Original Article

Prevalence of Coronary Atherosclerosis in Asymptomatic Healthy Subjects: An Intravascular Ultrasound Study of Donor Hearts

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Aim: At present, limited *in vivo* information is available on the prevalence and severity of coronary atherosclerosis in asymptomatic healthy subjects. The aim of this study was to examine the prevalence, extent and severity of coronary atherosclerosis in healthy individuals.

Methods: We performed an intravascular ultrasound (IVUS) examination on 198 heart transplant recipients 4 weeks after transplantation. The donor population consisted of 147 men and 51 women (31.4 ± 11.0 years). The left anterior descending coronary artery was imaged in all patients, and 3 vessel images were obtained for 99 patients.

Results: Angiographic appearance was completely normal in 177 of the 198 subjects (89.4%), while atherosclerotic luminal irregularities were observed in the remaining individuals. IVUS revealed that atherosclerotic lesions (defined as intimal thickness ≥ 0.5 mm at any site) were present in 96 patients (48.5%). The prevalence of coronary atherosclerosis rapidly increased with age (10-19 years, 5.9%; 20-29 years, 31.1%; 30-39 years, 59.0%; 40-49 years, 78.4%). In the diseased subgroup, atherosclerotic lesions were mostly eccentric (92.7%), with maximal intimal thickness of 0.99 ± 0.42 mm (area stenosis, $32.2 \pm 11.7\%$). All coronary arteries were predominantly located in the proximal third of each vessel. Donor age, male sex, and hypertension were the determinants of coronary atherosclerosis measured by IVUS examination. As more risk factors were present, the risk of atherosclerosis increased.

Conclusion: Coronary atherosclerosis is common in asymptomatic young healthy adults, supporting the need for preventive cardiology in the early stages of life.

J Atheroscler Thromb, 2013; 20:465-471.

Key words; Coronary atherosclerosis, Intravascular ultrasound, Prevalence

Coronary atherosclerosis begins early in life and progresses with age. Autopsy studies reveal that even individuals displaying no symptoms of cardiovascular disease may have coronary atheromatous lesions, and traditional risk factors are important determinants of the early stages of atherosclerosis¹⁻⁶. Despite their valuable contributions, autopsy studies have inherent limitations, including non-physiologic conditions and

fixation artifacts⁷.

Intravascular ultrasound (IVUS) generates detailed cross-sectional images of the vessel wall, allowing the accurate quantification of coronary plaques in living people⁸⁻¹⁰. Donor hearts are obtained from people with no known heart disease. Thus, IVUS analysis of transplant hearts may provide a unique insight into the prevalence and severity of atherosclerotic plaque in apparently healthy people; however, limited *in vivo* information is available on the extent and severity of coronary atherosclerosis in the healthy population¹¹⁻¹³. In this study, we determine the prevalence, extent, and severity of coronary atherosclerosis in heart transplant recipients at 4 weeks post-transplantation.

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Received: August 13, 2012

Accepted for publication: November 25, 2012

Table 1. Characteristics of donors

Characteristics	Total (n=144)	Atherosclerosis (n=68)	No atherosclerosis (n=76)	<i>p</i>
Age, years	30.8 ± 10.7	37.1 ± 7.7	25.0 ± 9.7	<0.001
Sex, male	105 (72.9)	56 (82.4)	49 (64.5)	0.024
BMI, kg/m ²	22.3 ± 3.6	23.2 ± 2.7	21.6 ± 4.1	0.002
Diabetes	0 (0)	0 (0)	0 (0)	–
Hypertension	13 (9.0)	12 (17.6)	1 (1.3)	0.001
Smoking	41 (28.5)	28 (41.2)	13 (17.1)	0.002

BMI: body mass index

Methods

Study Patients

Between July 1999 and December 2011, 202 consecutive patients who underwent heart transplantation at Asan Medical Center received cardiac catheterization with IVUS examination at 4 weeks after transplantation. Among these patients, 4 were excluded due to the inadequate quality of IVUS images ($n=1$) or inability to undergo IVUS examination ($n=3$). Consequently, the study population comprised 198 patients with no known coronary artery disease. Written informed consent was obtained from all patients, and the study protocol was approved by our institutional review board.

