In Vivo 16-Slice, Multidetector-Row Computed Tomography for the Assessment of Experimental Atherosclerosis Comparison With Magnetic Resonance Imaging and Histopathology

Juan F. Viles-Gonzalez, MD; Michael Poon, MD; Javier Sanz, MD; Teresa Rius, MD; Konstantin Nikolaou, MD; Zahi A. Fayad, PhD; Valentin Fuster, MD, PhD; Juan J. Badimon, PhD

Background—Noninvasive imaging can detect early atherosclerotic disease. Magnetic resonance imaging (MRI), because of its excellent spatial resolution, is already established as a tool for plaque characterization. Sixteen-slice, multidetector-row computed tomography (MDCT) was recently introduced into the field of cardiac imaging, with promising results for noninvasive angiography. We compared the capabilities of MDCT and MRI for the assessment of noncalcified, atherosclerotic plaques.

Methods and Results—Six atherosclerotic rabbits underwent in vivo imaging by MDCT and 1.5-T MRI. MDCT parameters were 120 kV, 120 mA/s, collimation 12×0.75, and spatial resolution 0.6×0.6 mm. MRI parameters were as follows: for proton density, repetition time/echo time (TR/TE) 2300/5.6; for T2, TR/TE 2300/62; and for T1, TR/TE 800/5.6; slice thickness was 3 mm and spatial resolution, 0.3×0.3 mm. Blinded analysis of 3-mm axial reconstructions from MDCT and the carefully matched MRI images (182 sections) showed excellent agreement between both modalities. MDCT yielded a slightly larger lumen area, anteroposterior diameters, and lateral diameters, with no significant differences in total vessel area. The sensitivity and specificity, respectively, to detect noncalcified, atherosclerotic plaques were 89% and 77% for MDCT and 97% and 94% for MRI. Fibrous-rich and lipid-rich plaque could not be differentiated visually, although they showed different attenuation properties (116±27 vs 51±25 Hounsfield units, P<0.01).

Conclusions—Both techniques allow reliable detection of noncalcified, atherosclerotic plaques and accurate assessment of vessel areas and diameters. MDCT offers the additive value of a very short image acquisition time when compared with MRI. The subtle measurement differences found between modalities may be due to the better spatial resolution of MRI, which probably explains its superiority for tissue characterization. (Circulation. 2004;110:1467-1472.)

Key Words: tomography ■ magnetic resonance imaging ■ atherosclerosis ■ vessels ■ coronary disease
temporal resolution. Consequently, we evaluated the capabilities of 16-slice MDCT to detect changes in vessel areas and diameters and its capacity to characterize and identify non-calcified, atherosclerotic lesions in comparison with high-resolution MRI and histopathology.

Methods

Experimental Model of Atherosclerosis

Aortic atherosclerosis was induced in male New Zealand White rabbits (n = 6, age = 3 months, weight = 3.5-4 kg; Covance, Princeton, NJ) by a combination of 9 months of a high-cholesterol diet (0.2% cholesterol–enriched diet, Research Diet, Inc) and double aortic balloon denudation injury (at 1 and 3 months after starting the high-cholesterol diet). Aortic injury was performed from the aortic arch to the iliac bifurcation with use of a 4F Fogarty embolectomy catheter introduced through the iliac artery, as previously described. All procedures were performed under general anesthesia by intramuscular ketamine injection (20 mg/kg, Fort Dodge Animal Health) and xylazine (10 mg/kg, Bayer Corp). The study protocol was approved by the internal review board of Mount Sinai School of Medicine.

