Noninvasive Quantitative Evaluation of Atherosclerosis Using MRI and Image Analysis


A new medical image analysis system to quantify atherosclerosis in the lower abdominal aorta using magnetic resonance imaging is described. This medical image analysis and display system permits the quantification of the three-dimensional (3D) properties of the vessel wall and lumen cross-sectional area and volumes. Preliminary results of employing this medical image analysis capability on magnetic resonance images demonstrated a twofold increase in wall volume per unit vessel length, corresponding to intimal thickening, before luminal narrowing was detected. This work demonstrated the feasibility and usefulness of quantitatively evaluating the 3D properties of the vessel lumen and wall by using a combination of magnetic resonance imaging and image analysis. The demonstration that intimal wall thickening is observed in images before observable occlusion of the lumen can be expected to provide an important early indicator of the future development of atherosclerosis. Such capability will permit detailed and quantitative studies to assess the effectiveness of therapies, such as drug, exercise, and dietary regimens. (Arteriosclerosis and Thrombosis 1993;13:1180-1186)

KEY WORDS • magnetic resonance imaging • multispectral pattern recognition • atherosclerosis • classification • 3D display

Imaging arterial lesions is proving to be a valuable tool for the study of atherosclerosis, both from the perspective of determining the natural history of the disease and detecting treatment-induced modifications.1-4 Current imaging methods have significant limitations. Some methods, such as angiography, are restricted to evaluating luminal encroachment, whereas atherosclerosis is predominantly an arterial wall disease.5 Additionally, luminal compromise is a late manifestation of atherosclerosis and not until encroachment is advanced is luminal patency predictive of future coronary events.6

Methods currently in clinical practice for diagnosing atherosclerosis include angiography and various ultrasound techniques. Angiography, an invasive procedure, is the "gold standard" in current clinical practice and is the examination of choice, particularly when surgical intervention is being considered.7-8 Several systems have been developed to automatically quantify the degree of stenosis by computerized analysis of angiograms.8 However, angiography carries the risks of high x-ray exposure and reaction to the contrast medium as well as potential embolism, which limits its usefulness for detection of early disease. Additionally, measurements of occlusion based on analysis of two-dimensional (2D) views have accuracy limitations without specific knowledge of the third dimension, limiting its usefulness for quantitative analysis. Intravascular ultrasound has significant possibilities for visualizing the three-dimensional (3D) characteristics of the lumen of coronary arteries as well as characteristics of the surrounding wall.1,9 However, both angiography and intravascular ultrasound are invasive techniques, which limit their usefulness for patients who exhibit no symptoms or only mild symptoms of circulatory insufficiency.

Two noninvasive techniques that can potentially evaluate the plaque constituents involved in atherosclerosis are digital ultrasound imaging and magnetic resonance imaging (MRI). Neither of these techniques uses ionizing radiation or requires a contrast medium, and both are considered safer than angiography. Techniques are just being developed to enable MRI to clinically and noninvasively visualize and diagnose atherosclerosis. Different MRI pulse sequences are able to enhance the contrast between certain atherosclerotic tissue types.11-13 Mohiaddin et al14 have used chemical shift imaging to assess arterial compliance, pulse wave velocity, and flow pattern in the aorta. Recently, Vinitski and coworkers15 have combined the use of in vivo MR chemical shift imaging and in vitro spectroscopic imaging of excised specimens to investigate atherosclerotic plaque formation in carotid arteries. This work has demonstrated the potential usefulness of MRI for visualizing many of the characteristics of atherosclerotic plaque. However, techniques have not been described for quantitatively analyzing this type of data, which is essential to studies involving diagnosis and staging of the disease as well as monitoring its progression and regression in response to various therapeutic interventions.

We have focused on developing MRI techniques in combination with image analysis techniques to noninvasive
sively quantify atherosclerosis. Interest has focused on using MRI to quantify the characteristics (ie, size and shape) of the lumen and wall noninvasively. Previous work has concentrated on application of these techniques to freshly excised human aorta specimens.\textsuperscript{16-18} This article describes the results of applying new techniques to quantify and characterize the vessel wall involved in human atherosclerosis. The ability to reliably identify different tissue types is an important goal because it will permit the stage of the disease process to be quantitatively evaluated and followed over time.

