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OCT Findings in Patients With Recanalization of Organized Thrombi in Coronary Arteries

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OBJECTIVES The purpose of this study was to determine the angiographic and optical coherence tomographic (OCT) characteristics of coronary lesions with recanalized thrombi.

BACKGROUND Although spontaneous recanalization of thrombi has been reported pathologically, it is rarely recognized in clinical practice.

METHODS Based on histopathologic features, recanalization of thrombi was defined by characteristics on OCT.

RESULTS Recanalization of thrombi was identified in 6 patients (3 male, 3 female; median age 63 years; age range 54 to 72 years). Based on symptoms, 3 patients were diagnosed with unstable angina; 2 were diagnosed with stable angina; and 1, who had mitral stenosis and huge left atrial thrombi, was diagnosed with post-infarct angina. All had normal serum concentrations of cardiac markers at admission. Angiography showed irregular linear filling defects and haziness. Two patients with near total occlusion had Thrombolysis In Myocardial Infarction (TIMI) flow grade 1 and collaterals, whereas 4 patients had TIMI flow grade 3 and no collaterals. All patients showed OCT findings consistent with recanalized thrombi, which consisted of signal-rich, high backscattered septa that divided the lumen into multiple small cavities communicating with each other. These structures, which had smooth inner borders, created a "Swiss cheese" appearance. Percutaneous coronary intervention was performed in 5 patients with angiographic slow flow or inducible-ischemia as documented by invasive or noninvasive stress tests. The remaining 1 patient with restored coronary flow underwent mitral valve surgery and left atrial thrombectomy.

CONCLUSIONS OCT provided details on the characteristics of the organization of thrombi in both chronic total occlusion and subtotal narrowing. Coronary lesions containing recanalized thrombi were characterized by multiple small channels, with most showing functional significance. (J Am Coll Cardiol Img 2012;5:725–32) © 2012 by the American College of Cardiology Foundation

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Although recanalization of coronary thrombi has been characterized pathologically, it is rarely recognized in real clinical practice (1–5). Because angiographic haziness and filling defects are common but nonspecific findings, it is speculated that a recanalized thrombus is often misdiagnosed as other pathological conditions such as fresh thrombosis by plaque rupture/erosion, spontaneous dissection, aneurysm, or heavy calcification. Despite several case reports addressing neovascularization within thrombi (6–9), its incidence and functional significance remain unclear.

Advances in high-resolution imaging modalities, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have provided new insights into evolving thrombotic lesions (6–9). As angiographic haziness does not always signify a fresh thrombus, intravascular imaging is necessary to differentiate the causative mechanisms in vivo and may provide information allowing an appropriate treatment approach specific to the underlying etiology. We have assessed the morphological characteristics on angiography, IVUS, and OCT of coronary lesions with spontaneous recanalization of thrombi.

ABBREVIATIONS AND ACRONYMS

IVUS = intravascular ultrasound

OCT = optical coherence tomography

METHODS

Angiographic analysis. From July 2010 to September 2011, OCT was performed in 271 patients. Recanalization of organized thrombi was found in 6 patients on the basis of OCT findings. Qualitative and quantitative angiographic measurements were performed using standard techniques with automated edge-detection algorithms (CAAS-5, Pie-Medical, Maastricht, the Netherlands) at the angiographic analysis center of the CardioVascular Research Foundation, Seoul, Korea (10,11).

OCT imaging and analysis. Before February 2011, OCT images were acquired by an occlusive technique using a commercially available system for intracoronary imaging and a 0.019-in ImageWire (LightLab Imaging, Westford, Massachusetts) before IVUS imaging. The artery was cleared of blood by continuous flushing with iodixanol 370 (Visipaque, GE Health Care, Cork, Ireland) at a flow rate of 3.0 ml/s (12). Since March 2011, OCT images were acquired by a nonocclusive technique with a C7XR system (DragonFly catheter and C7XR, LightLab Imaging). Based on previous histopathologic studies, recanalization or neovascularization of thrombi was defined as multiple channels divided by thin septa with or without communication with each other (3–8). Calcification was defined as a well-delineated, signal-poor region with sharp borders (13). Fresh thrombi were defined as masses ≥250 μm in diameter protruding into the vessel lumen and discontinuous from the surface of the vessel wall. Red thrombi were defined as high-backscattering protrusions with signal-free shadowing, and white thrombi as signal-rich, low backscattering projections into the lumen (14–17). The OCT analysis was performed by 2 independent observers (S.J.K. and H.G.S.).

