

Coronary Artery Disease in Asymptomatic Young Adults: Its Prevalence According to Coronary Artery Disease Risk Stratification and the CT Characteristics

Eun Ju Ha, MD
Yookyung Kim, MD
Joo Yeon Cheung, MD
Sung Shine Shim, MD

Index terms:

Coronary artery diseases
Computed tomography (CT)
Coronary angiography

DOI:10.3348/kjr.2010.11.4.425

Korean J Radiol 2010; 11: 425-432

Received November 12, 2009; accepted after revision March 11, 2010.

All authors: Department of Radiology, School of Medicine, Ewha Womans University, Seoul 158-710, Korea

Address reprint requests to:

Yookyung Kim, MD, Department of Radiology, Ewha Womans University Mokdong Hospital, 911-1 Mokdong, Yangcheon-gu, Seoul 158-710, Korea.
Tel. (822) 2650-5380
Fax. (822) 2650-5302
e-mail: yookkim@ewha.ac.kr

Objective: We aimed at evaluating the prevalence and CT characteristics of occult coronary artery disease (CAD) in young Korean adults under 40 years of age by performing coronary CT angiography (CCTA).

Materials and Methods: We retrospectively enrolled 112 consecutive asymptomatic subjects (90 men, mean age: 35.6 ± 3.7 years) who underwent CCTA as part of a general health evaluation. We classified the subjects into three National Cholesterol Education Program risk categories and we assessed the plaque characteristics on CCTA according to the number of involved vessels, the location and type of plaques and vascular remodeling.

Results: Twelve individuals had CAD (11%, 11 men). The prevalence of CAD was significantly higher in the subgroups with moderate (22%) or high (25%) risk than that in the low risk subgroup (5%) ($p < 0.05$). Nine patients had single-vessel disease and three patients had two-vessel disease. The most common location for plaque was the proximal left anterior descending coronary artery (60%). All the patients had non-significant stenosis and plaque, including the non-calcified (27%), mixed (47%) and calcified (27%) types. Positive vascular remodeling was identified in all the patients with non-calcified or mixed plaques.

Conclusion: The prevalence of occult CAD was not negligible in the asymptomatic young adults with moderate to high risk, and this suggests the importance of management and risk factor modification in this population. All the patients had non-significant stenosis, and one fourth of the plaques did not show calcification.

Coronary artery disease (CAD) is one of the leading causes of death in developed countries despite that there has been a significant reduction of the mortality rates during past decades (1, 2). CAD predominantly manifests in older individuals, and the incidence of symptomatic CAD in young adults is low; most studies have shown that only about 3% of all CAD cases and 2% to 6% of all infarctions involve individuals under the age of 45 (3).

Although young patients with myocardial infarction exhibit fewer comorbidities, lower rates of in-hospital mortality and more favorable outcomes on short-term follow-up than do the older patients (4), their long-term prognosis is often rather poor, with an overall 15-year mortality rate of 30% (5). Therefore, the early detection and treatment of subclinical CAD and the prevention of developing acute coronary events should be emphasized in young adults.

Because young, asymptomatic patients typically do not undergo medical evaluations

for CAD, not much data exists regarding the prevalence and characteristics of CAD in young asymptomatic individuals. In the current study, we used coronary CT angiography (CCTA) to evaluate the prevalence and CT characteristics of subclinical coronary atherosclerosis in asymptomatic Korean individuals who were under 40 years of age and who exhibited coronary risk factors.

MATERIALS AND METHODS

Study Population

We retrospectively evaluated 128 consecutive young adults who were under 40 years of age and who had undergone a CCTA evaluation with 64-slice multidetector CT (MDCT) as a screening test for detecting CAD during a general health evaluation from January 2006 to May 2008. We excluded 16 subjects who had chest pain or discomfort ($n = 15$) and those with a history of acute coronary syndrome ($n = 1$). None of the subjects were excluded due to nondiagnostic CCTA image quality. As a result, 112 asymptomatic young adults (90 men and 22 women) were finally enrolled. The mean age of the study population was 35.6 ± 3.7 years (range: 28–40 years). All the subjects had conventional coronary risk factors such as diabetes mellitus ($n = 8$), cigarette smoking ($n = 54$), hypertension ($n = 36$) or obesity ($n = 62$). There were 77 subjects with a low CAD risk, 27 with a moderate risk and eight with a high risk. Our Institutional Review Board approved this retrospective study and patient informed consent was waived.

