J Thromb Thrombolysis (2011) 32:150–157
DOI 10.1007/s11239-011-0585-6

Comparison of ruptured coronary plaques in patients with unstable and stable clinical presentation

Cheol Whan Lee · Chan-Sik Park · Ilseon Hwang · Hyangsin Lee · Duk-Woo Park · Su-Jin Kang · Seung-Whan Lee · Young-Hak Kim · Seong-Wook Park · Seung-Jung Park

Published online: 20 April 2011

Abstract It remains uncertain why some plaque ruptures trigger acute coronary syndrome (ACS), whereas others do not. We investigated the anatomic features and tissue factor (TF) expression at the sites of plaque rupture in 42 patients presenting with ACS ($n = 23$) or stable angina ($n = 19$). Intravascular ultrasound examination was performed before directional coronary atherectomy. Specimens were stained with antibodies against TF, CD68 positive phagocytic cells, and smooth muscle cells; and intravascular ultrasound and immunohistochemistry results were compared. Baseline demographic and clinical characteristics, as well as vessel and lumen sizes at both reference and lesion sites, were comparable in the two groups. However, the remodeling index and plaque burden at lesion sites were significantly greater in the ACS than in the stable angina group. The TF-immunopositive areas were significantly greater in the ACS than in the stable angina group (0.07%; IQR [0.02–0.16%] *vs.* 0.02%; IQR [0.01–0.05%], $P = 0.022$), whereas the proportions of CD68-positive and smooth muscle cell areas were similar. There was a significant correlation between areas positive for TF and those positive for CD68 ($r = 0.83$, $P < 0.001$). In conclusion, ruptured plaques in patients with ACS show stronger TF expression, a greater plaque burden, and a higher remodeling index than do plaques in those with stable angina, suggesting that both lesion morphology and local thrombogenicity are related to clinical symptoms after plaque rupture.

Keywords Acute coronary syndrome · Intravascular ultrasound · Plaque instability · Tissue factor

CW Lee and CS Park contributed equally to this paper.

C. W. Lee · D.-W. Park · S.-J. Kang · S.-W. Lee · Y.-H. Kim · S.-W. Park · S.-J. Park
Department of Medicine, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea

C.-S. Park
Department of Pathology, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea

I. Hwang
Department of Pathology, School of Medicine, Keimyung University, 194 Dongsan-Dong, Choong-Ku, Daegu, Korea

H. Lee
Asan Institute of Life Science, 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

Introduction

Plaque rupture and subsequent thrombus formation is considered the key event in the pathogenesis of acute coronary syndrome (ACS) [1]. However, plaque ruptures can occur not only in patients with ACS, but also in those with stable angina or no symptoms [3–6]. The severity of the culprit lesion or thrombus formation after plaque rupture may be responsible for the development of ACS [7], but the exact mechanisms remain unclear. Tissue factor is the principle in vivo initiator of coagulation, playing a critical role in determining plaque thrombogenicity [8–10]. Culprit lesions with abundant tissue factor may increase the plaque thrombogenicity after rupture, which in turn can lead to an ACS. To date, however, little has appeared

regarding the relationship between morphological characteristics and thrombogenicity in ruptured plaques and clinical symptoms. We therefore compared anatomic features and tissue factor expression at the sites of plaque rupture in patients presenting with ACS or stable angina.

Methods

Study patients

Tissue specimens were obtained from a biobank of our institution that collects atherectomy-derived specimens from patients with coronary artery disease. The demographic, clinical, and procedural characteristics of each patient were prospectively recorded in the biobank database. Patients with either non-ST-elevation ACS ($n = 23$) or stable angina (typical exertional angina without symptom change within one month before the procedure, $n = 19$) were included. All patients had ruptured coronary plaques as culprit lesions, and each specimen corresponded to the de novo lesion of a single patient that was responsible for the clinical presentation. Plaque rupture was diagnosed by angiographically determined lesion morphology showing an intimal flap (defined as a radiolucent extension of the vessel wall into the arterial lumen) and from intravascular ultrasound (IVUS) findings. Patients underwent directional coronary atherectomy using a FlexiCut catheter (Abbott Laboratories/Guidant Vascular Interventions, Santa Clara, CA) under intravascular ultrasound guidance. Specimens were immediately removed from the cutter housing, immersed in 2-methylbutane solution, and stored in a nitrogen tank. The study protocol was approved by our Institutional Review Committee, and all patients provided written informed consent.

