J Thromb Thrombolysis (2014) 38:503–509
DOI 10.1007/s11239-014-1062-9

Edge dissection of calcified plaque as a possible mechanism for acute coronary syndrome

Cheol Whan Lee · Soo-Jin Kang · Jung-Min Ahn · Sung-Han Yoon · Jong-Young Lee · Duk-Woo Park · Seung-Whan Lee · Young-Hak Kim · Seong-Wook Park · Seung-Jung Park

Published online: 21 February 2014

Abstract We evaluated the incidence and predictors of edge dissection of the calcified culprit plaque in patients with acute coronary syndrome (ACS) or stable angina (SA). Calcified plaque is not rare in patients with ACS, and compliance mismatch may create edge dissection of the calcified plaque to trigger ACS. However, little data are available on calcium edge dissection in relation to ACS. Pre-intervention intravascular ultrasound data were analyzed in 143 patients with ACS (n = 53) or SA (n = 90). Edge dissection of the calcified plaque was found in 14 patients (9.8 %). Patients were divided into two groups based on calcium edge dissection: group I (edge dissection, n = 14) and group II (no edge dissection, n = 129). Clinical and angiographic characteristics were largely similar between the two groups; however, ACS was more common in group I than in group II (64.3 vs. 34.1 %, respectively, $p = 0.039$). Intravascular ultrasound variables did not differ between the two groups except thrombus and reference measurements, with thrombus more frequently observed in group I than in group II (35.7 vs. 8.5 %, respectively, $p = 0.010$). Likewise, proximal and distal reference measurements were larger in group I than in group II. Multivariate analysis showed that ACS was the only independent predictor of calcium edge dissection (odds ratio 3.5, 95 % confidence interval 1.1–11.0, $p = 0.034$). Edge dissection of the calcified plaque was present and more common in ACS patients than in SA patients. Calcium edge dissection may play a role in the pathogenesis of ACS.

Keywords Acute coronary syndrome · Calcium · Dissection

Abbreviations

ACS	Acute coronary syndrome
CSA	Cross-sectional area
EEM	External elastic membrane
IVUS	Intravascular ultrasound

Introduction

Calcification frequently occurs in atherosclerotic lesions, with the extent and severity reflecting atherosclerotic plaque burden [1, 2]. Many studies have looked for a link between coronary artery calcification and plaque vulnerability, but the results have been conflicting [3–9]. Some studies have indicated that calcification increases the mechanical stability of coronary atherosclerotic plaques [3–6] while others found that it may increase the risk of plaque instability [7–9].

A calcified lesion is stiffer than the adjacent non-calcified tissue; therefore compliance mismatch may create dissection at the edge of the calcified plaque [10, 11]. Edge dissection of the calcified plaque is likely to expose the thrombogenic material and trigger acute coronary syndrome (ACS). A calcified plaque is not rare in patients with ACS, but there has been no report of its edge dissection in relation to ACS. In the present study, we investigated the incidence of edge dissection of the calcified culprit plaques

C. W. Lee · S.-J. Kang · J.-M. Ahn · S.-H. Yoon · J.-Y. Lee · D.-W. Park · S.-W. Lee · Y.-H. Kim · S.-W. Park · S.-J. Park
Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea

S.-J. Park (✉)
Division of Cardiology, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
e-mail: sjpark@amc.seoul.kr

in patients with ACS or stable angina, and its relation to clinical manifestations.

Methods

Study patients

The Asan Medical Center clinical database included 374 patients with ACS or stable angina, who had angiographically heavy calcification in culprit coronary lesions between January 2005 and September 2013. Of these, intravascular ultrasound (IVUS) examination during the procedure was performed in 338 patients (90.4 %). The culprit vessel was identified on the basis of clinical, electrocardiogram, and angiographic data.

Image acquisition and measurements

Intravascular ultrasound imaging was performed after intracoronary administration of 0.2 mg nitroglycerin using a motorized transducer pullback system (0.5 mm/s) and a commercial scanner (SCIMED/Boston Scientific, Natick, Mass) consisting of a rotating 40 MHz transducer within a 3.2F or 2.6F imaging sheath. IVUS images were recorded on a computer disc for off-line analysis.

