Master's Thesis of internal medicine

Morphological characteristics of Optical Coherence Tomography defined cholesterol crystal in patients with acute coronary syndrome

급성 관동맥 증후군 환자에서 광간섭단층촬영으로 정의한 콜레스테롤 결정의 형태학적 특성

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

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Background. Cholesterol crystal (CC) can induce an atherosclerotic inflammation, and cause mechanical instability, causing plaque rupture. However, the morphology of CCs was not clearly defined and often miss the interpretation. The relation between the CCs and plaque vulnerability was not clearly defined. We evaluated the morphologic characteristics of CCs to assess vulnerability using optical coherence tomography (OCT). **Methods.** We assessed the 194 CCs in 62 patients with acute coronary syndrome, and divided into two groups; a mature and immature form. The mature CC was defined as a linear and discrete high-intensity signal structure with sharp borders, and immature CC was defined a linear and discrete high-intensity signal with relatively unclear border surrounded by low signal lipid pools. We measured the size of CCs, the distance from the luminal surface, macrophage, plaque characteristics, and the presence of CCs in the ruptured plaque or plaque erosion. **Result.** The mean age of the subjects was 63.7±11.5 years. The immature CCs did not tend to be more frequent in culprit lesions of patients with ST-elevation myocardial infarctions. OCT characteristics of

coronary arteries with immature CCs showed larger maximum lipid arches. Immature CCs were significantly more common in the ruptured plaques (28.1% vs 47.4%, p-value 0.025). After adjusting the possible confounders, immature CCs were still the independent risk factor for plaque rupture (hazard ratio2.96, 95% confidence interval 1.44-6.06, p value = 0.003)

Conclusion. Immature CCs are significantly more frequent at the plaque rupture. A larger number of subjects is needed to secure statistical significance.

