Journal of Cardiology (2010) **55**, 224—231

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Original article

Age-related differences in virtual histology-intravascular ultrasound findings in patients with coronary artery disease

Young Joon Hong (MD), Myung Ho Jeong (MD, PhD, FESC, FACC, FAHA, FSCAI)*, Yun Ha Choi (RN), Eun Hye Ma (RN), Jum Suk Ko (MD), Min Goo Lee (MD), Keun Ho Park (MD), Doo Sun Sim (MD), Nam Sik Yoon (MD), Hyun Ju Youn (MD), Kye Hun Kim (MD), Hyung Wook Park (MD), Ju Han Kim (MD), Youngkeun Ahn (MD), Jeong Gwan Cho (MD), Jong Chun Park (MD), Jung Chaee Kang (MD)

Heart Center of Chonnam National University Hospital, Chonnam National University Research Institute of Medical Sciences, 671 Jaebongro, Dong-gu, Gwangju 501-757, Republic of Korea

Received 29 September 2009; received in revised form 31 October 2009; accepted 4 November 2009
Available online 14 January 2010

KEYWORDS
Coronary artery disease;
Aging;
Plaque;
Intravascular ultrasound

Summary
Background: We assessed the age-related differences in pre-intervention virtual histology-intravascular ultrasound (VH-IVUS) findings at target lesion sites in patients with coronary artery disease.
Methods: A total of 553 patients who underwent pre-intervention VH-IVUS imaging were grouped according to age: non-elderly (≤70 years, $n = 429$) and elderly (>70 years, $n = 124$); 191 had stable angina and 362 acute coronary syndrome. VH-IVUS classified the tissue into: fibrotic, fibro-fatty, dense calcium (DC), and necrotic core (NC).
Results: Overall, the absolute and percent volumes of DC ($11.0 \pm 11.0\,mm^3$ vs. $9.7 \pm 11.9\,mm^3$, $P = 0.033$; $11.7 \pm 8.1\%$ vs. $9.8 \pm 7.2\%$, $P = 0.014$, respectively) and NC ($18.5 \pm 17.6\,mm^3$ vs. $16.6 \pm 18.9\,mm^3$, $P = 0.020$; $18.8 \pm 8.8\%$ vs. $16.5 \pm 9.3\%$, $P = 0.026$, respectively) were significantly greater in the elderly than in the non-elderly. In stable angina patients, the absolute and percent volumes of DC ($10.4 \pm 9.9\,mm^3$ vs. $7.2 \pm 7.6\,mm^3$, $P = 0.022$; $13.4 \pm 10.0\%$ vs. $9.2 \pm 6.5\%$, $P = 0.011$, respectively) and NC ($14.8 \pm 11.2\,mm^3$ vs. $12.0 \pm 11.9\,mm^3$, $P = 0.035$; $19.6 \pm 8.8\%$ vs. $15.5 \pm 8.4\%$, $P = 0.006$, respectively) were significantly greater in the elderly.
However, in acute coronary syndrome patients, there were no significant differences in absolute and percent volumes of DC ($11.4 \pm 11.6\,mm^3$ vs. $10.9 \pm 13.4\,mm^3$, $P = 0.8$; $10.7 \pm 6.5\%$ vs. $10.1 \pm 7.5\%$, $P = 0.5$, respectively) and NC ($24.1 \pm 20.3\,mm^3$ vs. $23.9 \pm 21.2\,mm^3$, $P = 0.9$; $22.0 \pm 8.8\%$ vs. $21.3 \pm 9.6\%$, $P = 0.6$, respectively) between the elderly and non-elderly groups.

* Corresponding author. Tel.: +82 62 220 6243; fax: +82 62 228 7174.
E-mail address: myungho@chollian.net (M.H. Jeong).

0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2009.11.004

t Myocardial infarction (OR: 2.56, 95% CI: 1.45—4.12, $P = 0.003$), diabetes mellitus (OR: 2.23, 95% CI: 1.30—3.53, $P = 0.009$), and high-sensitivity C-reactive protein (OR: 1.44, 95% CI: 1.06—2.45, $P = 0.042$), but not age, were independent predictors of percent NC volume >20% in lesion site.
Conclusions: Myocardial infarction, diabetes mellitus, and high-sensitivity C-reactive protein, but not age, were associated with NC-rich lesions. Clinical presentation, risk factors, and inflammatory status, but not age, are important factors for plaque components.