IVUS imaging and analysis. IVUS imaging was performed after OCT imaging and after intracoronary administration of 0.2 mg nitroglycerin using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, Minnesota), consisting of a rotating 40 MHz transducer within a 3.2-F imaging sheath. Using computerized planimetry (EchoPlaque 3.0, Indec Systems, Mountain View, California), off-line quantitative IVUS analysis was performed in a core laboratory at the Asan Medical Center. External elastic membrane and minimal lumen areas were measured at the lesion site and reference segments (18).

RESULTS

Clinical characteristics. Based on the OCT findings, recanalization of organized thrombi was identified in 6 patients. The median age of the patients was 63 years (range 54 to 72 years) and 3 were female. Five patients had no history of previous percutaneous coronary intervention or coronary bypass surgery. Only 1 patient (Patient #6) showed in-stent restenosis after drug-eluting stent implantation 4 years earlier.

Table 1 summarizes the history and clinical presentation of the 6 patients. Three patients, with recently developed or aggravated angina symptoms for 1 to 8 weeks before admission, were diagnosed with unstable angina. Two patients presented with stable angina, and 1 patient (Patient #4) with mitral stenosis and huge left atrial thrombi 5 weeks after non–ST-segment elevation myocardial infarction was diagnosed with post-infarct angina. All 6 patients were admitted through the out-patient department. At admission, none had resting chest pain or presented with acute myocardial infarction. Their serum concentrations of creatine kinase-myocardial band and troponin were normal.

Table 1. Clinical Characteristics, Cases 1 Through 6

Patient #	Sex/Age	Clinical Presentation at Admission	Diagnosis	Risk Factors	Noninvasive Tests
1	F/72	Chest pain during exercise 8 months previously; aggravated symptoms for 1 month	Unstable angina	Hypertension, hyperlipidemia	ECG: Q-wave in II, III, aVF Echo: inferoposterior akinesia, EF 52% Thallium: partially reversible, large-sized severe perfusion defect in inferior wall
2	M/63	5-year history of angina; aggravated chest pain for 1 week	Unstable angina	Smoking, hypertension, hyperlipidemia	ECG: T-wave inversion in V4 to 6 Echo: inferoposterior wall akinesia, EF 58% FFR at maximal hyperemia 0.65
3	F/54	New onset of prolonged chest pain for 4 weeks	Unstable angina	None	ECG: T-wave inversion in inferior, lateral leads Thallium: partially reversible perfusion defect in apical septum and mid anteroseptum Echo: akinesia of anteroseptum, EF 53%
4	F/63	Non-STEMI 5 weeks earlier; mitral stenosis with LA thrombi atrial fibrillation	Old myocardial infarction	Hypertension	ECG: T-wave inversion in II, III, aVF Echo: severe mitral stenosis, LA thrombi (5 × 3 cm), hypokinesia of basal inferior wall, EF 50%
5	M/55	Effort-related chest pain for 1 year	Stable angina	Hypertension, hyperlipidemia, smoking	Thallium: reversible, large perfusion defect in apical septum and anterior wall ECG and Echo: normal findings, EF 65%
6	M/73	s/p DES implantation 4 years earlier; recurrent angina 1 year earlier	Stable angina	Diabetes mellitus	ECG: T-wave inversion, in II, III, aVF Echo: normal findings, EF 60%

DES = drug-eluting stent(s); ECG = electrocardiogram; Echo = echocardiography; EF = ejection fraction; FFR = fractional flow reserve; LA = left atrial; s/p = status post; STEMI = ST-segment elevation myocardial infarction.

