Positive Remodeling of the Coronary Arteries Detected by Magnetic Resonance Imaging in an Asymptomatic Population

MESA (Multi-Ethnic Study of Atherosclerosis)

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Objectives

The purpose of this study was to assess coronary arterial remodeling as a marker of subclinical atherosclerosis using coronary wall magnetic resonance imaging (MRI) in an asymptomatic population-based cohort.

Background

In early atherosclerosis, compensatory enlargement of both the outer wall of the vessel as well as the lumen, termed compensatory enlargement or positive remodeling, occurs before luminal narrowing.

Methods

One hundred seventy-nine participants in the MESA (Multi-Ethnic Study of Atherosclerosis) trial were evaluated using black-blood coronary wall MRI. Coronary cross-sectional area (vessel size), lumen area, and mean wall thickness of the proximal coronary arteries were measured.

Results

Men had a greater vessel size, lumen area, and mean wall thickness than women (38.3 ± 11.3 mm² vs. 32.6 ± 9.4 mm², 6.7 ± 3.2 mm² vs. 5.3 ± 2.4 mm², and 2.0 ± 0.3 mm vs. 1.9 ± 0.3 mm, respectively, p < 0.05). No significant coronary artery narrowing was present by magnetic resonance angiography. Overall, coronary vessel size increased 25.9 mm² per millimeter increase in coronary wall thickness, whereas lumen area increased only slightly at 3.1 mm² for every millimeter increase in wall thickness (difference in slopes, p < 0.0001). Adjusting for age and sex, participants with an Agatston score >0 were more likely to have wall thickness >2.0 mm (odds ratio: 2.0, 95% confidence interval: 1.01 to 3.84).

Conclusions

Coronary wall MRI detected positive arterial remodeling in asymptomatic men and women with subclinical atherosclerosis. (J Am Coll Cardiol 2009;53:1708–15) © 2009 by the American College of Cardiology Foundation

Coronary artery disease (CAD) is currently defined as clinically significant when luminal narrowing is present, typically at the 50% diameter reduction threshold. However, in early atherosclerosis the first arterial changes consist of compensatory enlargement of both the outer wall of the vessel as well as the lumen, termed compensatory enlargement or positive remodeling (1–3). Evidence from histopathological and clinical studies suggests that positive remodeling is associated with plaque vulnerability and plaque rupture (4–7). Prior studies have indicated that the process of positive remodeling can be prevented (8) and modulated (9) by statin therapy.

Whereas positive remodeling has been shown in patients with symptomatic CAD, it has not been shown in asymptomatic individuals and its relationship to other measures of subclinical atherosclerosis has not been established. This knowledge gap stems from the absence of noninvasive methods that allow for quantification of coronary vessel wall size in a large asymptomatic population. The most commonly used imaging technique to identify positive remodeling has been...
intravascular ultrasound. Intravascular ultrasound detects positive remodeling and can characterize plaque composition (2–7). The technique, however, is not suitable for a screening method because of its invasive nature. Multidetector computed tomography (MDCT) has been used to assess positive remodeling in patients with symptomatic CAD (10). Potential disadvantages of MDCT include ionizing radiation and injection of iodinated contrast.

Black-blood coronary wall magnetic resonance imaging (MRI) can detect increased wall thickness in patients with X-ray angiography–documented CAD with good reproducibility (11–14). Although coronary wall MRI is complex and sophisticated, the technology can be applied to an asymptomatic population because it is noninvasive and radiation-free. The purpose of this study was to detect and quantify subclinical atherosclerosis in a large asymptomatic population using coronary magnetic resonance angiography (MRA) and coronary arterial wall MRI.

Methods

Study participants. Study subjects were recruited from participants in the Baltimore and Chicago field centers of the MESA (Multi-Ethnic Study of Atherosclerosis) trial. The study design of the MESA trial has previously been described in detail (15). In brief, participants of 4 ethnic origins (Caucasian, African American, Hispanic, and Chinese) ages 45 to 84 years were enrolled from 6 U.S. field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). Individuals with known clinical cardiovascular disease at baseline were excluded.

One hundred seventy-nine participants from examination 4 of the MESA trial (October 2005 to February 2008) were enrolled in this prospective cohort study (Table 1). The mean age was 61 ± 9 years; 90 were men and 89 women. Sixty-four percent were Caucasian, and 36% were African American. We excluded participants with a heart rate above 85 beats/min (because of technical limitations of the MRI technique), claustrophobia, contraindications to MRI, and without sinus cardiac rhythm. Information on demographics, smoking, and medical history were collected, and the measurements of covariates, including plasma lipids, fasting glucose, resting blood pressure, Framingham risk score, and common carotid intima-media thickness (IMT) were obtained according to the MESA study design and methods (15). Left ventricular (LV) mass was determined by cardiac MRI as described previously (16). The study was approved by the respective institutional review boards. All participants provided written informed consent.