Introduction

Elderly individuals constitute an increasing segment of the population. Coronary artery disease is highly prevalent and accounts for the majority of morbidity and mortality in elderly people. Elderly patients have more comorbid conditions, including a history of diabetes mellitus, hypertension, atrial fibrillation, stroke or transient ischemic attack, myocardial infarction, and ischemic or nonischemic heart failure and are more likely to present with more complex lesions compared with younger patients [1—16].

Virtual histology-intravascular ultrasound (VH-IVUS) can provide quantitative information on plaque composition; it has been validated in studies of explanted human coronary segments [17]. VH-IVUS characterizes atherosclerotic plaque as fibrotic (FT), fibro-fatty (FF), dense calcium (DC), and necrotic core (NC) [17,18]. Previous grey-scale IVUS studies showed more calcified plaque and more negative remodeling in elderly patients [19—25]. However, few data are available about plaque components in elderly patients [26]. Therefore, the purpose of the present study was to investigate the age-related pre-procedural plaque components assessed by VH-IVUS.

Methods

Study population

This study was a retrospective, single-center study. From February 2007 to January 2009, we identified 553 consecutive patients who underwent pre-intervention VH-IVUS. The presence of stable angina was determined by typical effort-induced chest pain which was relieved by resting. The presence of unstable angina was determined by chest pain within the preceding 72 h with or without ST—T wave changes or positive cardiac biochemical markers. The presence of ST-segment elevation myocardial infarction was determined by >30 min of continuous chest pain, a new ST-segment elevation $\geq$2 mm on at least two contiguous electrocardiographic leads, and creatine kinase-MB >3 times normal. The presence of non-ST-segment elevation myocardial infarction was diagnosed by chest pain and a positive cardiac biochemical marker without new ST-segment elevation. We excluded patients with subacute or late stent thrombosis, restenosis after stenting, coronary artery bypass graft failure, factors associated with increased risk of bleeding, severe heart failure or cardiogenic shock, important systemic disease, or serum creatinine $\geq$2.5 mg/dl, and patients in whom adequate IVUS images could not be obtained. The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

Laboratory analysis

Peripheral blood samples were obtained before IVUS study using direct venipuncture. The blood samples were centrifuged, and serum was removed and stored at $-70\,^{\circ}C$ until the assay could be performed. The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by standard enzymatic methods. High-sensitivity C-reactive protein was analyzed turbidimetrically with sheep antibodies against human C-reactive protein; this has been validated against the Dade—Behring method [27]. Serum N-terminal pro-B-type natriuretic peptide was measured using an electrochemiluminescence sandwich immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Quantitative coronary angiography (QCA) analysis

Coronary angiogram was analyzed with validated QCA system (Phillips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, The Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter, reference diameter, and lesion length were measured in diastolic frames from orthogonal projections.

IVUS imaging and analysis

All pre-percutaneous coronary intervention VH-IVUS examinations were performed after intracoronary administration of 300 μg nitroglycerin. A 20-MHz, 2.9F IVUS imaging catheter (Eagle Eye, Volcano Corp, Rancho Cordova, CA, USA) was advanced >10 mm beyond the lesion; and automated pullback was performed to a point >10 mm proximal to the lesion at a speed of 0.5 mm/s.

Quantitative volumetric grey-scale and VH-IVUS analyses were performed across the entire lesion segment, and cross-sectional analyses were performed at the minimum lumen sites and at the largest NC sites. Grey-scale IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards

Table 1 Baseline characteristics.

	Non-elderly ($n = 429$)	Elderly ($n = 124$)	P-value
Age (years)	60 ± 13	76 ± 11	<0.001
Female gender	125 (29)	57 (46)	<0.001
Clinical presentation			0.012
Stable angina	145 (34)	46 (37)	
Unstable angina	157 (37)	59 (48)	
NSTEMI	52 (12)	9 (7)	
STEMI	75 (18)	10 (8)	
Diabetes mellitus	125 (29)	38 (31)	0.7
Hypertension	240 (56)	97 (78)	<0.001
Smoking	172 (40)	29 (33)	0.15
Ejection fraction (%)	63 ± 8	64 ± 8	0.5
White blood cells ($10^3/mm^3$)	7.7 ± 2.9	8.0 ± 2.3	0.3
Hemoglobin (g/dl)	13.8 ± 1.7	12.8 ± 1.3	<0.001
Platelet count ($10^3/mm^3$)	239 ± 85	212 ± 66	0.002
Creatinine (mg/dl)	0.85 ± 0.22	0.94 ± 0.62	0.008
NT-pro-BNP (pg/ml)	298 ± 558	586 ± 806	0.12
hs-CRP (mg/dl)	0.45 ± 1.23	0.56 ± 1.72	0.15
Total cholesterol (mg/dl)	180 ± 41	179 ± 47	0.8
Triglyceride (mg/dl)	114 ± 67	102 ± 54	0.072
LDL cholesterol (mg/dl)	115 ± 35	115 ± 42	0.9
HDL cholesterol (mg/dl)	49 ± 19	48 ± 12	0.6
Aspirin	420 (98)	118 (95)	0.4
Clopidogrel	385 (90)	112 (90)	0.9
Cilostazol	123 (29)	40 (32)	0.4
Statin	326 (76)	91 (73)	0.4
Beta-blocker	378 (88)	108 (87)	0.8
ACEI/ARB	365 (85)	100 (81)	0.3