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List of abbreviations

CC : cholesterol crystal

OCT: optical coherence tomography

ACS: acute coronary syndrome

PCI: percutaneous coronary intervention

STEMI: ST elevation myocardial infarction

NSTEMI: non-ST-segment elevation myocardial infarction

UA: unstable angina

TFCA: thin-cap fibroatheroma

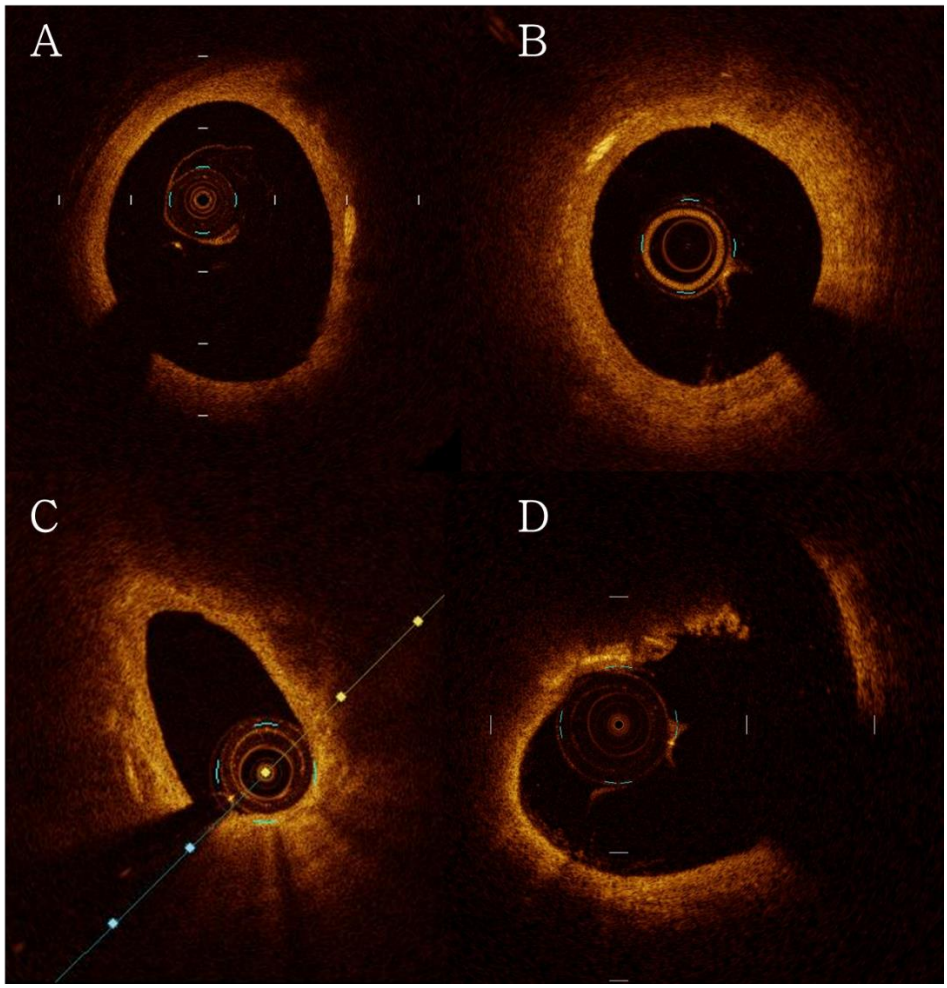
Chapter 1. Introduction

Understanding the mechanism of plaque rupture can greatly impact therapeutic approaches for both prevention and treatment of acute coronary syndrome, one of the leading causes of global morbidity and mortality (1, 2). Mortality and morbidity from acute coronary syndrome have reduced because of the development of coronary revascularization methods, especially percutaneous coronary intervention (3) These advances cannot be simplified to have occurred just dilating the stenotic coronary artery. Despite the recent advances in the coronary revascularizations, recent studies have highlighted that the initial interventional strategy with percutaneous coronary intervention or coronary artery bypass does not necessarily result in better clinical outcomes in stable coronary artery disease patients compared with optimal medical treatments (4). Since ruptured coronary plaques account for the majority of acute coronary syndrome, an improved understanding of the role of endothelial cells in the progression of atherosclerosis and early identification of high-risk plaques are anticipated to have considerable clinical impacts.

Cholesterol crystal (CC) imposes both mechanical and chemical stress on the plaque. Protrusion of CCs toward the lumen has been proposed as a possible cause of plaque rupture and thrombosis.

Moreover, intimal crystals have been identified as a possible therapeutic target for cardiovascular disease, due to the potential of these crystals to exacerbate inflammation through inflammasome-mediated cytokine production and activation (5-8) However, the morphology of CCs was not clearly defined and often miss the interpretation. Although CCs are defined as a linear and discrete high-intensity structure on optical coherence tomography (OCT) (9, 10), the size and the shape of the CCs are all different in the real world such as **Figure 1**. Thus, the relation between CCs and vulnerability was not yet clearly elucidated. We aimed to evaluate the morphology of CCs in patients with acute coronary syndrome using OCT-guidance.

Figure 1. Examples of cholesterol crystals found in patients with acute coronary syndrome



The mature cholesterol crystal was defined as a linear and discrete high-intensity signal with sharp borders (Figure 1A, 1B), and immature cholesterol crystal was defined a linear and discrete high-intensity signal surrounded by low signal lipid pools (Figure 1C, 1D).

Chapter 2. Body

Method

From January 2014 to August 2018, 170 consecutive patients with acute coronary syndrome (ACS), who underwent OCT examination on a native de novo coronary artery prior to percutaneous coronary intervention (PCI) at the Chung-Ang university hospital were eligible for the study. The subjects performed debulking or plaque modification before intravascular imaging were excluded. **Figure 2** described the study flow.

ST elevation myocardial infarction (STEMI) was diagnosed based on continuous chest pain for at least 30 min, arrival at the hospital within 6 h from the onset of symptoms, ST-segment elevation > 0.1 mV in two or more contiguous leads or new left bundle-branch block on the 12-lead electrocardiogram (ECG), and elevated cardiac marker (plasma creatine kinase-myocardial band or troponin I). Non-ST-segment elevation myocardial infarction (NSTEMI) was defined as ischemic symptoms in the absence of ST-segment elevation on the ECG with elevated cardiac markers. Unstable angina (UA) was defined as new onset/accelerating chest symptoms on exertion or rest angina within 2 weeks. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive treatment. Diabetes mellitus was defined as hemoglobin A1C ≥ 6.5mg/dL or medication treatment for diabetes mellitus. Dyslipidemia was defined as having

total cholesterol ≥ 240 mg/dl, low-density lipoprotein cholesterol ≥ 160 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or self-reported use of lipid-lowering drugs. The protocol was approved by the institutional review board, and written consent was obtained from all patients. Coronary angiography was performed after 200 μg of intracoronary nitroglycerin. The use of OCT is determined by the discretion of individual operators.

