Characterization of Human Atherosclerotic Plaques by Intravascular Magnetic Resonance Imaging

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Background—Development and validation of novel imaging modalities to assess the composition of human atherosclerotic plaques will improve the understanding of atheroma evolution and could facilitate evaluation of therapeutic strategies for plaque modification. Surface MRI can characterize tissue content of carotid but not deeper arteries. This study evaluated the usefulness of intravascular MRI (IVMRI) to discern the composition of human iliac arteries in vivo.

Methods and Results—Initial studies validated IVMRI against histopathology of human atherosclerotic arteries ex vivo. A 0.030-inch-diameter IVMRI detector coil was advanced into isolated human aortoiliac arteries and coupled to a 1.5-T scanner. Information from combined T1-, moderate T2-, and proton-density–weighted images differentiated lipid, fibrous, and calcified components with favorable sensitivity and specificity and allowed accurate quantification of plaque size. The validated approach was then applied to image iliac arteries of 25 human subjects in vivo, and results were compared with those of intravascular ultrasound (IVUS). IVMRI readily visualized inner and outer plaque boundaries in all arteries, even those with extensive calcification that precluded IVUS interpretation. It also revealed the expected heterogeneity of atherosclerotic plaque content that was noted during ex vivo validation. Again, IVUS did not disclose this heterogeneity. The level of interobserver and intraobserver agreement in the interpretation of plaque composition was high for IVMRI but poor for IVUS.

Conclusions—IVMRI can reliably identify plaque composition and size in arteries deep within the body. Identification of plaque components by IVMRI in vivo has important implications for the understanding and modification of human atherosclerosis. (Circulation. 2005;112:2324-2331.)

Key Words: atherosclerosis ■ intravascular ultrasound ■ magnetic resonance imaging

The composition of atherosclerotic plaques governs their vulnerability to disruption and hence their propensity to cause cardiovascular events. Current imaging techniques used in clinical practice, such as intravascular ultrasound (IVUS), can delineate plaque size but not content.

MRI can differentiate tissue content within atheroma on the basis of the magnetic properties of protons in water, by use of a range of imaging algorithms to optimize contrast, ie, T1-weighted (T1w), T2-weighted (T2w), and proton density–weighted (PDw) imaging. In human subjects, imaging the contents of atheromatous plaques has proved feasible in superficial arteries that lie in close proximity to the surface MR coils, principally the carotid arteries. However, surface MRI does not adequately visualize deeper vessels, such as the critically important coronary, renal, or iliac arteries because of a progressive drop-off in signal-to-noise ratio (SNR). We hypothesized that intravascular MRI (IVMRI), by virtue of the proximity of the MR detector coil to the arterial wall, would yield enhanced image quality and permit characterization of the fine structure of deep arteries of human subjects. This study tested this hypothesis in 2 steps. First, we correlated information about plaque composition and size derived from T1w, T2w, and PDw IVMRI with histopathology in human arteries ex vivo. Next, we applied in vivo the IVMRI approach validated ex vivo to characterize the structure of iliac arteries of 25 human subjects undergoing cardiac catheterization and compared the results with those of x-ray angiography and IVUS.

Methods

Preparation of Ex Vivo Specimens

Thirty-seven segments from 12 human iliac arteries and aortas obtained postmortem were available for analysis, ranging from apparently normal to severely atherosclerotic. The vessels were fixed immediately in 10% formalin and stored at room temperature before imaging. To address the potential effects of fixation on image characteristics, 2 of these arteries were initially placed in saline and imaged with IVMRI and then fixed in 10% formalin, handled identically to the remaining arteries from this point on, and
rescanned by IVMRI. Three sutures placed on the outer wall of each artery served as landmarks to ensure proper alignment and precise slice-by-slice correlation of MR images with histopathology.

**IVMRI Coil and Ex Vivo Imaging Protocol**

IVMRI was performed by use of the Intercept vascular internal MR coil (Surgi-Vision, Inc). The coil is a flexible loopless wire covered with silicone (outer diameter, 0.030 inches; total length, 100 cm) consisting of a distal receiving region 7 cm long. The proximal end attaches to the MR scanner through a radiofrequency interface box. Its appearance and handling characteristics resemble those of a standard 0.035-inch J-guide wire commonly used at cardiac catheterization.