Data are n (%), or mean ± SD. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies [28]. External elastic membrane (EEM) and lumen cross-sectional areas (CSA) were measured. Plaque plus media (P&M) CSA was calculated as EEM minus lumen CSA; and plaque burden was calculated as P&M divided by EEM CSA. Proximal and distal references were the single slices with the largest lumen and smallest plaque CSAs within 10 mm proximally and distally, but before any large

Table 2 Coronary angiographic findings.

	Non-elderly ($n = 429$)	Elderly ($n = 124$)	P-value
Target artery			0.2
Left main	26 (6)	5 (4)	
LAD	176 (41)	63 (51)	
LCX	77 (18)	17 (14)	
RCA	150 (35)	39 (32)	
Lesion location			0.6
Ostium	17 (4)	4 (3)	
Proximal	180 (42)	47 (38)	
Middle	163 (38)	55 (44)	
Distal	69 (16)	18 (15)	
Multivessel disease	163 (38)	64 (52)	0.007
Reference diameter (mm)	3.17 ± 0.85	3.15 ± 0.72	0.5
Pre-MLD (mm)	1.12 ± 0.32	1.06 ± 0.51	0.2
Lesion length (mm)	16 ± 12	19 ± 8	0.046

Data are n (%), or mean ± SD. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; MLD, minimal lumen diameter.

Table 3 Intravascular ultrasound findings.

	Non-elderly ($n = 429$)	Elderly ($n = 124$)	P-value
Proximal reference			
EEM CSA (mm^2)	17.0 ± 6.0	18.1 ± 7.1	0.11
Lumen CSA (mm^2)	10.7 ± 3.0	11.1 ± 3.1	0.3
P&M CSA (mm^2)	6.3 ± 3.1	7.0 ± 3.3	0.050
Plaque burden (%)	37 ± 8	39 ± 8	0.042
Minimum lumen site			
EEM CSA (mm^2)	15.4 ± 5.9	15.0 ± 6.5	0.3
Lumen CSA (mm^2)	4.5 ± 3.6	4.2 ± 4.0	0.2
P&M CSA (mm^2)	10.9 ± 4.2	10.8 ± 4.0	0.8
Plaque burden (%)	71 ± 14	72 ± 13	0.3
Largest necrotic core site			
EEM CSA (mm^2)	15.9 ± 6.3	15.9 ± 7.4	0.9
Lumen CSA (mm^2)	5.8 ± 4.0	5.5 ± 4.8	0.2
P&M CSA (mm^2)	10.1 ± 4.0	10.4 ± 3.9	0.3
Plaque burden (%)	64 ± 13	65 ± 11	0.3
Distal reference			
EEM CSA (mm^2)	13.9 ± 6.6	14.3 ± 6.8	0.4
Lumen CSA (mm^2)	8.9 ± 5.6	8.9 ± 5.7	0.9
P&M CSA (mm^2)	5.0 ± 3.1	5.4 ± 2.7	0.2
Plaque burden (%)	36 ± 8	38 ± 7	0.048
IVUS lesion length (mm)	20 ± 12	23 ± 8	0.032
Plaque morphology			0.077
Hypoechoic	291 (68)	69 (56)	
Hyperechoic, non-calcified	26 (6)	10 (8)	
Hyperechoic, calcified	99 (23)	38 (31)	
Mixed	13 (3)	7 (6)	
Superficial calcium	236 (55)	81 (65)	0.041
Volumetric analysis			
EEM volume (mm^2)	301 ± 265	292 ± 231	0.5
Lumen volume (mm^2)	127 ± 133	126 ± 114	0.9
P&M volume (mm^2)	174 ± 146	176 ± 123	0.8

Data are n (%), or mean $\pm$ SD. EEM, external elastic membrane; CSA, cross-sectional area; P&M: plaque plus media; IVUS, intravascular ultrasound.