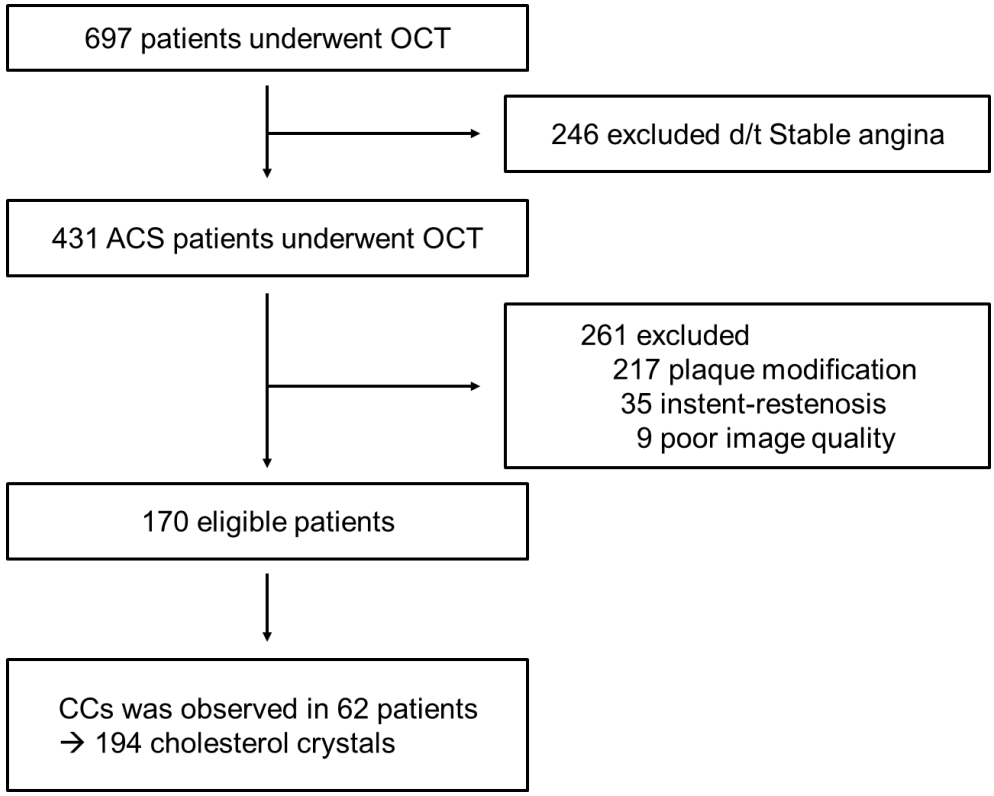
A commercially available frequency domain OCT system (C7-XR or Ilumien System, Light Lab Imaging, Inc., St. Jude Medical, Westford, Massachusetts) and a 0.014-inch wire-type imaging catheter (ImageWire, St. Jude Medical, Westford, Massachusetts) were used (9). Motorized ImageWire pull-back at 10mm/sec was performed during simultaneous injection of a viscous iso-osmolar contrast solution. Five-hundred frames of images in a 50mm coronary artery section was obtained through each OCT scan. Thrombus aspiration was performed prior to OCT imaging using an aspiration catheter (Thrombuster®, Kaneka Co, Osaka, Japan) according to the operator discretion, but generally for large thrombi in the setting of an ST-segment elevation myocardial infarction (STEMI). However, if balloon angioplasty was performed before OCT, it was considered not eligible for study.

OCT image was analyzed according to the previously established criteria for the plaque characterization. All OCT images were analyzed using a certified Offline Review Workstation (St. Jude Medical, Westford, Massachusetts) by two experienced analysts who were blinded to patient information. The mature CC was defined as a

linear and discrete high-intensity signal with sharp borders (**Figure 1A, 1B**), and immature CC was defined a linear and discrete high-intensity signal surrounded by low signal lipid pools (**Figure 1C, 1D**). An OCT image motion artifact such as a tangential and seam-line artifacts and vessel structure which create a mimicking linear structure were excluded. The definite and probable plaque erosion was defined as reported previously (1, 5, 9, 10). OCT-identified thin-cap fibroatheroma (TCFA) was defined as a fibrous cap thickness $\leq$ 65 μm at the thinnest part and an angle of the lipid $\geq$ 180°. The culprit lesion was identified based on the ECG, echocardiography, and angiographic findings which showed a lesion with complex features including a thrombus, ulcer with overhanging edges, extraluminal contrast, dissection or intraluminal flap, multiple irregularities, or acute occlusion. OCT plaque composition was analyzed as defined previously.