The arterial specimens were positioned in a container filled with either 10% formalin or normal saline as described above. The arteries were attached to Styrofoam with plastic pins. The IVMRI coil was placed coaxially inside the vessel and imaged in a commercially available 1.5-T CV/i scanner (General Electric Medical Systems, Inc). The imaging protocol was based on optimal sequences reported in studies of human carotid arteries by surface MRI and in investigations of tissue samples and animals in vivo by IVMRI.5,6 Accordingly, the protocol consisted of a T1w spin-echo sequence (TR, 500 ms; TE, 13 ms), a moderately T2w fast-spin-echo sequence (TR, 2550 ms; TE, 50 ms; echo train length, 8), and a PDw fast-spin-echo sequence (TR, 2550 ms; TE, 12 ms; echo train length, 8). All ex vivo intravascular MRI was performed with a slice thickness of 2 mm and skip of 1 mm. The protocol used a 9-cm field of view and a matrix of 256×256, yielding an in-plane resolution of 312 µm. We did not use fat saturation technique or image postprocessing.

**Histopathologic Analysis**

The 12 human aortoiliac arteries were sectioned into rings at 3-mm intervals using the sutures on the outer vessels for proper orientation. Each ring was frozen in Tissue-Tek OCT embedding medium, and 5-µm serial sections were cut from each block. Analyses included staining with hematoxylin and eosin for general morphology, picrossirius red for interstitial collagen, and oil red O for lipid. A total of 37 segments, primarily from iliac arteries, were examined.

**Correlation of IVMRI With Histopathology**

The ability of IVMRI to characterize the composition of atheroma was investigated by comparing MR images with distinct lipid, fibrous, and calcified areas identified with tissue-specific stains, as noted above. The corresponding regions of interest (ROIs) in each histological section were identified in matched IVMRI images. Three readers blinded to the histopathologic analysis independently scored a total of 171 ROIs in T1w, moderate-T2w, and PDw images using a standardized 5-point gray scale (Eastman Kodak Co).

To examine whether IVMRI could differentiate among various tissue components, the median MR scores for lipid, fibrous, and calcified ROIs were compared by use of separate Kruskal-Wallis tests for each imaging sequence (T1w, T2w, and PDw). In addition, because there may be an advantage to tissue characterization that relies on a multiparametric approach combining data from several sequences,² we developed combined tissue scores from multinomial logistic regression and simple regression models with histological tissue type as the dependent variable. Because there were no substantial differences in the ability of these models to discriminate between the tissue types, we chose a model with weights for each MR score based on the coefficients from a simple regression model. All statistical analyses were performed by use of Intercooled Stata, version 7.0 (Stata Corp).

The ability of IVMRI to measure plaque area was also evaluated by morphometric measurements in histopathologic sections and in corresponding MR images with ImagePro Software (Media Cybernetics Inc). The lumen, the outer vessel wall, and the calculated vessel wall areas were quantified. Linear regression and Bland-Altman analyses were used to correlate the measurements between the 2 techniques.

**Imaging of Human Iliac Arteries In Vivo**

The study protocol was approved by the Brigham and Women’s Hospital Institutional Review Board. Male and female subjects age 18 to 80 years undergoing a cardiac catheterization by the femoral artery approach were eligible. Exclusion criteria included general contraindications to MRI, hemodynamic instability, impaired renal or hepatic function, history of systemic bleeding, or stroke within the past 3 months. Twenty-five subjects enrolled into the study after giving written, informed consent.

At cardiac catheterization, angiographic definition of the distal abdominal aorta and iliac arteries was obtained by injecting 20 mL of nonionic contrast. An IVUS catheter with a 20-MHz rotating transducer (Sonicath 3.2 and Galaxy System, Boston Scientific) was introduced through the femoral sheath into the ipsilateral iliac artery, and imaging was performed during mechanized pullback at 0.5 mm/s. This catheter balances the requirement for fine resolution with the need for penetration of relatively large arteries. At the conclusion of the cardiac catheterization, the IVMRI coil was advanced into the ipsilateral iliac artery through the femoral sheath under fluoroscopic guidance. The 7-cm imaging segment was centered in the common iliac artery where the angiogram and IVUS were recorded earlier. The coil was secured in place, a sterile dressing was applied, and the subjects were transferred to a nearby MR suite. All subjects received systemic heparin for anticoagulation while the imaging coil remained in the artery.