Computed Tomography

Computed tomography angiography was performed with a 16-slice, multidetector-row computed tomography scanner (Sensation 16, Siemens Medical Solutions). An intravenous access was placed in the central vein of the ear with a 21-gauge line. Different dilutions of ioversol (Optiray 320, Mallinckrodt Inc), a nonionic, low-osmolar, iodinated contrast agent, were tested before initiation of the protocol to determine the optimal concentration creating an intra-aortic lumen attenuation similar to that routinely obtained in clinical human coronary computed tomography angiography examinations (250 to 300 Hounsfield units [HU]). The mixture used in this study was a 1:2 dilution of the contrast agent with saline, yielding a concentration of 106.6 mg iodine per milliliter. The animals were imaged in the craniocaudal direction and in the supine position. An initial localizer image served to confirm an adequate position of the animal (and to prompt modifications, if necessary) and to locate the area of interest, which was the segment of the abdominal aorta from the right renal artery to the iliac bifurcation. To cover this segment of 9 to 11 cm, 30 to 36 3-mm slices were acquired per animal. After an initial localizer plane, a single axial slice was acquired at the level of the aortic root. A total of 8 mL of the contrast dilution was administered at a rate of 0.5 mL/s with an upper pressure limit of 125 psi by using an automated infusion pump (Medrad Envision CT, Medrad Inc). Arrival of the contrast agent was monitored with a region of interest positioned in the center of the descending aorta between the right renal artery and the iliac bifurcation. After a threshold of 100 HU was reached in the vessel lumen, a fixed delay of 4 seconds was used to trigger image acquisition from the level of the diaphragm past the aortic bifurcation. Imaging parameters were as follows: 120 kV, 120 mA, rotation time 420 ms, 12° rotation collimation, and table feed 15 mm per rotation. The total acquisition time ranged from 6.5 to 7.5 seconds. Axial images were reconstructed by using a medium kernel (B30f), a field of view of 160×160 mm, a 512×512 matrix, and an inplane spatial resolution of 0.6×0.6 mm. A slice thickness of 3 mm with no overlap was chosen for reconstruction to allow direct comparison with MRI and histopathology sections.

Magnetic Resonance Imaging

All rabbits had MRI performed on the same day that they underwent MDCT with a 1.5-T MRI system (Siemens Medical Solutions) and a conventional phased-array volume coil. The MRI protocol used was based on previously validated work. Sequential axial images (3 mm thick) of the aorta from the celiac trunk to the iliac bifurcation were obtained by use of a fast spin-echo sequence with an inplane resolution of 300×300 μm (for proton density weighted [PDW], repetition time/echo time [TR/TE] 2300/17; for T2 weighted [T2W], TR/TE 2300/60; and for T1 weighted [T1W], TR/TE 800/5.6), field of view 9×9 cm, matrix 256×256, echo train length 8, and signal averages 4. Fat suppression and flow saturation pulses were used as previously described.

Histopathology

The rabbits were euthanized within 24 hours of MDCT and MRI by intravenous injection of 5 mL IV of 26% sodium pentobarbital (Sleppaway, Fort Dodge Animal Health) after receiving heparin (100 U/kg) to prevent postmortem thrombosis. The aortas were excised and perfusion-fixed as previously described. Serial sections of the aorta were cut at 3-mm intervals to match the corresponding MDCT and MRI images. Specimens were embedded in paraffin, and sections 5 μm thick were cut and stained with combined Masson’s trichrome elastin stain. To further characterize the lesions, all sections were stained immunohistochemically with anti-α-actin antibodies for vascular smooth muscle cells.

Image Analysis

The MDCT images were transferred to a dedicated workstation (Aquarius, Terrarecon Inc) for analysis. Before the protocol was started, an initial correlation of vessel diameters and areas between CT and MRI was performed in another animal with a variety of display parameters (data not shown). In slices with well-defined eccentric plaques visualized on MRI, an area of attenuation lower than the lumen but higher than the surrounding tissues was seen in the same position in the matching MDCT slices, suggesting that it corresponded to the plaque. Window settings were manipulated so that the MDCT image resembled in size and pattern the MRI depiction of the vessel lumen and wall. A window setting of 200 and a level setting of 100 were chosen for image analysis to enable standardized comparison. This combination generates a sharper central enhancement surrounded by a blurrier halo (Figure 1). The brighter central area was assumed to represent the lumen of the vessel and the peripheral halo, the vessel wall. In each axial section from the right renal artery to the iliac bifurcation, several measurements were manually traced: anteroposterior (in mm) and lateral luminal diameters (in mm), lumen area (LA; in mm²), and total vessel area (TVA; in mm²) (Figure 1). To match the image slices in the 3 modalities (histopathology, MRI, and MDCT), the right renal artery was taken as an anatomic reference. The slices for each rabbit were numbered craniocaudally, the first slice being the one containing the right renal artery and the last section the 1 containing the bifurcation into the iliac arteries (Figure 2). In each modality, 3-mm-thick sections were analyzed. In MRI, the slice thickness was 3 mm with no gap between slices. In MDCT, reconstructions of 3 mm with no overlap were performed after acquisition. Slices with matching numbers therefore corresponded to the same location, supported by the fact that each rabbit had the same number of slices covering this anatomic region with the 3 modalities.