The most common finding on electrocardiography was T-wave inversion, observed in 4 (67%) patients, whereas Q-wave was seen in only 1 patient. Regional wall motion abnormalities of the target vessel territory were observed in 4 patients (67%). The results of noninvasive and invasive stress tests are shown in Table 1.

Angiographic and grayscale IVUS. The involved vessel was the left anterior descending artery in 2 patients and the right coronary artery in 4 patients. All lesions presented with multiple speckled staining of contrast or filling defects with irregular lumen border. In each, the lumen included multiple linear structures mimicking a spontaneous dissection. Three patients showed only a mild degree of angiographic stenosis (diameter stenosis <50%). Angiography showed irregular linear filling defect and haziness. Two patients with near total occlusion had Thrombolysis In Myocardial Infarction (TIMI) flow grade 1 and collateral vessels, whereas the other 4 patients had TIMI flow grade 3 and no collateral vessels (Table 2).

Pre-procedural IVUS was performed in 4 of the 6 patients and showed multiple cavities of variable

Table 2. Angiographic Findings

Findings	Patient # 1	2	3	4	5	6
Lesion site	RCA	RCA	LAD	RCA	LAD	RCA
Lesion length, mm	29.3	19.5	65.0	20.4	15.9	11.2
Diameter stenosis, %	65	42	36	41	100	100
TIMI flow grade	3	3	3	3	1	1
Collaterals	None	None	None	None	From RCA	From LAD
Visible thrombi	−	+	−	+	−	−
Plaque rupture	+	+	+	+	−	+
Haziness or filling defect	+	+	+	+	+	+
Calcification	−	−	−	−	−	−
Dissection	+	+	+	+	+	+

Minus symbols indicate negative findings; plus symbols indicate positive findings.
LAD = left anterior descending artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

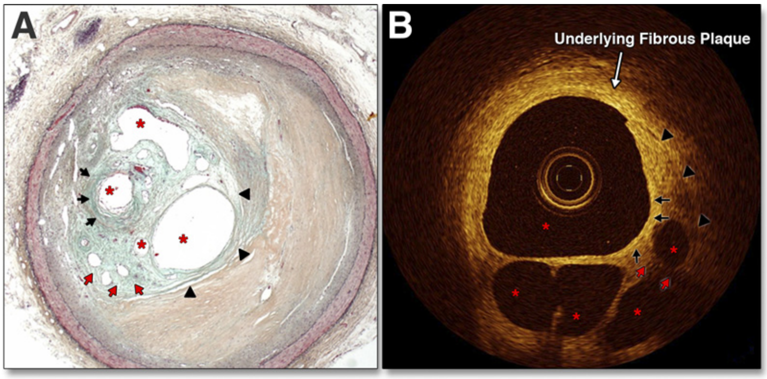

Figure 1. Histology and OCT Illustrations of Recanalization Within Thrombi

(A) The old lumen is occupied by an organized thrombus **(black arrowheads)**. The surface of septa of recanalized spaces are smooth and well endothelialized **(red asterisks)**. **(B)** The signal-poor, darker tissue in the deeper portion observed on optical coherence tomography (OCT) corresponds to a proteoglycan-rich area **(red arrows)**. Conversely, the areas near the lumen tend to be rich in smooth muscle cells and collagen, as well as being brighter on OCT **(black arrow)**.

size at the lesion site. There was vigorous blood speckling suggesting severe blood stasis in the lumen. The IVUS also revealed free-floating, huge intraluminal thrombi in 3 patients. All had markedly dilated vessels (external elastic membrane diameter >5.0 mm) with positive remodeling at the lesion segment and angiographic haziness.

