Potential Quantitative Magnetic Resonance Imaging Biomarkers of Coronary Remodeling in Older Hypertensive Patients

Kai Lin, Donald M. Lloyd-Jones, Ying Liu, Xiaoming Bi, Debiao Li, James C. Carr

Objective—To detect differences in potential magnetic resonance imaging biomarkers of coronary remodeling between older hypertensive patients and healthy controls.

Methods and Results—Two-dimensional black-blood coronary wall magnetic resonance imaging and 3-dimensional whole-heart coronary magnetic resonance angiography were performed on 130 participants (65–84 years), including 65 hypertensive patients and 65 healthy controls. Coronary segments derived from hypertensive participants had a higher mean coronary wall thickness, a smaller vessel area, a smaller coronary wall area, a smaller lumen area, a lower coronary distensibility index, and a higher percent of the coronary wall occupying the vessel area (PWOV) than those from healthy controls. When the average PWOV was set as an ad hoc cutoff point, coronary segments with a high PWOV had a significantly higher mean wall thickness, a higher maximum wall thickness, a smaller vessel area, a smaller lumen area, a higher coronary distensibility index, and a lower coronary plaque index compared with coronary segments with a low PWOV.

Conclusion—Magnetic resonance techniques are able to noninvasively detect significant differences in potential imaging biomarkers of coronary remodeling between older hypertensive patients and healthy controls. The PWOV is a promising remodeling feature for quantitatively evaluating the progression of coronary atherosclerosis. (Arterioscler Thromb Vasc Biol. 2012;32:00-00.)

Key Words: coronary remodeling ■ hypertension ■ imaging biomarker ■ magnetic resonance imaging

Vascular remodeling is considered to be an active modification of the vessel wall in response to changes in its milieu.1-3 Such a long-term alteration of the vascular structure has been linked to the development of atherosclerotic cardiovascular diseases.4 Various traditional cardiovascular risk factors, including hypertension, are able to remarkably accelerate vascular remodeling.3,4 In contrast, intensive treatments may retard or reverse this progression.3 Therefore, features of vascular remodeling are expected to serve as biomarkers for quantitatively evaluating the progression of cardiovascular diseases.6

The coronary artery is 1 of the most important components of the cardiovascular system, and its remodeling has been recognized as a strong predictor of clinical events.9 Although characterizations of coronary plaques have been described in patients with coronary artery disease,10,11 the morphological and biomechanical changes of the remodeled coronary wall have not been comprehensively investigated in apparently healthy individuals without documented or suspected cardiovascular disease. This knowledge gap exists mainly because of the limitations of clinical methodologies. X-ray exposure and invasive examinations are major drawbacks of various clinical methods, including intravascular ultrasound (IVUS), multidetector computed tomography, and x-ray angiography.

In the past decade, magnetic resonance (MR) has emerged as a noninvasive method for directly observing the coronary wall.12 Many indices affiliated with coronary remodeling, including coronary vessel area, lumen area, coronary wall thickening,12-13 and coronary wall distension,16,17 are reported to be acquired with adequate accuracy and reproducibility. Therefore, MR techniques provide a unique opportunity to assess coronary remodeling from multiple aspects in asymptomatic subjects at high risk for cardiovascular diseases, the main targets of preventive medicine. The aim of the present study was to detect differences in potential imaging biomarkers of coronary remodeling between older hypertensive patients and healthy controls using a single MR scan.

Methods

Patient Study

The present study was compliant with the Health Insurance Portability and Accountability Act, and approved by the Institutional Review Board. One hundred thirty participants (mean age 72.9±5.1 years,
range 65–84 years) of the Chicago Healthy Aging Low Risk MRI Angiography Study were enrolled. Informed consent was obtained from all the participants. The inclusion criterion was asymptomatic aging without a documented history of cardiovascular disease. The exclusion criteria were contradictions for MR scanning, heart rate >70 bpm, diabetes mellitus, and renal dysfunction (defined as a glomerular filtration rate <60 mL/min per 1.73 m²). There were 65 participants with primary hypertension (73.4±5.5 years) and 65 healthy controls (72.3±4.6 years). Primary hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or blood pressure controlled with medication. For each participant, the peripheral (brachial) blood pressure was measured within 2 hours before or after the MR scans. The pulse pressure (mm Hg) was defined as systolic blood pressure–diastolic blood pressure. The information on the participants is shown in the Table.