Data Acquisition

A single oral dose of 20 mg of a β -blocker (propranolol [Pranol; Daewoong, Korea]) was administered one hour before MDCT for the patients with a heart rate of > 65

beats per minute (bpm). For those with a heart rate that was still greater than 65 bpm, an additional 20 mg of oral propranolol was administered one hour after the administration of the first dose of oral β -blocker. CCTA was not performed for patients with heart rates more than 70 bpm after repeated drug administration or for those with an intermittent arrhythmia. Coronary vasodilatation was achieved by administering 0.6 mg nitroglycerin (Myung Moon, Seoul, Korea) sublingually before the CCTA to obtain the maximum coronary artery opacification.

All the examinations were performed using a 64-slice MDCT (SOMATOM Sensation 64, Siemens Medical Solutions, Germany) and the following scan parameters were used: tube voltage 120 kVp, tube current 750 effective mAs, detector collimation 64×0.6 mm, gantry rotation 370 msec and pitch 0.24. Retrospective electrocardiogram (ECG) gating and ECG-gated dose modulation were used. A bolus of 70 ml iopamidol (370 mg of iodine per milliliter; Iopamiro 370; Bracco, Milan, Italy) was injected intravenously into an antecubital vein at a flow rate of 4 ml/sec, and this was followed by a 40–50 ml saline chaser using the bolus tracking technique. The images were initially reconstructed at the mid-diastolic phase (60–70% of the RR interval) of the cardiac cycle, and they were then transferred to a computed workstation (Leonardo, Siemens Medical Solutions, Germany).

Image Analysis

All the scans were retrospectively analyzed on a three-dimensional workstation by two radiologists (14 and 7 years of experience in chest CT, respectively), using the multiplanar reformation technique, the maximum intensity projection technique and the volume-rendering technique with a short-axis and the two-chamber and four-chamber views. The coronary artery tree was segmented according

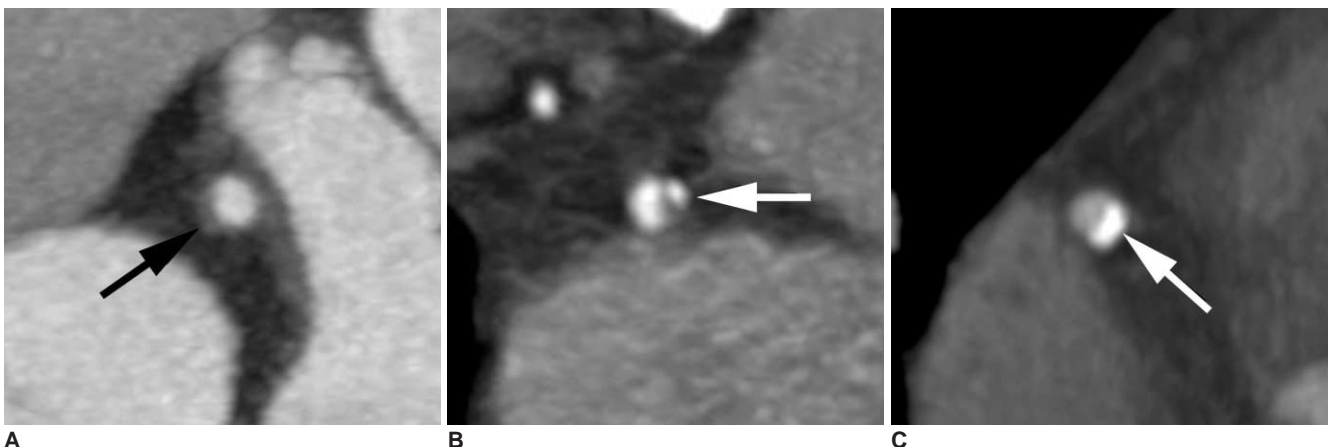


Fig. 1. Types of atheromatous plaques.
A-C. Noncalcified (A), mixed (B), and calcified (C) plaques (arrows).

to the modified American Heart Association classification (15 segments), and these segments were subsequently investigated for the presence and characteristics of coronary plaques (6).