Results are expressed as mean $\pm$ standard deviation or number (%). Student t-test (parametric statistical test) and Wilcoxon rank-sum test (nonparametric statistical test) are used to compare two independent continuous variables. When comparing more than three groups, one-way ANOVA test was performed to compare continuous variables. Categorial variables were compared using the X^2 test. Multivariate logistic regression analyses were performed to identify the independent predictors of the maturity of CCs. All analysis were performed using standard statistical software (SPSS version 23.0; IBM, Chicago, Illinois, USA), and $p < 0.05$ was considered statistically significant.

Figure 2. Study flow



Among 170 eligibile patients, 194 cholesterol crystals were observed in 62 patients and analyzed.

Result

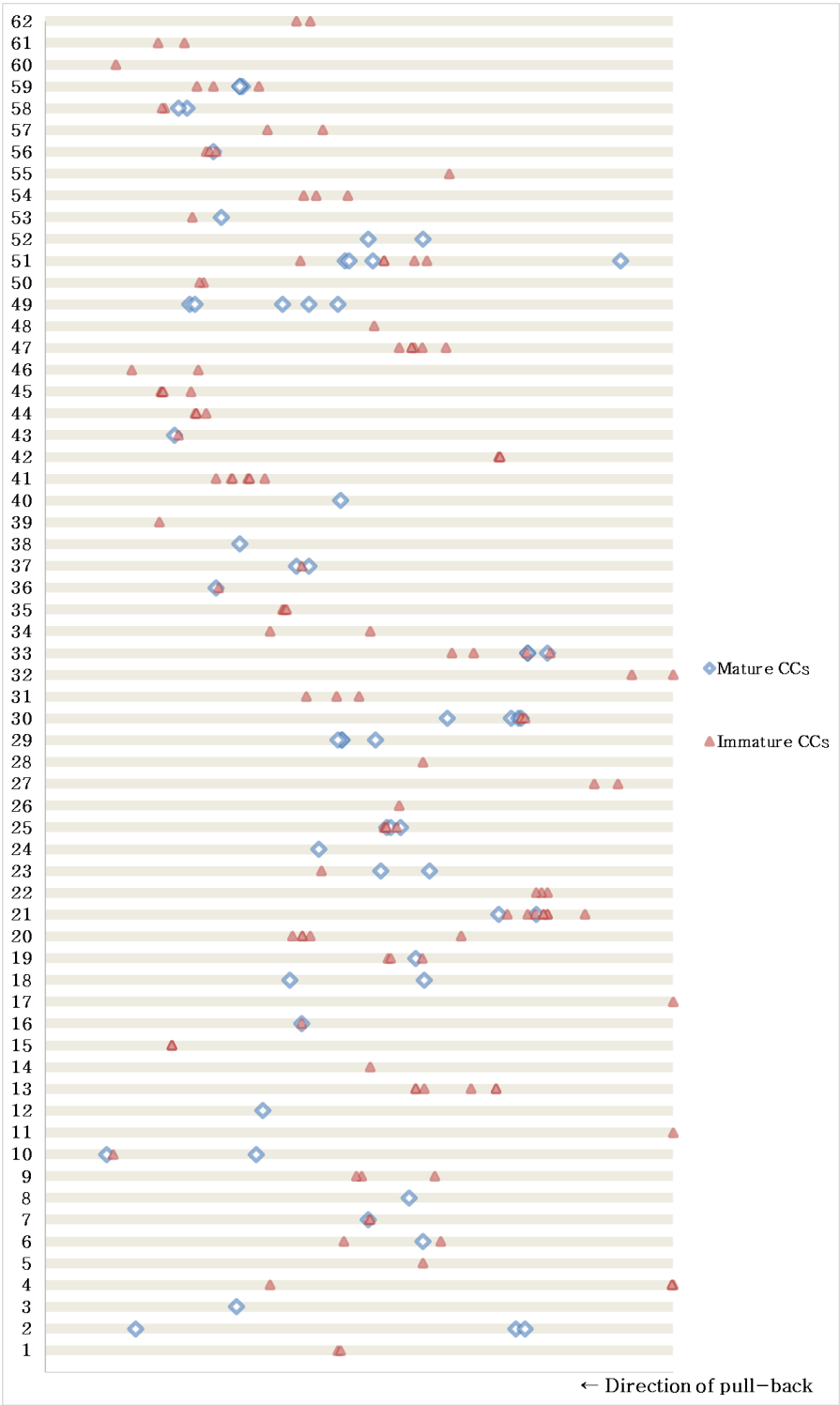
A total of 194 CCs were found in 62 patients. Subjects are divided in 3 groups according to the distribution of CCs: immature CCs without mature CCs (n=35), mature CCs without immature CCs (n=9), and mixed CCs (n=−18). The location where each CC was observed in the scanned 50 mm long coronary artery section in each patient is demonstrated in **Figure 3.** CCs are distributed in a specific location rather than widely spread. In the case of subjects with only immature CCs, there were median 2 CCs (interquartile range 1−3.5). In patients with mixed CC, there were 2 mature CCs (interquartile range 1−3.75) and 2 immature CCs (interquartile range 1−2.5). In patient with mature CCs, median 1 mature CC (interquartile range 1−2) was present **(Figure 4).** Mean age was 63.7 ± 11.5 years and 77.4% were male. Baseline clinical characteristics of the study population are shown in **Table 1**. There were no significant differences in incidence of STEMI and target vessels between the groups.