side branch. VH-IVUS analysis classified the color-coded tissue into four major components: green (FT); yellow-green (FF); white (DC); and red (NC) [17,18]. VH-IVUS analysis was reported in absolute amounts and as a percentage of plaque area or volume.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean value $\pm$ 1 SD; comparisons were conducted by Student's t-test or nonparametric Wilcoxon test if normality assumption was violated. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by chi-square statistics or Fisher's exact test as appropriate. Multivariable analysis was performed to identify independent predictors of percent NC volume >20% in lesion site. A P-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The baseline characteristics are summarized in Table 1. Elderly patients were more likely to be women and had more unstable angina and hypertension. The hemoglobin level and platelet counts were significantly lower, and creatinine level was significantly higher in the elderly group.

Coronary angiographic findings

Coronary angiographic findings are summarized in Table 2. There were no significant differences in target artery, lesion location, reference diameter, and minimal lumen diameter. However, multivessel disease was more common and the angiographic lesion length was significantly longer in the elderly group.

Grey-scale IVUS results

Grey-scale IVUS findings are summarized in Table 3. Plaque burdens at proximal and distal reference sites were significantly greater in the elderly group. However, no significant differences were found in the plaque mass at the minimum lumen and largest NC sites and by volumetric analysis. IVUS lesion length was significantly longer and superficial calcium was observed more frequently in the elderly group.

Overall VH-IVUS results

At the minimum lumen sites, the absolute and percent areas of DC ($0.67 \pm 0.62\,mm^2$ vs. $0.57 \pm 0.57\,mm^2$, $P = 0.032$; $11.8 \pm 10.9\%$ vs. $9.9 \pm 9.6\%$, $P = 0.039$, respectively) and NC ($1.29 \pm 1.17\,mm^2$ vs. $1.14 \pm 0.97\,mm^2$, $P = 0.014$; $20.8 \pm 11.8\%$ vs. $18.1 \pm 11.6\%$, $P = 0.023$, respectively) were significantly greater in the elderly group; conversely, percent FT area was significantly smaller in the elderly group ($56.6 \pm 15.7\%$ vs. $60.0 \pm 15.0\%$, $P = 0.026$). At the largest NC sites, the absolute and percent areas of DC ($0.94 \pm 0.73\,mm^2$ vs. $0.77 \pm 0.65\,mm^2$, $P = 0.012$; $15.2 \pm 10.6\%$ vs. $12.5 \pm 9.6\%$, $P = 0.009$, respectively) and NC ($1.77 \pm 1.24\,mm^2$ vs. $1.61 \pm 1.13\,mm^2$, $P = 0.018$; $27.2 \pm 11.6\%$ vs. $24.5 \pm 11.0\%$, $P = 0.016$, respectively) were significantly greater in the elderly group; conversely percent FT area was significantly smaller in the elderly group ($49.4 \pm 14.6\%$ vs. $54.3 \pm 13.6\%$, $P = 0.001$).

At the proximal reference sites, the percent areas of DC ($7.3 \pm 8.8\%$ vs. $5.5 \pm 8.0\%$, $P = 0.031$) and NC ($12.1 \pm 9.0\%$ vs. $10.0 \pm 9.0\%$, $P = 0.025$) were significantly greater in the elderly group. At the distal reference sites, and the percent areas of DC ($12.8 \pm 10.3\%$ vs. $10.2 \pm 9.2\%$, $P = 0.012$) and NC ($13.2 \pm 8.0\%$ vs. $10.3 \pm 10.6\%$, $P = 0.014$) were significantly greater in the elderly group; conversely percent FT area ($56.9 \pm 27.0\%$ vs. $60.8 \pm 28.3\%$, $P = 0.022$) was significantly smaller in the elderly group.

The absolute and percent volumes of DC and NC were significantly greater in the elderly group; conversely absolute FT volume was significantly smaller in elderly group (Fig. 1).

VH-IVUS results according to the clinical presentation

In patients with stable angina, the absolute and percent volumes of DC and NC were significantly greater in the elderly group (Fig. 2). However, in patients with acute coronary syndrome, there were no significant differences in absolute and percent volumes of DC and NC between the elderly and non-elderly groups (Fig. 3).