The degree of stenosis was classified as significant if the patient had more than a 75% area stenosis on the cross-sectional images or more than a 50% diameter stenosis on the longitudinal images.

Coronary plaques were classified as non-calcified (plaques without visible calcification), mixed (plaques with non-calcified and calcified components) or calcified plaques (completely calcified plaques), according to the calcified component of the plaques seen on CCTA. Plaque densities of more than 130 HU (Hounsfield unit) on the native scans were classified as calcified (Fig. 1).

Changes in the coronary artery diameter were measured to determine the remodeling index (RI). The maximum outer diameter at the lesion and at the proximal reference site was measured to calculate the RI (i.e., $RI = [\text{maximum outer diameter at the plaque site} - \text{maximum outer diameter at the reference vessel}] / \text{maximum outer diameter at the reference vessel}$). Positive remodeling was defined as an $RI > 0$ and negative remodeling as an $RI < 0$. The degree of remodeling was calculated by percentage (i.e., mean values \pm standard deviations). Measurements of the vascular diameter were obtained from the manually traced maximal diameters taken from the longitudinal source images (Fig. 2).

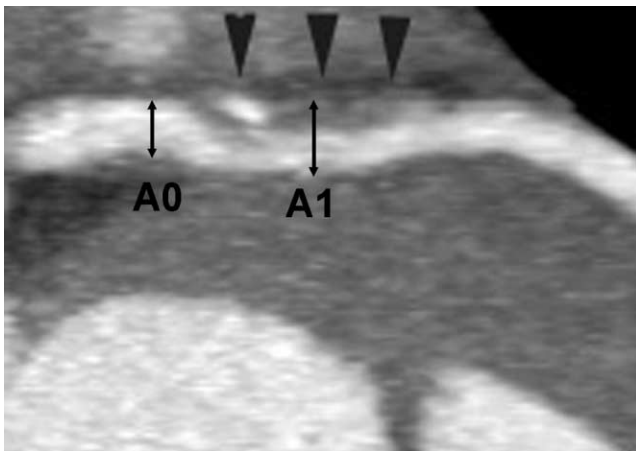


Fig. 2. Measurement of vascular remodeling. Vascular remodeling was measured on longitudinal image. Positive vascular remodeling is noted at site of plaque (arrowheads). Degree of vascular remodeling (%) = $(A_1 - A_0) / A_0 \times 100$ (A_1 = maximum outer diameter of coronary artery at site of plaque, A_0 = maximum outer diameter of coronary artery just proximal to plaque).

Coronary Artery Disease Risk Assessment and the Clinical Outcomes

All the study related data, including the demographics, symptoms, medical histories and laboratory results, was systemically acquired from the hospital database and a chart review. The conventional coronary risk factors such as obesity, cigarette smoking, hypertension, hypercholesterolemia and diabetes mellitus were assessed, and the serum biomarkers such as homocysteine, C-reactive protein and triglyceride were measured. The Framingham risk scores, as used by the National Cholesterol Education Program (NCEP) guidelines, were also calculated (7). All the subjects were assigned to one of three different risk groups according to the revised NCEP guidelines: the high-risk group (CAD risk equivalents or a 10-year risk $> 20\%$), the moderate-risk group (more than two risk factors and a 10-year risk $\leq 20\%$) and the low-risk group (0–1 risk factors).