OCT findings. On OCT, all patients with recanalized thrombi showed signal-rich, high backscattered septa dividing the lumen into multiple small cavities that communicated with each other (Fig. 1). The thin septa had smooth inner borders, and the multiple holes had a "Swiss cheese" appearance. The deeper portion contained signal-poor, darker tissue, corresponding to a proteoglycans-rich area with or without neovascularization on histology. In contrast, the areas near the lumen tended to be brighter, suggesting a relatively higher content of

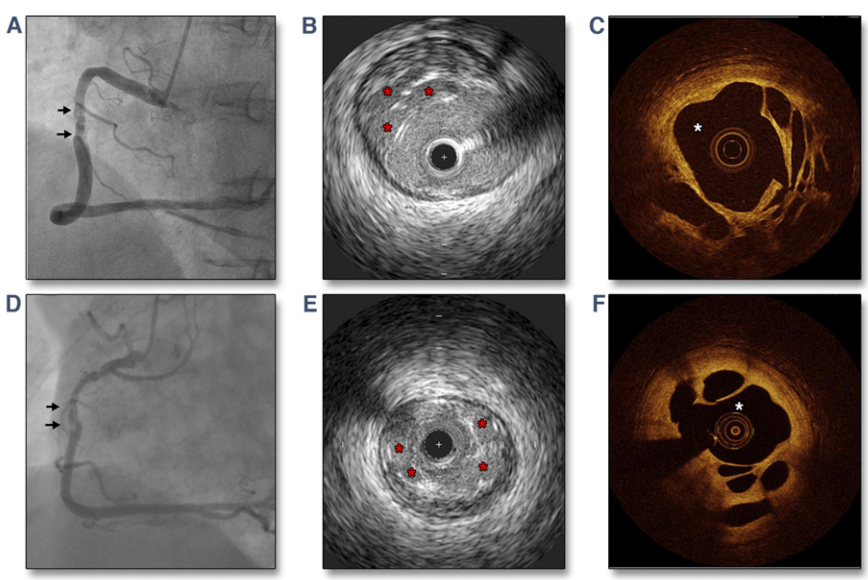

Figure 2. Angiographic and OCT Findings in Patient #1 and Patient #2

In both Patient #1 **(A to C)** and Patient #2 **(D to F)**, angiography **(A, D)** showed multiple filling defects and haziness in the mid portion of the right coronary artery **(black arrows)**. Intravascular ultrasonography **(B, E)** showed multiple cavities filled with blood speckling **(red asterisks)**. Optical coherence tomography (OCT) **(C, F)** showed multiple small channels, divided by thin septa, surrounding a larger central lumen **(white asterisk)**. The "Swiss cheese" appearance suggests recanalization of the thrombi.

smooth muscle cells and collagen. The angiographic, IVUS, and OCT findings of the 6 patients are shown in Figures 2 to 5. Fresh or organizing thrombi with signal attenuation were present in the areas adjacent to the lesion in 3 patients, whereas OCT-defined calcification was not observed. There was no definitive evidence of plaque rupture or dissection as a nidus of thrombotic occlusion.

Revascularization. Treatment strategy was based on the functional significance of stenosis. All 3 patients who underwent thallium scans (Patients #1, #3, and #5) showed reversible or partially reversible perfusion defects in the corresponding territories, and 1 (Patient #2) showed a reduced fractional flow reserve of 0.65. These 4 patients with documented inducible ischemia underwent percutaneous coronary intervention, with drug-eluting stents successfully implanted. In addition, a drug-eluting stent was implanted in Patient 6, who was diagnosed with total in-stent restenosis and angiographic slow flow. There was symptomatic improvement in all patients after treatment. The remaining patient (Patient #4) with restored coronary flow underwent mitral valve surgery and left atrial thrombectomy.

DISCUSSION

Three major findings were observed in coronary lesions with recanalization of organized thrombi: 1) common angiographic findings such as multiple irregular filling defects and intraluminal haziness were not specific for recanalization; 2) on OCT, the recanalization of organized thrombi was characterized by multiple small channels divided by thin septa communicating with each other; and 3) despite the neovascularization process, most of these lesions were functionally significant.