Intravascular Ultrasound (IVUS)

Following intracoronary administration of 0.2 mg nitroglycerin, and before coronary intervention, IVUS examinations were performed using a motorized transducer pullback system (0.5 mm/sec) and a commercial scanner (SCIMED/Boston Scientific, Natick, MA) consisting of a rotating 40 MHz transducer.

Qualitative and quantitative IVUS measurements were taken by a colleague blind to clinical data (S-J Kang). A ruptured plaque was defined as a plaque containing a cavity that communicated with the lumen, and that also 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 (microchannels) within the mass, and demonstrating speckling or scintillation. Using computerized planimetry, the external elastic membrane (EEM) and lumen cross-sectional area (CSA) (mm^2) were measured in culprit and reference segments. A reference segment was defined as the most normal-appearing cross-section within a region 5 mm proximal and distal to the lesion but before any side branch. The remodeling index was calculated as the lesion EEM CSA divided by the mean reference EEM CSA; area stenosis as mean reference CSA minus lesion lumen CSA divided by mean reference CSA; and plaque burden as plaque + media CSA divided by EEM CSA.

Tissue preparation

Tissue specimens were completely embedded in OCT compound (Miles Inc. Diagnostics Division, Elk-hart, IN, USA), snap-frozen in liquid nitrogen, and stored at −70°C prior to cryostat sectioning. Samples were cryosectioned into 4 μm sections, which were placed onto Superfrost-plus microscope slides, immediately fixed in cold acetone for 10 min, and stored at −70°C for subsequent staining.

Histological analysis

Sections were stained with hematoxylin and eosin to determine cellularity and general morphologic patterns. The area of each plaque was measured using a microscopy image analysis system (Motic Images Advanced 3.2, Motic, Xiamen, China). Plaques were classified as atheromatous (i.e., with necrotic cores and cholesterol clefts but without connective tissue matrix) or fibrocellular, and graded as paucicellular (<30 spindle cells per high-power field), moderately cellular (30–100 spindle cells) or hypercellular (≥100 spindle cells). All slides were graded by two pathologists (C–S Park and I Hwang), who had no knowledge of patient clinical status. Any discrepancy between the findings of the two pathologists was resolved by discussion.

Immunohistochemistry

Sections of each tissue specimen were stained with polyclonal anti-tissue factor antibody (1:200, American Diagnostica Inc, Stamford, CT) and monoclonal antibodies against smooth muscle actin (1:200, mouse anti-human macrophage antibody clone 1A4, DAKO, Carpinteria, CA) and CD68 (1:200, mouse anti-human macrophage antibody clone KP-1, DAKO), using an Envision-plus immunostaining kit (Envision+ Kits, DAKO) and 3,3-diaminobenzidine or 3-amino-9-ethylcarbazole (DAKO) as the chromogen, according to the manufacturer's instructions. Briefly, samples were incubated with primary antibodies (diluted in antibody diluent; DAKO) for 1 h, washed twice for 5 min each time with TBST, incubated with labeled polymer-HRP secondary antibodies (DAKO) for 1 h, and again washed. As

negative controls, adjacent sections were stained with species- and isotype-matched irrelevant antibodies, including normal rabbit IgG (Abcam, Cambridge, UK). The positive control for anti-tissue factor antibody was a sample of human placenta. Cell types positive for tissue factor were identified by immunostaining of serial sections with anti-tissue factor antibody. An immunopositive area was calculated as the ratio of a positively stained region to total plaque area.