The MRRs were transferred to a Macintosh computer for further analysis. We did not standardize the window parameters on MRI, and settings were chosen to produce adequate image quality (WW140-281 and WC370-814). Cross-sectional areas of the lumen and outer boundary of each section were determined by manual tracing with Image Pro-Plus (Media Cybernetics). From these measurements, LA (in mm²), TVA (in mm²), and anteroposterior and lateral luminal diameters (in mm) were calculated (Figure 1). Mean wall thickness (in mm) was derived by automated analysis of VA and TVA with use of the aforementioned software. The histopathologic sections were digitized to the same computer. Three experienced investigators blindly and randomly analyzed each of the MDCT and MRI sections (n = 182). There was good interobserver agreement for all variables for MDCT. Cohen’s 𝑘 was 0.82 for VA, 0.72 for LA, and 0.81 and 0.78 for lateral and anteroposterior luminal diameters, respectively. The intraobserver Cohen’s 𝑘 was 0.85, 0.77, 0.82, and 0.84 for VA, LA, and lateral and anteroposterior luminal diameters, respectively. An independent investigator blinded to the results of MDCT and MRI performed the histopathology analysis.
Statistical Analysis

The agreement between measurements for TVA, LA, and anteroposterior and lateral luminal diameters by MDCT, MRI, and histopathology was evaluated with the Bland-Altman test. Paired Student’s $t$ test was used to calculate mean differences between both techniques. Cohen’s $\kappa$ was calculated to determine interobserver agreement. All probabilities are 2-sided, with a statistical significance taken at a value of $P<0.05$.

Results

Quantification of Vessel Lumen and Wall Parameters

Overall, there was a highly significant agreement between MDCT and MRI measurements of vessel areas and diameters. A trend for a slight underestimation of TVA as measured by MDCT when compared with MRI was seen, although it did not reach statistical significance ($\text{mean} \pm \text{SD}, 0.029 \pm 0.159 \text{ mm}^2$, $P=0.079$). MDCT tended to provide larger values for LA to some extent (Figure 3). The mean difference between both modalities was $0.045 \pm 0.080 \text{ mm}^2$ ($P<0.001$). Both anteroposterior and lateral luminal diameters were slightly but consistently larger by MDCT than by MRI (Figure 3). The mean difference was $0.122 \pm 0.388 \text{ mm}$ ($P<0.001$) for the anteroposterior and $0.294 \pm 0.320 \text{ mm}$ ($P<0.05$) for the lateral luminal diameter (Table).

Sensitivity and Specificity for Detection of Plaque

The sensitivity and specificity of MDCT and MRI to detect noncalcified, nonstenotic atherosclerotic plaques was calculated by using the histopathology results as the “gold standard.” MDCT properly detected 134 of 151 sections (sensitivity 89%) that had atherosclerotic plaque, and the absence of lesions was correctly diagnosed in 24 of 31 sections (specificity 77%). The interobserver agreement determined by Cohen’s $\kappa$ was 0.81. When sections with a mean wall thickness $<0.6 \text{ mm}$ were excluded from analysis, the sensitivity and specificity increased to 96% and 84%, respectively.

MRI showed the presence of atherosclerotic plaques in 146 of 151 sections (sensitivity 97%) with noncalcified, nonstenotic lesions and correctly ruled out atherosclerosis in 29 of 31 normal sections (specificity 94%). The interobserver variability determined by Cohen’s $\kappa$ was 0.87.