Previous histopathologic studies found that older coronary thrombi undergo organization or recanalization to form a few large or several small lumens. Neovascularization is of variable sizes, endothelium-lined vascular channels within the thrombus, supported by a small amount of connective tissue (1–5). One-third of patients with thrombotic occlusion were reported to have some degree of recanalization, as confirmed by pathology (3,19). Although recanalization of thrombi was not infrequent in histopathologic studies (1,3,19), it was reported to be rare when assessed

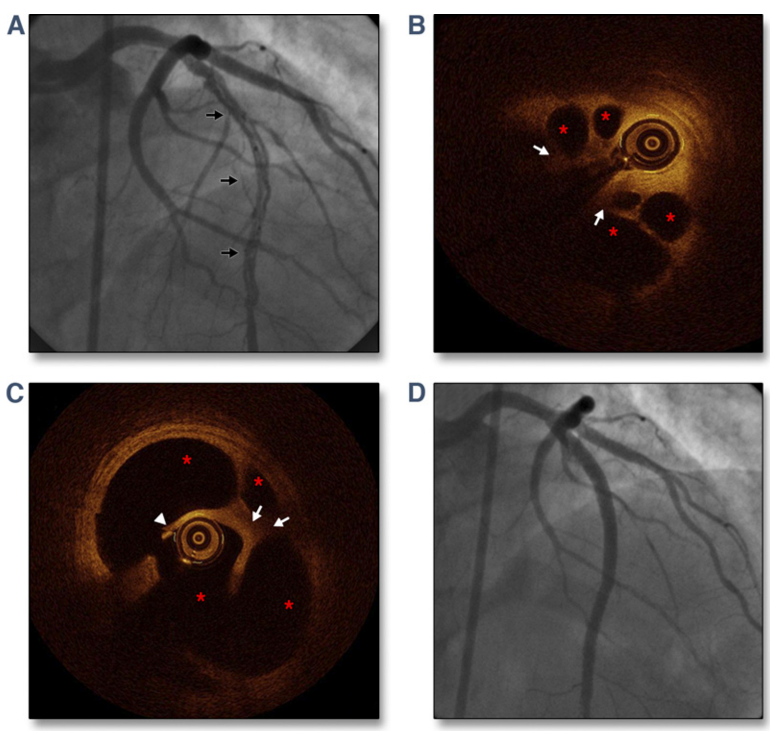

Figure 3. Angiographic and OCT Findings in Patient #3

(A) Intraluminal filling defects accompanied by a long flaplike structure in the entire left anterior descending artery **(black arrows)**, mimicking a spontaneous dissection. **(B, C)** On optical coherence tomography (OCT), multiple channels **(red asterisks),** with darker tissue in a deeper portion **(white arrows)**, represent neovascularization within organized thrombi. A disrupted septum is visible **(white arrowhead)**. **(D)** The lesion was successfully treated by placement of Nobori stents.

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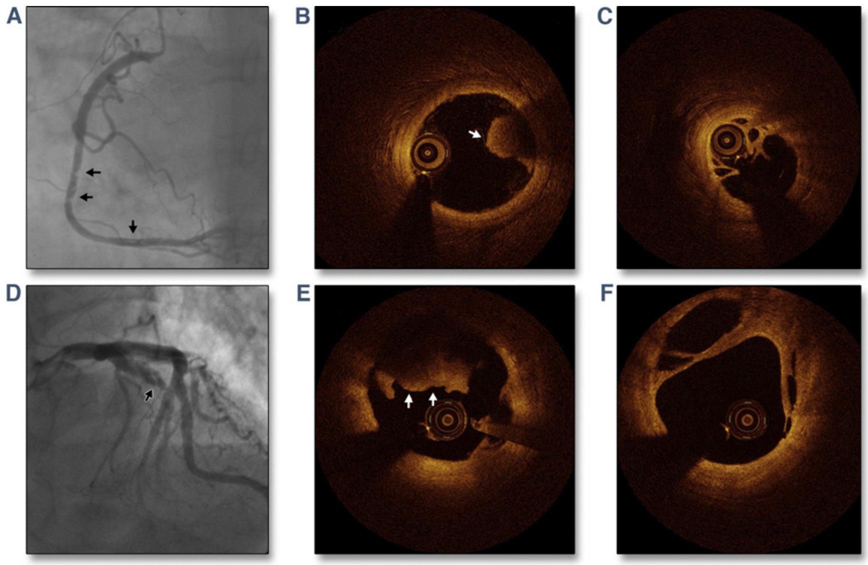