**Imaging Protocol**

The MR scans were performed with a 1.5-T scanner (Espree, Siemens, Germany). A 3-plane fast localization sequence was run for anatomic orientation for the whole scan. A black-blood half-Fourier acquisition single-shot turbo spin echo sequence was run to identify cardiac cine images in the 4-chamber view of the heart. The imaging parameters were as follows: repetition time/echo time = 2.8/1.1 ms; flip angle = 85°; and voxel size = 2.1×2.1×10 mm³. We acquired 22 reconstructive cardiac phases using retrospective gating. Two slices were acquired within each breath hold at the end of expiration. A motion-adapted navigator-gated, ECG-triggered, fat-saturated, T2-prepared, segmented 3-dimensional steady-state free precession sequence was used for noncontrast whole-heart coronary MR angiography (MRA). The 3-dimensional k-space data were collected by using a linear order in both the phase encoding direction and the partition encoding direction. The in-plane resolution = 1.1×1.1 mm²; the slice thickness = 0.7 mm (interpolated from 1.4 mm); repetition time/echo time = 3.7/1.7 ms; the flip angle = 90°; the lines per heart beat = 25 to 33; the readout bandwidth = 870 Hz/pixel; the parallel acquisition factor=2; and the field of view = 320×320 mm². The imaging time was 6–8 minutes for 88 to 104 slices. The whole-heart coronary MRA was run twice with the same parameters, aside from the different acquisition windows. The acquisition window for the first MRA scan was set at mid-diastolic. For the second MRA scan, segmented imaging data were acquired in end-systole.

A multiplanar reformation was performed on the 3-dimensional MRA data (acquired in mid-diastole) to localize the left main artery (LM), the left anterior descending artery (LAD), and the right coronary artery (RCA) for black-blood coronary wall imaging. Perpendicular to the long axes of the vessels and beginning at 5 mm from the ostia, we acquired 3 cross-sectional slices from the RCA (with 5-mm intervals), 1 slice from the LM, and 3 slices from the LAD (with 5-mm intervals) using a navigator-gated, ECG-triggered, double inversion recovery–prepared 2-dimensional turbo spin echo sequence. A spectral selective adiabatic inversion recovery pulse was applied to suppress the fat signal to improve the contrast between the coronary wall and the surrounding tissue. The imaging parameters were as follows: repetition time = 600 to 800 ms; echo time = 33 ms; echo train length = 9 to 13; in-plane resolution = 0.9×0.9 mm²; and slice thickness = 4.0 mm. In all cases, the duration of data acquisition was individually optimized to not exceed the coronary rest period duration and to begin after the onset of the coronary rest period in mid-diastole.

**Image Processing and Measurements**

Images were transferred to an imaging workstation (Dell Studio XPS 435T, installed with Linux operating system, Ubuntu 11.0) for analysis. The image qualities of the black-blood coronary wall MR imaging (MRI) and the whole-heart coronary MRA were graded with a modified 3-point system based on the following criteria: (1) bad image, vessel (wall) not eligible for analysis; (2) good image, vessel (wall) eligible for analysis, vessel (wall) may have some image artifacts or signal loss; and (3) excellent image, vessel (wall) observed continuously with little signal loss and with a clear border between the vessel (wall) and surrounding structures. Coronary (wall) images with a score (grade) of 2 or 3 were enrolled for quantitative analysis. The coronary wall images were then zoomed 10-fold (1000%). The outer (adventitial) and inner (luminal) boundaries of the coronary wall were manually traced by reader 1 (Kai Lin, with 5 years of experience in cardiovascular imaging) using dedicated region of interest tools from VesselMass software (Leiden University, Leiden, the Netherlands). The cross-sectional vessel area (outer contour area), luminal area, wall area (vessel area–lumen area), and wall thickness (mean and maximum) were also measured. The percent of the coronary wall occupying the vessel area (PWOW), defined as (wall area/ vessel area)×100%, was calculated for each coronary wall segment. The coronary plaque index was defined as the ratio of maximal coronary wall thickness to minimal vessel wall thickness. Cross-sectional images of the coronary arteries were reconstructed using multiplanar reformation, based on the eligible raw data of coronary MRA acquired at the end-systolic and mid-diastolic cardiac cycles. For the 2 sets of data/images, transverse segments of the RCA, LM, and LAD (at the 7 imaging planes where the black-blood coronary wall images were acquired) were carefully identified, and matched for the same anatomy based on the ostia of the coronary branches. The coronary lumen images were zoomed 10-fold (1000%), and traced manually by reader 1. The lumen areas in both systole and diastole were calculated according to their contours. The coronary distensibility index (CDI, mm Hg⁻¹) was calculated as follows: (lumen area max – lumen area min)/[lumen area min × pulse pressure]×100.0. The coronary plaque index, and PWOW, were compared (t tests) between participants with and without hypertension. The coronary wall indices, including wall thickness (mean and maximum), CDI coronary plaque index, and PWOW, were compared (t tests) between participants with and without hypertension. The coronary wall indices, including wall thickness (mean and maximum), CDI coronary plaque index, and PWOW, were compared (t tests) between

