Age-Related Differences in Intravascular Ultrasound Findings in 1,009 Coronary Artery Disease Patients

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Background The aim of this study was to assess the age-related differences in intravascular ultrasound (IVUS) findings of target lesions in patients with coronary artery disease.

Methods and Results The 1,009 patients who underwent IVUS imaging were grouped according to an increase of 10 years of age: Group I [<50 years (n=144)]; Group II [51–60 years (n=259)]; Group III [61–70 years (n=249)]; Group IV [71–80 years (n=264)]; and Group V [>80 years, (n=93)]. Calcified plaque (18%, 25%, 33%, 38%, and 46%, p<0.001) and negative remodeling (29%, 48%, 44%, 44%, and 66%, p<0.001) were most common, and reference segment plaque burden (35±11%, 35±10%, 39±10%, 38±10%, and 40±11%, p<0.001) was greatest in Group V. Plaque rupture (52%, 31%, 42%, 38%, and 20%, p=0.009) and thrombus (38%, 30%, 31%, 24%, and 11%, p=0.026) were most common in Group I. In the multiple logistic regression analysis, patient age was an independent predictor of calcified plaque (odds ratio (OR)=1.03, p=0.001), negative remodeling (OR= 1.04, p=0.001), and mean reference segment plaque burden >50% (OR=1.03, p=0.006).

Conclusion Elderly patients have more severe calcifications with negative remodeling and diffuse atherosclerosis, whereas younger patients have more unstable plaque morphology. (*Circ J* 2008; **72:** 1270 – 1275)

Key Words: Aging; Atherosclerosis; Coronary disease; Intravascular ultrasound

The elderly constitute an increasing segment of the population and cardiovascular disease is highly prevalent among them, accounting for most of their morbidity and mortality. Although age itself is a prominent marker of high risk for adverse events[1,2] the elderly have usually been underrepresented in clinical trials of coronary artery disease (CAD). Compared with the general population, elderly patients undergoing coronary revascularization have been more likely to present with more complex lesions, more unstable angina, and more comorbid conditions and a lower ejection fraction[3–17] However, the reasons for these adverse findings are not well understood, so the purpose of the present study was to assess the age-related differences in pre-percutaneous coronary intervention (PCI) intravascular ultrasound (IVUS) findings of target lesions treated with PCI in patients with CAD.

Methods

Study Population

From August, 2002 to July, 2007, we identified a total of 1,009 patients with CAD who underwent pre-intervention IVUS. We excluded patients with restenotic lesions, coronary artery bypass graft failure, and patients in whom adequate IVUS images could not be obtained. We divided the patients into 5 groups according to an increase of 10 years of age: Group I [<50 years (n=144)]; Group II [51–60 years (n=259)]; Group III [61–70 years (n=249)]; Group IV [71–80 years (n=264)]; and Group V [>80 years (n=93)].

Quantitative Coronary Angiography (QCA) Analysis

The location of the target coronary lesion was designated as proximal, middle or distal. Coronary angiograms were analyzed with a 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 and reference diameter were measured in diastolic frames from orthogonal projections.

IVUS Imaging and Analysis

All IVUS examinations were performed before PCI, after intracoronary administration of 300 μg nitroglycerin, using a commercially available IVUS system (Boston Scientific Corporation/SCIMed, Minneapolis, MN, USA). The IVUS catheter was advanced distal to the target lesion, and imaging was performed retrograde to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s.

IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies[18] Using planimetry software (TapeMeasure, INDEC Systems Inc, Mountain View, CA, USA), we measured the external elastic membrane (EEM) and lumen cross-sectional area (CSA). Plaque plus media (P&M) CSA was calculated as EEM CSA minus

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Table 1 Baseline Characteristics According to an Increase of 10 Years of Age

	Group I (n=144)	Group II (n=259)	Group III (n=249)	Group IV (n=264)	Group V (n=93)
Age (years)‡	43±6	55±5	64±6	75±5	84±6
Male gender†	112 (78%)	177 (68%)	173 (70%)	159 (60%)	54 (58%)
Stable angina	76 (53%)	150 (58%)	127 (51%)	132 (50%)	47 (51%)
Acute coronary syndrome	68 (47%)	109 (42%)	122 (49%)	132 (50%)	46 (49%)
Diabetes mellitus†	40 (28%)	67 (26%)	82 (33%)	87 (33%)	33 (35%)
Hypertension‡	72 (50%)	181 (70%)	184 (74%)	198 (75%)	75 (81%)
Smoking†	84 (58%)	130 (50%)	112 (45%)	63 (24%)	40 (43%)
Family history of CAD†	46 (32%)	98 (38%)	95 (38%)	66 (25%)	22 (24%)
Ejection fraction (%)†	47±11	48±12	43±13	44±14	41±11
Total cholesterol (mg/dl)*	192±42	183±46	181±48	168±40	151±40
Triglyceride (mg/dl)*	213±128	152±93	144±82	128±65	112±52
LDL-cholesterol (mg/dl)*	117±40	111±41	114±39	100±34	91±33
HDL-cholesterol (mg/dl)	40±10	44±13	45±13	45±15	40±13