Methods

We concentrated on imaging the lower abdominal aorta because of its large size as well as the relatively small movement artifacts due to aortic expansion/contraction and respiration. A group of normal subjects and a group of patients with significant signs of advanced disease were imaged using standard MR practice. The 3D lumen and wall volumes of the aortic vessel segment imaged in these subjects were obtained using semi-automated image analysis techniques. The 3D structure of the vessel segment was then reconstructed to demonstrate the spatial distribution of the lumen and wall.

Study Subject Groups

The normal subjects were asymptomatic adults without physical evidence of arterial disease and no risk factors for atherosclerosis. The patient group was selected after moderate to severe atherosclerosis was demonstrated by the presence of bruits during physical examination as well as the appearance of significant disease on abdominal angiogram. Twenty-three subjects were imaged, 16 of whom were “normal” and 7 of whom were “atherosclerotic.” Some normal and atherosclerotic subjects were imaged multiple times to obtain an estimate of the repeatability of the measurements.

MRI Protocol

Images were generated using the body coil on a Siemens 1.5-T Magnetom Imager. The present study employed transverse T1-weighted images obtained from approximately 10 different slice positions. The imaging protocol was designed to reduce artifacts that arise due to vessel motion and breathing during the acquisition process, as described below.

In attempting to produce images of the abdominal aorta, artifacts occur both from motion that takes place between phase-encoding steps (view to view) and from motion that occurs between radio frequency excitation and readout (in view). In-view motion artifacts arise because of incomplete rephasing of spins at the end of slice selection and/or in the middle of the readout period, and they become prominent at longer echo times (T2-weighted images). The spins can be effectively refocused by applying additional gradients using gradient moment rephasing (GMR).\textsuperscript{19} However, GMR is not highly effective at reducing artifacts from variable inflow enhancement because of pulsatile blood movement or at reducing artifacts generated by the motion of high-signal subcutaneous fat anterior to the aorta. To limit artifacts that arise from these motions, spatial presaturation is incorporated into the pulse sequences. T1-, T2-, and proton-density–weighted images of normal and atherosclerotic patients using the combined motion artifact–reducing techniques were greatly superior to those obtained by standard methods.

T1-weighted coronal scouts were used to determine the location of subsequent axial images such that they lay between the renal and aortic bifurcations. In addition, sagittal scouts were used to determine the placement of presaturation slabs in the slice-select and phase-encode directions. Presaturation in the phase-encode direction was used to limit the signal from high-intensity subcutaneous fat above the aortic region of interest (ROI). The presaturation slab in the slice-select direction was placed superior to the imaging ROI and was about the size of the ROI. This presaturation slab darkened blood that subsequently flowed into the ROI. A typical placement of presaturation slabs is shown in Fig 1. This presaturation scheme was used for the T1, proton-density, and T2 images acquired as described below. T1-weighted images were acquired with a standard spin-echo sequence using a repetition time (TR) of 650 milliseconds and an echo time (TE) of 15 milliseconds. Because the TE is so short, there is not enough time for significant in-view motion to occur, and thus no need to incorporate GMR in the T1 sequence. The image slices were 4 to 8 mm thick and the result of three averages. The averaging further helped to reduce artifacts due to random motion. To obtain a complete 3D data set, one set of images was obtained with a 100% gap between adjacent slices followed by another set of images centered in the gaps of the first image set. Acquiring the images in this interleaved fashion improved the signal-to-noise ratio. Proton-density– and T2-weighted images were obtained using a double spin-echo pulse sequence with variable bandwidth and presaturation slabs placed in the same positions as those

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Diagram showing presaturation (presat) pulse sequence for image acquisition. Imaging the wall of the abdominal aorta is hindered by artifacts that arise from various sources. Spatial presaturation is an extremely useful means by which to limit such artifacts. To show the placement of both presaturation slabs, the diagram is shown in a sagittal orientation. Motion artifacts that originate from the breathing motion of high-signal, anterior, subcutaneous fat can be alleviated by cancellation of the signal using spatial presaturation in the phase-encoding direction. The 100-cm slab is placed roughly 10 cm above the aorta. To saturate spins in the blood, another 100-cm presaturation slab is placed in the slice-select direction, upstream (superior) to the imaging plane of interest.} 
\end{figure}
for the T1-weighted images. Data were acquired for the proton-density images at a TE of 13 milliseconds and for the T2 image at a TE of 80 milliseconds. The readout time of the first echo was kept short to allow for a shorter TE to reduce motion artifacts. The readout time for the second echo was extended to improve signal-to-noise ratio. The length of this second acquisition period was adjusted to improve motion and chemical shift artifacts, which become increasingly severe as the readout period is lengthened (ie, as the bandwidth is reduced). Images were then transferred to the SUN Microsystems workstation for image analysis as described below.

