Quantification and 3D Reconstruction of Atherosclerotic Plaque Components in Apolipoprotein E Knockout Mice Using Ex Vivo High-Resolution MRI

Martina A. McAteer, Jürgen E. Schneider, Kieran Clarke, Stefan Neubauer, Keith M. Channon, Robin P. Choudhury

Objective—To investigate the ability of high-resolution MRI to determine composition and microanatomy of atherosclerosis in mouse aortic root and brachiocephalic artery.

Methods and Results—Aortic root and brachiocephalic arteries of apolipoprotein E knockout (apoE−/−) mice fed Western diet for 10, 20, or 30 weeks were imaged ex vivo (11.7 T; 3D multiecho sequence; resolution 47×47×62.5 μm). Using semiautomated histogram-based methods, MRI accurately quantified lipid-rich/necrotic areas in the aortic root (r²=0.84; P<0.001) and brachiocephalic artery (r²=0.90; P<0.001) compared with histology. Similarly, cell-rich caps in aortic roots, quantified by MRI and histology, correlated closely (r²=0.74; P<0.001). Reconstruction of segmented brachiocephalic arteries in 3D provided unique insights into plaque microanatomy and enabled volumetric quantification of plaque and lipid-rich/necrotic core. Between 10 and 30 weeks, 3D measurement identified an 11.6-fold increase in plaque volume (versus 4.1-fold for 2D) and a 21.3-fold increase in plaque lipid-rich/necrotic core volume (versus 6.4-fold for 2D), indicating superior power of 3D quantification.

Conclusions—Ex-vivo high-resolution 3D MRI accurately quantified lipid-rich/necrotic core and cell-rich cap areas in atherosclerotic lesions in apoE−/− mice. Reconstruction and volumetric quantification of segmented brachiocephalic arteries demonstrated greater sensitivity in detecting changes in plaque size and lipid composition over time than 2D analysis. (Arterioscler Thromb Vasc Biol. 2004;24:2384-2390.)

Key Words: atherosclerosis ■ brachiocephalic artery ■ apoE−/− mice ■ MRI ■ lipid-rich/necrotic core

Genetically engineered mice have become the animal model of choice for study of the pathogenesis of atherosclerosis.1–3 For example, apolipoprotein E knockout (apoE−/−) mice spontaneously develop atherosclerotic lesions throughout the arterial tree.4 The standard method for quantification and characterization of mouse atherosclerosis involves serial sectioning and histopathology of the aortic root.5 However, lesions at this site do not typically show defined lipid cores with thin fibrous caps, which characterize the “vulnerable” plaque in human atherosclerosis.6,7 More recently, advanced lesions showing features consistent with plaque rupture and intraplaque hemorrhage have been identified in the brachiocephalic artery of apoE−/− mice.8–11 Although histopathology can provide valuable information on plaque composition, it is tissue destructive and confined to 2D analyses of a relatively small number of 5 to 10 μm thick histological sections, giving limited insight into overall plaque structure and spatial distribution of plaque components. The brachiocephalic artery is technically demanding to embed and to section because of its small size (≈500 μm external diameter). Furthermore, preparation and processing for histology introduces size distortion during tissue dehydration and has the potential to disrupt the integrity of the plaque itself.

Using multicontrast MRI (T1-weighted [T1,W], T2,W, proton density-weighted [PDW]) with submillimeter spatial resolution, plaque components have been distinguished without tissue destruction in carotid artery specimens ex vivo12–14 and in human carotid artery15 and aorta16 in vivo. Magnetic resonance (MR) has also been shown to discriminate atherosclerotic plaque components in larger animal models including rabbits,17–19 pigs,20 and nonhuman primates.21

In apoE−/− mice, MRI accurately quantifies atherosclerosis in the abdominal aorta,22 aortic arch,23 aortic root,24 and brachiocephalic artery25 in vivo. However, genetic and pharmacological interventions affect not only plaque size but also composition.26 Therefore, plaque quantification alone does not fully capitalize on the power of MRI as a phenotyping tool in atherosclerosis. Itskovitch et al24 first demonstrated the potential of ex vivo MRI for characterization of mouse aortic

Original received June 11, 2004; final version accepted August 26, 2004.
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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

DOI: 10.1161/01.ATV.0000146811.19029.fb
root plaque, but no study has systematically evaluated this with histological validation, nor have lesions been examined in the brachiocephalic artery, where recent studies suggest that characterization is more important.\textsuperscript{8,9}

Accordingly, we developed a high-resolution 3D MRI method for analysis of atherosclerotic plaques in apoE\textsuperscript{−/−} mice ex vivo. We tested the ability of 3D MRI to quantify lipid-rich/necrotic cores and cell-rich caps in aortic roots and brachiocephalic arteries and to determine changes in composition in plaques of varying complexity.