IVUS Procedure

IVUS images were obtained using mechanical ultrasound imaging catheters at 30 or 40 MHz (Boston Scientific Corp/SCIMED, Natick, MA). After intracoronary administration of 0.2 mg nitroglycerin, IVUS catheters were advanced over a guidewire to the distal portion of each major epicardial coronary artery, and withdrawn at a constant speed of 0.5 mm/s using a motorized pull-back device. IVUS images were recorded on a super VHS videotape or computer disc for offline analysis.

IVUS Analysis and Definitions

IVUS images were analyzed offline, and each vessel divided into CASS segments from the ostium to the distal portion. For each segment, the investigator selected one site with the greatest intimal thickness, and performed quantitative IVUS analysis using computerized planimetry. Quantitative measurements included intimal thickness, external elastic membrane (EEM) area, lumen area, plaque, and media area. Percent area stenosis was calculated as: (EEM area-lumen area)/EEM area × 100. Obstructive coronary arteriosclerosis was defined as a ≥ 50% decrease. Atherosclerotic lesion was defined as any site with intimal thick-

ness ≥ 0.5 mm, and classified as eccentric at a maximum to minimum intimal thickness ratio of ≥ 2.

Statistical Analysis

Data are expressed as the means ± SD for continuous variables and frequencies for categorical variables. Continuous variables were compared using unpaired Student's *t* test and categorical variables with the chi-square test. Binary logistic regression analysis was performed to find donor risk factors associated with atherosclerosis. Backward variable selection approach was employed to determine independent predictors in the multivariable logistic model. The final multivariable model was assessed with C-statistics and the Hosmer-Lemeshow test to measure the discrimination and calibration ability of the logistic model. Furthermore, several multivariable models were evaluated to measure the discrimination power for risk factors. For this, the area under the curve (AUC) of receiver-operating characteristic (ROC) curves was compared using Delong's test for two correlated ROC curves¹⁴. All analyses were performed using SPSS software (SPSS Inc., Chicago, IL) and R software version 2.15.1. R package of pROC was used for Delong's test and statistical significance was defined as a two-sided *p*-value < 0.05.

Results

Baseline Characteristics

The donor population consisted of 147 men and 51 women with a mean age of 31.4 ± 11.0 years (range, 5–62 years). The medical histories were incomplete in 54 patients. The baseline characteristics of the donors whose information were fully acquired are shown in **Table 1**. In total, 41 of 144 donors were known smokers, 13 were hypertensive, and none of the donors had diabetes. The left anterior descending coronary artery was imaged in all patients, the left main in 165, the left circumflex in 115, and the right coronary artery in 118. Three vessel images were

Fig. 1. Frequency distribution of abnormal maximum intimal thickness (≥ 0.5 mm) in each patient.

obtained for 101 patients, 2 vessels for 32, and a single vessel for 65 patients.

Angiographic Findings

Angiographic appearance was completely normal in 177 of the 198 patients (89.4%). In the remaining patients, atherosclerotic luminal irregularity was observed, with a diameter stenosis of $31.4 \pm 17.5\%$ (15-90%). In two patients, angiography revealed a significant coronary lesion with diameter stenosis $\geq 50\%$, and one donor less than 30 years of age displayed angiographic evidence of atherosclerosis.

Prevalence of Atherosclerosis

IVUS examination revealed that atherosclerotic lesions (defined as intimal thickness ≥ 0.5 mm) were observed in 96 patients (48.5%) (**Fig. 1**): 25.5% (42 of 165) in the left main coronary artery, 42.4% (84 of 198) in the left anterior descending coronary artery, 21.7% (25 of 115) in the left circumflex artery, and 39.8% (47 of 118) in the right coronary artery. In the diseased subgroup, atherosclerotic lesions were mostly eccentric (92.7%), and maximal intimal thickness was 0.99 ± 0.42 mm. EEM area was 21.3 ± 6.6 mm² and lumen area was 14.4 ± 5.4 mm². Plaque area calculated by the difference between EEM area and lumen area was 6.8 ± 2.8 mm² (area stenosis $32.2 \pm 11.7\%$). The group with no atherosclerosis had lower maximal intimal thickness (0.28 ± 0.10 ; $p < 0.001$ than the group with atherosclerosis). Their EEM area, lumen area, plaque area, and area stenosis were 17.2 ± 6.5 mm²

($p = 0.006$), 14.1 ± 5.8 mm² ($p = 0.784$), 3.1 ± 1.1 mm² ($p < 0.001$), and 16.3 ± 7.2 mm² ($p = 0.100$), respectively. This shows positive vascular remodeling in response to plaque progression in the group with atherosclerosis. The prevalence of coronary atherosclerosis by age is presented in **Fig. 2**. The prevalence of coronary atherosclerosis rapidly increased with advancing age, and atherosclerotic lesions were detected in 78.4% of patients aged from 40 to 49 years and 100% of patients aged 50 years or older.