Independent predictors of percent NC volume >20% in lesion site

We performed multivariate analysis to determine independent predictors of percent NC volume >20% in lesion sites. All variables with $P < 0.2$ in univariate analysis (age, gender, myocardial infarction, diabetes mellitus, high-sensitivity C-reactive protein, and P&M volume) were tested for multivariate analysis. Myocardial infarction (OR: 2.56, 95% CI: 1.45—4.12, $P = 0.003$), diabetes mellitus (OR: 2.23, 95% CI: 1.30—3.53, $P = 0.009$), and high-sensitivity C-reactive protein (OR; 1.44, 95% CI: 1.06—2.45, $P = 0.042$), but not age, were the independent predictors of percent NC volume >20% in lesion sites.

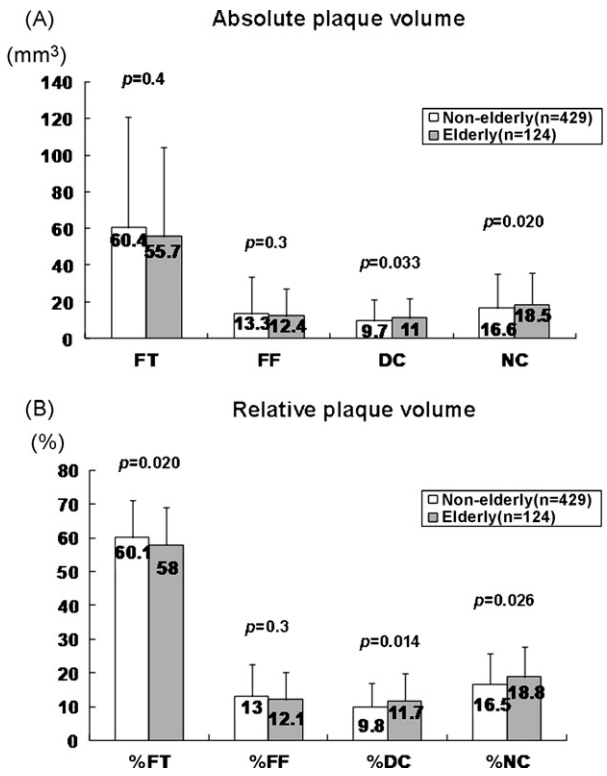

Figure 1 Overall volumetric absolute (A) and relative (B) plaque components. The absolute and percent volumes of dense calcium (DC) and necrotic core (NC) were significantly greater in the elderly group compared with the non-elderly group. FT, fibrotic; FF, fibro-fatty.

Discussion

Elderly patients with stable angina have more NC- and DC-containing plaques compared with younger patients with stable angina. However, these differences in plaque components between elderly and non-elderly patients were not observed in acute coronary syndrome patients. Only myocardial infarction, diabetes mellitus, and high-sensitivity C-reactive protein, but not age, were the independent predictors of percent NC volume >20% in lesion site.

Coronary artery disease is highly prevalent and accounts for the majority of mortality in elderly patients. Although the mechanism by which increasing age contributes to mortality is unknown, it has been postulated that the high mortality is precipitated in the elderly patients compared with younger patients by the presence of more comorbid conditions, more severe coronary lesion, and reduced cardiac and overall physiologic reserve in elderly patients [1—16].

As a part of the aging process, coronary arteries are prone to dilation, tortuosity, medial calcification, and endothe-

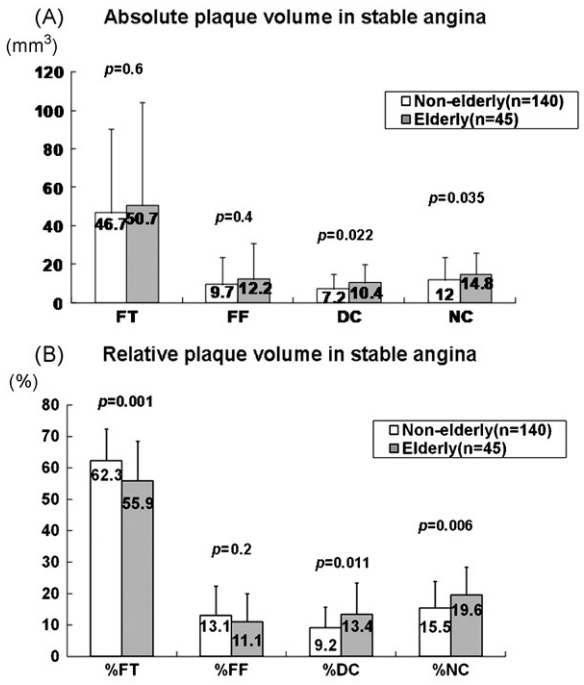

Figure 2 The volumetric absolute (A) and relative (B) plaque components in patients with stable angina. In patients with stable angina, the absolute and percent volumes of dense calcium (DC) and necrotic core (NC) were significantly greater in the elderly group compared with the non-elderly group. FT, fibrotic; FF, fibro-fatty.