### Methods

#### Animals

Homozygous apoE\textsuperscript{−/−} mice and wild-type C57BL/6 mice were bred in a specific pathogen-free room, with constant temperature and humidity (Wellcome Trust Centre for Human Genetics, Oxford, UK). Mice were weaned at 3 weeks of age. ApoE\textsuperscript{−/−} mice (n = 5 to 7 per group) were transferred to a “Western diet” (21% milk fat, 0.15% cholesterol; 100244 Dyets Inc), whereas control wild-type C57BL/6 mice (n = 3 per group) were fed a standard chow diet ad libitum for 10, 20, or 30 weeks. These time points were anticipated to produce a range of lesion severity from foam cells (American Heart Association [AHA] type I) to complex lesions (AHA type IV/V).\textsuperscript{6,27} All experiments were performed in accordance with the Scientific Procedures Act (1986).

#### Ex Vivo Sample Preparation

After each feeding period, mice were deeply anesthetized by inhalation of isoflurane. Hearts and aortas were perfused in situ with PBS followed by 4\% paraformaldehyde in PBS via the left ventricle. Perivascular tissue was removed from the aortic arch and its branches. The aortic tree and heart, attached to the spinal column, was removed en bloc and embedded in a glass MR tube containing 2\% agarose to secure tissue preparation during imaging. Fomblin, a liquid hydrocarbon (Ausimont), was instilled via the left ventricle and the tube sealed with a second layer of agarose to secure tissue preparation during imaging.

#### Ex Vivo MRI

Ex vivo MRI was performed using an 11.7-T (500 MHz) vertical magnet (Bruker) and a 13-mm H\textsuperscript{1} birdcage radiofrequency coil (RAPID Biomedical). Four echoes were acquired using a 3D multiecho sequence (\(\Delta\text{-echo time } 7 \text{ ms} \); repetition time 200 ms; number of averaged experiments 4; total experimental time \(\approx 7 \text{ hours} \) performed overnight, unattended). A field of view of 12\times12\times8 mm and a matrix size of 256\times256\times128 led to a voxel size of 47\times47\times62.5 \text{ \mu m} \text{ before zero filling.} MR data were acquired and reconstructed to generate a stack of 2D tiff images (16 bit) using purpose-written software.

#### Histological Processing of the Aortic Root and Brachiocephalic Artery

After imaging, the heart was removed from each specimen and transected at the level of the atria. The brachiocephalic artery was also dissected from the aortic arch to the bifurcation into right carotid and subclavian arteries. Specimens were dehydrated through graded ethanol solutions and Neo-clear (VWR International), paraffin-embedded, and serially sectioned (5-\mu m thick). Sections of aortic root and brachiocephalic artery (spaced \(=80 \text{ \mu m} \) apart; 3 sections per mouse per site) were dehydrated and stained with a combined Elastic kit (Sigma) to stain elastic laminae and nuclei black, and Masson's Trichrome (VWR International) to stain collagen green, cells red, and erythrocytes orange.\textsuperscript{28} Lipid within plaques, which dissolved out during tissue processing, appeared as white voids in histological sections.\textsuperscript{28} Digital light microscopy (LM) images of histological sections were captured with a Cool Snap Pro color video camera (Media Cybernetics) mounted on a light microscope (Leica) using ImagePro Plus image analysis software (version 4.5.1; Media Cybernetics).

#### Two-Dimensional MRI Segmentation and Quantification

Two-dimensional MR images and corresponding histopathologic sections were matched using surrounding anatomic structures, such as the atria and right ventricular outflow tract for the aortic root, whereas for the brachiocephalic artery, the origin at the aortic arch and the right carotid/subclavian bifurcation were used as fiducial references. Plaque area was quantified by manual tracing with ImagePro Plus. Lipid-rich/necrotic core and cell-rich cap areas were segmented and quantified using a semiautomated, histogram-based threshold method.