Image Analysis Procedure

Normalization of the transverse abdominal images. Due to the inherent interslice, interpatient, and intermachine variability of MR data, the success of segmentation and classification procedures depends on an effective gray-level normalization scheme. The normalization procedure used in the studies described depended on the determination of a tissue that could be readily detected in all images from all patients. The subcutaneous fat layer on the patient’s back was adopted for normalization of all intensity values because its high-intensity values and consistent spatial location between patients make it readily identifiable using simple edge-detection methods.

The subcutaneous fat is segmented by convolving the transverse abdominal image with a Laplacian of a Gaussian operator and then detecting contours in the image by locating zero-crossings in the convolved image.20 Since the subcutaneous fat is spatially consistent between patients, the corresponding contour is readily identifiable. The image can then be scaled to match the mean gray-level vector of the segmented fat region with the mean vector of a predetermined standard for subcutaneous fat.

Detection of aorta and segmentation of outer wall. After acquisition of transverse images of the abdominal aorta, the T1-weighted images were used for segmentation of the vessel. The T1-weighted images are appropriate for image segmentation because they have been found to emphasize the structural information involving the vessel wall boundaries. The segmentation was performed as shown in the sequence of steps outlined in Fig 2, which are described in more detail by Jackson and Merickel.21 The aorta is initially detected (step S-2 in Fig 2) by convolving the images with a Laplacian of a Gaussian operator. Peaks in the resulting image correspond to the position of the aorta, the vena cava, and various other structures. A subimage containing the
The aorta is then extracted and centered at the peak in the average of the sequence, and the resulting extracted regions are submitted to the aorta extraction procedure.

The goal of the aorta extraction procedure is to provide a better approximation to the center of the aorta than that obtained through spot detection of the images. An automatic threshold selection is performed on each of the extracted regions. This goal is achieved through an erosion process to find circular structures in the resulting binary images. The spatial average of the remaining points are taken as the center of the aorta. A smaller subimage is extracted about this center, further reducing the quantity of tissue outside the aorta.

The procedure to detect the aortic boundary uses these subimages as a starting point to accomplish the second major step in segmentation, the determination of the outer vessel boundary (step S-3 in Fig 2). A threshold for each of these subimages is automatically determined and thresholding is performed. The result is a region whose size, shape, and position correspond to that of the aorta. A one-pixel border is added to this region to ensure inclusion of all of the aortic wall.

**Aortic lumen segmentation using 3D region growing.** In an effort to segment the lumen of the lower abdominal aorta more accurately, a segmentation technique using 3D region growing has been developed (step S-4 in Fig 2). Using the T1-weighted MR image volume, a seed point is selected within the lumen of the aorta. If the gray level of the selected voxel is within acceptable limits, it is labeled as lumen. All eight in-plane neighbors as well as those directly above and below the seed-point voxel are likewise examined for lumen membership. If any of these neighbors are accepted as lumen voxels, then their neighbors are also examined. This process continues recursively until no new neighbors are found that are accepted as lumen voxels. The result of this process, the 3D lumen of the vessel, is used to calculate lumen volume based on knowledge of the voxel dimensions and also as the basis for the 3D reconstruction of the vessel.

**3D vessel reconstruction.** The lumen segmentation results provide the 3D-identified regions representing the lumen as well as the wall and the surrounding adventitial fat. Traditional volume-rendering techniques, such as those used in the Sun Microsystems’s voxel package, can be used to produce a 3D reconstruction of the vessel segment. An attribute table is first established describing the color and opacity of each tissue type in the vessel segment to be rendered. The volume-rendering technique works by spawning a ray from each voxel in the 3D data set. As the ray traverses the volume, the encountered voxel values are summed according to the values for the particular tissue type in the attribute table. If the ray intersects the boundary between two regions, a surface normal is calculated and a shading model is applied. The final color of the voxel in the rendered frame depends on the number of pixels encountered, their color and opacity, and any surface boundaries crossed.