We verified the position of the IVMRI coil by low-resolution 3D “localizer” images from surface MRI. We also used the localizer images to target the common iliac artery for orthogonal high-resolution IVMRI imaging at 3-mm intervals. The iliac artery was imaged by use of the IVMRI coil with sequences similar to those used in the ex vivo studies. Black-blood imaging⁷,⁸ was performed by applying a superior saturation pulse, because the standard double-inversion recovery technique resulted in too great a loss of efficiency and prolonged scan times for multislice acquisition. Fat saturation was abandoned after pilot experiments because of poor signal homogeneity induced by the presence of the metallic imaging wire. Cardiac gating was used to set TR equal to 2 R-R intervals and to acquire image data during diastole, resulting in an imaging time of 42 seconds per slice at a heart rate of 80 bpm. Effective images were acquired with an echo train length of 4 to 8, field of view of 9 cm, slice thickness of 2 mm, 8 excitations, and a 256×256 matrix yielding in-plane resolution of 312 µm. No image postprocessing was performed.

**Analysis of IVUS and IVMRI In Vivo**

Angiographic, IVUS, and MR images were uploaded to a workstation (Hewlett Packard) for review using eFilm Workstation software v.1.5.3 (Merge eFilm) and for morphometric measurements using Image J software v.1.33 (National Institutes of Health). Images were matched precisely on the basis of the distance from the common iliac artery ostium. Adjacent veins and contralateral iliac arteries clarified the artery ostium. Adjacent veins and contralateral iliac arteries clarified the boundaries were identified on T1w images. Two investigators determined specific ROIs within the vessel wall that were visually distinct
structures present in at least 2 of the 3 imaging sequences. Three readers blinded to the angiographic and IVUS results then interpreted the IVMRI images in the T1w, moderate T2w, and PDw sequences. The readers scored each specific ROI on the basis of the 5-point gray scale, as described earlier under ex vivo studies. Each reader scored the ROIs independently twice, 2 weeks apart, to determine intraobserver variability.

Using matched images, we compared the tissue characteristics of the ROI from IVUS to the same ROI defined by IVMRI using scores validated from our ex vivo data. Intraobserver and interobserver agreement to within 1 score were assessed by use of Cohen’s weighted $\kappa$ statistics. In those arterial segments in which IVUS images satisfied ACC/AHA criteria for interpretability, we compared lumen and outer vessel areas by IVMRI and IVUS using Wilcoxon signed-rank tests.

Results

Validation of IVMRI Against Histopathology Ex Vivo

Comparison of images from 12 cross sections of 2 aortoiliac arteries placed initially in saline and then in formalin did not reveal appreciable alterations in signal intensities by the fixation process. Compared with histopathology, IVMRI of 37 arterial segments discerned fine details of plaque composition and morphology (Figures 1 and 2). The lumen, the outer vessel, and the vessel wall areas imaged by IVMRI correlated closely with histomorphometric measurements (all $r>0.96$ and $P<0.001$) (Figure 3). Bland-Altman analyses confirmed good agreement: for an average lumen area of 44.6 mm$^2$, the mean difference (IVMRI minus histopathology) was 4.2 mm$^2$ (limits of agreement, 2.7 to 5.7 mm$^2$); for an average outer vessel area of 98.3 mm$^2$, the mean difference was 11.5 mm$^2$ (limits of agreement, 9.4 to 13.6 mm$^2$); and for an average vessel wall area of 53.7 mm$^2$, the mean difference was 7.1 mm$^2$ (limits of agreement, 6.2 to 20.5 mm$^2$).

