ultrasonography, magnetic resonance imaging, and multidetector computed tomography—or invasive imaging modalities—including IVUS or VH-IVUS—to study the correlation between the cardiovascular risk factors and the morphological characteristics of atherosclerotic plaques (17–20). Among them, IVUS provides high-resolution tomographic visualization and quantifies atherosclerotic plaque area and volume and plaque burden. However, other recent studies have suggested that grayscale IVUS has limited value for the identification of specific plaque components (6,7) that lead to the development of VH-IVUS (21–24).

Previous IVUS studies had reported that male sex and DM are strong independent predictors of the atherosclerotic burden in coronary disease patients, either at severely narrowed segments or at mildly narrowed segments (20,25). Some investigators also showed that in culprit lesions, the plaque burden was significantly associated with age, male sex, and DM (26). Using multidetector computed tomography, DM patients had more coronary segments with atherosclerosis per patient (27).

An IVUS study showed that subjects with MS had a significantly higher percentage of plaque volume and as well as more frequent eccentricity, calcification, and lipid pool-like images than subjects without MS (28). In a multidetector computed tomography study, MS was independently associated with the presence and extent of both calcified and noncalcified coronary atherosclerotic plaques (29).

Several VH-IVUS studies have demonstrated for the relationship between risk factors and plaque composition. The proportion of NC and DC increased with increasing age, and more advanced calcified lesions were observed in

men than in women (30,31). In a study from a global VH registry, patients with diabetes and hypertension had an increased proportion of NC and DC, and high-density lipoprotein–cholesterol level negatively correlated with fibrofatty tissue and NC. Also, greater amounts of NC were associated with diabetes, hypertension, myocardial infarction, and low high-density lipoprotein cholesterol (32). However, previous studies analyzed plaque composition at target lesions or nonobstructive lesions, but not from the entire coronary arterial tree. Compared with these previous studies, the present study extends the association between cardiovascular risk factors (age, DM, and MS) and plaque burden and plaque composition, especially as it affects the entire coronary tree. Therefore, analysis of the whole plaque burden as performed in the current study is more representative than focal plaque analysis for assessing risk factors and the prognosis of at-risk patients.

Until now, few studies have depicted the pathohistological relation between NC or TCFA and DM or MS. Pathologically, the NC size was positively correlated with the diabetic status, independent of other risk factors (33). Another study showed that MS was independently correlated with the percentage of lipid volume at the nontarget coronary lesions that had mild to moderate stenosis (34). Similarly, our study found patients with DM or MS had more NCs and more frequent VH-TCFAs than did patients without DM or MS. NC or TCFA have currently become the surrogate for assessing the vulnerability of plaque. The strong relations of the P+M burden, the %NC, and the number of VH-TCFAs with increased MS scores suggest that the plaque vulnerability might be increasing with the severity of MS.

Study limitations. This study was a single-center study, and the findings of this study were based on a small patient population. These patients are not typical of patients presenting to catheterization laboratories in the United States, and the results thus may not fully apply to a U.S. patient population. Even though pathological correlations of VH-IVUS versus ex vivo coronary arteries and directional coronary atherectomy specimens have been published (8,21), a recent comparison of VH-IVUS versus a model of porcine atherosclerosis found no correlation in the assessment of necrotic core (35). Also, there are limited data on the reproducibility of VH-IVUS or the ability of VH-IVUS to predict future events. VH-IVUS is limited in analyzing small vessels, including distal vessels or those typical of diabetic patients. On one hand, the system imposes at least a 300-μm thick gray "media" obscuring small amounts of plaque; by contrast, there are limitations in imaging near the 20-MHz transducer used during VH analysis. The VH-IVUS differences between patients with versus without DM and between patients with versus without MS were small, may not be clinically meaningful or predictive of future events, and must be studied prospectively in larger patient populations. We imaged only the proximal 56.1 ± 17.4 mm of the left anterior descending, 51.9 ± 19.0 mm of the left circumflex, and 74.2 ± 18.8 mm of the right coronary arteries; thus, whereas earlier studies suggested that vulnerable plaques are mostly proximal, the recent PROSPECT (Providing Regional Observations to Study predictors of Events in the Coronary Tree) study indicated that a significant percentage of vulnerable plaques are more distal than previously thought. This study contains a great number of independent *t* tests comparisons raising the specter of type I error.

Conclusions

Three-vessel VH-IVUS volumetric analysis showed that there are more NCs and TCFAs and a greater plaque burden in DM and MS patients. This implies higher plaque vulnerability in these groups.

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