Of the 112 subjects, 109 underwent abdominal ultrasonography as part of a general health evaluation within one week of CCTA, and the presence or absence of a fatty liver was determined. The degree of fatty liver on ultrasonography was classified as follows: 1) a mild, minimal diffuse increase of the hepatic echogenicity with normal visualization of the diaphragm and intrahepatic vessel borders; 2) a moderate, moderate diffuse increase of the hepatic echogenicity with slightly impaired visualization of the intrahepatic vessels and diaphragm; 3) a severe, marked increase of the echogenicity with poor visualization or nonvisualization of the hepatic vessels and diaphragm. We also compared the patients with CAD to the normal subjects with respect to the coronary risk factors and a fatty liver.

The clinical follow-up data (range: 10–39 months) was obtained from the patients who exhibited CAD on CCTA, based on the cardiac events, the treatment and the laboratory findings.

Statistical Analysis

All the statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL). The differences between categorical variables were analyzed using Chi-square or Fisher's exact tests, and the differences between continuous variables were analyzed using the unpaired Student's *t*-test or Mann-Whitney test, as appropriate. A $p < 0.05$ was considered significant.

RESULTS

Atheromatous plaques were noted in 15 segments in 12 of 112 subjects (11%). Nine patients had single-vessel

disease, and three had two-vessel disease. There were 11 men and one woman with an age range from 31 to 40 years (mean age: 36.8 ± 2.6 years) with atheromatous plaques. The patient population included four of 77 subjects (5%) with a low CAD risk, six of 27 (22%) with a moderate risk and two of eight (25%) with a high CAD risk. The prevalence of CAD was significantly higher in the moderate CAD risk group than that in the low risk group

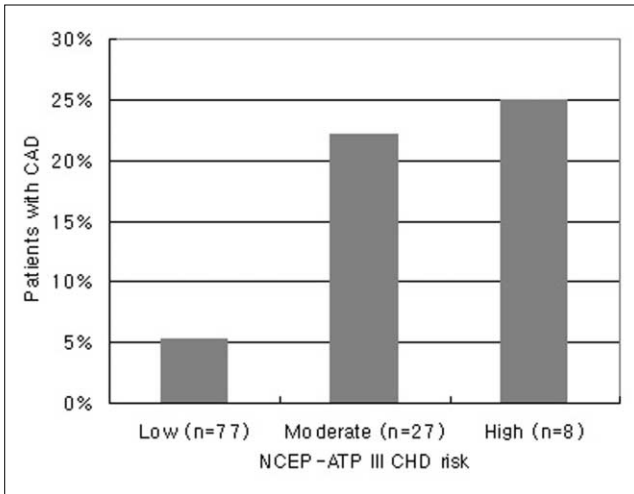


Fig. 3. Frequency of coronary artery disease in each coronary artery disease risk group. Percentage of patients with coronary artery disease is shown on ordinate. CAD = coronary artery disease, Low = low-risk group, moderate = moderate-risk group, high = high-risk group, NCEP-ATP III CAD risk = National Cholesterol Education Program-Adult Treatment Panel III coronary artery disease risk

($p = 0.018$); however, there was no significant difference between the moderate and high risk groups ($p = 0.604$) (Fig. 3).

The presence of obesity, hypertension, hypercholesterolemia, high triglycerides and fatty liver was significantly higher in the patients with CAD than that in the normal individuals. There also tended to be a higher incidence of cigarette smoking, high LDL (low-density lipoprotein) cholesterol, low HDL (high-density lipoprotein) cholesterol, diabetes mellitus and high C-reactive protein in the patients with CAD; however, any statistical significance was not identified (Table 1).

The location and degree of stenosis as well as the type of plaque are shown in Table 2. The coronary plaques were located in the left anterior descending (LAD) ($n = 11$, 73%) and the left main (LM) ($n = 4$, 27%) arteries, with the most common location being the proximal LAD ($n = 9$, 60%) (Fig. 4). All the coronary segments with plaque exhibited non-significant stenosis. The types of plaque included non-calcified ($n = 4$, 27%), mixed ($n = 7$, 47%) and calcified ($n = 4$, 27%).