All CCs were divided into 2 groups according to the morphology of CCs within the lesion segment: mature CCs (n= 57) and immature CCs (n=137). OCT findings at the site of cholesterol crystals are described in **Table 2**. Immature CCs were thinner and shorter in length than mature CCs. There was no significant difference in macrophage depth between the two groups, but macrophages length was wider in the mature CCs. Maximum lipid arc was significantly increased in immature CCs, but no significant difference was found in lipid length, average lipid arc, and lipid index. Plaque rupture was

significantly more frequent in the immature CCs than in the mature CCs (47.4% vs 28.1%, p-value = 0.013). Plaque erosion and TFCA tended to be more in the immature CCs, but there was no statistical significance. Lipid plaques were not statistically significant, but tended to be more common in immature CC.

Table 3 shows the results of multiple linear regression analysis of factors associated with the plaque rupture. The maturity of the CCs was an independent risk factor for the plaque rupture (hazard ratio 2.96, 95% confidence interval 1.44-6.06, p-value 0.003) after adjusting the potential confounders. Maximum lipid arch was another statistically significant risk factor for the plaque rupture (hazard ratio 3.46, 95% confidence interval 1.82 - 6.56, p-value <0.001).

Figure3.Intracoroanry distribution of cholesterol crystals of each subject.



While performing pull-back, the OCT scan obtained 500 frames of coronary artery images in a 50 mm section. The location of the both mature and immature crystal in each patient is indicated on the figure 3.