In 171 ROIs from 37 arterial segments, the median gray-scale signal from calcium was significantly different from both lipid and fibrous tissues in all 3 imaging sequences ($P<0.001$). Lipid was distinct from fibrous tissue in the T1w and moderate T2w sequences but not in the PDw sequence (Table 1). On the basis of these observations in 171 ROIs, we devised a 5×5 table that integrates T1w and T2w gray-scale scores to optimally differentiate lipid, calcified, and fibrous tissue (Table 2). When characterizing tissue composition using this simplified schema that incorporates information from T1w and T2w sequences only, we identified lipid with 68% sensitivity and 79% specificity, fibrous tissue with 76% sensitivity and 72% specificity, and calcium with 100% sensitivity and 100% specificity. Although this ap-

![Figure 1. Correlation of IVMRI and histopathology for morphology and tissue type in an iliac artery with eccentric plaque. IVMRI of a human arterial specimen in 3 imaging sequences and corresponding histopathology with hematoxylin and eosin (a) demonstrates accurate definition of plaque morphology. In the region enclosed by the dark rectangle, picrosirius red staining (b) demonstrates collagen-rich areas (white arrow), and oil red O staining (c) demonstrates lipid-rich area (black arrow). IVMRI defines plaque morphology accurately and identifies distinct signal patterns from lipid and fibrous tissues.](http://circ.ahajournals.org/)

![Figure 2. Correlation of IVMRI and histopathology for morphology and tissue type in an iliac artery with mild circumferential plaque. IVMRI of a human arterial specimen in 3 imaging sequences and corresponding histopathology with hematoxylin and eosin (a) demonstrates accurate definition of plaque morphology. In the region enclosed by the dark rectangle, picrosirius red staining (b) demonstrates collagen-rich area (white arrow), and oil red O staining (c) demonstrates lipid-rich area (black arrow). IVMRI defines plaque morphology accurately and identifies distinct signal patterns from lipid and fibrous tissues.](http://circ.ahajournals.org/)
proach allowed straightforward interpretation of tissue content by IVMRI, we also sought to optimize sensitivity and specificity by integrating information from all 3 sequences using a combined tissue score. Cutpoints for the score were defined with optimal sensitivity and specificity for identifying each tissue. The tissue score (TS) equation 

\[
TS = \frac{T1w}{0.4} - (PDw - T2w) 
\]

identified lipid (TS, 0.5 to 1.3) with 73% sensitivity and 85% specificity, fibrous tissue (TS>1.3) with 83% sensitivity and 81% specificity, and calcium (TS<0.5) with 100% sensitivity and 97% specificity.

### Characterization of Human Iliac Arteries by IVMRI In Vivo

We imaged a common iliac artery in 25 subjects by IVUS and IVMRI successively. Their demographics are presented in Table 3. Angiographic evidence of coronary artery disease was present in 72% and symptomatic peripheral artery disease in 28% of subjects. No complications were noted during IVMRI or IVUS examinations.

IVMRI imaging of a 20-mm segment of the iliac artery in T1w, T2w, and PDw sequences was typically performed in 21 minutes at a heart rate of 60 bpm. Fewer than 10% of the gated images showed mild motion artifact, typically because of poor cardiac gating associated with a rapid or irregular heart rate despite the use of β-blockers, but this did not preclude image interpretation. Black-blood imaging greatly facilitated luminal border identification and was entirely successful in 90% of images. When black-blood imaging was only partly successful (<10%), interpretation of vessel wall images was still feasible. Whereas ex vivo imaging demonstrated an intense signal adjacent to the coil that potentially obscured a portion of the artery wall, this was rarely a problem in vivo, with a more central luminal location of the coil. We abandoned surface imaging, initially compared with IVMRI in 2 subjects, because of increased imaging time after it became clear that the quality of the iliac artery images with surface MRI was much inferior to that of IVMRI (Figure 4).

