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Optical Coherence Tomography Assessment of Morphological Characteristics in Suspected Coronary Artery Disease, but Angiographically Nonobstructive Lesions☆

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ABSTRACT

Background/purpose: We sought to evaluate the morphological characteristics of nonobstructive coronary lesions in patients with ischemic symptoms and/or signs.
Materials/methods: We used optical coherence tomography (OCT) to assess the presumed culprit lesion in 142 patients with suspected coronary artery disease in whom coronary angiography showed no lesion with a diameter stenosis ≥50%. Patients with a clinical diagnosis of acute coronary syndrome (ACS, $n = 31$, including 2 ST-elevation myocardial infarction, 9 non-ST-elevation myocardial infarction, and 20 unstable angina pectoris) were compared to those with stable coronary artery disease (CAD) ($n = 111$) including 79 patients with stable angina and 32 patients with silent ischemia (positive non-invasive stress test only).
Results: The overall prevalence of thrombus, plaque rupture, intimal laceration, or calcified nodule in the combined groups was 23.2% (33/142) including 15 thrombus, 12 plaque rupture, 9 calcified nodule, and 8 intimal laceration (not mutually exclusive) without differences between ACS and stable CAD patients. Also the prevalence of thin-cap fibroatheroma was not significantly different between ACS and stable patients (12.9% vs 6.3%, $p = 0.22$). Minimum lumen area (3.1 mm^2 [2.3, 4.1] versus 3.2 mm^2 [2.4, 4.7], $p = 0.7$) and area stenosis (49.9% [37.1, 56.4] versus 48.1% [37.8, 55.8], $p = 0.9$) were similar between ACS and stable CAD patients.
Conclusion: In patients presenting with ischemic symptoms and/or signs, but angiographically nonobstructive culprit lesions, approximately 25% had abnormal findings by OCT—whether patients presented with acute/unstable or stable CAD.

1. Introduction

Nonobstructive coronary artery disease (CAD) has been found in 40–60% of patients with stable angina undergoing coronary angiography (CAG) [1] and in 10% of patients with non-ST elevation myocardial infarction [2]. Patients with nonobstructive CAD can have adverse outcomes including cardiovascular death and myocardial infarction [1,3]. Nonobstructive CAD has several distinct, potential underlying pathophysiologies [4]. Optical coherence tomography (OCT) provides detailed visualization of intraluminal coronary artery structures including morphology related to acute coronary syndrome (ACS) such as plaque rupture, thin-cap fibroatheroma, plaque erosion, calcified nodule, or significant anatomic stenosis [5,6]. We use OCT to assess patients undergoing diagnostic coronary angiography for suspected CAD who had angiographic nonsignificant lesions and compared patients with ACS to patients with stable CAD.

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2. Materials and methods

This was a retrospective observational study at St Francis Hospital (Roslyn, New York, USA) from January 2014 to September 2015 to determine coronary OCT morphology in 142 patients with previously undocumented CAD who underwent CAG for suspected CAD, but in whom no vessels had ≥50% diameter stenosis (visual estimation). Indications for CAG included clinical symptoms of angina pectoris, abnormal electrocardiogram indicating myocardial ischemia, elevated cardiac biomarker(s), cardiac wall motion abnormalities by echocardiography, positive nuclear stress test, or coronary stenosis by coronary computed tomography angiography. ACS included myocardial infarction [7] and unstable angina pectoris [8]. Patient demographic data were confirmed by hospital chart review. Coronary risk factors included hypertension (medication treated only), diabetes mellitus (diet controlled, oral agent treated, or insulin treated), hyperlipidemia (medication treated or total cholesterol >220 mg/dL), current cigarette smoking, and family history of coronary artery disease. Written informed consent was obtained from all patients.

CAGs were assessed visually by independent observers who were blinded to the clinical and OCT findings. Qualitative evaluation included thrombolysis in myocardial infarction (TIMI) flow grade, calcification, thrombus, ulceration, and haziness using standard definitions [9].