Figure 4. Comparison of the number of cholesterol crystals by maturity

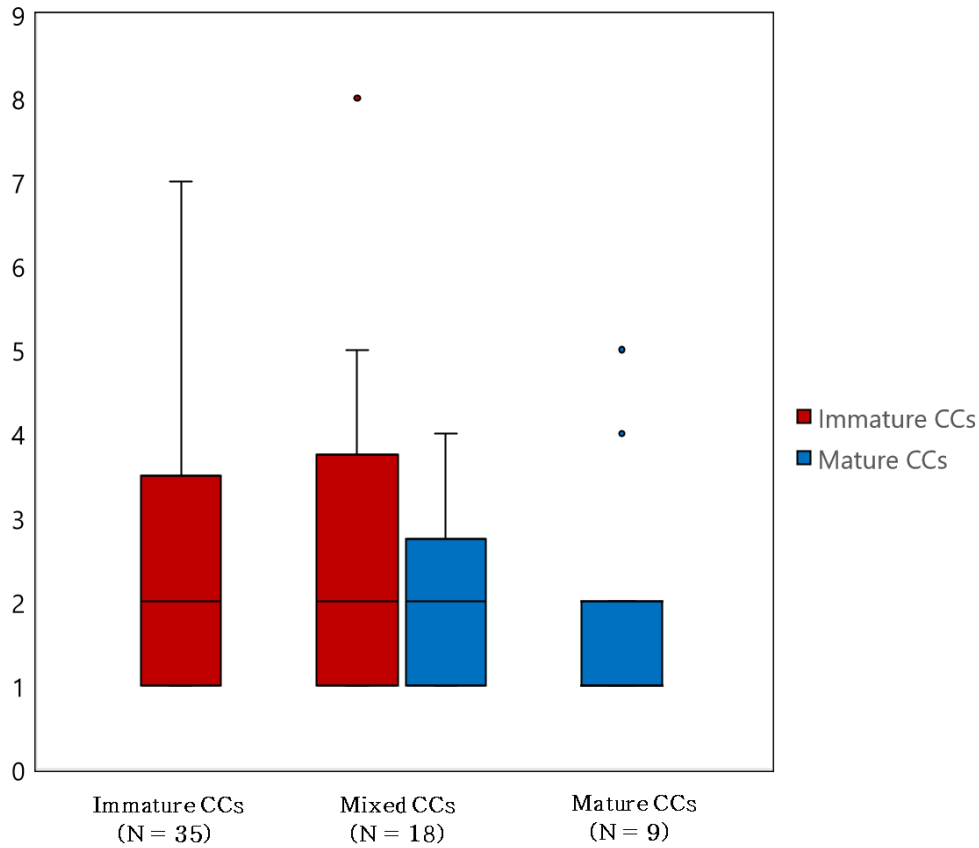


Table 1. Baseline clinical characteristics of subjects according to the distribution of cholesterol crystals

	Immature CCs (N = 35)	Mixed CCs (N = 18)	Mature CCs (N = 9)	*p*-value
Age (years)	62.6 ± 12.1	64.2 ± 2.5	66.1 ± 3.6	*0.682*
Male gender, n (%)	26 (78.8%)	13 (72.2%)	9 (81.8%)	*0.804*
DM n (%)	8 (24.2%)	7 (38.9%)	3 (27.3%)	*0.540*
Hypertension, n (%)	17 (51.5%)	11 (61.1%)	4 (36.4%)	*0.433*
IHD, n (%)	6 (18.2%)	5 (27.8%)	2 (18.2%)	*0.701*
Current smoker	17 (51.5%)	8 (44.4%)	4 (36.4%)	*0.665*
Clinical Presentation, n (%)				
Unstable angina	15 (45.5%)	14 (77.8%)	5 (45.5%)	*0.167*
NSTEMI	8 (24.2%)	2 (11.1%)	4 (36.4%)	
STEMI	10 (30.3%)	2 (11.1%)	2 (18.25)	
Culprit vessel				
LAD	20 (60.6%)	9 (50.0%)	7 (63.6%)	*0.150*
LCX	2 (6.1%)	5 (27.8%)	5 (27.3%)	

RCA	11 (33.3%)	4 (22.2%)	1 (9.1%)	
LDL-C (mg/dL)	114.8 ± 41.1	104.2 ± 28.7	113.3 ± 24.7	0.583
HDL-C (mg/dL)	40.1 ± 11.2	47.0 ± 11.4	43.7 ± 9.6	0.126
Triglyceride (mg/dL)	173.3 ± 152.3	134.9 ± 84.7	119.6 ± 44.8	0.354
Total cholesterol (mg/dL)	165.8 ± 78.6	144.9 ± 77.5	151.2 ± 79.9	0.639
HbA1c (%)	6.3 ± 1.7	6.1 ± 1.9	5.7 ± 2.2	0.637
Glucose (mg/dL)	147.2 ± 64.7	134.2 ± 62.2	143.5 ± 50.2	0.772
BUN (mg/dL)	17.1 ± 5.5	17.8 ± 4.1	15.1 ± 3.7	0.348
Creatinine (mg/dL)	0.93 ± 0.23	0.86 ± 0.17	0.84 ± 0.18	0.302
WBC (ug/L)	8288 ± 2474	6901 ± 3046	8127 ± 3088	0.224
Hemoglobin (g/dL)	14.2 ± 1.8	14.1 ± 1.9	14.8 ± 1.8	0.560
CRP (mg/dL)	2.6 ± 2.9	2.1 ± 2.3	2.0 ± 2.8	0.787
LV ejection fraction (%)	53.2 ± 13.8	61.2 ± 5.0	54.0 ± 9.9	0.055
E/e'	11.4 ± 5.6	10.4 ± 3.2	13.6 ± 7.3	0.301

DM, diabetes mellitus, IHD, ischemic heart disease; NSTEMI, non-ST

elevation myocardial infarction, STEMI, ST elevation myocardial infarction; LAD left anterior descending artery, LCX left circumflex artery, RCA right coronary artery, LDL-C low density lipoprotein cholesterol, HDL-C, high density lipoprotein cholesterol, BUN, blood urea nitrogen; WBC, white blood cell count, CRP, C-reactive protein; LV, left ventricular

Table 2. Comparison of optical coherence tomographic findings according to the morphology of cholesterol crystals