For immunofluorescent staining, fixed sections were hydrated in phosphate- buffered saline for 10 min at room temperature, incubated with DakoCytomation Protein Block (DakoCytomation, Carpinteria, CA) for 5 min at room temperature, and washed three times in phosphate-buffered saline Tween (PBST). Sections were next incubated with mouse anti-human CD68 monoclonal antibody (DakoCytomation), mouse anti-human smooth muscle actin monoclonal antibody (DakoCytomation), or rabbit anti-human tissue factor polyclonal antibody (American Diagnostica Inc., Greenwich, CT, USA) for 60 min at room temperature. After three additional washes in PBST, sections were incubated with FITC-conjugated anti-rabbit IgG or APC-conjugated anti-mouse IgG for 60 min at room temperature, and washed three times with PBST. Coverslips were mounted onto glass slides using DAKO fluorescent mounting medium (DakoCytomation). FITC was excited using an argon laser at 488 nm and APC was excited by a helium–neon laser at 633 nm. Detector slits were configured to minimize any cross-talk between channels. Images were collected on a Leica TCS_NT/SP confocal microscope (Leica Microsystems, Mannheim, Germany) using the 40× objective model NA 0.75, and a Zoom 1-4×, and processed using Leica TCS-NT/SP software (version LCS) and Adobe Photoshop 7.0.

Statistical analysis

Continuous variables are expressed as means (± standard deviations) or medians (with interquartile ranges), whereas categorical variables are expressed as frequencies. Continuous variables were compared using Student's t test or the Mann–Whitney U test, and categorical variables were analyzed using the Chi-squared or Fisher's exact test. Linear regression analysis was used to correlate areas positive for tissue factor with those containing CD68 positive phagocytic cells or smooth muscle cells. Statistical significance was defined as a two-sided P value <0.05.

Results

Clinical characteristics

The demographic and clinical characteristics of the two groups were similar (Table 1). Of the 42 patients, 34 (81%) were men and 9 (21.4%) had diabetes mellitus. Mean patient age was 57.8 ± 8.5 years (range, 42–78 years). Of the 23 patients with ACS, 8 (31.8%) had acute rest angina (Braunwald's classification IIIB), and the remaining 15

Table 1 Patient demographic and clinical characteristics

	ACS ($n = 23$)	Stable angina ($n = 19$)	P-value
Age, years	59.9 ± 7.8	55.1 ± 8.8	0.070
Gender, male/female	17/6	17/2	0.258
Current smoker	9 (39.1%)	8 (42.1%)	1.000
Diabetes mellitus	5 (21.7%)	4 (21.1%)	1.000
Hypertension	14 (60.8%)	9 (47.4%)	0.535
Hypercholesterolemia (>200 mg/dl)	7 (30.4%)	8 (42.1%)	0.525
Multivessel disease	9 (39.1%)	9 (47.4%)	0.756
Target artery			0.538
Left anterior descending coronary	18 (78.3%)	14 (73.7%)	
Left circumflex	1 (4.3%)	0 (0%)	
Right coronary	4 (17.4%)	5 (26.3%)	
Medications at the time of DCA			
Aspirin	23 (100%)	19 (100%)	1.000
Clopidogrel	23 (100%)	19 (100%)	1.000
Angiotensin-converting enzyme inhibitor	4 (17.4%)	1 (5.3%)	0.456
β-blockers	4 (17.4%)	8 (42.1%)	0.098
Calcium antagonists	11 (47.8%)	13 (68.4%)	0.221
Statins	6 (26.1%)	6 (31.6%)	0.742
Left ventricular ejection fraction (%)	57.1 ± 8.9	61.0 ± 6.5	0.115

DCA directional coronary atherectomy

(65.2%) had non-ST-elevation myocardial infarction. Concomitant medications at the time of directional coronary atherectomy were similar in the two groups.

Intravascular ultrasound

Qualitative and quantitative IVUS data are summarized in Table 2. A thrombus was observed in 69.6% of patients with ACS, compared with 42.1% of those with stable angina ($P = 0.118$). Most ruptured plaques were proximal to or at the minimal lumen site. Proximal and distal reference measurements were similar for the two groups. Likewise, there were no significant differences in EEM CSA or lumen CSA at the rupture and minimal lumen sites, and the ruptured cavity area was similar in the two groups. However, the remodeling index (1.08 ± 0.20 *vs.* 0.91 ± 0.18, $P = 0.008$) and the plaque burden at minimal lumen sites (90.45 ± 3.13 vs. 85.11 ± 6.92, $P = 0.002$) were significantly greater in patients with ACS than in those with stable angina.