OCT images were acquired using ILUMIEN OPTIS System with Dragonfly Duo OCT Imaging Catheter or Dragonfly OPTIS Imaging Catheter (Abbott Vascular, Santa Clara, California, USA) [10,11]. OCT was used to examine the presumed culprit lesion (the artery with the single worst stenosis in each patient, even if that stenosis was mild) after diagnostic CAG. Alternatively, a positive non-invasive ischemic test was used to select the presumed culprit. Minimum lumen area and the average of proximal and distal reference lumen area were recorded; and area stenosis was calculated. Morphological evaluation of the worst stenosis included underlying plaque composition, plaque rupture, intimal laceration, calcified nodule, and thrombus. Lipidic plaque was defined as a region with strong signal attenuation and diffuse borders with lipid-rich plaque having a ≥ 90° arc of lipid. Thin-cap fibroatheroma (TCFA) was defined as lipid-rich plaque with <65 μm fibrous cap thickness. Macrophages were signal-rich, distinct, or confluent punctate regions exceeding the intensity of background speckle noise. Calcium was defined by signal-poor or heterogeneous regions with sharply delineated borders. Plaque rupture was a disrupted fibrous cap with intra-plaque cavity formation. Intimal laceration was characterized by disruption of the superficial intimal lining without fibrous cap rupture [12]. Calcified nodule was defined as an accumulation of small nodular calcifications with disruption of the fibrous cap and an underlying calcified plate [13]. Thrombus was an irregular mass protruding into the lumen with a measured dimension ≥250 μm [14].

Statistical analysis was performed with SPSS version 20.0 (IBM, Armonk, New York, USA). Continuous variables were presented as median [first quartile, third quartile] and compared using the Mann-Whitney *U* test. Categorical variables were expressed as frequency (%) and compared with χ^2 statistics or the Fisher exact test. *p*-Value <0.05 was considered statistically significant.

Table 1
Baseline clinical characteristics.

	Patients diagnosed as ACS ($n = 31$)	Patients diagnosed as stable CAD ($n = 111$)	*p* value
Age, years	66 [58, 71]	67 [61, 75]	0.32
Women	13 (41.9%)	37 (33.3%)	0.38
Hypertension	16 (51.6%)	69 (62.2%)	0.29
Diabetes mellitus	8 (25.8%)	23 (20.7%)	0.54
Hyperlipidemia	19 (61.3%)	77 (69.4%)	0.40
Current smoking	2 (6.5%)	6 (5.4%)	1.0
Family history of coronary artery disease	7 (22.6%)	31 (27.9%)	0.55
Aspirin and/or thienopyridine	15 (48.4%)	65 (58.6%)	0.31
ACE-I/ARB	10 (32.3%)	41 (36.9%)	0.63
Beta blocker	10 (32.3%)	35 (31.5%)	0.94
Statin	16 (51.6%)	65 (58.6%)	0.49
Low-density lipoprotein cholesterol, mg/dL	104 [91, 131]	91 [74, 119]	0.02
High-density lipoprotein cholesterol, mg/dL	44 [39, 60]	44 [36, 52]	0.18
Triglyceride, mg/dL	133 [90, 185]	111 [78, 156]	0.40
eGFR, mL/min/1.73 m^2	78 [71, 87]	78 [68, 87]	0.67

Values are *n* (%) or median [first quartile, third quartile]. ACE-I = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate using the modification of diet in renal disease study.

Table 2
Angiographic findings.

	Patients diagnosed as ACS ($n = 31$)	Patients diagnosed as stable CAD ($n = 111$)	*p* value
Diameter stenosis, %	30 [20, 40]	30 [20, 30]	0.35
Vessel studied with OCT			0.56
Right	6 (19.4%)	17 (15.3%)	
Left anterior descending	19 (61.3%)	79 (71.2%)	
Left circumflex	6 (19.4%)	15 (13.5%)	
Proximal lesion location	9 (29.0%)	39 (35.1%)	0.67
Calcification (moderate/severe)	10 (32.3%)	30 (27.0%)	0.57
Thrombus	0 (0.0%)	0 (0.0%)	
Ulceration	0 (0.0%)	2 (1.8%)	1.0
Haziness	1 (3.2%)	6 (5.4%)	1.0

Values are *n* (%) or median [first quartile, third quartile].
OCT = optical coherence tomography; other abbreviations as in Table 1.