	Immature CCs (N = 137)	Mature CCs (N = 57)	p value
Crystal Thickness (μm)	46 ± 26	58 ± 31	0.006
Crystal Length (μm)	301 ± 132	371 ± 187	0.012
Depth from lumen surface (μm)	783 ± 4256	233 ± 126	0.331
Minimal lumen area (mm2)	3.8 ± 3.5	3.3 ± 2.6	0.002
Macrophage length (μm)	755 ± 253	846 ± 269	0.030
Macrophage depth (μm)	200 ± 79	210 ± 98	0.527
Lipid length (mm)	13.4 ± 6.2	14.6 ± 6.9	0.233
Maximum lipid arc (°)	315 ± 394	240 ± 66	0.034
Average lipid arc (°)	145 ± 39	148 ± 34	0.700
Lipid index	2027 ± 1185	2253 ± 1392	0.255

Plaque rupture, n (%)	65 (47.4%)	16 (28.1%)	0.013
Plaque erosion, n (%)	50 (40.7%)	20 (38.5%)	0.787
Thin cap fibroatheroma, n (%)	90 (65.7%)	29 (50.9%)	0.054
Plaque characteristics			
Fibrotic, n (%)	40 (29.2%)	20 (35.1%)	0.779
Lipidic, n (%)	84 (61.3%)	33 (57.9%)	
Calcific, n (%)	12 (8.8%)	4 (7.0%0	

Lipid index lipid length multiplied with mean lipid arc, STEMI ST-segment elevation myocardial infarction

Table 3. Multivariable linear regression analysis showing independent predictors for plaque rupture

	Hazard ratio	95% confidence interval	*p*-value
Immature cholesterol crystal	2.96	1.44 - 6.06	*0.003*
Crystal length > 280μm	1.05	0.57 - 1.93	*0.883*
Macrophage length > 560μm	1.26	0.68 - 2.34	*0.460*
Maximal lipid arch > 235O	3.46	1.82 - 6.56	*<0.001*

Chapter 3. Discussion

This study demonstrated that the maturity of the cholesterol crystal can predict the plaque rupture in patients with acute coronary syndrome. We confirmed that the cholesterol crystals found at the plaque rupture were relatively thin, short, and had less clear margin with small lipid pools.

Preceding studies demonstrated that cholesterol crystallization is strongly influenced by the size and composition of the cholesterol pool within the atheromatous plaque. From that point of view, larger lipid pool could create larger and sharper crystals enough to pierce the fibrous cap of the plaque. However, according to our report, large maximum lipid arch was still independent risk factor for plaque rupture, but small and amorphous crystal which thought to be immature during crystallization would be more dangerous than large and sharp ones. It suggests that the role of mechanical stress by volume expansion during crystallization is smaller than expected.

A plaque rupture does not always cause a heart attack or stroke in every patient. In patients with myocardial infarction, multiple plaque ruptures may occur simultaneously, but not all plaque ruptures cause thrombotic occlusion. (11). Therefore, other factors are involved in determining the event severity and outcome. Based on the current proposed role of CC in plaque rupture, it would be expected that plaques with large necrotic cores will release greater amounts of CC into the circulation causing more injury and arterial thrombosis. (5)

Thus, plaque burden is of critical importance and this has been recognized in clinical studies (11, 12).

Free cholesterol is transported in and out of cells. When the equilibrium between esterified and free cholesterol is stable, HDL cholesterol reversely transports free cholesterol from the extracellular membrane through membrane transporters. When the cell membrane of dead foam cells is damaged, overloaded esterified cholesterol are released into the extracellular space, causing crystallization. During this process, various inflammatory mediators are activated, triggering aggravation of atherosclerosis. (13-15) Thus, developing agents that dissolve CCs and/or that target inflammatory pathways may provide alternative approaches for stabilizing vulnerable plaques. The current data would support observations that a large plaque burden that contains more crystals is a critical feature of plaque ruptures with an associated inflammatory state that is reflective of a systemic condition with localized events (11, 12, 16).

Based on studies regarding the role of CC, pharmacological compounds that have the potential of dissolving CC or inhibiting their formation may provide an effective therapeutic approach to reduce the incidence of acute cardiovascular events. In our studies, the observations by electric microscopy were made possible by avoiding tissue processing with ethanol, because ethanol dissolves CC rendering them and their role in atherosclerosis invisible. (17, 18) Also, recent studies have demonstrated that statins can dissolve CC and interfere with crystal formation. (4) Thus, maximizing inhibition

of CC formation and their dissolution could prove to be an effective therapy in stabilizing vulnerable plaques. Also, the recent introduction of proprotein convertase subtilisin/kexin type 9 inhibitors that are very effective in lowering LDL may greatly impact CC formation (18, 19).