Immunocytochemistry

Detailed morphometric data are shown in Table 3. Total plaque area was significantly smaller in patients with ACS than in those with stable angina (82.1 mm^2 [IQR, 51.1–164.4 mm^2] vs. 175.1 mm^2 [84.6–280.6 mm^2], $P = 0.033$). However, there were no between-group differences in the proportions of areas for atheroma, thrombi, or calcium. Thrombi were identified in 60.9% of specimens (fresh thrombi 64.3%, lytic or organized thrombi 37.7%) [11] from patients with ACS and in 43.4% of specimens (fresh thrombi 33.3%, lytic or organized thrombi 66.7%) from those with stable angina ($P = 0.535$).

Figures 1 and 2 show representative immunohistochemical staining data for tissue factor, CD68 positive phagocytic cells, and smooth muscle cells in plaques obtained from a patient with ACS and from a patient with stable angina. The relative area immunopositive for tissue factor was significantly greater in patients with ACS than in those with stable angina (0.07% [0.02–0.16%] vs.

Table 2 Intravascular ultrasound findings

	ACS ($n = 23$)	Stable angina ($n = 19$)	P-value
Plaque morphology			0.355
Hyperechoic	6 (26.1%)	9 (47.4%)	
Mixed		5 (26.3%)	
Hypoechoic	8 (34.8%)	5 (26.3%)	
Thrombus (%)	16 (69.6%)	8 (42.1%)	0.118
Rupture location *vs.* minimal lumen site			0.809
Proximal, %	11 (47.8%)	11 (57.9%)	
Same, %	9 (39.1%)	6 (31.6%)	
Distal, %	3 (13.0%)	2 (10.5%)	
Proximal reference			
EEM CSA, mm^2	18.49 ± 5.14	17.02 ± 3.91	0.323
Lumen CSA, mm^2	10.20 ± 3.41	10.04 ± 3.25	0.882
Distal reference segment			
EEM CSA, mm^2	12.58 ± 5.22	12.89 ± 6.18	0.864
Lumen CSA, mm^2	7.01 ± 3.31	8.42 ± 4.49	0.225
Minimal lumen site			
EEM CSA, mm^2	16.37 ± 4.19	13.91 ± 6.43	0.148
Lumen CSA, mm^2	1.49 ± 0.42	2.13 ± 1.79	0.103
Plaque burden (%)	90.45 ± 3.13	85.11 ± 6.92	0.002
Area of stenosis (%)	81.4 ± 5.9	77.2 ± 14.1	0.197
Remodeling index	1.08 ± 0.20	0.91 ± 0.18	0.008
Lesion length, mm	17.91 ± 10.01	15.51 ± 6.68	0.398
Rupture site			
EEM CSA, mm^2	16.74 ± 5.13	14.92 ± 6.35	0.316
Lumen CSA, mm^2	3.64 ± 5.37	3.14 ± 1.85	0.705
Plaque burden (%)	80.54 ± 19.06	78.80 ± 7.05	0.716
Area of stenosis (%)	62.6 ± 32.8	65.24 ± 14.07	0.754
Remodeling index	1.09 ± 0.22	0.98 ± 1.68	0.088
Cavity area, mm^2	1.59 ± 1.17	1.27 ± 1.06	0.195

Table 3 Histological findings

	ACS ($n = 23$)	Stable angina ($n = 19$)	P-value
Histology			
Atheroma	6.72 (2.01–23.51)	7.13 (2.68–16.95)	0.742
Fibrocellular area			
Paucicellular	72.06 (38.16–93.71)	88.88 (70.10–95.46)	0.050
Moderately cellular	2.54 (0–10.58)	0 (0–1.03)	0.003
Hypercellular	0 (0–1.06)	0 (0–0)	0.109
Thrombi	0.97 (0–5.18)	0 (0–2.46)	0.307
Calcium	0.19 (0.04–1.17)	0.09(0–0.54)	0.141
Immunohistochemistry			
α-smooth muscle actin	0.49 (0.09–4.74)	0.41(0.16–1.71)	0.464
CD68	1.25 (0.67–8.44)	1.26 (0.12–2.81)	0.202
Tissue factor	0.07 (0.02–0.16)	0.02 (0.01–0.05)	0.022