**Results**

**Basic Characteristics of the Aorta Viewed With MRI**

Fig 3 shows a set of T1-, proton-density-, and T2-weighted transverse images through a representative section of a normal subject and a 60-year-old man with advanced atherosclerosis. In general, the lumen of the vessels appears dark, with all pulse sequences due to the presaturation pulse in the slice-select direction that was employed as described in “Methods.” The T1- and proton-density–weighted images through the diseased vessel clearly show the wall of the aorta to be thickened, particularly on the dorsal side next to the vertebral column. The intimal wall thickening and distribution of plaque tissues can be quite complex in patients with advanced disease. Fig 4 shows an aortogram of the same diseased patient demonstrating the irregularity and narrowing of the lumen, which is especially noticeable near the iliac bifurcation.

**Measurement of Lumen and Wall Cross-sectional Area**

Approximately 10 to 18 transverse contiguous slices were imaged in the region between the bifurcation of the aorta into the iliac arteries and the renal arteries. The cross-sectional area of the vessel occupied by lumen and wall was determined for each slice in the aortic segment imaged by using the image analysis procedure. Cross-sectional area profile plots were generated for both the lumen and wall area measurements by plotting cross-sectional area vs slice position for each subject. Normal subjects generally had a relatively thin smooth wall and constant luminal area (Fig 5, top). Atherosclerotic subjects demonstrated much greater variability in both their lumen and wall cross-sectional area profiles. Fig 5, bottom shows an example of a cross-sectional area profile for a patient's aorta that demonstrates a region...
of increased wall thickening (ie, intimal thickening) that is also accompanied by increased luminal area.

**Measurement of Lumen and Wall Volume**

The total volume occupied by the lumen and wall was determined by multiplying the cross-sectional area for the lumen and wall in each slice by the slice thickness and summing the measurements across all contiguous slices in the imaged segment. The lumen and wall volume measurements were divided by the length of the vessel segment imaged to facilitate comparison between patients. The average lumen volume per unit length of vessel was determined to be 2.0±0.4 mL/cm for normal subjects (n=16) and 1.6±0.9 mL/cm for the patient group (n=7) (Table 1), which is not significantly different at the 95% confidence level using a two-tailed t test (t=1.35, P<.05). However, the average wall volume per unit length of vessel for the patient group (2.7±1.4 mL/cm) was found to be significantly (t=4.27, P<.05) greater than the volume for the normal group (1.2±0.3 mL/cm).

Several of the subjects, particularly from the normal group, were imaged multiple times to gain an estimate of the repeatability of the lumen and wall volume measurements. Table 2 shows the repeated measurements that were made on normal subjects 6, 7, and 8 (imaged 2, 4, and 3 times, respectively) and patient 9 (imaged twice). The repeatability of the volume measurements for both the lumen and wall were analyzed with a one-way analysis of variance that demonstrated that the between-subject variance was greater than the within-subject variance at the 99% confidence level.

**TABLE 1. Summary of Volume Measurements for Normal and Atherosclerotic Subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Lumen (mL/cm)</th>
<th>Wall (mL/cm)</th>
<th>Lumen (%)</th>
<th>Wall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>16</td>
<td>2.0±0.4</td>
<td>1.2±0.3</td>
<td>60.9±7.2</td>
<td>39.1±7.2</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>7</td>
<td>1.6±0.9</td>
<td>2.7±1.4</td>
<td>36.8±2.5</td>
<td>63.2±2.5</td>
</tr>
</tbody>
</table>

Volume is expressed as lumen (mL/cm) or wall (mL/cm) volume per unit vessel length and as the percent of the total vessel volume occupied by lumen (% lumen) and wall (% wall). Note that the percent of vessel occupied by lumen and wall add up to 100%.
TABLE 2. Summary of Repeatability of Wall and Lumen Measurements