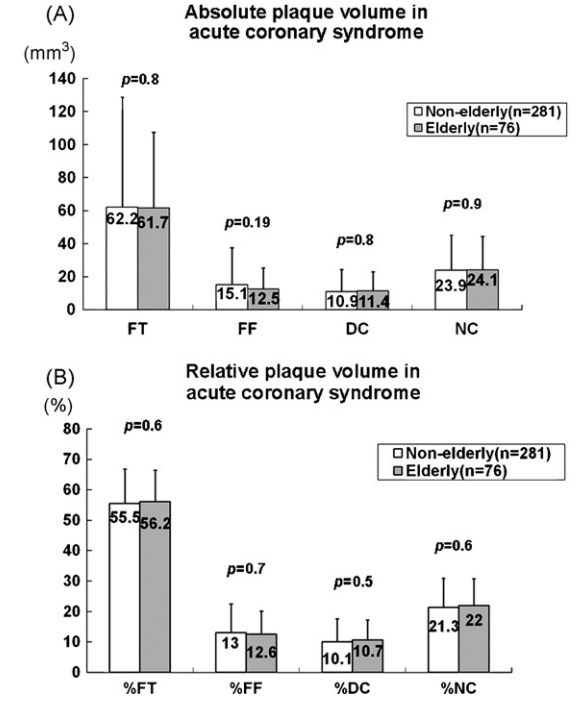

Figure 3 The volumetric absolute (A) and relative (B) plaque components in patients with acute coronary syndrome. In patients with acute coronary syndrome, there were no significant differences in absolute and percent volumes of dense calcium (DC) and necrotic core (NC) between the elderly and non-elderly groups. FT, fibrotic; FF, fibro-fatty.

lial dysfunction [29—32]. Previous grey-scale IVUS studies have demonstrated more calcified plaque and more negative remodeling in elderly patients [19—25]. In the present study, plaque burdens at reference segments were significantly greater and lesion length was significantly longer and superficial calcium was observed more frequently in the elderly group compared with the younger group.

VH-IVUS can provide detailed qualitative and quantitative information about plaque composition and it can identify four specific plaque components. In the present study, in the overall coronary artery disease population, the DC and NC components were significantly greater in the elderly group; conversely absolute FT volume was significantly smaller in the elderly group compared with the younger group. In patients with stable angina, the DC and NC components were significantly greater in the elderly group, however, in patients with acute coronary syndrome, there were no significant differences in plaque components between elderly and non-elderly patients. Several studies have demonstrated the differences in coronary plaque components assessed by VH-IVUS between patients with stable angina and those with acute coronary syndrome [18,33,34]. Rodriguez-Granillo et al. [18] reported that VH-IVUS identified thin-cap fibroatheroma as a more prevalent finding in acute coronary syndrome patients than in stable angina patients. Hong et al. [33] reported that the NC components were greater and the FT and FF components were less in acute coronary syndrome patients compared with stable angina patients. Missel et al. [34] reported that the percentage of NC and its ratio to DC in diseased coronary segments are associated with a high-risk acute coronary syndrome presentation. The present study showed that myocardial infarction, diabetes mellitus, and high-sensitivity C-reactive protein were independent predictors of NC-rich lesion, however age was not. Our results suggest that clinical presentation, risk factors, and inflammatory status, but not age, are important factors for determining plaque components.

Study limitations

First, this was a retrospective single-center study. The results of this study should be verified by further prospective investigation. Second, IVUS and VH-IVUS imaging were performed at the discretion of the individual operators leading to potential selection bias. Third, heavily calcified plaques may induce an artifact regarding the codification of plaques by VH-IVUS resulting in an increase in NC content. Fourth, we excluded the patients with serious conditions like increased risk of bleeding, severe heart failure, cardiogenic shock, important systemic disease, or renal dysfunction. Thus, the present study might not represent the whole spectrum of patients with coronary artery disease.

Conclusions

The present study demonstrates that myocardial infarction, diabetes mellitus, and high-sensitivity C-reactive protein, but not age, were associated with NC-rich lesions. Our results suggest that clinical presentation, risk factors, and inflammatory status, but not age, are important factors for

determining plaque components. Therefore, age is not an important factor for determining plaque components.

Acknowledgments

This study was supported by a grant of the Korea Healthcare Technology R&D Project (A084869), Ministry for Health, Welfare & Family Affairs, Republic of Korea, and the Cardiovascular Research Foundation, Asia.

