High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults
Evidence From Intravascular Ultrasound

E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

Background—Most of our knowledge about atherosclerosis at young ages is derived from necropsy studies, which have inherent limitations. Detailed, in vivo data on atherosclerosis in young individuals are limited. Intravascular ultrasonography provides a unique opportunity for in vivo characterization of early atherosclerosis in a clinically relevant context.

Methods and Results—Intravascular ultrasound was performed in 262 heart transplant recipients 30.9 ± 13.2 days after transplantation to investigate coronary arteries in young asymptomatic subjects. The donor population consisted of 146 men and 116 women (mean age of 33.4 ± 13.2 years). Extensive imaging of all possible (including distal) coronary segments was performed. Sites with the greatest and least intimal thickness in each CASS segment were measured in multiple coronary arteries. Sites with intimal thickness ≥ 0.5 mm were defined as atherosclerotic. A total of 2014 sites within 1477 segments in 574 coronary arteries (2.2 arteries per person) were analyzed. An atherosclerotic lesion was present in 136 patients, or 51.9%. The prevalence of atherosclerosis varied from 17% in individuals < 20 years old to 85% in subjects ≥ 50 years old. In subjects with atherosclerosis, intimal thickness and area stenosis averaged 1.08 ± 0.48 mm and 32.7 ± 15.9%, respectively. For all age groups, the average intimal thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in men and 51.7% in women).

Conclusions—This study demonstrates that coronary atherosclerosis begins at a young age and that lesions are present in 1 of 6 teenagers. These findings suggest the need for intensive efforts at coronary disease prevention in young adults.

Key Words: atherosclerosis • ultrasonics • plaque • coronary disease

Although patients with coronary artery disease typically become symptomatic after age 40 years, necropsy studies have demonstrated that atherosclerotic changes in the vessel wall begin early in life.1–5 Characterization of coronary disease through postmortem examination of young subjects has important limitations, however, particularly the presence of nonphysiological conditions (arteries not pressure-distended) and fixation artifacts.6 Few in vivo data have documented the extent and severity of atherosclerosis in young, healthy subjects.7,8

Miniaturization of high-frequency transducers has allowed the development of intravascular ultrasound (IVUS), a unique imaging modality that permits direct examination of the vessel wall in living humans.9–12 Comparative studies have documented a close correlation between ultrasound measurements of atherosclerosis performed in vitro and histological measurements performed in pressure-distended arteries.8,13,14

We sought to determine the prevalence of atherosclerosis in subjects with no clinical or angiographic evidence of significant coronary disease. The population for this investigation consisted of patients who had recently undergone cardiac transplantation. We used IVUS to determine the presence, extent, and distribution of atherosclerosis in the donor coronary arteries within weeks of transplantation. Because most donors are relatively young, this approach provided the opportunity to characterize the early atherosclerotic disease process.

Methods

Patient Population

Between December 1992 and May 1999, IVUS examination was performed in 262 heart transplant recipients 30.9 ± 13.2 days after transplantation. The donor population consisted of 116 women (44%) and 146 men (56%) with a mean age of 33.4 ± 13.2 years. None of the patients had known coronary artery disease because potential donors were screened for heart disease before proceeding with transplantation. The hospital’s Institutional Review Board approved the study protocol. All participants provided informed consent.
IVUS Examination
The method of IVUS imaging has been reported previously in detail. After coronary angiography, patients received anticoagulation with heparin, and 100 to 200 μg nitroglycerin IC was administered. A 30-MHz, 3.5F monorail ultrasound catheter (Boston Scientific) was advanced over an angioplasty guidewire to a distal location in the coronary artery, and the position of the transducer was documented by angiography. Ultrasound images were displayed with a dedicated scanner (Hewlett-Packard Corp) and recorded on S-VHS tape during a slow, distal-to-proximal manual pullback. During pullbacks, voice annotation and frequent angiography were used to document the location of imaging sites of interest.

Offline IVUS Analysis
Images were reviewed on a video monitor in the IVUS core laboratory. Using an image-processing computer, a technician digitized full-motion IVUS sequences (30 frames per second) at a 640×480 pixel matrix with 24 bits per pixel. Images were considered suitable for analysis if they were free of ultrasound artifacts, such as extreme catheter angulation or nonuniform rotational distortion. For each segment, defined according to Coronary Artery Surgery Study (CASS) classification, the operator selected 2 sites, one with the least intimal thickness and another with the greatest intimal thickness. Although single frames were selected for analysis, the operator examined the full-motion sequence to facilitate optimal border delineation. The lumen and external elastic membrane (EEM) borders of the selected frames were manually traced to yield measurements of maximum intimal thickness, minimum intimal thickness, and both luminal and EEM cross-sectional areas.