Intravascular ultrasound images were analyzed by a single individual, blinded to the clinical data. The culprit lesion site and reference site were selected for measurement. A reference segment was defined as the most normal-appearing cross-section within a 5 mm region proximal and distal to the lesion, but before any side branch. Using computerized planimetry (EchoPlaque 3.0, Indec Systems, Mountain View, CA), the external elastic membrane (EEM) and lumen cross-sectional area (CSA) (mm^2) were measured in culprit and reference segments. When acoustic shadowing in the culprit image slice made identification of the EEM difficult, two types of extrapolation methods were used, according to a previously described method [2]. Calcium was identified by the presence of a bright echogenic signal with acoustic shadowing, and its distribution pattern was classified as superficial, deep or mixed [2]. A length of calcified lesion was measured between the proximal and distal edges of target lesion calcium, and the largest arc of target lesion calcium was measured from the middle of the lumen. The remodeling index was calculated as the lesion EEM CSA divided by the mean reference EEM CSA, and the plaque burden was calculated as plaque + -media CSA divided by EEM CSA.

Definitions

Unstable angina was defined as new onset or worsening of previous angina, with a severity of at least III based on the Canadian Cardiovascular Society Classification system, or rest angina. Acute myocardial infarction was diagnosed as a typical rise and fall of cardiac injury markers with the sudden onset of resting chest pain lasting >20 min and new ischemic electrocardiographic changes [12]. ST-segment elevation myocardial infarction was defined as ST elevation at the J point in at least two contiguous leads ≥2 mm in precordial leads ands or ≥1 mm in limb leads. Calcified nodules were defined as the presence of luminal protruding calcified masses with a convex irregular surface [13–16]. Edge dissection of the calcified plaques was defined as abrupt discontinuity of the luminal surface in the edge of superficial calcium. A ruptured plaque was defined as a plaque containing a cavity that communicated with the lumen, which showed an overlying residual fibrous cap fragment. A thrombus was defined as an intraluminal mass with a layered or lobulated appearance, showing evidence of blood flow within the mass, and demonstrating speckling or scintillation.

Statistical analysis

Data are expressed as medians with interquartile ranges (IQRs) for continuous variables and frequencies for categorical variables. Continuous variables were compared using the Mann–Whitney *U* tests, and categorical variables were analyzed using the Chi squared test. Multivariate logistic regression analysis was performed to assess independent predictors for calcium edge dissection. Statistical significance was defined as a two-sided p value <0.05.

Results

Of all the IVUS images, 46.7 % were obtained before any coronary intervention. Of these, 15 patients were excluded from the analysis due to inadequate quality of IVUS images (n = 11) or incomplete IVUS studies (n = 4). Thus, the remaining 143 patients (53 in ACS, 90 in stable angina) constituted the study population.

Clinical characteristics

The mean age of the patients was 65.7 ± 9.3 years (range 38–87 years), and 69.2 % were men. Edge dissection of the calcified plaque was found in 14 patients (9.8 %), and patients were divided into two groups based on calcium edge dissection: group I (edge dissection, n = 14) and group II (no edge dissection, n = 129). As shown in Table 1, clinical characteristics were largely similar between the two groups and, likewise, the angiographic characteristics and lesion distributions were comparable between the two groups. However, ACS was more

Table 1 Clinical characteristics

Characteristics	Dissection (n = 14)	No dissection (n = 129)	*p* value
Age (years)	68.5 (65.0–74.8)	67.0 (61.0–72.0)	0.586
Sex, male/female	9/5	90/39	0.762
Current smoker	3 (21.4 %)	33 (25.6 %)	1.000
Diabetes mellitus	4 (28.6 %)	45 (34.9 %)	0.772
Hypertension	11 (78.6 %)	91 (70.5 %)	0.757
Estimated GFR[a]	65.6 (34.5–84.9)	70.6 (58.4–85.9)	0.321
Total cholesterol (mg/dl)	157.0 (150.0–207.0)	160.0 (138.0–184.0)	0.589
Triglyceride (mg/dl)	98.0 (61.0–129.0)	109.0 (88.0–161.0)	0.139
HDL cholesterol (mg/dl)	47.5 (41.5–60.0)	43.0 (37.0–52.0)	0.077
Hs-CRP (mg/dl)	1.9 (0.5–4.6)	1.3 (0.6–3.1)	0.965
Diagnosis			
Acute coronary syndrome	9 (64.3 %)	44 (34.1 %)	0.039
STEMI	1 (7.1 %)		
NSTEMI	2 (14.3 %)		
Unstable angina	6 (42.9 %)		
Stable angina	5 (35.7 %)	85 (68.9 %)	
Culprit coronary artery			0.339
Left main	1 (7.1 %)	18 (14.0 %)	
Left anterior descending	8 (57.1 %)	90 (69.8 %)	
Left circumflex	1 (7.1 %)	4 (3.1 %)	
Right	4 (28.6 %)	17 (13.1 %)	
Multivessel disease	6 (42.9 %)	58 (45.0 %)	1.000
TIMI flow grade 3 at baseline+	14 (100 %)	124 (96.1 %)	1.000