*p<0.05, †p<0.01, ‡p<0.001.
CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2 Coronary Angiographic Findings According to an Increase of 10 Years of Age

	Group I (n=144)	Group II (n=259)	Group III (n=249)	Group IV (n=264)	Group V (n=93)
Target artery					
Left main	4 (3%)	8 (3%)	15 (6%)	16 (6%)	4 (4%)
LAD	62 (43%)	111 (43%)	102 (41%)	108 (41%)	47 (51%)
LCX	24 (17%)	39 (15%)	46 (18%)	55 (21%)	13 (14%)
RCA	54 (38%)	101 (39%)	86 (35%)	85 (32%)	29 (31%)
Lesion location					
Proximal	58 (40%)	116 (45%)	113 (46%)	134 (54%)	38 (41%)
Middle	74 (51%)	106 (41%)	95 (38%)	91 (35%)	41 (44%)
Distal	12 (8%)	36 (14%)	40 (16%)	31 (12%)	14 (15%)
Multivessel disease†	37 (30%)	67 (29%)	77 (33%)	91 (39%)	44 (52%)
Reference diameter (mm)	3.15±0.63	3.02±0.60	3.07±0.63	2.97±0.62	3.05±0.80
Pre-MLD (mm)	1.29±0.66	1.29±0.67	1.32±0.61	1.28±0.63	1.26±0.53

†p<0.01.
LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; MLD, minimal lumen diameter.

lumen CSA, and plaque burden was calculated as P&M CSA divided by EEM CSA. The lesion was the site with the smallest lumen CSA; if there were multiple image slices with the same minimum lumen CSA, then the image slice with the largest EEM and P&M was measured.

Coronary artery remodeling was assessed by comparing the lesion site to the reference segment EEM CSA. The reference EEM area was calculated by averaging the proximal and distal EEM areas. Proximal and distal references were the single slices with the largest lumen and smallest plaque burden within 10-mm proximally and distally, but before any large side branch. The remodeling index was the lesion site EEM CSA divided by the average of the proximal and distal reference segment EEM CSA. Positive remodeling was defined as a remodeling index >1.05, intermediate remodeling as a remodeling index between 0.95 and 1.05, and negative remodeling as a remodeling index <0.95[19]

Soft plaque was less bright than the reference adventitia; fibrotic plaque was as bright as or brighter than the reference adventitia without acoustic shadowing; calcified plaque was hyperechoic with shadowing. A calcified lesion contained >90° of circumferential lesion calcium. The location of calcium (superficial vs deep) was noted, and the arc (in degrees) and length (in millimeters) of calcium were measured. Extensive calcification was defined as a lesion calcium arc >270°. When there was no dominant plaque composition, the plaque was classified as mixed.

A ruptured plaque contained a cavity that communicated with the lumen and had an overlying residual fibrous cap fragment. A fragmented and loosely adherent plaque without a distinct cavity and without a fibrous cap fragment was not considered as a plaque rupture[20,21] The plaque cavity was measured and extrapolated to the ruptured capsule area. Thrombus was an intraluminal mass with a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation[21,22]

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (Chicago, IL, USA) was used for all analyses. Continuous variables are presented as the mean value±SD; comparisons were conducted with Student's t-test or the nonparametric Wilcoxon test or P ANOVA. Discrete variables are presented as percentages and relative frequencies; comparisons were conducted using chi-square statistics or Fisher's exact test as appropriate. Pearson's correlation coefficient was used to evaluate the associations between patient age vs calcium arc, remodeling index, and reference segment plaque burden. Logistic regression analysis was used to identify the independent predictors of calcified plaque, negative remodeling, and reference segment plaque burden >50%. Variables used in the multivariate model were determined from a univariate analysis with any parameter meeting p<0.2. A p-value <0.05 was considered