The following definitions were used to describe lesion characteristics and severity:

- **Atherosclerotic lesion**: Any site with an intimal thickness ≥0.5 mm.
- **Normal site**: Within any CASS segment, the site with the least intimal thickness among the sites without atherosclerosis.
- **Eccentric lesion**: A lesion was classified as eccentric if the maximum intimal thickness was more than twice the value for the minimum intimal thickness.
- **Calcified lesion**: A lesion containing an echogenic structure that blocked penetration of ultrasound, thereby producing acoustic shadowing.

**Percent area stenosis**: EEM area−lumen area/EEM area×100

Angiographic Analysis
Coronary angiography was performed by standard techniques. Angiograms were reviewed on a screen at a fixed distance with a rear projection system (Tagarno 35 Ax) and classified as normal or abnormal by experienced angiographers blinded to the donor clinical data and ultrasound findings. For each vessel, the CASS segment classification system was used to identify the most distal site imaged by ultrasound. In abnormal angiograms, stenosis severity at sites showing any luminal narrowing or abnormality was measured with a digital caliper system (Sandhill Scientific, Inc). For each identifiable lesion, the operator determined vessel diameter at the stenosis site and at an adjacent angiographically normal reference site to quantify percent diameter stenosis.

Statistical Analysis
Normally distributed data were reported as mean±SD, and categorical variables were expressed as number and percentage of the cohort.

Results
Patient Population and Extent of Imaging
All donors in the study were free of known heart disease, the mean age was 33±13.2 years, and 56% were male. Other donor characteristics are listed in the Table. In the 262 subjects, 574 major epicardial coronary arteries other than the left main trunk were imaged (2.2 arteries per patient). The left anterior descending coronary artery (LAD) was visualized in 238 patients (90% of the cohort), the left circumflex (LCx) in 180 (69%), and the right coronary artery (RCA) in 156 (56%). All 3 arteries were imaged in 97 patients (37% of subjects), 2 arteries in 118 (45%), and only 1 vessel in 47 (18%). From these arteries, ultrasound images were analyzed for a total of 1477 CASS segments.

Intimal Thickness at the Normal Sites
Figure 1 shows the frequency distribution of the normal site with least intimal thickness in each patient for different age cohorts. If the donor was <40 years of age, the smallest intimal thickness in each patient was always <0.3 mm. Even when the donor age was >40 years, the normal intimal thickness was always <0.5 mm. Therefore, in the present study, we used the threshold of 0.5 mm to define the presence of an atherosclerotic lesion and to determine the prevalence of atherosclerosis. We also present the data according to the less stringent criterion of 0.3 mm.

Prevalence of Atherosclerosis
Of 262 individuals, 136 (51.9%) had ≥1 atherosclerotic site (intimal thickness >0.5 mm) (Figure 2). In these 136 subjects, the intimal thickness at the lesion was 1.08±0.48 mm, and percent stenosis averaged 32.7±15.9%. Figure 3 shows the frequency distribution of greatest intimal thickness in each patient for different age groups, demonstrating that intimal thickness increases progressively with advancing age. In all age groups, a portion of the cohort had ≥1 site with intimal thickness exceeding the 0.3-mm or 0.5-mm thresholds used for the definition of atherosclerosis (Figure 4). Strik-
ingly, when the more stringent definition of >0.5 mm was used, even the 12- to 19-year-old age group showed atherosclerosis in 17% of subjects. By age 40 years, >70% of individuals showed ≥1 coronary site with an intimal thickness >0.5 mm. With a less conservative threshold of 0.3 mm, 21% of teenagers and 91% of individuals 40 years old had ≥1 atherosclerotic lesion.

**Intimal Thickness and Stenosis Severity**

From each of the 1477 CASS segments, the sites with the largest value for intimal thickness, whether normal or diseased, were selected. The intimal thickness and percent area stenosis at these sites were 0.35±0.34 mm and 12.4±11.8%, respectively. The distribution of these values by age group is shown in Figure 5. The intimal thickness and percent area stenosis at these sites correlated with donor age (r=0.55, P<0.001 and r=0.56, P<0.001, respectively).