Data are shown as % positive area (immunostaining area/total plaque area ×100), and as median values with IQRs

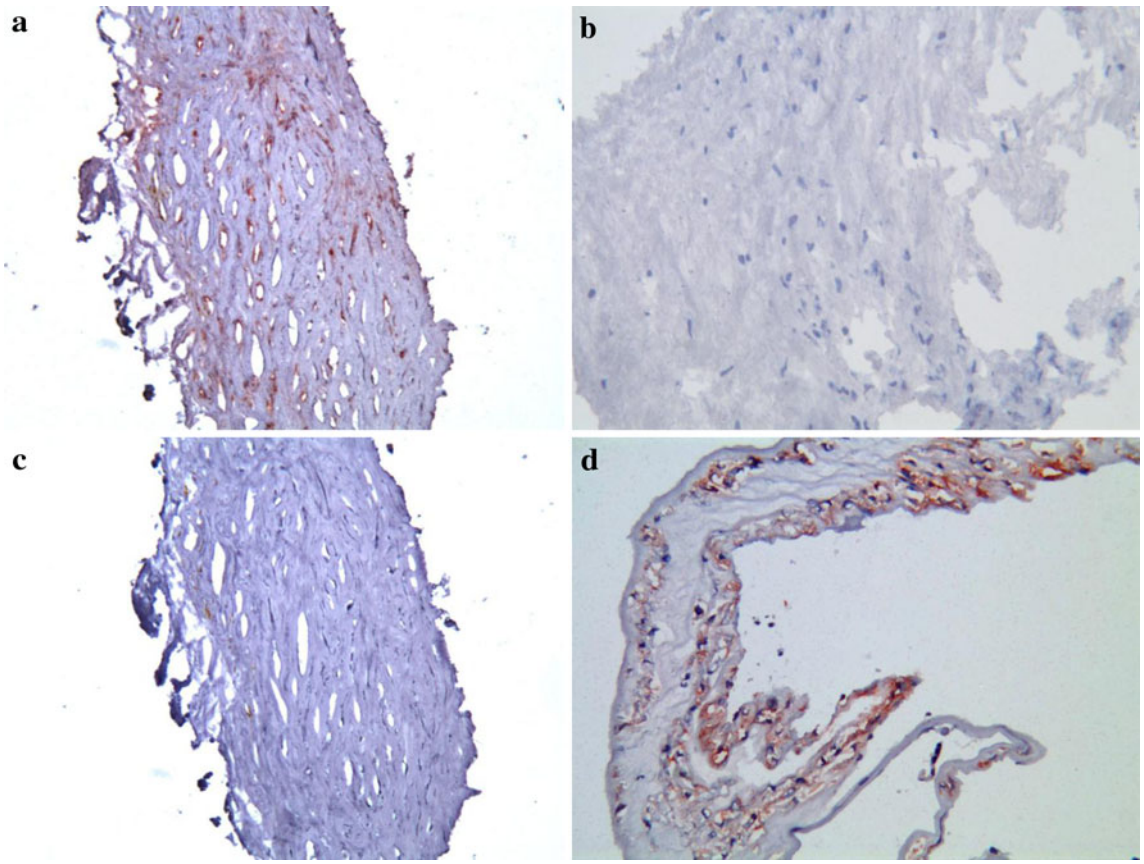

Fig. 1 Immunohistochemical staining for tissue factor in ruptured coronary plaques of atherectomy specimens taken from patients with **a** unstable angina and **b** stable angina. Immunopositivity for tissue factor is shown in *red*. **c** Negative control; staining of these specimens employed rabbit isotype primary antibody. **d** Positive control; staining of a placenta sample with antibody to tissue factor antibody (×200)

0.02% [0.01–0.05%], $P = 0.022$), but there were no between-group differences in relative areas positive for CD 68 or smooth muscle cells. The areas positive for tissue factor coincided with those positive for CD68, and double immunostaining confirmed the co-localization of tissue factor and CD68 (Fig. 2). Likewise, some areas positive for smooth muscle cells co-localized with areas positive for tissue factor (Fig. 2). We observed a significant correlation between areas positive for tissue factor and CD68 phagocytic cells ($r = 0.83$, $P < 0.001$), but not between areas positive for tissue factor and smooth muscle cells.