Coronary MRI. All participants were imaged on a 1.5-T whole-body magnetic resonance scanner (Avanto, Siemens, Erlangen, Germany) with a gradient strength of 45 mT/m, slew rate of 200 T/m/s, and 12-channel receive coils (6 anterior and 6 posterior). The period of coronary diastasis was determined for each participant based on a 4-chamber cine steady-state free precession sequence. The MRAs were acquired during free breathing using an axial 3-dimensional (3D) whole-heart, navigator and electrocardiogram-gated, fat-suppressed, T2-prepared steady-state free precession sequence. Sequence parameters were: TR/TE 3.8/1.7 ms, bandwidth 975 Hz/pixel, flip angle 90°, field of view 320 × 320 mm², matrix 288 × 288 interpolated to 512 × 512, slice thickness 3.0 mm interpolated to 1.5 mm, navigator acceptance window ±2 mm.

The 3D multiplanar reformations were performed on MRA images to localize the left main (LM), the proximal left anterior descending (LAD), and the right coronary artery (RCA). Cross-sectional coronary wall MRIs were acquired at 5-mm intervals from the origins of the LM (1 image), the proximal portions of the LAD and RCA (3 images for each artery at 5-mm intervals) as previously described (17). Coronary wall MRIs were acquired with a double inversion recovery, motion adapted navigator gated, asymmetric adiabatic spectral inversion pulse for fat suppression, T2 turbo spin-echo sequence with the parameters: TR 2 R–R intervals, TE 33 ms, echo-spacing 6.6 ms, bandwidth 305 Hz/pixel, matrix 512 × 512, field of view 420 × 420 mm², slice thickness 5 mm, navigator acceptance window ±2 mm. The examination time was limited to 60 min or less to complete the protocol. MRI analysis. For coronary MRA analysis, the images were transferred to a 3D image analysis workstation (Leonardo, Siemens). Image analysis of 3D multiplanar reformations and maximum intensity projections for LM, the proximal portions of LAD, and RCA were performed by 2 experienced observers to detect any significant luminal narrowing (>50% diameter reduction). Black-blood images were graded on a 3-point scale: 1 = nonvisualization; 2 = adequate; and 3 = good. Coronary wall images with a score of 2 or 3 were analyzed using VesselMASS software (Division of Image Processing, Radiology Department, Leiden University Medical Center, Leiden, the Netherlands (18)) by an observer blinded to coronary MRA results and other clinical information. The images were zoomed to 1,000%. The outer (adventitial) and inner (luminal) boundaries of the coronary wall were traced manually using a region-of-interest tool. The outer contour area (cross-sectional vessel size), lumen area, and mean vessel wall...
Coronary artery calcium (CAC) measurement. Computed tomography (CT) scanning of the chest was performed with a prospectively electrocardiogram-triggered scan acquisition at 50% of each RR interval with an MDCT system (Volume Zoom, Siemens) that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential axial scan mode. Each participant was scanned twice consecutively. Scans were read centrally at the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center to identify and quantify coronary calcification (19). CAC measurements were adjusted with a standard calcium phantom scanned simultaneously with each participant. The mean Agatston score was used in all analyses.

Statistical analysis. All of the statistical analyses were performed with the use of statistical software SAS version 9.2 (Statistical Analysis System, SAS Institute Inc., Cary, North Carolina). Continuous variables are presented as means with standard deviations. When multiple measurements of a single coronary artery were available, they were averaged for that vessel to constitute a single data point. Both procedures UNIVARIATE and CAPABILITY in SAS were used to assess normality of the variables of interest. An unpaired t test was used to compare with group mean values after assessing for normality of the distributions. Because the CAC score was not normally distributed, log-transformed CAC was used in the comparisons. A chi-square test was used to compare categorical variables. Linear regression analysis was used to investigate the relationship between coronary artery wall thickness and: 1) outer contour area; and 2) lumen area before and after adjustment for measures of body and heart size (body mass index, LV mass, respectively). Logistic regression analysis was used to evaluate the relationship between dichotomized CAC and coronary arterial wall thickness. To examine whether 2 correlation coefficients were equal, a method proposed by Cohen and Cohen (20) was used and the SAS procedure covariance analysis of linear structural equations (CALIS) was used to perform the analysis.

Results

Participant characteristics. The characteristics of the study population are summarized in Table 1. The number of participants with dyslipidemia, smoking history, or non-0 coronary Agatston calcium score in men was greater than those in women (p < 0.05). Agatston calcium score and common carotid IMT were greater in men than in women (p < 0.05). Framingham risk score was greater in women than in men (p < 0.05). All participants meeting the enrollment criteria completed coronary artery MRA and coronary wall MRI. The image quality of all MRAs was adequate for analysis at the sites at which coronary artery...
Wall images were obtained. No significant stenoses (≥50% luminal diameter reduction) in the LM and the proximal portions of RCA and LAD were identified.