3. Results

Patients with ACS symptoms ($n = 31$, ST-elevation myocardial infarction [MI], $n = 2$; non-ST-elevation MI, $n = 9$; unstable angina pectoris, $n = 20$) were compared with patients having stable CAD ($n = 111$) including 79 with clinical symptoms of angina pectoris (31 with symptoms only and 48 with symptoms and a positive non-invasive test) and 32 with a positive non-invasive test only. The reason for performing a non-invasive test was because of atypical symptoms and/or for pre-operative assessment. A positive non-invasive test included 40 with a positive nuclear stress test, 20 with coronary stenosis by computed tomography angiography, 11 with an abnormal

Table 3
OCT findings.

	Patients diagnosed as ACS ($n = 31$)	Patients diagnosed as stable CAD ($n = 111$)	*p* value
Any high-risk finding	8 (25.8%)	25 (22.5%)	0.70
Plaque rupture	2 (6.5%)	10 (9.0%)	0.65
Calcified nodule	2 (6.5%)	7 (6.3%)	0.63
Intimal laceration	2 (6.5%)	6 (5.4%)	0.55
Thrombus	4 (12.9%)	11 (9.9%)	0.42
Reference lumen area, mm^2	5.5 [4.3, 7.0]	5.5 [3.7, 6.9]	0.55
Minimum lumen area, mm^2	3.1 [2.3, 4.1]	3.2 [2.4, 4.7]	0.69
Area stenosis, %	49.9 [37.1, 56.4]	48.1 [37.8, 55.8]	0.91
Thin-cap fibroatheroma	4 (12.9%)	7 (6.3%)	0.22
Lipid-rich plaques	9 (29.0%)	35 (31.5%)	0.79
Maximum angle of lipidic plaque, °	186 [115, 288]	138 [110, 203]	0.26
Thinnest cap thickness, mm	0.08 [0.06, 0.12]	0.13 [0.08, 0.20]	0.04
Macrophage	16 (51.6%)	61 (55.0%)	0.74
Calcium	24 (77.4%)	80 (72.1%)	0.55
Maximum angle of calcium, °	115 [71, 214]	111 [73, 179]	0.50

Values are *n* (%) or median [first quartile, third quartile]. Abbreviations as in Table 1.

electrocardiogram indicating myocardial ischemia, or 9 with cardiac wall motion abnormalities by echocardiography.

As shown in Table 1, the median patient age was 67 [60, 74] years; 35% were female; and there were no significant differences in clinical characteristics between the two groups except low-density lipoprotein cholesterol was significantly higher in the ACS group than in the stable angina group (104 mg/dL [91, 131] versus 91 mg/dL [74, 119], $p = 0.02$). Among ACS patients, 11 had troponin I elevation (0.51 ng/mL [0.18, 1.60]).

Angiographic findings have been shown in Table 2. TIMI flow was grade 3 in all vessels. The worst angiographic diameter stenosis was located in the left anterior descending coronary artery in 98 patients, right coronary artery in 23 patients, and circumflex coronary artery in 21 patients; and 48 lesions were in a proximal segment without significant differences between groups.

OCT findings have been shown in Table 3. The overall prevalence of plaque rupture, intimal laceration, calcified nodule, and/or thrombus in the combined groups was 23.2% (33/142), with no differences between ACS and stable CAD patients. OCT showed atherosclerotic plaque in all lesions. Reference lumen area (5.5 mm^2 [4.3, 7.0] versus 5.5 mm^2 [3.7, 6.9], $p = 0.55$), minimum lumen area (3.1 mm^2 [2.3, 4.1] versus 3.2 mm^2 [2.4, 4.7], $p = 0.69$), and area stenosis (49.9% [37.1, 56.4] versus