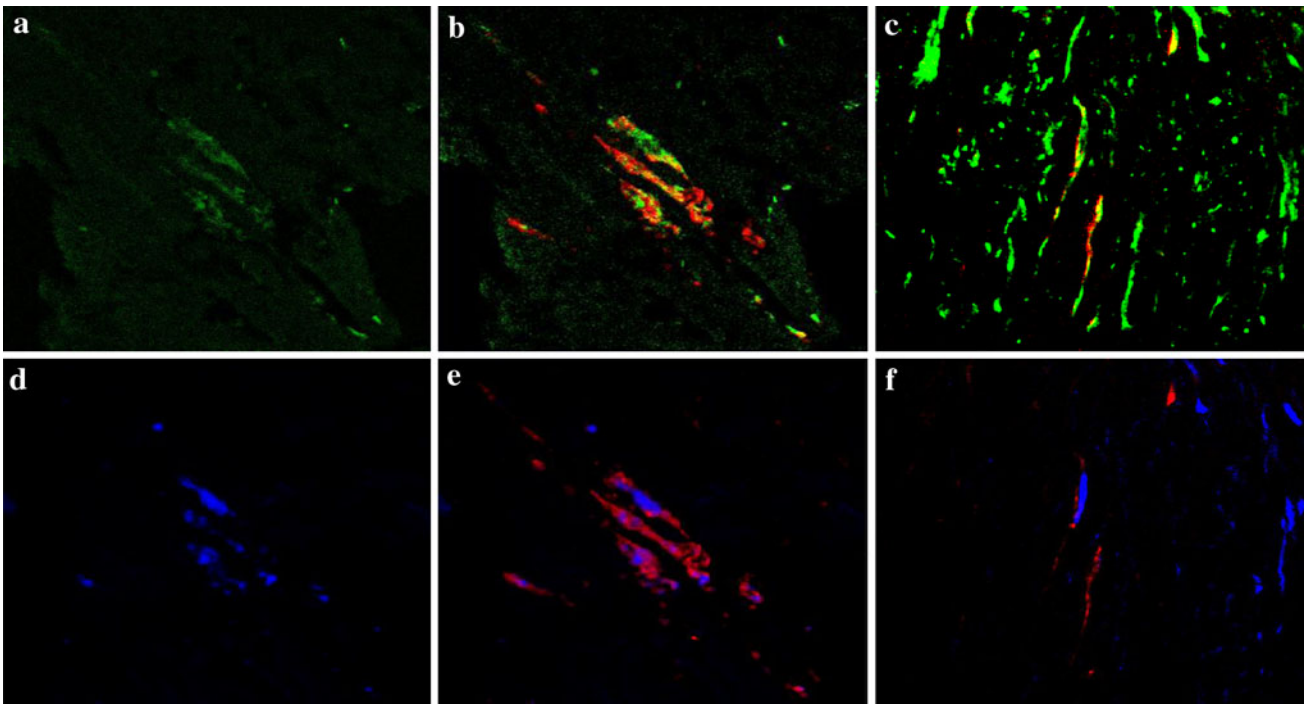

Fig. 2 Immunofluorescence staining of coronary plaques of a patient with unstable angina using antibodies to tissue factor, CD68, and smooth muscle actin (SMA). Specimens were incubated with rabbit anti-human tissue factor polyAb, mouse anti-human CD68 mAb, and/or mouse anti-SMA mAb, and subsequently with FITC-conjugated anti-rabbit IgG (*green*) and/or APC-conjugated anti-mouse IgG (*red*) antibodies. **a** tissue factor, **b** tissue factor and CD68, **c** tissue factor and SMA, **d**–**f** DAPI nuclear counterstaining. Original magnification ×1,200

Discussion

We have shown here that ruptured plaques from patients with ACS have greater levels of tissue factor, a higher plaque burden, and a greater remodeling index than do ruptured plaques from patients with stable angina. These findings are in good agreement with the clinical manifestations of these two conditions, indicating that such manifestations depend on the nature of plaque components as well as local hemorheologic and systemic blood factors, and not just on plaque rupture *per se*.