**Coronary arterial wall remodeling.** A total of 365 coronary wall MRIs (LM 108, LAD 121, and RCA 136) with grade 2 and 3 of image quality scores in 179 participants were evaluated. The imaging protocol was not completed for 52 arterial locations primarily because of patient tolerance or examination time exceeding 60 min. The coronary artery wall could not be visualized at 129 locations. The overall image quality scores of 365 coronary wall images were 2.6 ± 0.24, 2.6 ± 0.24, and 2.7 ± 0.21 for the LM, LAD, and RCA, respectively. There was no significant difference in image quality score among the coronary artery segments (p > 0.05). Coronary arterial wall MRI measurements are summarized in Table 2. Coronary vessel size, expressed as either outer contour area or lumen area, had a normal distribution. Men had a greater mean outer contour area and lumen area than women (38.8 ± 11.3 mm² and 6.7 ± 3.2 mm² vs. 32.6 ± 9.4 mm² and 5.3 ± 2.4 mm², respectively, p < 0.05). Mean wall thickness in men was greater than that in women (2.0 ± 0.3 mm vs. 1.9 ± 0.3 mm, respectively, p < 0.05). The LM outer contour area and lumen area were greater than that of the LAD or RCA (p < 0.0001). There was no significant difference in coronary artery wall thickness between LM and LAD or RCA.

As coronary artery wall thickness increased, the overall vessel size (outer contour area) increased at a greater rate than the change in the lumen area. Specifically, the outer contour area increased by 25.9 mm² for every millimeter increase in mean wall thickness (p < 0.0001). Lumen area also increased, but at a smaller rate of 3.1 mm² for every millimeter increase in mean wall thickness (p < 0.0001). This indicated that the coronary vessel size enlarged to compensate for atherosclerotic change, that is, positive remodeling (examples in Figs. 1 and 2).

For men, the outer contour area increased 26.2 mm² for every millimeter increase in wall thickness, whereas the lumen area increased 3.2 mm² per millimeter increase in wall thickness (difference between slopes, p < 0.0001) (Fig. 3A). For women, the relationship was similar: outer contour area increased 23.9 mm² per millimeter increase in wall thickness, whereas lumen area increased 2.3 mm² per millimeter increase in wall thickness (difference between slopes, p < 0.0001) (Fig. 3B).

To consider the possibility that increased vessel size and wall thickness could be explained by body size alone, the regression analyses were repeated after adjustment for body mass index or LV mass. After adjustment, the relationships of mean wall thickness to outer contour area and lumen area for both men and women remained statistically significant. Adjusting for LV size (mass), the outer contour area increased 0.141 mm²/g and the lumen area index increased 0.018 mm²/g per millimeter increase in wall thickness in men (p < 0.0001). When the LM, LAD, and RCA were examined individually, the positive correlations between outer contour area and vessel wall thickness remained significant (p < 0.0001, all territories).

**Coronary calcification and positive remodeling.** Eighty-two participants (82 of 179, 46%) had coronary calcification. The mean calcium scores in men and women were 163 and 50 Agatston units, respectively, indicating mild atherosclerosis. The distribution of CAC (or log CAC +1) versus wall thickness was nonlinear because of wide variation in wall thickness for participants with a CAC score of 0 (i.e., noncalcified plaque). To test the hypothesis that CAC was associated with increased wall thickness, logistic regression was used to relate Agatston score to median wall thickness of the study population (1.96 mm). Arterial wall thickness greater than the median was significantly associated with positive CAC score (odds ratio: 2.1, 95% confidence interval: 1.1 to 3.8) in univariate logistic regression analysis. There was little change
after adjustment for age and sex (odds ratio: 2.0, 95% confidence interval: 1.01 to 3.8).

**Discussion**

This is the first study to noninvasively show positive coronary wall remodeling in asymptomatic individuals with no history of CAD as well as the relationship between coronary calcification and arterial wall thickness by black-blood coronary MRI. Positive remodeling was present in the coronary arteries of both men and women. Mean coronary wall thickness was assessed by MRI as a measure of atherosclerosis, and the lumen area on average showed a
slight increase as wall thickness increased (Figs. 3A and 3B). However, the predominant change in the vessel size was a more substantial increase in the outer contour area of the vessel wall (Figs. 3A and 3B). These relationships persisted after adjusting for body size or heart size. The combination of these findings is consistent with positive arterial remodeling in early atherosclerosis (1–3). Glagov et al. (1) observed that human coronary artery cross-sectional area increased with increasing plaque area to maintain the lumen area until plaque occupied 40% of the potential lumen area. For vessels with <20% stenosis, cross-sectional vessel area enlarged at a faster rate than plaque area increased, consequently lumen area also increased a small amount (Fig. 4). In the present study, the outer contour area of the vessel wall increased with increasing mean wall thickness and the lumen area also increased, but at a much slower rate than the outer contour area. This indicated overcompensation, consistent with the previously mentioned histopathological studies.