#### Three-Dimensional Reconstruction and Volumetric Quantification of Brachiocephalic Artery Plaque

MR image stacks for the entire brachiocephalic artery and its segmented plaque and segmented lipid-rich/necrotic core “masks” were assigned to red, blue, and green color channels, respectively, and reconstructed in 3D using the 3D Constructor plug-in for ImagePro Plus. Isosurfaces for the color channels corresponding to plaque and lipid-rich/necrotic cores were added and the enclosed volumes quantified.

#### Statistical Analyses

Correlations of measurements by MRI and histopathology were tested by linear regression analysis using Prism software version 3.02 (GraphPad). Bland–Altman plots\textsuperscript{30} were constructed to determine the level of agreement between MRI and LM measurements. Intraobserver and interobserver coefficients of variation (CVs) for plaque lipid-rich/necrotic core and cell-rich cap areas were calculated by analyzing random MR images (n = 15). Differences in area and volume measurements for each parameter between 10, 20, and 30 weeks were determined using Student t test. Statistical significance was attributed to P values <0.05.

#### Results

### Histopathology of Aortic Root and Brachiocephalic Artery Plaques

Typical histopathologic sections and matched MR images of aortic root and brachiocephalic artery plaques in apoE\textsuperscript{−/−} mice fed Western diet for 10, 20, or 30 weeks are shown in supplemental Figure I (available online at http://atvb.ahajournals.org) and Figure 1, respectively. At 10 weeks, atherosclerotic lesions were identified in all aortic roots (n = 7) and 57\% of brachiocephalic arteries (ie, 4 of 7 mice). After 20 and 30 weeks, advanced lesions were found in all specimens. Within plaques, some areas appeared as white voids in histological sections, reflecting the loss of soluble lipid during tissue processing. In the aortic root, lesions were mainly fibrofatty, with a distinctive cell-rich cap at the luminal edge of the plaque. Brachiocephalic artery lesions had larger, more defined lipid-rich/necrotic cores and thin acellular caps. No intraplaque hemorrhage was observed. No lesions were found in control wild-type mice fed standard chow diet (images not shown).

#### Two-Dimensional Segmentation of Plaque Components and Correlation With Histopathology

MRI showed excellent correlation with histopathology for quantification of plaque area in the aortic root (\(r^2 = 0.90; P < 0.0001\)) and brachiocephalic artery (\(r^2 = 0.90; P < 0.0001\)). Areas of atherosclerotic plaque showed MR signal heteroge-
neity. Based on anatomic distribution, we tested the hypothesis that low signal (black and dark gray) areas within the plaque represented lipid-rich/necrotic cores, whereas high signal (light gray) areas reflected cell-rich cap regions. These areas were segmented using a semiautomated histogram-based approach. Figure 2 shows a typical signal intensity histogram derived from an MR image of a brachiocephalic artery from an apoE−/− mouse fed Western diet for 20 weeks. Three peaks were identified on the histogram, representing black, dark gray, and light gray regions in the MR image. Accordingly, within the arterial wall, the number of pixels comprising the first 2 peaks was quantified as lipid-rich/necrotic core, whereas pixels comprising the light gray peak were taken to be cell-rich areas. Using this approach, we found excellent correlation between MRI and histological measurements for lipid-rich/necrotic core areas in aortic root ($r^2=0.84; P<0.0001$) and in brachiocephalic artery plaques ($r^2=0.80; P<0.0001$). Quantification of cell-rich areas present in the caps of aortic root lesions by MRI also correlated well with histopathology measurements ($r^2=0.74; P<0.0001$). Cell-rich caps were not quantified in brachiocephalic arteries because they were not typically present in these lesions at the time points studied.