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### Table. Information of Study Population

<table>
<thead>
<tr>
<th>Hypertensive Patients (n=65)</th>
<th>Normal Controls (n=65)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y±SD</td>
<td>73.4±5.5</td>
<td>72.3±4.6</td>
</tr>
<tr>
<td>Men, %</td>
<td>38 (58)</td>
<td>41 (63)</td>
</tr>
<tr>
<td>Heart rate, bpm±SD</td>
<td>61.3±7.1</td>
<td>60.1±7.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>140.0±17.3</td>
<td>121.2±11.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85.2±13.8</td>
<td>73.8±8.6</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>54.7±8.6</td>
<td>47.4±5.4</td>
</tr>
<tr>
<td>Diagnosed with hypertension</td>
<td>11.3±5.2</td>
<td>N/A</td>
</tr>
<tr>
<td>BP under control, %</td>
<td>59 (90.7)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

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**Repeatability and Reproducibility Tests**

Two readers (Kai Lin and Ying Liu; reader 2 had 8 years of experience in clinical radiology, and was blinded to the research design) independently reviewed, and measured the coronary indices using the same protocol in 10 randomly chosen hypertensive patients to test interobserver agreement. Reader 1 repeated the coronary measurements 1 month after the first analysis to test intraobserver variation. Coronary MRI was repeated on 10 participants with subject repositioning to test the reproducibility of the coronary indices measured by reader 1.

**Data Analysis and Statistical Methods**

The data were presented as mean±1 SD. On a per-patient basis, sex composition and age were compared (χ² tests and t tests) between participants with and without hypertension. The coronary wall indices, including wall thickness (mean and maximum), CDI coronary plaque index, and PWOW, were compared (t tests) between participants with and without hypertension.
coronary segments derived from the 2 patient groups. Correlations among coronary measurements were investigated (Pearson correlation coefficients). Coronary indices were compared (t tests) between the coronary segments using mean PWOW as a cutoff point. Bland-Altman plots were used to show the interobserver, intraobserver, and scan-rescan coronary measurement agreement based on coronary MRI/angiography. Statistical significance was set at a 2-tailed \( P < 0.05 \). All the statistical processing in the present study was performed with the SPSS software (version 13.0, SPSS Inc, Chicago, IL).

**Results**

The imaging data from 6 participants were excluded for analysis because of incomplete scanning due to uncontrollable body motion (n=3), irregular breath mode (n=1), hypertensive emergency (n=1), or scanner malfunction (n=1). In total, 124 MR scans were completed, and 525 coronary wall segments were eligible for quantitative analysis, including 259 segments (42 LM, 105 LAD, and 112 RCA) from 61 hypertensive participants and 266 segments (45 LM, 116 LAD, and 105 RCA) from 63 healthy controls. The acquisition windows in a single heart beat (time resolution) for the coronary MRA (the same in systole and diastole) and the coronary wall MRI were 85±2 ms and 91±8 ms, respectively. The image quality and scan efficiency were 2.39±0.42, 34±17% for coronary wall MRI and 2.55±0.56, 37±12% for coronary MRA.

No significant stenosis (>50%) was presented in our study. Coronary segments derived from hypertensive participants have a higher mean coronary wall thickness (1.43±0.26 mm versus 1.35±0.21 mm, \( P < 0.001 \)), a smaller vessel area (25.06±7.66 mm\(^2\) versus 29.62±10.15 mm\(^2\), \( P < 0.001 \)), a smaller coronary wall area (18.49±5.32 mm\(^2\) versus 20.15±5.91 mm\(^2\), \( P = 0.001 \)), a smaller lumen area (6.57±3.44 mm\(^2\) versus 9.48±5.39 mm\(^2\), \( P < 0.001 \)), a lower CDI (5.30±2.60 mm\(^2\) versus 7.49±3.33, \( P < 0.001 \)), and a higher PWOW (74.59±8.30% versus 69.38±8.99%, \( P < 0.001 \)) than those from healthy controls.