Table 3 IVUS Findings According to an Increase of 10 Years of Age

	Group I (n=144)	Group II (n=259)	Group III (n=249)	Group IV (n=264)	Group V (n=93)
Proximal reference					
EEM CSA (mm^2)	15.3±4.7	15.4±5.0	16.0±4.8	14.9±5.0	17.9±5.9
Lumen CSA (mm^2)	9.9±2.9	9.7±2.7	9.7±3.2	9.1±3.1	10.3±3.5
P&M CSA (mm^2)†	5.4±3.2	5.6±3.4	6.2±2.8	5.9±2.9	7.5±3.8
Plaque burden (%)‡	33.7±13.5	34.4±11.9	38.4±11.1	38.6±10.9	41.0±12.4
Distal reference					
EEM CSA (mm^2)	12.8±5.0	13.1±4.9	13.9±4.6	13.4±4.6	14.2±6.0
Lumen CSA (mm^2)	8.2±3.2	8.2±3.0	8.4±2.7	8.3±2.7	8.6±3.9
P&M CSA (mm^2)†	4.6±2.6	4.9±2.8	5.6±2.8	5.1±2.7	5.7±3.4
Plaque burden (%)‡	34.9±11.5	35.7±11.0	36.8±11.4	36.9±11.3	38.6±12.1
Minimum lumen site					
EEM CSA (mm^2)	14.3±4.4	13.8±4.8	14.5±4.9	13.3±4.5	14.0±5.1
Lumen CSA (mm^2)	2.6±1.4	2.5±1.3	2.6±1.1	2.6±1.2	2.7±1.0
P&M CSA (mm^2)	11.6±4.3	11.3±4.6	11.9±4.8	10.7±4.5	11.3±5.0
Plaque burden (%)	80.1±10.0	80.0±10.5	80.7±10.0	78.7±11.4	78.4±9.7
Plaque cavity area (mm^2)†	2.9±1.8	2.4±1.3	2.3±1.2	2.3±1.4	2.0±1.2
Plaque rupture length (mm)†	3.3±1.9	2.8±1.1	2.6±1.5	2.7±1.1	2.1±1.6
Calcium arc (°)‡	71±99	85±90	105±99	110±104	158±112
Calcium length (mm)‡	3.3±5.4	4.6±7.5	5.4±5.9	5.5±5.6	6.1±3.9
Extensive calcification (calcium arc >270°)‡	12 (8%)	13 (5%)	20 (8%)	24 (9%)	18 (19%)
Superficial calcium‡	40 (28%)	113 (44%)	107 (43%)	111 (42%)	57 (61%)
Remodeling index‡	1.05±0.23	0.99±0.23	1.00±0.26	0.97±0.21	0.90±0.23
IVUS lesion length (mm)‡	12.2±10.1	13.4±10.9	15.2±7.1	15.3±7.5	16.0±8.1

†$p<0.01$, ‡$p<0.001$.
IVUS, intravascular ultrasound; EEM, external elastic membrane; CSA, cross-sectional area; P&M, plaque plus media.

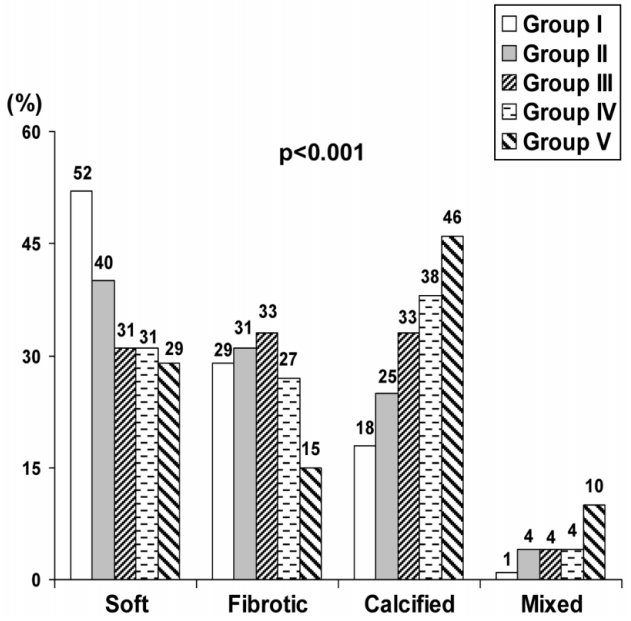

Fig 1. Plaque morphology according to age group.

statistically significant.

Results

Patient Characteristics

The baseline characteristics of the patients are summarized in Table 1. There were no significant differences in the clinical presentations of the groups. Females were predominant in Group V. The prevalence of both diabetes mellitus and hypertension was most frequent in Group V, whereas Group I had the most smokers. The ejection fraction was lowest in Group V. Total cholesterol, triglyceride, and low-density lipoprotein-cholesterol levels were highest in Group I.