### Agreement and Reproducibility of MRI Data

Bland–Altman plots for testing agreement of MRI and histopathological measurements of plaque, lipid-rich/necrotic core, and cell-rich cap areas in the aortic root and brachiocephalic artery are shown in supplemental Figure II (available online at http://atvb.ahajournals.org) and Figure 3, respectively. Overall agreement between the 2 methods was excellent. For aortic root and brachiocephalic artery plaque areas, 89 (94%) and 73 (100%) fell within one (two) SD of the mean difference, respectively. Similar values were obtained for lipid-rich/necrotic core areas (82 [94%] and 81 [92%], respectively) and for aortic root cell-rich cap areas (83 [96%]).

For MRI, intraobserver CVs for aortic root and brachiocephalic artery plaque areas (8.2% and 7.0%, respectively) and lipid-rich/necrotic core areas (12.7% and 10.1%, respectively) were reproducible. Interobserver assessment also demonstrated similar reproducibility (plaque area 13.1%; lipid-rich/necrotic core area 10.0%). Cell-rich cap area measurements by MRI gave good intraobserver and interobserver agreement (10.4% and 17.2%, respectively). One value for cell-rich caps was excluded from the interobserver readings because the valve cusp, which also appeared as a bright...
between measurements by the 2 techniques was very good. Because of tissue shrinkage during dehydration, agreement was consistent bias toward smaller measurements by histopathology.

Western diet for 10, 20, or 30 weeks. Although there was a consistent bias toward smaller measurements by histopathology because of tissue shrinkage during dehydration, agreement between measurements by the 2 techniques was very good.

signal on the MR image, was misinterpreted by an observer as a cell-rich cap.

Three-Dimensional Reconstruction and Volumetric Quantification of Brachiocephalic Artery Plaque and Lipid-Rich/Necrotic Cores

To establish the distribution of lipid-rich/necrotic cores within the plaque and their variation with increasing plaque complexity, segmented images of the brachiocephalic artery were reconstructed in 3D. Figure 4 shows typical 3D-reconstructed and surface-rendered image stacks of segmented plaque and lipid-rich/necrotic cores in the brachiocephalic artery of an apoE−/− mouse fed a Western diet for 10, 20, or 30 weeks. To determine the sensitivity of 3D MRI in detecting changes in the plaque size and composition, plaque and lipid-rich/necrotic core volumes were quantified and compared with their respective 2D area measurements (Table). Three-dimensional volumetric measurements were more sensitive than 2D area quantification in detecting plaque progression over time (6.8-fold versus 2.9-fold between 10 and 20 weeks; 17-fold versus 1.4-fold between 20 and 30 weeks; 11.6-fold versus 4.1-fold between 10 and 30 weeks, respectively). Lipid-rich/necrotic core volume also increased significantly between 10 and 20 weeks but not thereafter. Volumetric 3D quantification of lipid-rich/necrotic cores again detected greater increases than 2D area measurements (12.0-fold versus 4.7-fold between 10 and 20 weeks and 21.3-fold versus 6.4-fold between 10 and 30 weeks, respectively). The proportion of plaque occupied by lipid-rich/necrotic cores significantly increased from 5% to 22% between 10 and 20 weeks (P<0.01) but did not increase further between 20 and 30 weeks.

Volumetric analysis identified differences in plaque distribution through the brachiocephalic artery with time. At 10 weeks, the majority of plaque and lipid-rich/necrotic core volumes were localized in the proximal half of the artery (88% and 91%, respectively). Plaque and lipid-rich/necrotic core volumes in all mice appeared to extend progressively in a continuous fashion along the right (but not the left) side of the artery, starting at the junction with the aortic arch and extending distally in continuity with the existing lesion rather than in random or isolated regions. At 20 and 30 weeks, 47% and 54% plaque volume and 52% and 52% lipid-rich/necrotic volume, respectively, were in the proximal half of the artery.

Discussion

This study demonstrates the ability of ex vivo high-resolution, 3D MRI to accurately characterize atherosclerosis in the aortic root and brachiocephalic artery of apoE−/− mice. Using much smaller voxels than described previously in this context, it was possible to reproducibly quantify lipid-rich and cell-rich areas of plaque in excellent agreement with measurements made by histopathology. Acquisition of very small, near-isotropic voxels also enabled volumetric data to be calculated with minimal distortion from partial volume effects. Accordingly, MRI identified marked changes in lesion size and composition between time points. Significantly, compared with 2D analysis, volumetric quantification by MRI identified an 11.6-fold versus 4.1-fold increase in plaque size and a 21.3-fold versus 6.4-fold increase in lipid-rich/necrotic core between 10 and 30 weeks, respectively, suggesting that 3D analysis would substantially enhance statistical power and reduce the numbers of mice required for progression/regression studies. In addition, 3D reconstruction of segmented images of brachiocephalic arteries has allowed more detailed interrogation of plaque structure and microanatomy than can be accomplished by 2D techniques.