GFR glomerular filtration rate, *hs-CRP* high-sensitivity C-reactive protein, *NSTEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction, *TIMI* thrombolysis in myocardial infarction

[a] Estimated GFR by Cockcroft–Gault method. +Antegrade TIMI flow grade 3 through the coronary culprit lesion before coronary angioplasty

Table 2 Intravascular ultrasound findings

	Dissection (n = 14)	No dissection (n = 129)	*p* value
Lesion length (mm)	29.1 (24.1–35.7)	29.2 (19.8–39.2)	0.918
Thrombus (%)	5 (35.7 %)	11 (8.5 %)	0.010
Plaque rupture	3 (21.4 %)	42 (32.6 %)	0.300
Plaque morphology			0.334
Fibrocalcific	5 (35.7 %)	45 (34.9 %)	
Soft	1 (7.1 %)	30 (23.3 %)	
Mixed	8 (57.1 %)	54 (41.9 %)	
Calcium deposits			
Location			0.397
Superficial	8 (57.1 %)	55 (42.6 %)	
Mixed	6 (42.9 %)	74 (57.4 %)	
Shape			0.305
Concave	9 (64.3 %)	100 (77.5 %)	
Convex	1 (7.1 %)	5 (3.9 %)	
Mixed	4 (28.6 %)	24 (18.6 %)	
Surface irregularity			0.083
Regular	9 (64.3 %)	105 (81.4 %)	
Irregular	4 (28.6 %)	22 (17.1 %)	
Mixed	1 (7.1 %)	2 (1.6 %)	
Calcified nodules	4 (28.6 %)	19 (14.7 %)	0.245
Dissection location versus minimal lumen site			
Proximal	8 (57.1 %)		
Same	1 (7.1 %)		
Distal	5 (35.7 %)		

common in group I than in group II (64.3 vs. 34.1 %, respectively, $p = 0.039$).

IVUS findings

Intravascular ultrasound characteristics are summarized in Table 2, and examples of calcium edge dissection are shown in Fig. 1. Calcified lesions were mostly a concave shape with a regular luminal surface. Calcium edge dissection was located proximal to the minimal lumen area site (57.1 %), distal to the minimal lumen area site (35.7 %), and at the corresponding minimal lumen area site (7.1 %). Calcified nodules were observed in 23 patients (16.1 %) with no difference between the two groups. A thrombus was more frequently identified in group I than in group II (35.7 vs. 8.5 %, respectively, $p = 0.010$). Plaque morphology and plaque rupture did not differ between the two groups.

The arc of maximum calcium measured 200.0° (IQR 120.0°–315.0°); 44.1 % was superficial, and 55.9 % was mixed. The arc, area, and length of calcification were similar between the two groups (Table 3). There were also no differences in EEM CSA, lumen CSA, plaque burden, or remodeling index at the minimal lumen sites between the two groups. However, proximal and distal reference measurements were larger in group I than in group II. Multivariate analysis showed that ACS was the only independent predictor of calcium edge dissection (odds ratio 3.5, 95 % confidence interval 1.1–11.0, $p = 0.034$).