Angiographic Results

Angiographic findings are summarized in Table 2. There were no significant differences in the target artery or lesion location among the 5 groups. However, multivessel disease was most frequently observed in Group V. There were no significant differences in the reference diameter or minimal lumen diameter among the groups.

IVUS Results

IVUS findings are summarized in Table 3. Proximal and distal reference segment P&M CSAs and plaque burden were greatest, and the IVUS lesion was longest, in Group V. There were no significant differences in lesion site EEM, lumen, P&M CSA, and plaque burden among the 5 groups. Soft plaque was most common in Group I and calcified plaque was most common in Group V (Fig 1). The calcium arc was greatest and calcium length was longest in Group V. Superficial calcium and extensive calcification were observed most frequently in Group V. The remodeling index was lowest and negative remodeling was most common in Group V, whereas positive remodeling was most common in Group I (Fig 2). Plaque rupture and thrombus were most common (Fig 3), plaque cavity area was greatest, and plaque rupture length was longest in Group I.

Predictors of Calcified Plaque, Negative Remodeling, and Reference Segment Plaque Burden

Univariate predictors of calcified plaque were patient age, diabetes mellitus, stable angina, serum creatinine, multivessel disease, reference segment plaque burden, and negative remodeling. Using multiple logistic regression analysis, independent predictors of calcified plaque were patient age (odds ratio (OR)=1.03; 95% confidence interval (CI) 1.01–

1.04, p=0.001), multivessel disease (OR=1.53; 95% CI 1.07–2.21, p=0.021), and reference segment plaque burden (OR=1.07; 95% CI 1.01–1.13, p=0.021).

Univariate predictors of negative remodeling were patient age, diabetes mellitus, lesion location, calcified plaque, and superficial calcium location. Using multiple logistic regression analysis, the only independent predictor of negative remodeling was patient age (OR=1.04; 95% CI 1.01–1.06, p=0.001).

Univariate predictors of mean reference segment plaque burden >50% were patient age, male gender, diabetes mellitus, multivessel disease, and calcified plaque. Using multiple logistic regression analysis, independent predictors of mean reference segment plaque burden >50% were male gender (OR=3.48; 95% CI 1.70–7.14, p=0.001), patient age (OR=1.03; 95% CI 1.01–1.05, p=0.006), diabetes mellitus (OR=1.95; 95% CI 1.09–3.48, p=0.024), and multivessel disease (OR=1.84; 95% CI 1.07–3.15, p=0.027).

Discussion

The present IVUS study demonstrated that elderly patients have more severe calcification with negative remodeling and diffuse atherosclerosis, whereas younger patients have more unstable plaque morphology (positive remodeling with more plaque rupture and thrombus). In particular, patient age was an independent predictor of calcified plaque, negative remodeling, and diffuse atherosclerosis (greater reference segment plaque burden).

CAD is highly prevalent, and accounts for the majority of deaths, in elderly patients. Although the mechanism by which increasing age contributes to mortality is unknown, it has been postulated that the high mortality in the elderly compared with younger patients is precipitated by the presence of more comorbidities, more severe CAD, and reduced cardiac and overall physiologic reserve in these patients.[3–17] Elderly patients have a higher incidence of diabetes mellitus and hypertension, whereas younger patients have a higher incidence of hyperlipidemia, family history of CAD, and current or former smoking.[16] The results of the present study are consistent with those from previous studies reporting more comorbidities in elderly patients.

The present study demonstrated that age may be related to the differences in plaque morphology. As part of the aging process, coronary arteries are prone to dilation, tortuosity, medial calcification, and endothelial dysfunction.[23–26] These pathophysiologic alterations might be associated with differences in plaque morphology (ie, more calcified plaque) and more diffuse disease in elderly patients. Vascular calcification causes a reduction in the elasticity of the vessel wall and thus reduced compliance, and vascular calcification generally occurs with advanced age. The presence of calcium deposits in the vessel wall indicates advanced atherosclerosis, and the extent of coronary calcification has been found to add incremental prognostic significance to conventional risk factors for CAD.[27,28]

Previous studies showed more calcified plaque and more negative remodeling in elderly patients.[29–34] Positive remodeling is associated with plaque rupture, yellow plaque color, and thrombus formation,[35–37] whereas negative remodeling may be related to superficial calcium deposition and the amount of calcium.[38] Previous studies have shown greater amounts of fibrocalcified plaque elements at the lesion site,[39–41] and the results of the present study suggest that extensive calcification, especially superficial calcium accu-