Autopsy studies have shown the presence of plaque rupture in ~70% of individuals who died after acute myocardial infarction, with the remaining ~30% of deaths associated with plaque erosion or calcified nodules [12, 13]. Several IVUS studies have shown that 20–79% of patients with ACS have at least one ruptured plaque at a site other than the culprit lesion [3–7]. High-resolution optical coherence tomography has shown at least one noninfarct-related/nontarget plaque rupture in 31% of patients with acute myocardial infarction and in 15% of those with stable angina [14]. In addition, plaque ruptures can be found incidentally in the coronary arteries of patients after noncardiac death [6]. These findings indicate that plaque rupture may occur during the course of atherosclerosis, but that only some patients with ruptured plaques develop ACS. Extracellular matrix degradation including collagen is generally considered a prelude to rupture. However, it is largely unknown why some plaque ruptures trigger ACS, whereas others do not. Thus, a better understanding of these processes may contribute to more accurate identification of high-risk individuals who are valid targets for therapy.

Earlier angiographic studies showed that most underlying lesions in patients with acute myocardial infarction are mild to moderate luminal stenosis [2]. In contrast, IVUS has shown that ruptured plaques in culprit lesions of patients with ACS have smaller lumens, greater plaque burdens, and more thrombi than do ruptured plaques in non-culprit lesions [7], indicating that plaque rupture in a region of smaller lumen area, and/or thrombus formation, causes lumen compromise and ACS. The results presented here also show that both of plaque burden and the remodeling index were greater in patients with ACS than in those with stable angina. However, the lumen area of the culprit site was similar in the two groups, because only significant lesions can be treated with coronary angioplasty. Overall, the IVUS findings indicate that the culprit lesions in ACS are not mild, but rather have a high plaque burden, a large necrotic core, and a small lumen area.

Tissue factor is the principal activator of the coagulation cascade, leading to the generation of thrombin and

subsequent thrombus formation [8–10]. We have shown here that tissue factor was strongly expressed at the site of ruptures in ACS patients, with a significant correlation between areas positive for tissue factor and CD68, suggesting that CD68 phagocytic cells are the major source of tissue factor in ruptured plaques. Tissue factor was also present in smooth muscle cells, and extracelluar space, indicating that tissue factor can be derived from multiple sources [15]. In addition, our findings agree with previous results, showing that expression of tissue factor is higher in plaques from patients with unstable compared to stable angina [16, 17]. However, we observed thrombi only in ~60% of specimens from patients with ACS. Several factors may be responsible for this observation, including the use of anticoagulant therapy and the nature of the specimen collection process. Anticoagulants are routinely used in patients with non-ST-elevation ACS waiting for coronary intervention, and thrombi on the surface of a plaque may thus be rapidly lysed. A forceful saline flush is also required to collect specimens from the cutter housing, causing the thrombi to dissolve. Autopsy studies have demonstrated that organized thrombi were incorporated into atherosclerotic lesions, and were thus involved in plaque progression [18, 19]. In our study, fresh thrombi were more commonly observed in patients with ACS, but old thrombi in those with stable angina. Hence, ruptured plaques in patients with ACS may be more thrombogenic and active, with fresh thrombi; whereas ruptured plaques in patients with stable angina may be less thrombogenic and already healed, with old thrombi. Thus, biologic factors, including tissue factor, may modulate the thrombogenicity of culprit plaques, and both plaque thrombogenicity and lesion severity may contribute to the development of ACS.

Study limitations

This study had several limitations. First, atherectomy tissues were extracted primarily from lesions in large vessels, because calcified, tortuous, or small vessels are not suitable for directional coronary atherectomy. Thus, it may not be possible to generalize our findings to lesions at sites other than large vessels. Second, because of the small sizes of specimens, tissue factor expression could not be confirmed by Western blot analysis. Finally, we did not assay for systemic blood factors that increase thrombogenicity around ruptured plaques. Nevertheless, this is the first comprehensive study to show that both anatomic features and local thrombogenicity play a key role in determining clinical symptoms after plaque rupture.