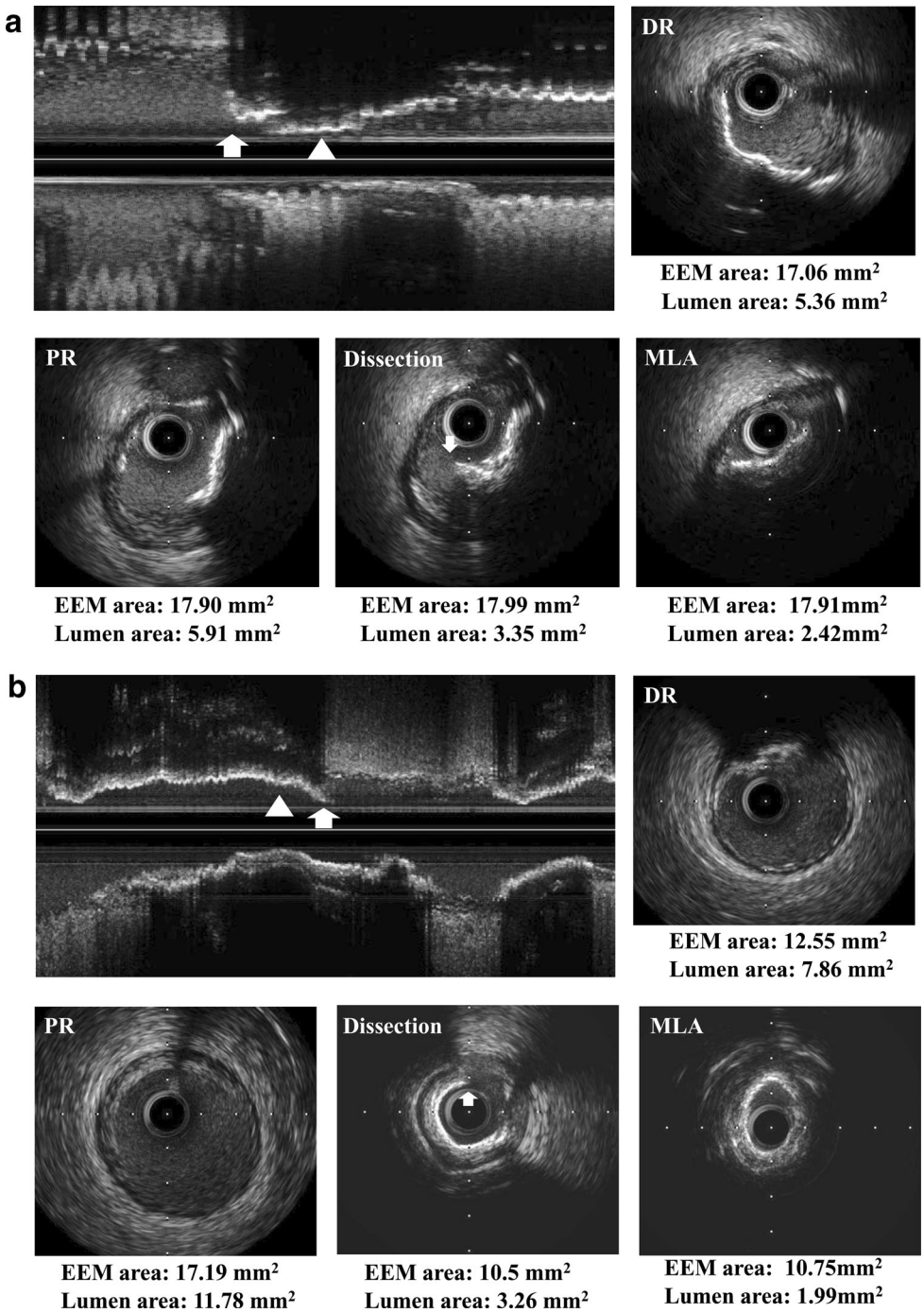

Fig. 1 Representative IVUS images showing edge dissection of the calcified plaque from patients with ST elevation (**a**) or non-ST elevation (**b**) myocardial infarction. Longitudinal and cross-sectional IVUS images showed calcified coronary plaques with edge dissection (*arrows*). *Arrowheads* indicate an MLA site. *DR* distal reference, *EEM* external elastic membrane, *IVUS* intravascular ultrasound, *MLA* minimal lumen area, *PR* proximal reference

Discussion

This study shows that calcium edge dissection is not rare in calcified culprit coronary lesions, and is more common in patients with ACS than in those with stable angina. These findings suggest that edge dissection of the calcified plaque may be related to plaque instability responsible for ACS.

Plaque rupture followed by luminal thrombosis is the most common cause of ACS. In autopsy studies, plaque rupture is present in $\sim$70 % of cases of acute myocardial infarction, and the remaining cases include plaque erosion or calcified nodules [13, 14]. Calcified nodules are found in sudden coronary death victims and introduced as a rare cause of coronary thrombosis [13–15]. However, calcified nodules identified by IVUS caused fewer major adverse cardiac events during a 3-year follow-up, raising questions about their roles in ACS [16]. In our study, calcified nodules were relatively common among patients with heavy calcified lesions, but not different between ACS and stable angina patients (11.3 vs. 18.9 %, respectively, $p = 0.346$).