Donor Risk Factors Associated with Atherosclerosis

On univariate analysis, age, male sex, hypertension, smoking history, and BMI were significantly associated with coronary atherosclerosis (**Table 2**). Using multivariate analysis, age and male sex were independently associated with atherosclerosis. Regarding hypertension, the significance was on the borderline. We assessed whether the risk of atherosclerosis might increase with more risk factors by comparing the AUC of ROC curves (**Table 3**). As more risk factors accumulated, the AUC increased as expected. In particular, when hypertension was added to the model composed of age and sex, the prediction ability for atherosclerosis increased with statistical significance (from 0.836 to 0.855, $p = 0.044$).

Distribution of Atherosclerosis

For each of the major epicardial coronary arteries, the site with the greatest intimal thickness was selected. The frequency distribution of these sites according to distance from each coronary ostium is shown in **Fig. 3**. All coronary arteries were predominantly located in the proximal third of each vessel (left anterior descending coronary artery, 72.2%, within 20 mm from the ostium; left circumflex lesion, 67.0%, within 20 mm from the ostium; right coronary artery lesions, 71.2%, within 30 mm from the ostium). Within the subgroup of 101 patients receiving 3-vessel IVUS imaging, atherosclerotic lesions were present in the left anterior descending coronary artery of 46 patients (45.5%), the left circumflex artery of 21 patients (20.8%), and the right coronary artery of 39 patients (38.6%).

Discussion

In this study, we demonstrated frequent coronary atherosclerosis in asymptomatic young adults, which increased in prevalence with age. Our results are consistent with previous reports¹¹⁻¹³ supporting the theory that early prevention of atherosclerosis is critical for vascular health.

Fig. 2. Prevalence of coronary atherosclerotic lesions according to age.

Table 2. Clinical characteristics predictive of atherosclerosis defined by abnormal maximum intimal thickness (≥ 0.5 mm)

	Univariate Analysis			Multivariate Analysis [†]		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Age, years	1.15	1.10-1.21	<0.001	1.15	1.09-1.21	<0.001
Sex, male	2.57	1.18-5.61	0.018	3.25	1.19-8.92	0.022
Hypertension	16.07	2.03-127.26	0.009	7.75	0.89-67.60	0.064
Smoking	3.39	1.57-7.31	0.002			
BMI, kg/m ²	1.15	1.03-1.28	0.013			

OR: odds ratio; CI: confidence interval; BMI: body mass index

[†]C-statistics (95% CI)=0.855 (0.795 to 0.916) and *p*-value based on the Hosmer-Lemeshow test=0.135)

Autopsy studies have disclosed that atherosclerotic plaque formation starts early in life, and the extent of atherosclerosis is markedly increased in young people with multiple risk factors¹⁻⁶. An autopsy study on 300 American soldiers aged between 18 and 48 years who died in the Korean War revealed grossly visible atherosclerosis in the coronary arteries of 77.3% of these individuals¹⁵. This study highlighting the frequent incidence of atherosclerosis in young adults was a major step forward in research in this field. A multicenter study on *Pathobiological Determinants of Atherosclerosis in Youth* (PDAY) in 390 young men (15-34 years of age) initially showed that serum lipoprotein cholesterol concentrations and smoking are important determinants of the early stages of atherosclerosis in adolescents and young adults⁴. In the Bogalusa autopsy study, the influence of multiple risk factors on the extent of atherosclerosis was examined in the aorta and coronary arteries of 204 young people who died prematurely of non-cardiac causes³. Tradi-

tional risk factors, including body-mass index, systolic blood pressure, low-density lipoprotein cholesterol levels, triglyceride levels, and cigarette smoking, were significantly associated with the extent of lesions in both the aorta and coronary arteries. These landmark autopsy studies clearly demonstrate a strong relationship between cardiovascular risk factors and the extent of atherosclerotic plaque formation in young people.