Acknowledgments This study was supported by grants from the Asan Institute for Life Science (W08-408) and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A090264).

Conflict of interest None.

References

1. Davies M, Thomas A (1984) Thrombosis and acute coronary artery lesions in sudden cardiac ischemic death. N Engl J Med 310:1137–1140
2. Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. Circulation 92:657–671
3. Maehara A, Mintz GS, Bui AB, Walter OR, Castagna MT, Canos D, Pichard AD, Satler LF, Waksman R, Suddath WO, Laird JR Jr, Kent KM, Weissman NJ (2002) Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. J Am Coll Cardiol 40:904–910
4. Rioufol G, Gilard M, Finet G, Ginon I, Boschat J, Andre-Fouet X (2004) Evolution of spontaneous atherosclerotic plaque rupture with medical therapy: long-term follow-up with intravascular ultrasound. Circulation 110:2875–2880
5. Hong MK, Mintz GS, Lee CW, Kim YH, Lee SW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Park SW, Park SJ (2004) Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. Circulation 110:928–933
6. Thomas AC, Knapman PA, Krikler DM, Davies MJ (1988) Community study of the causes of "natural" sudden death. BMJ 297:1453–1456
7. Fujii K, Kobayashi Y, Mintz GS, Takebayashi H, Dangas G, Moussa I, Mehran R, Lansky AJ, Kreps E, Collins M, Colombo A, Stone GW, Leon MB, Moses JW (2003) Intravascular ultrasound assessment of ulcerated ruptured plaques: a comparison of culprit and nonculprit lesions of patients with acute coronary syndromes and lesions in patients without acute coronary syndromes. Circulation 108:2473–2478
8. Wilcox JN, Smith KM, Schwartz SM, Gordon D (1989) Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. Proc Natl Acad Sci USA 86:2839–2843
9. Tremoli E, Camera M, Toschi V, Colli S (1999) Tissue factor in atherosclerosis. Atherosclerosis 144:273–283
10. Steffel J, Lüscher TF, Tanner FC (2006) Tissue factor in cardiovascular diseases molecular mechanisms and clinical implications. Circulation 113:722–731
11. Murakami T, Mizuno S, Takahashi Y, Ohsato K, Moriuchi I, Arai Y, Mifune J, Shimizu M, Ohnaka M (1998) Intracoronary aspiration thrombectomy for acute myocardial infarction. Am J Cardiol 82:839–844
12. Davies MJ (1990) A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 82(suppl II):II-38–II-46
13. Virmani R, Burke AP, Farb A, Kolodgie FD (2006) Pathology of the vulnerable plaque. J Am Coll Cardiol 47(8 Suppl):C13–C18
14. Fujii K, Masutani M, Okumura T, Kawasaki D, Akagami T, Ezumi A, Sakoda T, Masuyama T, Ohyanagi M (2008) Frequency and predictor of coronary thin-cap fibroatheroma in patients with acute myocardial infarction and stable angina pectoris a 3-vessel optical coherence tomography study. J Am Coll Cardiol 52:787–788
15. Moreno PR, Bernardi VH, Lopezcuellar J, Murcia AM, Palacios IF, Gold HK, Mehran R, Sharma SK, Nemerson Y, Fuster V, Fallon JT (1996) Macrophages, smooth muscle cells, and tissue factor in unstable angina: implications for cell-mediated thrombogenicity in acute coronary syndromes. Circulation 94:3090–3097

16. Annex BH, Denning SM, Channon KM, Sketch MH, Stack RS, Morrissey JH, Peters KG (1995) Differential expression of tissue factor protein in directional atherectomy specimens from patients with stable and unstable coronary syndromes. Circulation 91: 619–622
17. Kaikita K, Ogawa H, Yasue H, Takeya M, Takahashi K, Saito T, Hayasaki K, Horiuchi K, Takizawa A, Kamikubo Y, Nakamura S (1997) Tissue factor expression on macrophages in coronary plaques in patients with unstable angina. Arterioscler Thromb Vasc Biol 17:2232–2237
18. Mann J, Davies MJ (1999) Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart 82:265–268
19. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R (2001) Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 103:934–940