Plaque Characterization

A total of 60 lipid-rich and 60 fibromuscular aortic atherosclerotic plaques were selected from the histopathology analysis. These images were matched (anatomically and visually) with the corresponding cross-sectional images on MRI and MDCT. As in previous reports that used the same MRI sequence, lipid-rich plaques showed low signal intensity
in T2W and high signal intensity in T1W and PDW, whereas fibrous plaques were hyperintense on T1W, T2W, and PDW (Figure 4). Mean±SD MDCT attenuation of all lipid-rich lesions was 51±25 HU and for predominantly fibrous plaques, was 116±27 HU (Figure 5). The difference found in CT densities between lipidic and fibrotic atherosclerotic plaques was statistically significant (unpaired Student’s t test, P<0.01). Of note, we were unable to distinguish lipid-rich areas from fibrous areas within the same atherosclerotic lesion on the cross-sectional images of MDCT.

Discussion

The introduction of noninvasive imaging modalities for the early detection and reliable assessment of atherosclerosis would be of great clinical importance. Given their noninvasive approach, MRI and MDCT are emerging as promising tools in the field of cardiovascular imaging for detecting and characterizing atherosclerotic lesions. Therefore, our objective has been to compare 16-slice MDCT and MRI for the assessment of experimental atherosclerosis by using a vessel with a caliber comparable to that of human coronary arteries. MDCT and MR images obtained from atherosclerotic animals were compared, and the observations were corroborated by histologic evaluation of the lesions.

Vessel Areas and Diameters for MDCT and MRI

<table>
<thead>
<tr>
<th></th>
<th>MDCT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LA</td>
<td>TVA</td>
</tr>
<tr>
<td>Mean</td>
<td>0.502</td>
<td>1.323</td>
</tr>
<tr>
<td>SD</td>
<td>0.139</td>
<td>0.489</td>
</tr>
<tr>
<td>Mean</td>
<td>0.461</td>
<td>1.327</td>
</tr>
<tr>
<td>SD</td>
<td>0.138</td>
<td>0.478</td>
</tr>
</tbody>
</table>

Values are expressed in cm² for the areas and in cm for the diameters. AP indicates anteroposterior; LAT, lateral.

Quantification of Vessel Lumen and Wall Parameters

We found close correlations between MDCT and MRI for all vessel measurements, which were stronger for the areas than the diameters. Both techniques demonstrated good accuracy to detect variations in vessel lumen along the course of the vessel. These differences were documented histopathologically. Importantly, MDCT was very sensitive for the detection of subtle differences in vessel diameters between contiguous segments. In this way, it allows the localization of areas of stenosis as well as those of negative and positive remodeling (Figure 6). Therefore, MDCT appears to be adequate for the assessment of differences in vessel wall and LAs between adjacent sections. Potential applications include the quantification of stenosis and follow-up during the natural history of the disease or in response to therapeutic measures. LA values were consistently larger with MDCT, but no significant differences were noted for TVA between techniques. Hence, there was a slight underestimation of the vessel wall area when compared with MRI (vessel wall area=TV-A LA). Nevertheless, there was very good agreement between both techniques, with a mean bias of only 0.1 to 0.3 mm for diameters and 0.04 mm² for LA. These findings might be explained by the different spatial resolution of both imaging modalities and in turn can justify the difference found in the analysis of sensitivity and specificity. Additionally, the measured diameters and areas in MDCT depend on the image display settings, which in this study were selected empirically.