In our study, patients had coronary angiograms that were normal in 89.4%, but the IVUS revealed atherosclerotic lesions in a significant portion of the patients with normal angiograms. IVUS is employed for the *in vivo* identification and characterization of atherosclerotic lesions in arteries of transplanted donor hearts, which may reflect those of the asymptomatic healthy population. Tuzcu and colleagues investigated 262 heart transplant recipients (mean donor age of 33.4 ± 13.2 years) 30.9 $\pm$ 13.2 days after transplantation. The group showed that 136 of the patients (51.9%) had ≥ 1 atherosclerotic sites (intimal thick-

Table 3. Comparison of the areas under the curve (AUCs) for the prediction of atherosclerosis

ROC analysis	AUC (95% CI)
Model 1 (age)	0.823 (0.757-0.889)
Model 2 (age + sex)	0.836 (0.771-0.901)
Model 3 (age + hypertension)	0.840 (0.777-0.903)
Model 4 (age + sex + hypertension)	0.855 (0.795-0.916)
Delong's test for two correlated ROC curves	<i>p</i>
Model 1 vs Model 2	0.3836
Model 1 vs Model 3	0.0796
Model 1 vs Model 4	0.0554
Model 2 vs Model 4	0.0443
Model 3 vs Model 4	0.2412

ROC: receiver-operating characteristic; CI: confidence interval

ness ≥ 0.5 mm), and intimal thickness increased progressively with advancing age¹³. The authors concluded that coronary atherosclerosis begins at a young age, with lesions present in 1 out of 6 teenagers. In our study, the prevalence of coronary atherosclerosis was 48.5%, and rapidly increased with age; however, compared with previous reports, the incidence of coronary atherosclerosis in the young age donor group was relatively low (5.9% in teenage donors), and lesions were prevalent in the older age group. The reasons for this discrepancy remain unclear, but may be explained by the difference in donor clinical characteristics and ethnicity between the two studies. Compared to Tuzcu's study, our patients had a similar age, but included more males, fewer smokers, and patients with lower hypertension incidence and BMI values. The possibility of ethnic differences should be also considered as a reason for discrepancy and needs further investigation¹⁶. The geographic distribution of lesions was similar to previous reports. Atheromatous lesions tended to cluster within the proximal third of the coronary arteries^{17, 18}. Local regional factors, including shear stress, may be responsible for this difference¹⁹.

While we performed limited analysis of risk factors, our results clearly imply a significant association between classical risk factors and atherosclerosis. Among them, age was the most significant factor. Coronary atherosclerosis was only identified in 5.9% of the donors aged between 10 and 19 years; however, in patients 20 years or older, coronary atherosclerotic lesions rapidly increased and progressed with age (31.1% of donors aged 20 to 29 years, and 59.0% of donors aged 30 to 39 years). About 78.4% of the 40- to 49-year-old donors displayed clear evidence of coronary atherosclerosis, which may explain the recent

Fig. 3. Frequency distribution of maximum intimal thickness according to distance from each coronary ostium is shown for the left anterior descending coronary artery (LAD), left circumflex (LCX) and right coronary artery (RCA).

increase in heart attacks within this age group in Korea. Limited information is currently available on the distribution and extent of coronary atherosclerosis in asymptomatic healthy young adults. The present study provides unique *in vivo* data in this population.

This study had limitations. First, the number of study subjects was relatively small; hence, the findings require further confirmation in a large population. Second, the threshold of abnormal intimal thickness (0.5 mm), selected on the basis of its use in several previous studies¹¹⁻¹³⁾, was rather stringent. Third, we cannot exclude the effect of cardiac transplantation or its immunologic mechanism on the development of atherosclerosis 1 month after transplantation. It is known that cardiac allograft vasculopathy progresses through immunologic and non-immunologic mechanisms; however, it is usually defined as newly developed atherosclerosis on the 1-year coronary angiogram and IVUS study. In addition, this seems to be insufficient time for the transplantation-mediated immunologic mechanism to develop *de-novo* atherosclerosis and vascular remodeling. Finally, risk factor information was incomplete and the effects of risk factors on atherosclerosis could not be adequately analyzed. Nevertheless, our findings demonstrate a high prevalence of coronary atherosclerosis in the asymptomatic healthy young population, supporting the rationale for early prevention of atherosclerosis.

Acknowledgements

This study was supported by grants from the CardioVascular Research Foundation, and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (0412-CR02-0704-0001).

Conflicts of Interest

None.

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