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lumen (mL/cm)</th>
<th>Wall (mL/cm)</th>
<th>Lumen (%)</th>
<th>Wall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVN6</td>
<td>2.0±0.4</td>
<td>1.5±0.4</td>
<td>58.5±2.1</td>
<td>41.5±2.1</td>
</tr>
<tr>
<td>AVN7</td>
<td>1.6±0.2</td>
<td>0.9±0.1</td>
<td>62.5±4.4</td>
<td>37.5±4.4</td>
</tr>
<tr>
<td>AVN8</td>
<td>2.0±0.1</td>
<td>1.3±0.2</td>
<td>59.6±4.9</td>
<td>40.4±4.9</td>
</tr>
<tr>
<td>AV9</td>
<td>2.5±0.3</td>
<td>4.4±0.5</td>
<td>36.6±0.3</td>
<td>63.4±0.3</td>
</tr>
</tbody>
</table>

Normal subjects AVN6, AVN7, and AVN8 were imaged 2, 4, and 3 times respectively; atherosclerotic patient AV9 was imaged twice.

These results suggest that the measurements are reasonably repeatable. Some variability between repeated measurements is expected due to the difficulty of ensuring that exactly the same segment of vessel is imaged each time.

To minimize effects of variations in overall vessel size due to variations in subject size, the wall and lumen volume measurements were expressed as percentages of the total vessel volume occupied by the wall and lumen. The results (Table 1) show a clear separation between the normal and patient groups, such that all normal subjects have a percentage of vessel occupied by wall of less than 55%, whereas all patients have a corresponding value greater than 55%. The standard deviation of the normalized percentage measurements was the same for the lumen and wall, since these measurements are from the same data sets and add up to 1. These data were graphed by plotting the percentage of total vessel volume occupied by wall vs lumen volume per unit vessel length (Fig 6).

Visualization of 3D Vessel Structure

The 3D spatial characteristics of the lumen and wall regions were observed by creating a 3D reconstruction of the lumen and wall regions. Fig 7 shows a 3D reconstruction of an aorta from a normal subject and an aorta from a patient with advanced atherosclerosis; the latter clearly depicts the increase in wall volume and buildup of plaque.

Discussion

The results presented demonstrated the feasibility of using MRI to noninvasively quantify and visualize the 3D structural characteristics of major human arteries such as the aorta. The results clearly demonstrated that the patient group has an approximately twofold increase in wall volume with no significant change in average luminal volume. This lack of change in luminal volume for the entire vessel segment is attributed to the phenomenon of compensation, which has been observed in human and primate carotid and coronary arteries. It is believed that the aorta has a significant ability to compensate because of its size and the fact that it is not significantly restricted by surrounding structures. The significant increase in wall volume, which does not significantly impinge on the lumen, demonstrates that the extent of plaque buildup could be greatly underestimated by diagnostic methods that only visualize the lumen, such as angiography. The potential for underestimating plaque buildup with angiography has also been suggested by other investigators of coronary artery disease.

The lumen and wall volumes were also expressed as percentages of total vessel volume to minimize effects of vessel size. The difference between the normal and patient groups was even greater using these percentage measurements. The normal group had an average of 39.1±7.2% of their vessel occupied by wall compared with 63.2±2.5% for the patient group, with no overlap in values between the two groups. The percentage of the total vessel volume due to wall can be considered as an
estimate of the degree of stenosis. The normal group showed the expected negative correlation between percent stenosis and lumen volume (Fig 6) that has been observed in coronary arteries.13 However, all of the patients showed very high values for percentage of vessel occupied by wall (>55% of vessel occupied by wall), but did not demonstrate the same negative correlation with lumen volume observed in the normal group. This result is also consistent with the phenomenon of compensation described above, since the lumen volume did not decrease in the patient group in the presence of significant wall thickening (ie, >55% vessel occupied by wall).

These results are consistent with the significant effect of the disease process on wall volume, which is obscured by measurements of lumen properties alone. The measurement of wall volume described can be expected to provide an early, noninvasive indicator of disease before luminal compromise is observed with angiographic techniques. This ability will permit a much more direct and quantitative method of diagnosing and monitoring the presence of atherosclerosis as well as its progression and/or regression in response to various therapeutic interventions, such as cholesterol-lowering drugs.

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