Sensitivity and Specificity for Detection of Plaque

In agreement with previous reports, MRI showed a higher sensitivity (97%) and specificity (94%) than MDCT for plaque detection. Our assessment of sensitivity (89%) and specificity (77%) of MDCT to detect noncalcified, atherosclerotic lesions with the pathologic result as the gold standard is consistent with previous work. The sensitivity and specificity to identify stenotic (≥50% lumen reduction)
plaques in native coronary arteries in selected populations by 16-slice MDCT have been reported to be 92% to 95% and 86% to 93%, respectively. In a recent in vivo human study, a comparison of MDCT with intravascular ultrasound yielded a sensitivity of 92% and a specificity of 88% for the detection of segments with any nonstenotic plaque, but the sensitivity decreased to 53% when noncalcified plaques were considered exclusively. In our study, the sensitivity and specificity of MDCT became closer to that of MRI (96% and 84%, respectively) when lesions with a mean wall thickness <0.6 mm (limit of the spatial resolution of MDCT) were excluded. This observation suggests that the sensitivity of MDCT for plaque detection is strongly limited by spatial resolution. Hence, this may impede early detection of atherosclerotic disease and might affect its use as a screening tool.

A major limitation of this analysis is the high prevalence of sections with atherosclerotic lesion (151 of 182) as a result of utilization of an animal model of atherosclerosis, which may result in overestimation of the sensitivity of the technique. Nevertheless, the specificity was good, even before exclusion of smaller plaques.

**Plaque Characterization**

Analysis of MDCT images showed a statistically significant difference of attenuation between lipid and fibrous plaques, in line with prior reports indicating the potential of MDCT for tissue characterization. However, the high standard deviation of our results combined with the variability reported in previous work supports the idea that a reliable differentiation between lipid-rich and fibrotic plaques with MDCT may not be possible. In an ex vivo study, the mean attenuation was 47±9 for lipid-rich plaques (with 38 HU being the lowest attenuation) and 104±28 HU for fibrous plaques. The difference between lipid and fibrous plaques was statistically significant. With in vivo MDCT, a mean attenuation of 12±26 HU was found for lipid-laden plaques. Similarly, others have reported a density of 6±28 HU for soft plaques and of 83±17 HU for intermediate, noncalcified plaques. Additionally, the ability of MDCT to depict atherosclerotic plaque microarchitecture seems to be very poor, especially when compared with that of MRI. The differences found between reports and the high standard deviation of our study may be due to the complexity of atherosclerotic lesions and the still-limited spatial resolution of MDCT.

In summary, the present study provides the first assessment of the capabilities of 16-slice MDCT in comparison with high-resolution MRI and histopathology for arterial lumen and wall evaluation. Our results suggest that MDCT correlates very well with MRI in the measurement of vessel areas and diameters and that it reliably identifies noncalcified, nonstenotic, atherosclerotic plaques, although with poorer sensitivity and specificity than MRI. It can therefore be of potential utility in the detection of preclinical atherosclerotic lesions and assessment of the severity of stenosis and vessel remodeling with the additive advantage of a very short examination time when compared with MRI. A major drawback of MDCT is the radiation dose, which is on the order of 2 to 4 times that of conventional angiography. Moreover, despite the increased spatial resolution of the current generation of MDCT scanners, MRI still appears to be the modality of choice in the field of noninvasive “plaque characterization.” It is noteworthy that given that the rabbit aorta is a straight vessel that does not move (as opposed to the coronary arteries), it is uncertain how our results will translate into the clinical setting. Therefore, application of these imaging tech-
techniques to human coronary arteries may possibly not attain the same level of accuracy.

Acknowledgments
This study was supported by grants from the National Institutes of Health (National Institutes of Health Specialized Center of Research grant HL54469 to Drs Fuster and Badimon) and the National Heart, Lung, and Blood Institute (HL61801 to Dr Fuster). Dr Sanz’s work is supported in part by a research grant from the Spanish Society of Cardiology. We are grateful for the technical assistance of Jose Rodriguez and Anthony Lopez. We thank Frank Macaluso and Paul Wisdom for their collaboration and support.

References
In Vivo 16-Slice, Multidetector-Row Computed Tomography for the Assessment of Experimental Atherosclerosis: Comparison With Magnetic Resonance Imaging and Histopathology

Juan F. Viles-Gonzalez, Michael Poon, Javier Sanz, Teresa Rius, Konstantin Nikolaou, Zahi A. Fayad, Valentin Fuster and Juan J. Badimon

_Circulation_. 2004;110:1467-1472; originally published online September 7, 2004; doi: 10.1161/01.CIR.0000141732.28175.2A

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/11/1467

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/