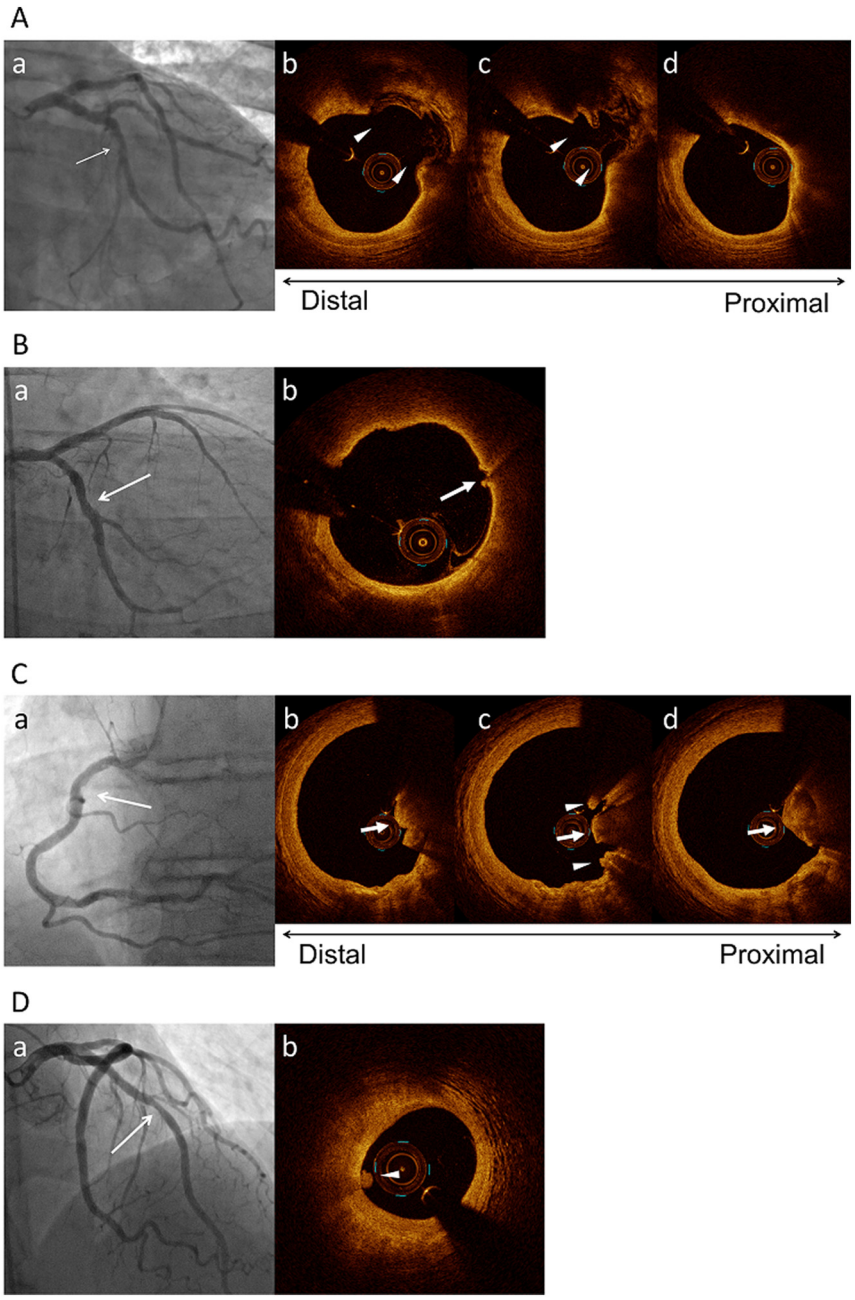

Fig. 1. Representative cases of OCT findings. A: Example of plaque rupture. Left coronary angiogram (a) shows a mild stenosis in the mid-left circumflex artery (arrow) in a patient with symptoms of stable coronary artery disease (CAD). By optical coherence tomography (OCT) (b–d), there was intimal disruption with an empty cavity (arrowheads in b and c) at 2 o'clock. B: Example of intimal laceration. Left coronary angiogram (a) shows a mild stenosis in the mid-left circumflex coronary artery (arrow) in a patient with symptoms of acute coronary syndromes (ACS). By optical OCT (b), there was disruption of the superficial intimal lining without rupture of the fibrous cap (2 o'clock, arrow). C: Example of calcified nodule. Right coronary angiogram (a) showed a mild stenosis in the proximal right coronary artery (arrow) in a patient with symptoms of stable CAD. By OCT (b–d), there was a protruding calcified nodule (arrows in b and c) with thrombus (arrowheads in c) at 3 o'clock. There was a calcium plate proximal to the calcified nodule (arrow in d). D: Example of thrombus. Left coronary angiogram (a) shows a mild stenosis in the mid-left anterior descending artery (arrow) in a patient with symptoms of stable CAD. By OCT (b), there was a small thrombus (310 μm in diameter) without any intimal disruption at 9 o'clock (arrowhead).

48.1% [37.8, 55.8], $p = 0.91$) were similar between ACS and stable CAD patients. The underlying plaque composition was not different between the 2 groups. While the fibrous cap thickness was thinner in ACS patients compared with stable CAD patients (0.08 mm [0.06, 0.12] vs 0.13 mm [0.08, 0.20], $p = 0.04$), the prevalence of an TCFA (12.9% versus 6.4%, $p = 0.22$) was not different between the 2 groups. Representative cases of OCT findings are shown in Fig. 1.