Figure 4. Angiographic and OCT Findings in Patient #4 and Patient #5

In both patients, **(A to C)** Patient #4 and **(D to F)** Patient #5, **(A, D)** angiography showed multiple irregular filling defects **(black arrows)** with luminal haziness. **(B, C, E, F)** Optical coherence tomography (OCT) showed many channels with smooth inner border of multiple septa, as well as protruding intraluminal thrombi with attenuation **(white arrows)**.

angiographically (4). Because of poor resolution, coronary "luminography" has been unable to differentiate multiple vascular channels from more common pathological conditions causing angiographic haziness (3,9,20). Although IVUS provides cross-sectional images of atherosclerotic plaque and vessel walls, its relatively low resolution limits proper diagnosis and accurate tissue characterization. Because of its better resolution, OCT can clarify the etiology of angiographic ambiguity and potentially guide an optimal therapeutic approach.

All 6 of our patients showed multiple linear filling defects on coronary angiography mimicking spontaneous dissection. Although neovascularization is based on pathological diagnosis, OCT clearly demonstrated the unique features of recanalized thrombi in vivo, described as a Swiss cheese–like or spider web–like appearance. These findings suggest that the organization of thrombi is either complete or ongoing (7–9). Figure 1 illustrates the pathological findings of recanalized thrombi that were similar to the OCT findings.

Although the functional significance of recanalization of organized thrombi has been unclear, previous studies have reported that blood flow through recanalized channels is insufficient. Because the growth of vascular channels takes several weeks or months (5,21,22), the role of recanalization in the restoration of blood flow may be insignificant, especially soon after infarction. We found that angiographic diameter stenosis varied from 36% to 100%. Irrespective of the degree of angiographic stenosis, all patients who underwent invasive or noninvasive functional tests had inducible ischemia revealed. Despite the recanalization, the stenosis remained functionally significant in most of our patients, and it is also suggested by an autopsy study that recanalized thrombi may be responsible for terminal coronary events (2). However, it remains unclear how recanalization affects early and long-term prognosis after myocardial infarction; therefore, more investigations are definitely needed in this matter.

Study limitations. As a limitation of retrospective observation, the general incidence of thrombus with recanalization or the accuracy of angiographic findings was not shown. Also, the accuracies of gray-scale IVUS with 40 MHz and 20 MHz catheters in identifying thrombi were not compared in the study. Because the sample size of this study was small and there was no histological confirmation, our observations cannot be generalized. Moreover, we could not determine the possible causes of initial thrombotic occlusion, such as plaque rupture or spontaneous dissection, as a nidus for thrombus formation. The presence of clinical

Figure 5. Angiographic and OCT Findings in Patient #6

(A) In-stent restenosis with total occlusion **(black arrows)** in Patient #6. **(B)** Grayscale intravascular ultrasonography showing multiple cavities **(red asterisks)** and suspicious thrombi **(white arrows)**. **(C, D)** Optical coherence tomography (OCT) showing neovascularization within huge thrombi **(red asterisks)**.

plaque rupture or focal dissection may be obscured by organized thrombi or other structures. In addition, the entry site of a dissection is usually small and may not show re-entry into the true lumen. Finally, the composition of the extracellular matrix including its collagen/proteoglycan content depends on duration of thrombus, location, and other factors, and this small study did not address the various stages of evolving thrombi over time.

CONCLUSIONS

An OCT evaluation provided details on the characteristics of the evolution of thrombi. Recanalization of these thrombi was characterized by multiple small channels, with most showing functional significance.

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Key Words: angiographic haziness ■ optical coherence tomography ■ recanalized thrombi.