The changes in the vascular diameter at the CAD site were measured in four coronary segments with noncalcified plaque and in seven with mixed plaques. This measure was not evaluated in segments with calcified plaques because the exact measurement of the vascular diameter was unavailable due to beam-hardening and blooming artifacts. Positive remodeling was identified in all the segments with noncalcified or mixed plaques, and

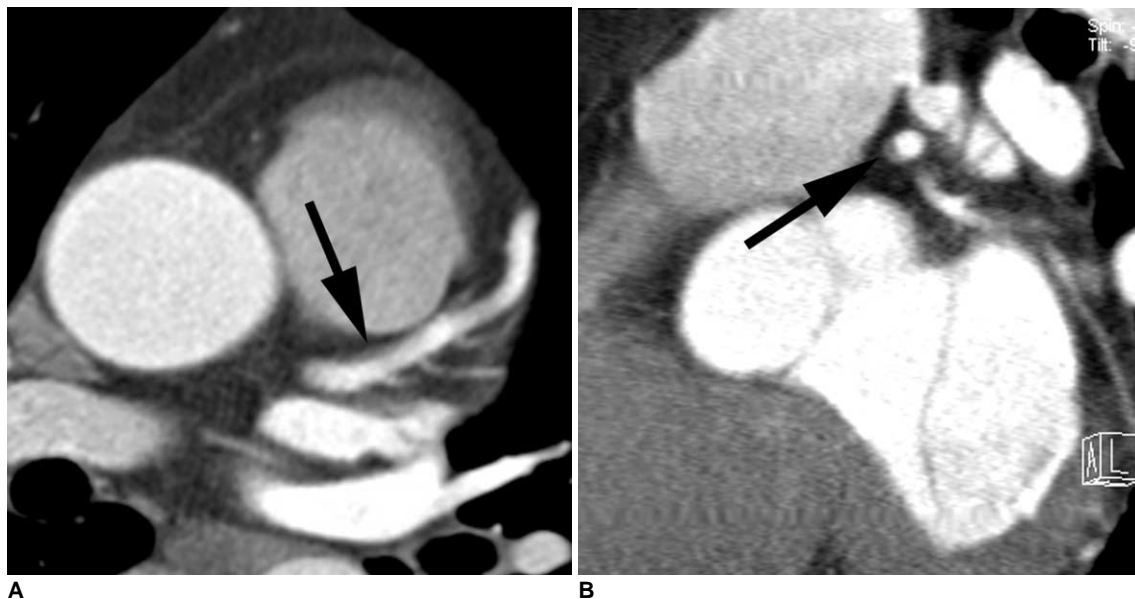


Fig. 4. 35-year-old man with hypertension and history of cigarette smoking. **A, B.** Longitudinal (**A**) and cross-sectional (**B**) multiplanar reconstruction images of proximal left anterior descending coronary artery show mild degree of stenosis due to noncalcified plaque (arrows). Longitudinal image indicates slightly increased vascular diameter at site of plaque compared with proximal normal vessel (positive vascular remodeling).

Coronary Artery Disease in Asymptomatic Young Adults

the degree of positive remodeling tended to be higher in the patients with noncalcified plaques than in those with mixed plaques (Table 3); however, there was no statistically significant difference between the two groups ($p = 0.471$).

Twelve patients with CAD have been free of cardiac events 10–39 months after CCTA. Four of the five patients with hypercholesterolemia started antihypercholesterolemic medication, based on the results of the CCTA, and they showed improvement of their hypercholesterolemia on the follow-up tests.

DISCUSSION

Early detection of CAD provides the opportunity to initiate interventions that will stabilize existing lesions, including LDL-lowering drug therapy (statins), smoking cessation intervention for cigarette smokers, blood pressure lowering for persons with hypertension, and lifestyle intervention for the physically inactive and obese. Such interventions can reduce the risk of developing acute coronary syndromes later in life.