**Figure 2.** A, Example of atherosclerosis in LAD of 17-year-old man. Eccentric intimal thickening representing early atherosclerosis is evident. Note normal intima opposite diseased arc. Right, Magnified view of same lesion. B, Evidence of advanced atherosclerosis in 32-year-old woman.

**Figure 3.** Frequency distribution of greatest intimal thickness in each patient for all age cohorts.

**Figure 4.** Prevalence of coronary atherosclerosis by age with 0.5- and 0.3-mm thresholds for defining atherosclerotic lesions.
Lesions in Patients With 3-Vessel Imaging
To assess the distribution patterns of atherosclerosis in the young, lesions were investigated separately in the subgroup of 97 patients (1026 sites) in whom ultrasound imaging was performed in all 3 epicardial coronaries. The mean age of these patients was 32.4±13.2 years, and 58% were male (similar to entire cohort). A lesion was present in the LAD in 41 patients (42%), the RCA in 38 (39%), and the LCx in 26 (27%). The proportion of segments with a lesion was 19±25% for the LAD, 12±23% for the LCx, and 18±26% for the RCA.

Distribution and Composition of Lesions
Atherosclerotic lesions were identified in proximal segments more frequently (59%) than mid and distal segments, and the vast majority of lesions were eccentric (91%). The most diseased site involved a coronary bifurcation in 43% of patients. Calcification at ≥1 site by ultrasound was observed in 33 patients (12.6%).

Discussion
Atherosclerotic coronary disease is the leading cause of death and a major source of morbidity in developed countries, resulting in nearly 1 million deaths and $100 billion in annual costs in the United States alone.6 Necropsy studies have demonstrated that atherosclerosis begins at a very early stage in life. The present study provides unequivocal in vivo evidence of atherosclerosis in young asymptomatic individuals with no evidence of clinical coronary artery disease (Figure 3). This study is unique because it provides detailed, clinically relevant, quantitative, in vivo information on early atherosclerosis from an asymptomatic young population.

Necropsy studies dating back to 1948 describe coronary atherosclerosis in a young population, but none have provided quantitative measures of disease severity.1–5 In Korean and Vietnam war victims, the degree of obstruction was judged by gross inspection and microscopic examination performed without pressure fixation. Stary, in an elegant study,17a performed light and electron microscopy on pressure-fixed segments of the proximal LAD and LCx in 565 subjects <29 years old. The focus of this careful investigation, however, was lesion morphology, not measurement of plaque thickness, area stenosis, or lesion distribution. In the Pathological Determinants of Atherosclerosis in Youth (PDAY) study, the RCA was the only vessel examined.4 In the Korean War study, as well as the Bogalusa and PDAY studies, dissection of coronary arteries was longitudinal, not cross-sectional.1,3,17b In contrast to these studies, the present investigation assessed atherosclerosis in vivo and quantified lesions with methods used in clinical practice.

Limited data are available to describe the range of normal intimal thickness in humans. Using vessels that were not pressure-fixed, a necropsy study showed an age-related dependency of intimal thickness, averaging 0.21 mm for ages 21 to 25 years, increasing slightly to 0.25 mm for ages 36 to 40 years.18 Other small studies report normal intimal thickness ranging from 0.1 to 0.35 mm and medial thickness from 0.15 to 0.25 mm.7,12,19

In the present study, we thought it particularly important to rigorously define the threshold for presence of atherosclerosis. Previous ultrasound studies have established that intimal thickness detected within 8 weeks of transplantation represents preexisting coronary atherosclerosis in the donor.7,20,21 Furthermore, there was no difference in the prevalence and severity of intimal thickness in hearts that were examined 2 to 4 or 6 to 8 weeks after transplantation. Because all of the 262 subjects showed ≥1 site with an intimal thickness <0.5 mm, we felt justified in using this threshold as a conservative definition of atherosclerosis. Because all patients <40 years of age showed ≥1 site with intimal thickness <0.3 mm, this latter value may actually represent a less stringent but more reasonable definition for atherosclerosis. It is important to recognize, however, that intimal thickness is a continuous variable and that defining atherosclerosis as a categorical variable has limitations. Furthermore, intimal thickness does not necessarily indicate atherosclerosis. Morphological characteristics of intimal thickening observed in this study helped to identify the atherosclerotic origin of these findings. The majority of the areas with intimal thickening were eccentric, located proximally, adjacent to bifurcations.