For all cross-sectional segments, the PWOW (71.95±9.03%) was correlated with the mean wall thickness (1.39±0.24 mm, \( r = 0.589, P < 0.001 \)), maximum wall thickness (1.76±0.33 mm, \( r = 0.553, P < 0.001 \)), vessel area (27.37±9.28 mm\(^2\), \( r = 0.436, P < 0.001 \)), lumen area (8.04±4.76 mm\(^2\), \( r = 0.786, P < 0.001 \)), and CDI (6.41±3.21 mm Hg\(^{-1}\), \( r = 0.452, P < 0.001 \)). The CDI was correlated with the mean coronary wall thickness (\( r = 0.609, P < 0.001 \)) and maximum wall thickness (\( r = 0.466, P < 0.001 \)). Figure 1 presents the relationships among mean wall thickness, CDI, and PWOW.

When the average PWOW was set as an ad hoc cutoff point, 248 coronary segments with a high PWOW (>71.95%) had a significantly higher mean wall thickness (1.50±0.22 mm versus 1.22±0.20 mm, \( P < 0.001 \)), a higher maximum wall thickness (1.90±0.31 mm versus 1.60±0.28 mm, \( P < 0.001 \)), a smaller vessel area (24.20±7.07 mm\(^2\) versus 30.92±10.15 mm\(^2\), \( P < 0.001 \)), a smaller lumen area (5.18±2.18 mm\(^2\) versus 11.25±4.84 mm\(^2\), \( P < 0.001 \)), a higher CDI (7.52±3.30 mm Hg\(^{-1}\) versus 5.41±2.78 mm Hg\(^{-1}\), \( P < 0.001 \)), and a lower coronary plaque index (1.70±0.39 versus 1.78±0.41, \( P = 0.035 \)).

**Figure 1.** Relationships among mean coronary wall thickness, coronary distensibility index (CDI), and percent of the coronary wall occupying the vessel area (PWOW). **A**, A moderate correlation was found between the PWOW and the mean coronary wall thickness (\( r = 0.589, P < 0.001 \)). **B**, A moderate correlation was found between the PWOW and the CDI (\( r = 0.452, P < 0.001 \)). **C**, A good correlation was found between the CDI and the mean coronary wall thickness (\( r = 0.609, P < 0.001 \)).
compared with 277 coronary segments with a low PWOV (<71.95%).

A set of images for multiple coronary segments with various remodeling patterns from a single hypertensive patient is shown in Figure 2.

For the 10 randomly chosen cases, good intraobserver (r=0.866 for CDI and r=0.911 for wall thickness, P<0.001) and interobserver agreement (r=0.812 for CDI and r=0.898 for wall thickness, P<0.001) were found in 43 coronary segments. The scan-rescan test showed low variation between coronary measurements in 38 coronary segments from the 10 randomly chosen cases (r=0.751 for CDI and r=0.816 for wall thickness, P<0.001, Figure I in the online-only Data Supplement).

Discussion

In the present study, we found that asymptomatic hypertensive elders have a thicker coronary wall, a smaller coronary vessel area, a smaller wall area, a smaller lumen area, a higher CDI, and a higher PWOV than healthy controls. There are close correlations among those measurements of coronary walls. Compared with existing publications, our study is a noninvasive exploration of coronary remodeling with both morphological and functional measurements using coronary MRI.

Generally, the manifestations of coronary remodeling are defined jointly by changes in the vessel size and the plaque burden. Positive remodeling (a normal lumen gauge with compensatory vessel enlargement) and negative remodeling (a reduced lumen area with vessel shrinkage) are main remodeling patterns in multiple stages of atherosclerosis. Both
pathology and IVUS have been accepted as clinical standards for defining coronary remodeling. According to the classic theory of coronary remodeling developed by Glagov et al.,

the coronary wall area enlarges, but the coronary lumen may remain nearly normal until 40% of the internal elastic lamina is occupied. After the point of inflexion (40%), the coronary artery lumens begin to narrow because the plaque burden continues to grow. In another histological investigation, Varnava et al defined percent vessel remodeling using the difference in the cross-sectional area at the plaque from the mean of the reference vessel area. Plaque sites, in which vessel remodeling was $\geq 0\%$, were considered to have positive remodeling, and those with remodeling $<0\%$ were considered to have negative remodeling. The authors found that positive remodeling was associated with the plaque with a larger lipid core and a higher macrophage count. Such plaques were considered to be vulnerable lesions.21

IVUS identifies remodeled vessel walls in vivo by comparing target segments with adjacent sites (references); a remodeling index (lesion vessel area/reference vessel area) $>1$ indicates positive remodeling (enlargement), and a remodeling index $<1$ indicates negative remodeling. Positive remodeling was associated with acute cardiovascular events, and negative remodeling was linked with diabetes mellitus, hypertension, stenosis, and ischemia.22–26 In a recently published clinical trial, the percent atheroma volume (PAV, defined as $\left( \Sigma \text{(external elastic membrane area−lumen area)}/\Sigma \text{(external elastic membrane area)} \right) \times 100$) was acquired with IVUS as the primary efficacy endpoint to evaluate the variations in the remodeling of the coronary wall under 2 statin regimens.6