The current approach for managing the asymptomatic individuals who are at risk for CAD is based on traditional clinical risk assessments such as the Framingham risk score

Table 2. Coronary Artery Disease Detected on Screening Coronary CT Angiography in Young Adults Under 40 Years of Age

	Number of Plaques (n = 15)
Location of plaque	
LAD	11 (73)
pLAD	9 (60)
mLAD	2 (13)
LM	4 (27)
Degree of stenosis	
Non-significant	15 (100)
Significant	0
Plaque type	
Noncalcified	4 (27)
Mixed	7 (47)
Calcified	4 (27)

Note.— Numbers in parentheses are percentages.
LAD = left anterior descending coronary artery, LM = left main coronary artery, m = middle, p = proximal

Table 1. Demographic Data and Coronary Risk Profile of Study Group

	Patients with CAD (n = 12)	Normal Individuals (n = 100)	P Value
Age, years			
Mean	36.8 ± 2.6	35.8 ± 3.8	
Range	31–40	19–40	
Gender			
Male	11 (92)	79 (79)	
Female	1 (8)	21 (21)	
NCEP-ATP III risk stratification			
Low-risk group	4 (33)	73 (73)	
Moderate-risk group	6 (50)	21 (21)	
High-risk group	2 (17)	6 (6)	
Coronary risk factors			
Obesity	12 / 12 (100)	50 / 99 (51)	0.001*
Cigarette smoking	8 / 12 (67)	46 / 98 (47)	0.163
Hypertension	8 / 12 (67)	28 / 99 (28)	0.009*
Hypercholesterolemia #			
Total cholesterol	4 / 12 (33)	7 / 98 (7)	0.018*
LDL cholesterol	5 / 12 (42)	34 / 95 (36)	0.690
HDL cholesterol	5 / 12 (42)	19 / 96 (20)	0.086
Diabetes	2 / 12 (17)	6 / 100 (6)	0.205
Triglyceride	8 / 12 (67)	36 / 98 (37)	0.047*
CRP	3 / 11 (27)	12 / 90 (13)	0.632
Fatty liver	10 / 12 (83)	37 / 94 (39)	0.005*
Mild	3 (25)	18 (19)	
Moderate	7 (58)	16 (17)	
Severe	0 (0)	3 (3)	

Note.— Numbers in parentheses are percentages.

CAD = coronary artery disease, CRP = C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NCEP-ATP = National Cholesterol Education Program-Adult Treatment Program

* $p < 0.05$, # Normal range: total cholesterol, 130–240 mg/dL; LDL cholesterol, ≤ 120 mg/dL; HDL cholesterol, 42–72 mg/dL

Table 3. Vascular Remodeling of Coronary Artery in Young Adults with Coronary Artery Disease

Plaques	Vascular Remodeling	Degree of Remodeling (%) ($p = 0.471$)
Noncalcified	4 (100%)	26.8 ± 11.62 (13.7–38.71)
Mixed	7 (100%)	21.6 ± 8.74 (11.4–32.14)
Total	11 (100%)	

Note.— Degree of remodeling (%) = $(A_1 - A_0) / A_0 \times 100$ (A_1 = maximum outer diameter of coronary artery at site of plaque, A_0 = maximum outer diameter of coronary artery just proximal to plaque). Data are expressed as mean values \pm standard deviations. Numbers in parentheses are ranges.

Remodeling was not evaluated in calcified plaques because of beam-hardening and blooming artifacts.

or the NCEP guidelines (7). However, there is growing evidence that these traditional risk assessment tools, which are based on risk factor analysis, have substantial limitations when they are used to guide individual therapy (8, 9). In a recently published study by Choi et al. (10) in which CAD was evaluated using CCTA in 1,000 middle-aged asymptomatic adults (mean age: 50 years), CAD was noted in 215 subjects (22%). This rate is higher than that observed in earlier studies (3–5%), and the results were confirmed by coronary angiography in the asymptomatic individuals (11–13).