Itskovich et al24 first demonstrated the potential of ex vivo MRI to characterize lipid and fibrous plaque components in murine atherosclerotic lesions in the aortic root. With in-plane resolution of 50 μm/pixel (slice thickness 300 μm), areas of heterogeneity in T2W, T1W, and PDW images of aortic root were proposed to represent lipid cores and fibrous caps in corresponding histopathologic sections. To build on this previous work, significant improvements in MR spatial resolution have been achieved using a 3D rather than a 2D acquisition matrix (256×256×128) that led to near-isotropic voxel size of 47×47×62.5 μm³ (23.5×23.5×31.8 μm³ after interpolation). The significantly longer imaging time (7 hours) was efficiently accommodated by running unsupervised overnight scans.
Images generated in this way showed excellent within the same experiment provided optimal tissue volumetric quantification and are shown isolated from the back-ground image.

In earlier systematic evaluation, we found that summation of T2W images combining multiple echo images obtained within the same experiment provided optimal tissue contrast. Images generated in this way showed excellent agreement with histopathology. Bland–Altman tests of agreement between MRI and histopathology data showed systematically higher measurements of plaque areas and its components by MRI. This represents a distortion in tissue prepared for histology. For example, increasing cell cap area was associated with a progressive increase in the discrepancy between the cap area measured by MRI and by LM. During tissue processing for histology, water-rich tissues shrink because of dehydration. In contrast, MRI measurements, made on nonprocessed tissue, more closely reflected tissue architecture in vivo. An incremental pattern resulted because the effects of dehydration became increasingly prominent with increasing cellular (water-rich) content. Similar effects have been noted previously. Consistent with this, a similar error increment was not observed in the measurement of lipid-rich/necrotic area using the 2 techniques.

Histological processing may introduce further artifacts. The brachiocephalic artery is small, fragile, and difficult to manipulate. In some instances, vessel disruption that was apparent during histology was not seen on the corresponding previous MR images (Figure 1). This may indicate damage to this vulnerable vessel segment during preparation and sectioning and further cautions on histological analysis of plaque Micro-anatomy.

Three-dimensional reconstruction of segmented brachiocephalic artery images enabled us to examine, for the first time, changes in plaque distribution throughout the entire artery, with time. Previously, plaque progression in the brachiocephalic artery has been investigated in 2D histological sections, which provide valuable information on plaque morphology but cannot fully interrogate plaque distribution in relation to the entire artery. Our observation from 3D-reconstructed images that only the right side of the brachiocephalic artery was affected during plaque progression may have implications for mechanisms of atherogenesis, including flow dynamics, and may focus attention on these regions in future studies.

Clearly, in vivo plaque characterization in mice is a desirable goal but has not yet been accomplished. Previous in vivo studies have shown high resolution in plane (109 × 109 μm), but slice thickness (500 μm) led to disabling partial volume effects. Furthermore, anisotropic voxels preclude the type of 3D reconstruction and analyses performed in the current study. Hockings et al used a 3D

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**Figure 4. Images of a 3D-reconstructed brachiocephalic artery of an apoE−/− mouse fed Western diet for 20 weeks. A, Reconstruction in a plane transverse to the axis of the artery. The vessel wall appears green, whereas segmented plaque is yellow, and lipid-rich/necrotic core appears red. B, A second reconstructed plane orthogonal to the first has been introduced to highlight the artery structure, which demonstrates the lesion extending in a cranial direction along only 1 side of the artery. Isolated lipid-rich/necrotic pools are apparent within the plaque. C, Identical slices to those shown in the previous panel with additional surface rendering of plaque volume. D, Plaque and lipid-rich/necrotic cores have been 3D surface rendered for volumetric quantification and are shown isolated from the back-ground image.**

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**Table 1. Volume and Area Measurements in the Brachiocephalic Artery of apoE−/− Mice**