Readers independently identified luminal and outer vessel borders by IVMRI and IVUS. The entire circumference and full thickness of the arterial wall were visible in all 35 sections in all 3 MRI sequences (total, 105 images). In contrast, matched IVUS images interpreted by 3 experienced readers were deemed to be of acceptable quality (defined as the region of the external elastic membrane being visible for at least 270°) in only 54% of images (P<0.001 versus IVMRI) (Figures 5 and 6). Among the limited number of images acceptable by IVUS, mean lumen areas for IVMRI were similar to those for IVUS (44.5±21.6 and 43.5±22.6 mm², respectively; mean difference, 0.952 mm², P=0.0534), whereas the mean outer vessel wall areas were consistently larger by IVMRI compared with IVUS (116.4±4.7 and 86.6±5.8 mm², respectively; mean difference, 29.7 mm², P=0.0001).

### TABLE 1. Gray-Scale Scores According to Tissue Type and Imaging Sequence

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>T1w</th>
<th>PDw</th>
<th>Moderate T2w</th>
<th>P Value for Lipid vs Fibrous</th>
<th>P Value Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>3 (3–4)</td>
<td>2 (2–3)</td>
<td>2 (1–2)</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrous</td>
<td>4 (4–5)</td>
<td>3 (2–3)</td>
<td>2 (2–2)</td>
<td>0.1805</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcified</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
<td>0.0031</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Median (interquartile range) gray-scale scores for the 3 tissues were compared in each imaging sequence by use of the Kruskal-Wallis test. Although calcium was visually distinct in all sequences, lipid and fibrous tissues were readily discriminated in T1w and moderate T2w, but not PDw.
Readers independently interpreted the tissue composition in 35 iliac artery sections of 8 subjects with extensive atheromatous plaque by both IVUS and IVMRI. Three readers interpreted IVMRI using the combined T1w and moderate T2w gray-scale scores in the table format and all 3 sequences in the tissue score equation (Figure 5). The presence of calcium by IVMRI and IVUS was highly correlated, as was localization of calcium either deeply or superficially within plaque (P < 0.001 by Fisher’s exact test for both calcium presence and localization) (Figure 7).

IVMRI revealed the expected complexity of plaque content, with distinct lipid, fibrous, and calcified regions observed previously in the validated ex vivo studies. Intraobserver agreement among the 3 readers for 2 readings 2 weeks apart varied from 76.5% to 84.3%, and κ values ranged from 0.68 to 0.79 (a κ value of >0.40 represents good reliability and >0.60 very good reliability). Agreement between readers for IVMRI was also very good for both gray-scale scores (κ=0.63) and tissue interpretation (κ=0.62). In contrast, the reliability of IVUS interpretation of tissue composition was poor (κ=0.21).

**Discussion**

In this study, IVMRI accurately quantified the size of human atherosclerotic plaques and differentiated lipid, fibrous, and calcified components with favorable sensitivity and specificity ex vivo. We then applied the approach we validated ex vivo to imaging of human iliac arteries in vivo and compared the results with those of IVUS. IVMRI readily visualized inner and outer plaque boundaries in all arteries, even those with extensive calcification that barred IVUS interpretation. The IVMRI approach also revealed the expected heterogeneity of atherosclerotic plaque content noted during ex vivo validation, a capability not shared by IVUS. IVMRI had a high level of interobserver and intraobserver agreement in the interpretation of plaque composition, whereas agreement was poor for IVUS. Accordingly, the results indicate that IVMRI can characterize the composition and size of atherosclerotic plaques in “deep” arteries in humans.

Imaging techniques that visualize the presence, evolution, and stabilization of vulnerable plaques are much needed.10–13

**Figure 4.** Comparison of IVMRI and surface MRI. T1w surface MRI (a) and IVMRI (b) of a common iliac artery in a subject with an atheromatous plaque illustrates better image quality with IVMRI compared with surface MRI. Both images were produced by use of identical parameters (TR, 500 ms; TE, 13 ms; band width, 16 kHz; field of view, 9 cm; matrix, 256×256; no phase wrap) and in-plane resolution of 316 μm, but the relative SNR is far superior for IVMRI.