4. Discussion

The main finding of the present study was that approximately 25% of patients with suspected CAD, but insignificant lesions by CAG, had abnormal findings by OCT, whether presenting with ACS or stable CAD.

Increasing lesion severity by CAG has been related to future adverse events regardless of whether obstructive or nonobstructive disease is present [3,15], possibly explained by an intravascular ultrasound study showing that more severe lesions not only had more plaque burden, but also more fibroatheromas [16,17]. Furthermore, patients with angina symptom and non-obstructive CAD have elevated risks for cardiovascular events whether presenting as ACS or stable CAD [18,19]. Increased risks of future cardiac events are seen in patients with angina symptom and diffuse non-obstructive CAD and even normal coronary arteries compared to a patient population without ischemic heart disease [1]. Possible explanations cover a broad range of pathophysiologies. European Society of Cardiology guidelines in 2013 on the management of stable coronary artery disease state that the mechanisms of myocardial ischemia include not only epicardial stenosis, but also coronary spasm (that invariably occurs at sites with subclinical atherosclerosis [20], microvascular dysfunction, or the combination [21]). Cardiac ischemia from a myocardial bridge and endothelial dysfunction are other possible causes. Noncoronary causes include tako-tsubo syndrome, myocarditis, cardiomyopathies, and mismatch between oxygen supply and demand resulting from other organ dysfunction and affect the worse outcomes [4,22,23]. Finally, atherosclerosis with plaque rupture and thrombosis do not always lead to a severe stenosis [24].

An OCT meta-analysis [25] showed that ACS patients had plaque rupture in 70.4% with ST-elevation MI, 55.6% with non-ST-elevation MI, and 39.1% with unstable angina while stable CAD patients had plaque rupture in 6.2%. On the other hand, there was a report using intravascular ultrasound that plaque rupture was common (38%) in women patients with non-obstructive ACS [26]. Furthermore, among obstructive ACS patients, complex angiographic lesions were related to OCT features of plaque rupture superimposed with thrombus [27]. Nevertheless, in this current study the frequency of plaque rupture was only 8.5%, lower than in previous studies, possibly explained by only 6% of angiographic complex lesions (haziness and irregularity). TCFA, the precursor of plaque rupture, has been observed in 76.6% of patients with ST-elevation MI, 56.3% of non-ST-elevation MI, and 52.9% of unstable angina patients, but in only 22.8% of stable CAD patients [25]. In current study, we found TCFAs in only 7.7% of nonobstructive lesions without significant differences between ACS and stable CAD patients.

OCT plaque characteristics of thrombus, plaque rupture, and calcified nodule have been associated with ACS [5,6], and intimal laceration has been related to plaque erosion [12]. In the current study, we found abnormal findings (thrombus, plaque rupture, intimal laceration, or calcified nodule) in 23.2% without significant differences between ACS and stable CAD patients, much less frequent than in patients with obstructive CAD [5,6,25,28]. Our cohort was different from previous studies in that there were no significant lesions in any vessel angiographically.

Several OCT studies have showed that statin use (mediated by a low LDL) was associated with increased fibrous cap thickness [29,30] which has been related to plaque stabilization, similar to obstructive CAD [31]. Moreover, statin therapy was related to better outcome even in patients with non-obstructive CAD [32]. Thus, optimal medical therapy should be considered when abnormal OCT findings are found, irrespective of coronary angiographic findings. Finally, OCT could play a role in delineating the underlying ischemia-causing pathology in ACS patients who have unremarkable coronary angiograms.

The study had several limitations. First, this was a retrospective study with a modest number of patients. Second, the indication to perform CAG was decided by physician's discretion, and coronary stenosis severity was assessed visually. Third, we did not assess coronary endothelial function, microvascular dysfunction, or coronary artery spasm. Fourth, we did not perform three vessel OCT imaging, thereby missing findings in other vessels. Fifth, no clinical follow-up data were collected in this study.

5. Conclusions

In patients presenting with ischemic symptoms and/or signs, but angiographically nonobstructive culprit lesions, approximately 25% had abnormal findings by OCT - whether patients presented with acute/unstable or stable CAD.

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