Table 3 Quantitative intravascular ultrasound data

	Dissection (n = 14)	No dissection (n = 129)	*p* value
Calcium deposits			
Arc of calcium (°)	290.0 (150.0–313.0)	180.0 (120.0–320.0)	0.211
Area of calcium (mm^2)	1.7 (0.8–2.5)	1.1 (0.8–1.6)	0.048
Length of calcium (mm)	23.6 (16.2–30.2)	19.0 (10.7–29.1)	0.147
Proximal reference			
EEM CSA (mm^2)	18.7 (14.6–22.6)	16.7 (12.9–20.7)	0.080
Lumen CSA (mm^2)	10.4 (6.7–11.9)	7.0 (5.6–10.6)	0.034
Distal reference segment			
EEM CSA (mm^2)	12.3 (11.0–19.9)	10.0 (7.4–14.3)	0.012
Lumen CSA (mm^2)	7.4 (6.2–9.9)	5.1 (3.6–6.5)	0.002
Minimal lumen site			
EEM CSA (mm^2)	11.7 (9.2–18.2)	12.1 (9.2–15.1)	0.625
Lumen CSA (mm^2)	2.1 (1.6–2.5)	1.8 (1.3–2.4)	0.423
Plaque burden (%)	82.8 (76.6–86.5)	84.4 (77.8–89.2)	0.356
Remodeling index	0.74 (0.61–1.01)	0.86 (0.75–1.05)	0.125
Dissection site			
EEM CSA (mm^2)	14.7 (11.3–19.5)		
Lumen CSA (mm^2)	5.3 (3.3–7.2)		
Plaque burden (%)	67.9 (61.6–72.9)		
Remodeling index	0.93 (0.77–1.08)		

CSA cross-sectional area, *EEM* external elastic membrane

In contrast, edge dissection of the calcified plaque was more common in a culprit coronary lesion in ACS patients than in patients with stable angina. Our findings seem to be consistent with a pathological study showing that coronary atherosclerotic plaques can be torn without connection to a lipid core at the junction of fibrous tissue with a plate of calcium within the intima [17]. Although there is no direct evidence linking calcium edge dissection to acute luminal thrombosis, these findings suggest that a portion of ACS is potentially related to calcium edge dissection. Plaque rupture is classically defined as the disruption of a fibrous cap over a lipid core, with communication between the lipid core and the lumen; whereas plaque erosion is the disruption of the plaque without communication. Similarly, we propose that calcium edge dissection, as well as calcified nodules, may cause plaque disruption with or without communication between the lipid core and the lumen (Fig. 2). However, calcium edge dissection may not always lead to ACS, just as plaque rupture does not always result in ACS.

Calcium is commonly found in patients with atherosclerosis, and is a reliable marker for atherosclerosis. Coronary artery calcification scoring provides incremental value over conventional risk factors, with a score <100 considered low risk, while a score >300 is considered high risk [18–21] In the Multi-Ethnic Study of Atherosclerosis, the adjusted risk of a coronary event was increased by a factor of 7.73 among participants with coronary artery calcification scores between 101 and 300, and by a factor of 9.67 among participants with scores >300, compared to individuals without coronary artery calcification [20]. Furthermore, there is a linear relationship between the extent of coronary artery calcification and all-cause mortality [21], highlighting the prognostic value of the coronary artery calcification score. However, the impact of calcification on plaque vulnerability still remains controversial. Calcification seems to have complex effects on plaque vulnerability, depending on the patterns and location of calcium deposits within the vessel wall. In a computational model, calcification within a thin fibrous cap increases peak stress in the cap, whereas calcification in regions more distant from the lumen has no significant effect on peak stress [22, 23]. An IVUS study showed that patients with ACS have many spotty calcifications compared with stable angina [6]. A recent OCT study also revealed that calcium is spotty and more superficial in the culprit lesions of ACS [9], supporting the idea that the shape and location of calcification may be related to plaque vulnerability. Taken together, superficial calcium may cause edge dissection of the calcified fibrous cap, leading to plaque rupture with ACS.