**Figure 5.** IVMRI of common iliac artery in vivo. Angiogram (left) of a common iliac artery and corresponding IVUS and IVMRI images of the iliac artery at its origin (top half) and 6 mm distal to the bifurcation (bottom half). In both segments, the artery is characterized by angiographic narrowing and IVUS that images the outside edges of the artery and plaque incompletely, whereas the corresponding IVMRI depicts the entire plaque morphology. The validated approach to tissue characterization ex vivo applied to this in vivo study demonstrates a predominantly lipid core with overlying fibrous cap at the origin of the iliac artery (top half) and a large lipid core with a calcium nodule in the more distal segment (bottom half).
MRI can differentiate the principal tissue components of atherosclerotic plaques on the basis of proton magnetic properties. MRI coils have provided accurate information on plaque size in human carotid arteries and reliably distinguished the lipid from the fibrotic regions in vivo compared with histopathology on the carotid specimen subsequently excised. MRI also provides insights into mechanisms of alterations in atheroma characteristics considered to be related to plaque “stabilization.” In a small case-control study of intensive lipid-lowering therapy, MRI of carotid arteries showed a marked reduction in the lipid content, consistent with the known effects of this therapy on plaque composition from experimental studies.

Although MRI has yielded acceptable visualization of carotid plaques, current surface MR techniques do not permit investigation of deeper arteries because of poor SNR associated with the increased distance between the detector coil and the vessel under study. Placement of the intravascular detector coil adjacent to the atheromatous plaque offers one potential solution for acquiring high-quality images. In addition, the relatively stable location of the MR antenna within the artery in the effective field of view reduces artifacts related to body and respiratory motion. Any artifacts caused by the motion of the catheter relative to the artery during the cardiac cycle are effectively reduced by acquiring images only in diastole through ECG gating.

Several designs for IVMRI detector coils exist: some incorporate a loop (twin-lead design) or a solenoid (single or paired) to maximize SNR, but at present, these devices are too bulky for clinical application; a loopless detector coil...
permits miniaturization while still maintaining SNR by a factor of 4 or more over surface coils. Such detectors are relatively flexible, enhance safety, and permit imaging over longer segments (up to 7 cm). Although the loopless antenna used here is too large to fit into the coronary arteries, it can be scaled down to the size of a coronary angioplasty guidewire (0.35 mm/0.014 inches). Moreover, unlike with other coil designs, this coil can detect signal when parallel or perpendicular to the main magnetic field of the MRI scanner. Thus, angulated coronary arteries should not preclude imaging. For all of these reasons, we favored this loopless design over others with the potential of coronary applications in the future. Clearly, more research into the design of the receiver coil will advance clinical applications.

Previous studies used IVMRI to image excised human arteries and animals with atherosclerosis, and their results have held promise for plaque characterization in humans in vivo. The present study presents IVMRI for vascular imaging in human subjects in vivo. We initially evaluated the signal from our IVMRI system with reference to histopathologic examination. Our results agree with those of Worthley and colleagues, using surface MRI, that fibrous tissues in human atheroma yield bright signal in T1w sequences compared with lipid and for lipid compared with calcium. Our data also reinforce those of Zhao and colleagues, who described T2 signals as brighter for fibrous tissue compared with lipid. In accord with previous studies, we also found that a combination of different weightings differentiates optimally among the various tissue components. Because PD weighting contributed relatively little, we were able to judge tissue composition solely from T1w and T2w signals from a convenient table (Table 2) with favorable specificity and sensitivity. Addition of PD weighting into a more cumbersome equation improved specificity and sensitivity only marginally. Although our correlation of IVMRI to histopathologic examination was of necessity obtained ex vivo, MR signal characteristics are for all practical purposes identical when vascular imaging is performed on an excised atheroma solely from T1w and T2w images demonstrated many of the same fibrous, lipid, and calcified atheroma features as validated in the ex vivo studies compared with histopathology. However, although IVUS imaging readily identifies calcifications, its difficulties in differentiating lipid from fibrous tissue reliably are well known (sensitivity and specificity, <50%).

In conclusion, IVMRI can reliably identify plaque composition and size in iliac arteries, vessels deep within the body not readily characterized by surface MRI. The development of a novel imaging technique that can differentiate the principal components of atherosclerotic plaques in humans in vivo will aid in the development of novel therapeutic approaches that favor plaque stabilization. As this technology continues to improve, IVMRI should evolve into an important investigational and clinical tool.

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References


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