To date, there is a paucity of data regarding the prevalence of atherosclerotic plaques as detected on CCTA in asymptomatic young adults, and this is largely because these asymptomatic young adults typically do not undergo medical evaluations for CAD. In this study that enrolled asymptomatic young adults (i.e., < 40 years of age) who were at risk for CAD, coronary plaques were demonstrated in 11% of the subjects, and the prevalence of CAD was significantly higher in the subjects with moderate (22%) or high (25%) risk than in those subjects with low risk (5%).

Positive remodeling was noted in all the coronary segments that exhibited noncalcified or mixed plaques with non-significant stenosis. This finding may indicate an important cause for underestimating CAD on coronary angiography and it may explain the acute coronary syndrome of young patients with angiographically normal coronary arteries (14–16). Positive remodeling occurs in the early stages of coronary plaque development, and it is well known that positive remodeling is related to plaque instability, suggesting it is more prone to rupture and erosion with subsequent coronary events (17–19). Nakamura et al. (19) reported that positive remodeling was observed more frequently in patients with acute coronary syndrome (78–82%) than in patients with stable

CAD (33–40%), and a significantly higher degree of positive remodeling was noted in patients with acute myocardial infarction (remodeling index, 1.26 ± 0.15) than in elderly patients with unstable angina pectoris (1.11 ± 0.10) or stable angina pectoris (0.94 ± 0.11) (mean age, 63 ± 10 years). Tanaka et al. (18) demonstrated that all lipid core plaques showed positive vascular remodeling, which is in contrast to the severely calcified plaques that did not show positive remodeling. Furthermore, it is well known from angiographic studies that most myocardial infarctions occur at sites that previously caused only mild to moderate luminal stenosis (20, 21). Taken together, these studies demonstrate the clinical significance and importance of early plaques with mild stenosis.

This study found the highest frequency of coronary plaques in the proximal LAD. Choi et al. (10) also reported that 85% of CAD presented at the LAD. In our study, plaques were not observed in the left circumflex artery, the peripheral branches of the coronary arteries or the diagonal branches. This may have resulted from the limited temporal resolution of CCTA, which would underestimate the small branches of the coronary arteries, or it may also result from a lower prevalence of plaques in those segments in patients with early-stage CAD.

The coronary calcium score is intimately associated with the total plaque burden (22) and it is a strong predictor of coronary events, and the coronary calcium score is independent of the traditional coronary risk factors or risk-factor scores (23). However, it sometimes fails to predict acute coronary events or significant stenosis because a significant numbers of vulnerable plaques tend to be predominantly noncalcified and nonstenotic lesions (20). The absence of coronary calcification has been described in 1% of the male patients with significant coronary stenosis (24) and in 4% of the patients suffering from an unheralded myocardial infarction (25). In our study, 27% of the patients with CAD had only noncalcified plaques, which is slightly higher than the 19% reported by Choi et al. (10). This may be linked to the observation that the plaques in young patients are probably in the early stages, so they have less calcification than those of older individuals. Therefore, the coronary calcium score may underestimate CAD in young adults to a greater degree than that in older individuals.

Obesity, smoking, hypertension and hypercholesterolemia are well known risk factors for CAD, and their incidences were significantly higher in the patients with CAD than that in the normal subjects of our study. In a recent report, fatty liver was demonstrated to be associated with the risk of CAD and early atherosclerosis in

middle-aged individuals (26). In the current study, we were able to evaluate the incidence of fatty liver because almost all the subjects underwent abdominal ultrasonography and CCTA as a part of a general health evaluation. As such, we also found that a fatty liver was significantly more prevalent in the patients with CAD (83%) than that in the normal individuals (39%).

Our study had some limitations. The study population was small, it included only Koreans living in urban areas and all the subjects were self-referred. Therefore, the actual prevalence of CAD in the young asymptomatic subjects in various ethnic groups and geographic regions may differ from our results, although this was evaluated in relation to the NCEP CAD risk categories.