The edge portion of the calcified plaque is exposed to mechanical stress, and thus expected to be more susceptible to dissection. During the cardiac cycle, the calcified lesion

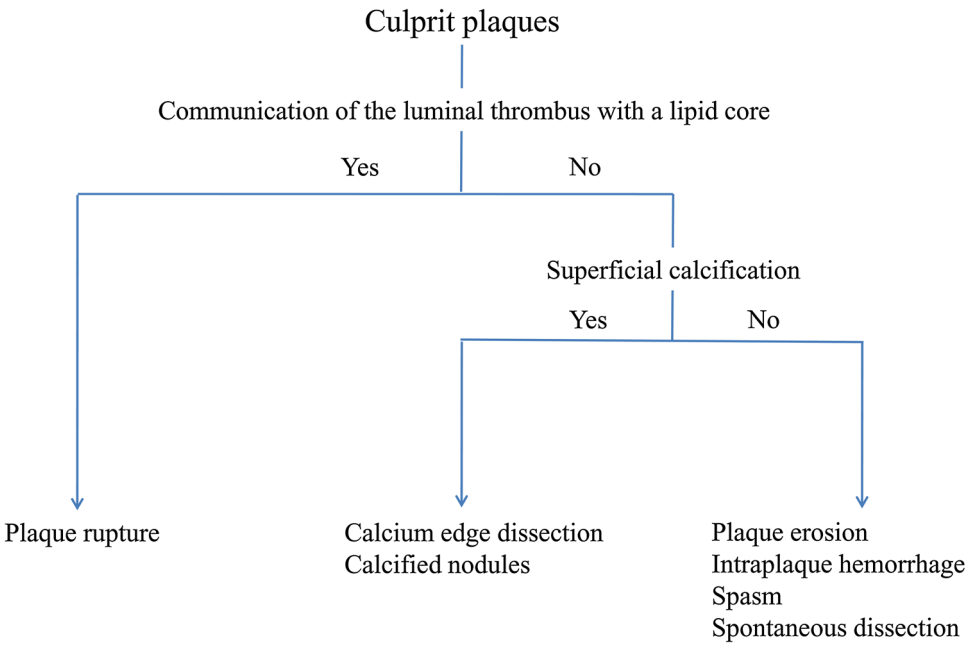

Fig. 2 Proposed classification of culprit plaques causing acute coronary syndrome

is relatively fixed, but the adjacent compliant tissue is moving, creating a point for dissection between the calcified lesion and the adjacent distensible tissue. It is well demonstrated that in patients with calcified plaques, dissection after balloon angioplasty usually occurs along the edge of the calcium deposits [22]. Likewise, edge dissection of the calcified plaques may spontaneously occur due to mechanical forces exerted by the radial force of blood pressure, and the shear stress of blood flow. Interestingly, plaque rupture during exercise occurs more frequently in the shoulder portion with a thick fibrous cap [24], supporting the concept that mechanical stress can cause plaque disruption in regions of compliance mismatch [8, 23]. Similarly, mechanical stress during acutely altered hemodynamic states may induce edge dissection of the calcified plaques, and expose the thrombogenic tissues (lipid core or underlying media), triggering ACS. Thus, avoidance of triggering factors including vigorous physical activity or emotional stress may be helpful to prevent ACS in high-risk patients. Further studies are needed to better understand the role of calcium edge dissection in relation to ACS.

The present study had several limitations. Firstly, the relatively low resolution of IVUS precludes a detailed assessment of the culprit plaques, including fibrous cap thickness, plaque composition, and thrombus. Secondly, pre-intervention IVUS was not available in many patients because it was difficult to move the IVUS catheter across the calcified lesions. Thirdly, only patients with angiographically calcified lesions were included in this study. The coronary angiogram is relatively insensitive to the presence of lesion calcification and thus, it may not be possible to generalize our findings to coronary artery lesions without angiographic calcification. Nevertheless, our findings firstly suggest that edge dissection of calcified plaques is a possible mechanism by which calcification may lead to ACS.

Acknowledgments This study was supported by a grant from the Cardiovascular Research Foundation, and the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (HI12C00300000).

Conflict of interest None.