<table>
<thead>
<tr>
<th></th>
<th>10 wks (n=7)</th>
<th>20 wks (n=5)</th>
<th>30 wks (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3D MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA length (mm)</td>
<td>0.661±0.072</td>
<td>1.228±0.176†</td>
<td>1.075±0.179†</td>
</tr>
<tr>
<td>Plaque volume (mm³)</td>
<td>0.045±0.058</td>
<td>0.304±0.055‡</td>
<td>0.516±0.120‡,‡</td>
</tr>
<tr>
<td>LRC volume (mm³)</td>
<td>0.005±0.008</td>
<td>0.065±0.023†</td>
<td>0.116±0.081*</td>
</tr>
<tr>
<td>% LRC in plaque</td>
<td>5±7</td>
<td>22±7†</td>
<td>22±11*</td>
</tr>
<tr>
<td><strong>2D MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque area (mm²)</td>
<td>0.070±0.073</td>
<td>0.193±0.025†</td>
<td>0.279±0.051‡,‡</td>
</tr>
<tr>
<td>LRC area (mm²)</td>
<td>0.008±0.012</td>
<td>0.039±0.012†</td>
<td>0.053±0.038*</td>
</tr>
<tr>
<td>% LRC of plaque</td>
<td>4±6</td>
<td>20±3†</td>
<td>19±9*</td>
</tr>
</tbody>
</table>

BA indicates brachiocephalic artery; LRC, lipid-rich/necrotic core. Data are mean±SD.

*P<0.05; †P<0.01; and ‡P<0.001 compared with 10-week mice.

**P<0.05; †P<0.01; and ‡P<0.001 compared with 20-week mice.**
technique (7-T) for in vivo imaging in mice but with significantly larger voxels (187 × 187 × 140 μm) than reported here. Prolonged imaging protocols of the sort described here are not feasible in vivo; therefore, we anticipate that further advances in microscopic plaque characterization will require new contrast agents. Gadolinium-conjugated nanoparticles that are targeted to specific molecules have been used to image thrombus and integrins in larger animals. Such imaging in mice is keenly anticipated and will greatly enhance in vivo studies by introducing the possibility for functional and serial imaging. However, molecular imaging is unlikely to match the detailed, very high resolution information on plaque composition achieved with ex vivo MRI.

Lesions in the brachiocephalic artery of mice often possess a large lipid-rich/necrotic core and thin fibrous cap, and these types of lesion are particularly well suited to analyses of plaque composition, which assess plaque responses to pharmacological and genetic interventions in mice. Ex vivo MRI provides a means to accurately and efficiently quantify plaque and its components in small numbers of mice without need for histology. With minor methodological modification to the embedding process, it would be possible to image multiple arteries simultaneously, analogous to the method described for imaging mouse fetuses, thus presenting the possibility for high-throughput phenotyping. Importantly, the technique is tissue nondestructive, and imaged tissue can be recovered for subsequent histological or immunohistochemical analysis if required.

Conclusions
This study demonstrates that ex vivo, very high-resolution 3D MRI facilitates reliable visualization and quantification of lipid-rich/necrotic cores and cellular caps in atherosclerotic lesions in apoE−/− mice. In addition, 3D reconstruction and volumetric quantification of plaque and lipid-rich/necrotic cores in brachiocephalic arteries enabled differences in the extent and composition of atherosclerosis to be distinguished at different time points, with greater sensitivity than was possible using 2D slices and without tissue distortion that can be caused during processing for histological examination. As such, 3D high-resolution MRI is a potentially useful additional tool for the study of mouse atherosclerosis.

Acknowledgments
This work was supported by the British Heart Foundation. The authors gratefully acknowledge the contributions of Phil Townsend, Carol Williams, and Ian Oliver.

References


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Arterioscler Thromb Vasc Biol. 2004;24:2384-2390; originally published online September 30, 2004;
doi: 10.1161/01.ATV.0000146811.19029.fb
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/24/12/2384

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Figure I

Aortic root

10 wks

20 wks

30 wks

1 mm
Figure II

(A) Mean MR and LM plaque area (mm²)

(B) Mean MR and LM lipid-rich/necrotic area (mm²)

(C) Mean MR and LM cellular area (mm²)