In conclusion, the prevalence of occult CAD was not negligible in asymptomatic young adults, and the prevalence of CAD was significantly higher in those subjects with moderate to high risks than in those with low risk. Additionally, most of the patients had single-vessel disease, plaques of various composition, non-significant stenosis and positive vascular remodeling and one fourth of the patients had non-calcified plaques. Finally, the most common location for plaques was the proximal LAD. This study suggests the importance of management and risk factor modification for the asymptomatic young adults who have a moderate or high risk for CAD.

References

- Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med* 1998;339:861-867
- Beaglehole R. Global cardiovascular disease prevention: time to get serious. *Lancet* 2001;358:661-663
- Jalowiec DA, Hill JA. Myocardial infarction in the young and in women. *Cardiovasc Clin* 1989;20:197-206
- Hoit BD, Gilpin EA, Henning H, Maisel AA, Dittrich H, Carlisle J, et al. Myocardial infarction in young patients: an analysis by age subsets. *Circulation* 1986;74:712-721
- Cole JH, Miller JI 3rd, Sperling LS, Weintraub WS. Long-term follow-up of coronary artery disease presenting in young adults. *J Am Coll Cardiol* 2003;41:521-528
- Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5-40
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421
- Johnson KM, Dowe DA, Brink JA. Traditional clinical risk assessment tools do not accurately predict coronary atherosclerotic plaque burden: a CT angiography study. *AJR Am J Roentgenol* 2009;192:235-243
- Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol* 2003;41:1475-1479
- Choi EK, Choi SI, Rivera JJ, Nasir K, Chang SA, Chun EJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol* 2008;52:357-365
- Thaulow E, Erikssen J, Sandvik L, Erikssen G, Jorgensen L, Cohn PF. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). *Am J Cardiol* 1993;72:629-633
- Froelicher VF, Thompson AJ, Longo MR Jr, Triebwasser JH, Lancaster MC. Value of exercise testing for screening asymptomatic men for latent coronary artery disease. *Prog Cardiovasc Dis* 1976;18:265-276
- Pilote L, Pashkow F, Thomas JD, Snader CE, Harvey SA, Marwick TH, et al. Clinical yield and cost of exercise treadmill testing to screen for coronary artery disease in asymptomatic adults. *Am J Cardiol* 1998;81:219-224
- Ammann P, Marschall S, Kraus M, Schmid L, Angehrn W, Krapf R, et al. Characteristics and prognosis of myocardial infarction in patients with normal coronary arteries. *Chest* 2000;117:333-338
- Pecora MJ, Roubin GS, Cobbs BW Jr, Ellis SG, Weintraub WS, King SB 3rd. Presentation and late outcome of myocardial infarction in the absence of angiographically significant coronary artery disease. *Am J Cardiol* 1988;62:363-367
- Klein LW. Acute coronary syndromes in young patients with angiographically normal coronary arteries. *Am Heart J* 2006;152:607-610
- Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 2000;101:598-603
- Tanaka M, Tomiyasu K, Fukui M, Akabame S, Kobayashi-Takenaka Y, Nakano K, et al. Evaluation of characteristics and degree of remodeling in coronary atherosclerotic lesions by 64-detector multislice computed tomography (MSCT). *Atherosclerosis* 2009;203:436-441
- Nakamura M, Nishikawa H, Mukai S, Setsuda M, Nakajima K, Tamada H, et al. Impact of coronary artery remodeling on clinical presentation of coronary artery disease: an intravascular ultrasound study. *J Am Coll Cardiol* 2001;37:63-69
- Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-671
- Kullo IJ, Edwards WD, Schwartz RS. Vulnerable plaque: pathobiology and clinical implications. *Ann Intern Med* 1998;129:1050-1060
- Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995;92:2157-2162
- Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336-1345

24. Haberl R, Becker A, Leber A, Knez A, Becker C, Lang C, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001;37:451-457
25. Raggi P, Callister TQ, Coil B, He ZX, Lippolis NJ, Russo DJ, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850-855
26. Gastaldelli A, Kozakova M, Højlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. *Hepatology* 2009;49:1537-1544