References

[1] Gurwitz JH, Osganian V, Goldberg RJ, Chen ZY, Gore JM, Alpert JS. Diagnostic testing in acute myocardial infarction: does patient age influence utilization patterns? The Worcester Heart Attack Study. Am J Epidemiol 1991;134:948—57.
[2] Peterson ED, Jollis JG, Bebchuk JD, DeLong ER, Muhlbaier LH, Mark DB, Pryor DB. Changes in mortality after myocardial revascularization in the elderly. The National Medicare Experience. Ann Intern Med 1994;121:919—27.
[3] Myler RK, Webb JG, Nguyen KP, Shaw RE, Anwar A, Schechtmann NS, Bashour TT, Stertzer SH, Zapolanski A. Coronary angioplasty in octogenarians: comparisons to coronary bypass surgery. Cathet Cardiovasc Diagn 1991;23:3—9.
[4] Little T, Milner MR, Lee K, Constantine J, Pichard AD, Lindsay Jr J. Late outcome and quality of life following percutaneous transluminal coronary angioplasty in octogenarians. Cathet Cardiovasc Diagn 1993;29:261—6.
[5] O'Keefe Jr JH, Sutton MB, McCallister BD, Vacek JL, Piehler JM, Ligon RW, Hartzler GO. Coronary angioplasty versus bypass surgery in patients >70 years old matched for ventricular function. J Am Coll Cardiol 1994;24:425—30.
[6] Morrison DA, Bies RD, Sacks J. Coronary angioplasty for elderly patients with ''high risk'' unstable angina: short-term outcomes and long-term survival. J Am Coll Cardiol 1997;29:339—44.
[7] Thompson RC, Holmes Jr DR, Grill DE, Mock MB, Bailey KR. Changing outcome of angioplasty in the elderly. J Am Coll Cardiol 1996;27:8—14.
[8] Forman DE, Berman AD, McCabe CH, Baim DS, Wei JY. PTCA in the elderly: the ''young—old'' versus the ''old—old''. J Am Geriatr Soc 1992;40:19—22.
[9] Santana JO, Haft JI, LaMarche NS, Goldstein JE. Coronary angioplasty in patients eighty years of age or older. Am Heart J 1992;124:13—8.
[10] Thompson RC, Holmes Jr DR, Gersh BJ, Mock MB, Bailey KR. Percutaneous transluminal coronary angioplasty in the elderly: early and long-term results. J Am Coll Cardiol 1991;17:1245—50.
[11] Lindsay Jr J, Reddy VM, Pinnow EE, Little T, Pichard AD. Morbidity and mortality rates in elderly patients undergoing percutaneous coronary transluminal angioplasty. Am Heart J 1994;128:697—702.
[12] Klein LW, Block P, Brindis RG, McKay CR, McCallister BD, Wolk M, Weintraub W, ACC-NCDR Registry. Percutaneous coronary interventions in octogenarians in the American College of Cardiology-National Cardiovascular Data Registry: development of a nomogram predictive of in-hospital mortality. J Am Coll Cardiol 2002;40:394—402.
[13] Cohen HA, Williams DO, Holmes Jr DR, Selzer F, Kip KE, Holubkov R, Kelsey SF, Detre KM, NHLBI Dynamic Registry. Impact of age on procedural and 1-year outcome in percutaneous transluminal coronary angioplasty: a report from the NHLBI Dynamic Registry. Am Heart J 2003;146:513—9.
[14] De Gregorio J, Kobayashi Y, Albiero R, Reimers B, Di Mario C, Finci L, Colombo A. Coronary artery stenting in the elderly: short-term outcome and long-term angiographic and clinical follow-up. J Am Coll Cardiol 1998;32:577—83.
[15] DeGeare VS, Stone GW, Grines L, Brodie BR, Cox DA, Garcia E, Wharton TP, Boura JA, O'Neill WW, Grines CL. Angiographic and clinical characteristics associated with increased in-hospital mortality in elderly patients with acute myocardial infarction undergoing percutaneous intervention (a pooled analysis of the primary angioplasty in myocardial infarction trials). Am J Cardiol 2000;86:30—4.
[16] Alexander KP, Anstrom KJ, Muhlbaier LH, Grosswald RD, Smith PK, Jones RH, Peterson ED. Outcomes of cardiac surgery in patients > or = 80 years: results from the National Cardiovascular Network. J Am Coll Cardiol 2000;35:731—8.
[17] Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation 2002;106:2200—6.
[18] Rodriguez-Granillo GA, García-García HM, Mc Fadden EP, Valgimigli M, Aoki J, de Feyter P, Serruys PW. In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. J Am Coll Cardiol 2005;46:2038—42.
[19] Dangas G, Mintz GS, Mehran R, Lansky AJ, Kornowski R, Pichard AD, Satler LF, Kent KM, Stone GW, Leon MB. Preintervention arterial remodeling as an independent predictor of target-lesion revascularization after nonstent coronary intervention: an analysis of 777 lesions with intravascular ultrasound imaging. Circulation 1999;99:3149—54.
[20] Fuessl RT, Kranenberg E, Kiausch U, Baer FM, Sechtem U, Hopp HW. Vascular remodeling in atherosclerotic coronary arteries is affected by plaque composition. Coron Artery Dis 2001;12:91—7.
[21] Farb A, Weber DK, Kolodgie FD, Burke AP, Virmani R. Morphological predictors of restenosis after coronary stenting in humans. Circulation 2002;105:2974—80.
[22] Gyongyosi M, Yang P, Hassan A, Weidinger F, Domanovits H, Laggner A, Glogar D. Coronary risk factors influence plaque morphology in patients with unstable angina. Coron Artery Dis 1999;10:211—9.
[23] Hassani SE, Mintz GS, Fong HS, Kim SW, Xue Z, Pichard AD, Satler LF, Kent KM, Suddath WO, Waksman R, Weissman NJ. Negative remodeling and calcified plaque in octogenarians with acute myocardial infarction: an intravascular ultrasound analysis. J Am Coll Cardiol 2006;47:2413—9.
[24] Higashikuni Y, Tanabe K, Yamamoto H, Aoki J, Nakazawa G, Onuma Y, Otsuki S, Yagishita A, Yachi S, Nakajima H, Hara K. Relationship between coronary artery remodeling and plaque composition in culprit lesions: an intravascular ultrasound radiofrequency analysis. Circ J 2007;71:654—60.
[25] Hong YJ, Jeong MH, Ahn Y, Sim DS, Chung JW, Cho JS, Yoon NS, Yoon HJ, Moon JY, Kim KH, Park HW, Kim JH, Cho JG, Park JC, Kang JC. Age-related differences in intravascular ultrasound findings in 1,009 coronary artery disease patients. Circ J 2008;72:1270—5.
[26] Qian J, Maehara A, Mintz GS, Margolis MP, Lerman A, Rogers J, Banai S, Kazziha S, Castellanos C, Dani L, Fahy M, Stone GW, Leon MB. Impact of gender and age on in vivo virtual histology-intravascular ultrasound imaging plaque characterization (from the global Virtual Histology Intravascular Ultrasound [VH-IVUS] registry). Am J Cardiol 2009;103:1210—4.
[27] Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, Rifai N. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications, Part 2. Clin Chem 2001;47:418—25.
[28] Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and

reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478—92.

[29] Tokunaga O, Yamada T, Fan JL, Watanabe T. Age-related decline in prostacyclin synthesis by human aortic endothelial cells. Qualitative and quantitative analysis. Am J Pathol 1991;138:941—9.

[30] Lee TJ, Shirasaki Y, Nickols GA. Altered endothelial modulation of vascular tone in aging and hypertension. Blood Vessels 1987;24:132—6.

[31] Taddei S, Virdis A, Mattei P, Ghiadoni L, Gennari A, Fasolo CB, Sudano I, Salvetti A. Aging and endothelial function in normotensive subjects and patients with essential hypertension. Circulation 1995;91:1981—7.

[32] Kirma C, Akcakoyun M, Esen AM, Barutcu I, Karakaya O, Saglam M, Kargin R, Turkmen M, Boztosun B, Izgi A, Sonmez K. Relationship between endothelial function and coronary risk factors in patients with stable coronary artery disease. Circ J 2007;71:698—702.

[33] Hong MK, Mintz GS, Lee CW, Suh J, Kim JH, Park DW, Lee SW, Kim YH, Cheong SS, Kim JJ, Park SW, Park SJ. Comparison of virtual histology to intravascular ultrasound of culprit coronary lesions in acute coronary syndrome and target coronary lesions in stable angina pectoris. Am J Cardiol 2007;100:953—9.

[34] Missel E, Mintz GS, Carlier SG, Sano K, Qian J, Kaple RK, Castellanos C, Dangas G, Mehran R, Moses JW, Stone GW, Leon MB. Necrotic core and its ratio to dense calcium are predictors of high-risk non-ST-elevation acute coronary syndrome. Am J Cardiol 2008;101:573—8.