References

1. Alexopoulos N, Raggi P (2009) Calcification in atherosclerosis. Nat Rev Cardiol 6:681–688
2. Mintz GS, Pichard AD, Popma JJ, Kent KM, Satler LF, Bucher TA, Leon MB (1997) Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic and intravascular ultrasound study. J Am Coll Cardiol 29:268–274
3. Shemesh J, Stroh CI, Tenenbaum A, Hod H, Boyko V, Fisman EZ, Motro M (1998) Comparison of coronary calcium in stable angina pectoris and in first acute myocardial infarction utilizing double helical computerized tomography. Am J Cardiol 81:271–275
4. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT (1993) Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. Circulation 87:1179–1187
5. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT (2001) The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation 103:1051–1056
6. Ehara S, Kobayashi Y, Yoshiyama M, Shimada K, Shimada Y, Fukuda D, Nakamura Y, Yamashita H, Yamagishi H, Takeuchi K, Naruko T, Haze K, Becker AE, Yoshikawa J, Ueda M (2004) Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. Circulation 110:3424–3429

7. Schmermund A, Erbel R (2001) Unstable coronary plaque and its relation to coronary calcium. Circulation 104:1682–1687
8. Li ZY, Howarth S, Tang T, Graves M, U-King-Im J, Gillard JH (2007) Does calcium deposition play a role in the stability of atheroma? Location may be the key. Cerebrovasc Dis 24:452–459
9. Mizukoshi M, Kubo T, Takarada S, Kitabata H, Ino Y, Tanimoto T, Komukai K, Tanaka A, Imanishi T, Akasaka T (2013) Coronary superficial and spotty calcium deposits in culprit coronary lesions of acute coronary syndrome as determined by optical coherence tomography. Am J Cardiol 112:34–40
10. Vengrenyuk Y, Carlier S, Xanthos S, Cardoso L, Ganatos P, Virmani R, Einav S, Gilchrist L, Weinbaum S (2006) A hypothesis for vulnerable plaquerupture due to stress-induced debonding around cellular microcalcifications in thin fibrous caps. Proc Natl Acad Sci USA 103:14678–14683
11. Hoshino T, Chow LA, Hsu JJ, Perlowski AA, Abedin M, Tobis J, Demer LL (2009) Mechanical stress analysis of a rigid inclusion in distensible material: a model of atherosclerotic calcification and plaque vulnerability. Am J Physiol Heart Circ Physiol 297:H802–H810
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction (2012) Third universal definition of myocardial infarction. Circulation 126:2020–2035
13. Virmani R, Burke AP, Farb A, Kolodgie FD (2006) Pathology of the vulnerable plaque. J Am Coll Cardiol 47:C13–C18
14. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R (2013) Update on acute coronary syndromes: the pathologists' view. Eur Heart J 34:719–728
15. Lee JB, Mintz GS, Lisauskas JB, Biro SG, Pu J, Sum ST, Madden SP, Burke AP, Goldstein J, Stone GW, Virmani R, Muller JE, Maehara A (2011) Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. Am J Cardiol 108:1547–1551
16. Xu Y, Mintz GS, Tam A, McPherson JA, Iñiguez A, Fajadet J, Fahy M, Weisz G, De Bruyne B, Serruys PW, Stone GW, Maehara A (2012) Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). Circulation 31(126):537–545
17. Richardson PD, Davies MJ, Born GV (1989) Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 2(8669):941–944
18. Grayburn PA (2012) Interpreting the coronary-artery calcium score. N Engl J Med 366:294–296
19. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC (2004) Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 291:210–215
20. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 358:1336–1345
21. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS (2007) Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 49:1860–1870
22. Fitzgerald PJ, Ports TA, Yock PG (1992) Contribution of localized calcium deposits to dissection after angioplasty. An observational study using intravascular ultrasound. Circulation 86:64–70
23. Hoshino T, Chow LA, Hsu JJ, Perlowski AA, Abedin M, Tobis J, Tintut Y, Mal AK, Klug WS, Demer LL (2009) Mechanical stress analysis of a rigid inclusion in distensible material: a model of atherosclerotic calcification and plaque vulnerability. Am J Physiol Heart Circ Physiol 297:H802–H810
24. Tanaka A, Imanishi T, Kitabata H, Kubo T, Takarada S, Tanimoto T, Kuroi A, Tsujioka H, Ikejima H, Ueno S, Kataiwa H, Okouchi K, Kashiwaghi M, Matsumoto H, Takemoto K, Nakamura N, Hirata K, Mizukoshi M, Akasaka T (2008) Morphology of exertion-triggered plaque rupture in patients with acute coronary syndrome: an optical coherence tomography study. Circulation 118:2368–2373