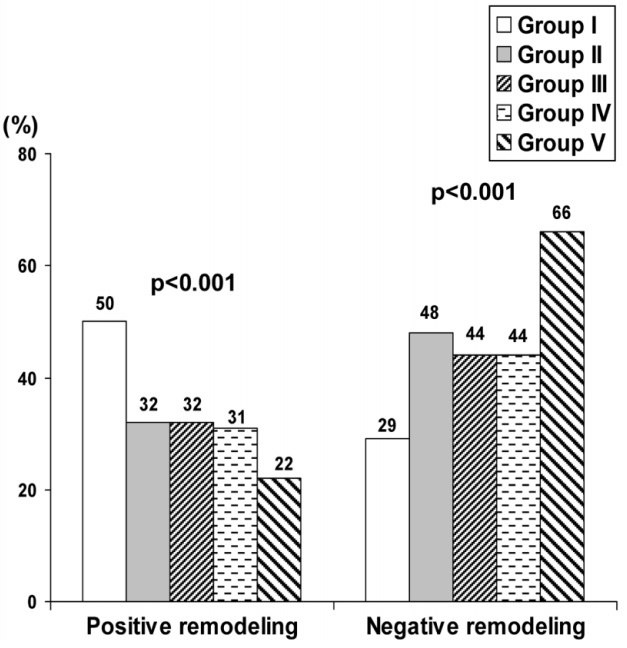

Fig 2. Incidence of positive and negative remodeling according to age group.

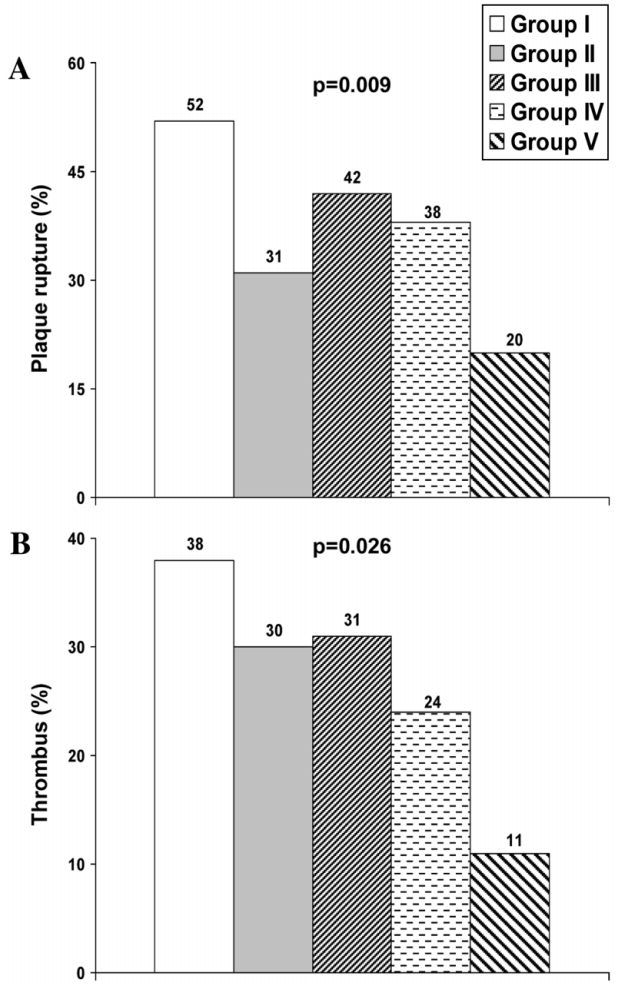

Fig 3. Incidence of plaque rupture (A) and thrombus (B) according to age group.

mulation, may limit the vessel's adaptive response to plaque accumulation.

A previous IVUS study demonstrated that independent predictors of reference segment plaque burden were male gender, patient age, diabetes mellitus, hypercholesterolemia and presence of multivessel disease in angiographically "normal" reference segments of 884 patients undergoing transcatheter therapy for symptomatic CAD.[42] The present study suggests that atherosclerosis occurs progressively and diffusely with aging, and that this process may be associated with more comorbidities (many of the conventional risk factors for CAD) in elderly patients.

Study Limitations

Firstly, the present study was a retrospective single-center study, so it is subject to the limitations inherent in this type of clinical investigation. Secondly, the number of octogenarians was small, so selection bias cannot be excluded entirely. Thirdly, long-term clinical follow-up was not available. Fourthly, the results may only apply to patients who are selected for PCI. Importantly, there was a selection bias against elderly patients undergoing revascularization, so it is unclear whether they were referred for PCI for the same reasons as the younger patients.

Conclusions

Elderly patients have more severe calcification with negative remodeling and diffuse atherosclerosis, whereas younger patients have more unstable plaque morphology (positive remodeling with more plaque rupture and thrombus).

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