Another therapeutic target is reduction of the inflammation induced by CC. Recently, a clinical trial, Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), was designed to evaluate the efficacy of an antibody that selectively inhibits IL-1b, canakinumab, in reducing plaque inflammation and cardiovascular events. (20) Canakinumab is used in the treatment of out and other inflammatory conditions. However, the results of the effects of canakinumab in cardiovascular disease are still pending. The use of other anti-inflammatory agents for atherosclerotic disease is being evaluated. Low-dose methotrexate is currently under investigation in patients with high cardiovascular risk in the Cardiovascular Inflammation Reduction Trial (CIRT) (21). Also, colchicine can interfere with macrophage and neutrophil activity and has been shown in a small trial to reduce cardiovascular events (22). Anti-leukotrienes agents are currently being investigated for reducing cardiovascular inflammation, and free fatty acid derivates such as lipoxins and resolvins are being proposed for their anti-inflammatory and pro-resolution properties.

There are several limitations in this study. This study was a small observational study and has limitations in defining the causal relationship. Maturity is an ambiguous terminology that can be

affected by the subjective bias of the researchers without histopathologic correlations. Although the actual crystal structure is three-dimensional, we had no choice but to evaluate in only the cross-sectional area. There is a possibility that the CCs that really pierced the endothelium may have poured into the lumen of coronary artery and washed out. Moreover, some patients with acute coronary syndrome had limitations to be evaluated in our study. First, OCT has not been favored in patients with acute kidney injury or chronic kidney disease because of concerns about contrast induced nephropathy. OCT is not a preferred method in patients with multivessel disease or ostial lesions. Second, we excluded the patients underwent balloon angioplasty prior to OCT images. Cholesterol crystals are likely to be present in coronary arteries with more severe stenosis, but these vessels are difficult to evaluate prior to balloon angioplasty.

Conclusion

Immature cholesterol crystals were more frequently existed in the ruptured plaque than mature cholesterol crystals. Further prospective study with larger number of subjects would be needed to confirm the temporal relationship between the morphology of the crystal and the acute coronary syndrome.

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Abstract

배경. 콜레스테롤 결정은 동맥경화성 염증을 유발하고 기계적 불안정성을 유발하여 동맥경화반 파열을 유발할 수 있다. 그러나 파열을 유발할 수 있는 콜레스테롤 결정의 형태는 명확하게 정의되지 않았으며 크리스탈이 존재하여도 관찰하지 못하고 놓치는 경우도 많다. 이러한 콜레스테롤 결정과 취약한 동맥경화반의 관계는 명확하게 규명되지 않았다. 우리는 광간섭단층촬영을 사용하여 콜레스테롤 결정의 형태학적 특성을 평가하였다. **방법.** 우리는 급성 관상동맥 증후군 환자 62명에서 194개의 콜레스테롤결정을 평가하고, 결정을 성숙한 결정과 미성숙한 결정의 두 그룹으로 나누었다. 날카로운 경계를 가진 선형 및 고강도 신호를 발산하는 구조물을 성숙한 결정이라고 정의하였고, 낮은 신호의 지질로 둘러싸인 상대적으로 불분명한 경계를 보이는 선형 및 고강도 신호를 발산하는 구조물을 미성숙하다고 정의하였다. 우리는 콜레스테롤 결정의 크기, 대식세포의 분포, 지질의 혈관내 분포를 측정하고 파열된 동맥경화반 또는 미란이 발생한 동맥경화반에서 결정이 존재하는지를 관찰하였다. **결과.** 피험자의 평균 연령은 63.7± 11.5세였다. 미성숙 결정이 발견되는 빈도는 ST분절 상승 심근경색 환자군에서 차이가 없었다. 미성숙 결정이 발견된 관상동맥은 최대 지질각도가 유의하게 증가되어 있었다. 미성숙 결정은 동맥경화반 파열 부위 (28.1% vs 47.4%, p−value 0.025)에서 유의하게 더 많이 존재하였다. 교란 인자를 보정한 로지스틱 회귀분석에

서도 미성숙 결정과 최대 지질각도는 동맥경화반 파열의 독립적인 위험 인자라는 것이 확인되었다 (위험 비 2.96, 95% 신뢰구간 1.44 – 6.06, p-value = 0.03). **결론.** 미성숙 콜레스테롤 결정은 동맥경화반 파열의 통계적으로 유의하나 위험인자이다. 인과관계를 공고히 하기 위하여는 향후 더 많은 수의 환자를 대상으로 한 전향적인 연구가 필요하겠다.