Arterial calcium by CT is an established marker of coronary atherosclerosis. Prior studies have shown that CAC is closely correlated with plaque burden (21,22). Although CT CAC measures only a fraction of the total plaque burden, we may expect to see an overall relationship with arterial wall thickness defined by MRI. In the present study, CAC score using the Agatston score was positively associated with increased arterial wall thickness before and after adjustment for age and sex.

The use of MRI presents several advantages as well as limitations for identification of early coronary atherosclerosis. The method is noninvasive without ionizing radiation, and a contrast agent is not used. The arterial wall signal is readily identified because of its relatively high signal intensity compared with the low signal of adjacent periadventitial fat and lumen. This high level of conspicuity for the arterial wall is offset by several disadvantages. Each image of the arterial wall takes 2 to 3 min to acquire, and we excluded patients with elevated heart rates caused by short periods of coronary diastasis. Low image quality is present when respiratory patterns are irregular, because imaging is simultaneously gated to both the electrocardiogram and the motion of the diaphragm. Also, our protocol was challenging to implement: 2 MESA sites in Baltimore and Chicago with multiple technologists were used for a sophisticated protocol that required near-real-time reformation of the coronary angiogram and precise placement of perpendicular image slices with avoidance of coronary branches. The spatial resolution of MRI is much worse than intravascular ultrasound, although contrast resolution is generally better. Ultrasound methods have defined a remodeling index based on identification of the external elastic membrane, but this structural detail is not present on MRI. Factors such as partial volume effects and insufficient blood flow suppression currently limit this method to determine a threshold for normal coronary artery wall thickness. Current MRI methods have not resolved plaque components of the coronary artery in vivo. Despite these issues, evidence of positive coronary arterial remodeling was detected in both men and women without symptomatic CAD and no significant (>50%) coronary luminal narrowing as assessed by whole-heart MRA.
A previous study by Fayad et al. (12) used 2-dimensional black-blood MRI to evaluate coronary arteries in 8 normal participants and 5 patients with ≥40% stenosis of coronary arteries as assessed by X-ray angiography. The results showed that the average maximum coronary wall thickness in patients was significantly greater than that in normal participants (4.38 ± 0.71 mm vs. 0.75 ± 0.17 mm, p < 0.0001). In another study, 2-dimensional black-blood coronary wall MRI showed that both mean vessel wall thickness and mean wall area were greater in CAD patients than in healthy participants (1.5 ± 0.2 mm vs. 1.0 ± 0.2 mm and 21.2 ± 3.1 mm² vs. 13.7 ± 4.2 mm², p < 0.02) (11) as well as in patients with diabetic nephropathy (23).

Worthley et al. (24) used serial MRI at baseline and 6 months after aortic balloon denudation in a Watanabe heritable hyperlipidemic rabbits model to show positive arterial remodeling. Their results showed that the vessel wall area increased significantly after treatment. The outer arterial wall area showed much larger changes compared with proportionately smaller increases in lumen area. These MRI results were confirmed by histopathology. Kim et al. (14) used 3D black-blood coronary wall MRI to detect positive arterial remodeling in the RCA of 6 patients in areas of nonsignificant CAD (10% to 50% diameter reduction). Both mean coronary wall thickness and wall area were significantly increased in the patients compared with 6 healthy participants, whereas the lumen diameter and lumen area were similar, indicating positive arterial remodeling.

Positive arterial remodeling may be related to accumulation of plaque in the arterial wall, with overcompensation of nondiseased areas caused by endothelium-dependent vaso-dilatation in response to increase of shear stress (25,26). Based on this mechanism, eccentric plaque should contribute more to the positive arterial remodeling than diffuse atherosclerosis. Early coronary artery plaques are usually eccentric (27), therefore positive remodeling mostly occurs in the early stage of atherosclerosis.

Clinical significance. These results suggest progress in using noninvasive imaging for the detection of early atherosclerosis. Currently most noninvasive imaging studies using CT or MRA are focused on detection of coronary artery narrowing because 50% coronary narrowing is the current threshold for angiographic treatment. If the reliability and spatial resolution of MRI can be improved, early and potentially more treatable atherosclerotic disease could be evaluated and monitored noninvasively.

Conclusions

Positive remodeling of the coronary artery wall was detected in asymptomatic men and women using MRI. With further development, MRI has potential as a noninvasive method for assessing plaque burden and coronary artery size.

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REFERENCES


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