In the present study, we noninvasively described remodeled coronary wall using MR techniques. For the first time, we introduced the PWOV, an MR-specific index combining changes in both the lumen and the wall area to describe remodeled coronary wall, using both Glagov method and the PAV as prototypes. We found a significant difference in the PWOV between subjects with and without hypertension, and there were obvious disparities in major morphological and biomechanical characteristics between coronary segments with distinct PWOVs. Our results suggest that the PWOV has the potential to serve as a quantitative imaging biomarker that is affiliated with pathophysiological properties of remodeled coronary arteries. Therefore, it is promising to match the PWOV with established pathological biomarkers of coronary remodeling to estimate the progression of cardiovascular diseases and individual responses to cardiovascular regimens in clinical studies.

Nevertheless, it is worth noting the differences in describing coronary lesions between MRI and existing clinical methods. The vessel wall measurements described by Glagov et al included only the intima. However, it is almost impossible to define the internal elastic lamina with current MR techniques. Hence, the cutoff point (40%) of the Glagov model could not be directly applied in MRI studies. In a study of the carotid artery, remodeling was observed with black-blood MRI in a population of 2204 subjects, and a knot of remodeling patterns was found when the vessel wall occupied 64% of the whole vessel area.27 Therefore, population studies are warranted to find out cutoff point of PWOV for discriminating coronary remodeling patterns. PAV is also an index reflecting the ratio of coronary wall to vessel size. However, PAV is a measurement for plaque volume whereas PWOV is for plaque area. Further studies are needed to investigate relations between PAV and PWOV in the assessment of atherosclerosis burdens.

Our study has several limitations. First, we did not use clinical examinations, such as IVUS or x-ray angiography, as references for the MRI angiography because it was difficult to justify using invasive methods on asymptomatic subjects without clinical indicators. Although cardiac motion blurring may affect the accuracy of depiction for vessel wall, various existing publications proved the accuracy of MR techniques (black-blood and bright-blood) in detecting coronary lesions.14,28–31 In addition, we routinely tested the reproducibility of coronary measurements to determine the reliability of our methods. Second, we were unable to discriminate certain subtle structures in the coronary plaques, such as the lipid core or calcification, due to limited spatial resolution. Therefore, the effect of those lesions on local coronary biomechanical properties could not be excluded. However, such a spatial resolution was sufficient for the quantitative evaluation of morphological changes, such as thickening of the coronary wall.13,15,16,19 Third, we only imaged the proximal portions (as far as 15 mm from the ostia) of the coronary branches at predefined locations because 2-dimensional black-blood coronary wall MRI is unable to cover the whole coronary tree. Although remodeling of the distal parts may be missed, proximal lesions on the coronary wall are generally recognized as a focus of clinical concern. Fourth, a portion of the coronary wall images (343 segments) was excluded from the quantitative analysis due to poor image quality. Using MR to observe the coronary wall is challenging. The image quality is jointly affected by various technical and physiological factors. Nevertheless, our success rate is still comparable with that of other published studies of coronary MRI.13

Conclusion

MR techniques are able to noninvasively detect significant differences in potential imaging biomarkers of coronary remodeling between older hypertensive patients and healthy controls. The PWOV is a promising remodeling feature for quantitatively evaluating the progression of coronary atherosclerosis.

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Disclosures

One coauthor, Dr Bi, is an employee of Siemens Healthcare, Chicago, IL. The data and information of the present study are under control by authors who are not Siemens employee. The other authors have no conflicts to report.

References


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Supplemental Materials

Figure I The repeatability and reproducibility of coronary measurements on MR images.

I-a, b For reader #1, good intra-observer agreement was found between CDI (r = 0.866, $P < 0.001$) and mean coronary wall thickness (r = 0.911, $P < 0.001$) measurements.

I-c, d Good agreement in CDI (r = 0.812, $P < 0.001$) and mean coronary wall thickness (r = 0.898, $P < 0.001$) measurements was found between reader #1 and #2.

I-e, f Low scan-rescan variations were found on CDI (r = 0.751, $P < 0.001$) and mean coronary wall thickness (r = 0.816, $P < 0.001$) measurements by reader #1 (r = 0.811, $P < 0.001$).
Figure I-a
Figure I-b

A scatter plot showing the relationship between average wall thickness (mm) and the difference of wall thickness (mm). The data points are distributed around the mean, with confidence intervals at ±1.96 SD.
Figure I-d
Figure I-e