Ultrasound techniques for quantification of intimal thickness measure different boundaries than classic necropsy studies. An ultrasound reflection occurs at a tissue interface whenever there is an abrupt change in acoustic impedance. Normally, 2 strong acoustic interfaces are visualized by ultrasound: the leading edge of the intima (at the interface between the blood-filled lumen and the endothelium) and the outer border of the media (at the junction of the media and the EEM). Accordingly, ultrasound techniques measure intimal thickness from the intimal leading edge to the EEM, thus including the media. This practice is used routinely in all
other ultrasound techniques, such as carotid or peripheral vascular imaging, for quantification of atherosclerosis.22

Few lesions were detected by angiography, the traditional “definitive” method for in vivo evaluation of the vascular lumen. Angiograms were abnormal in only 8% of the full cohort of 262 patients. No angiogram was abnormal in any patient <30 years old, yet 28% of these subjects had ultrasound evidence of atherosclerosis. Angiography provides excellent resolution but does not depict the vessel wall.7,23–25

Because compensatory remodeling is evident in many early lesions, the lumen is usually preserved in the early phase of the disease.26 Accordingly, angiography is insensitive for early detection and estimation of lesion severity. The greater sensitivity of IVUS is a result of its ability to provide tomographic images of the vessel wall, which permits detection of disease before the onset of luminal narrowing.8,9,11,13,14

The present study represents a thorough interrogation of the epicardial coronary arteries, including distal coronary segments. No statistically significant differences were observed in distribution of lesions within the different coronary arteries, although there was a trend toward higher prevalence in the LAD and the lower prevalence within the LCx, with intermediate probability for the RCA. We were also able to confirm the finding of previous necropsy studies that most early lesions occur in proximal segments.27,28 Early disease is highly eccentric (91% of lesions), with a strong predilection for involvement at bifurcation sites (nearly half of lesions). These findings suggest that flow patterns in the coronary arteries may be particularly important in the genesis of the early lesion.

Our findings regarding the high prevalence of atherosclerosis in young people are consistent with those of most other studies, including 2 small IVUS investigations. Examining only the proximal LAD, St Goar et al8 reported a 24% prevalence in 40 patients but no atherosclerosis in donors <25 years old. We previously reported on multivessel imaging in 50 patients with a prevalence rate of 56%.7 Gross inspection of coronaries of the American soldiers killed in the Korean and Vietnam wars demonstrated atherosclerosis in 77% and 45% of autopsies, respectively.12 In the Bogalusa Heart Study, the prevalence in children <15 years old was 8%, reaching 69% in adults between 26 and 40 years old.17

With a conservative definition of disease and imaging in vivo, the prevalence rates in our study were similar, showing unequivocal evidence of atherosclerosis in 28% of subjects <30 years old and 17% of individuals <20 years old. It is possible that incidence of atherosclerosis in the young population is even higher because many potential donors were rejected during pretransplant screening on the basis of clinical or angiographic evidence of coronary artery disease. It is important to recognize that coronary atherosclerosis described in these studies represent early phases of a continuous process. Some of those with atherosclerosis later develop clinical coronary artery disease, frequently as a result of a complication, such as plaque rupture.

In this study, the risk factor information was incomplete. Thus, the impact of the risk factors other than age on the development of atherosclerosis could not be adequately assessed. In the PDAY and Bogalusa studies, however, the strong correlation between the conventional risk factors and coronary atherosclerosis was documented.29–31 It remains unproven whether early intervention to curtail atherosclerosis in this young population can limit the development of symptomatic disease. The compelling in vivo data from this study, however, along with previously published necropsy data, emphasize the need to focus societal strategies to limit death and disability from coronary heart disease on the young population.

References


High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults: Evidence From Intravascular Ultrasound

E. Murat Tuzcu, Samir R. Kapadia, Eralp Tutar, Khaled M. Ziada, Robert E. Hobbs, Patrick M. McCarthy, James B. Young and Steven E. Nissen

Circulation. 2001;103:2705-2710
doi: 10.1161/01.CIR.103.22.2705

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/22/2705