The Prevalence and Quantification of Atherosclerosis in an Elderly Population Assessed by Whole-Body Magnetic Resonance Angiography


Objective—The principal aim of the present study was to explore the feasibility of using whole-body magnetic resonance angiography to assess atherosclerosis in different vascular territories in a cohort of elderly.

Methods and Results—Three hundred six 70-year-old subjects (145 women, 161 men) recruited from a population-based cohort study (Prospective Investigation of the Vasculature in Uppsala Seniors, ie, the PIVUS study) underwent 1.5-T whole-body magnetic resonance angiography with gadodiamide. The arteries were divided into 26 segments. In total, 7956 vessel segments were evaluated with 7900 segments (99.3%) possible to evaluate. Of these, 7186 segments (91%) were normal. Luminal narrowing of ≥50% was observed in 9 (1.5%) of the renal arteries, 12 (1.8%) of the carotid arteries, in 31 segments (1.1%) of the pelvic/upper leg territories, and in 136 segments (6.2%) of territories in the lower leg. Approximately one-third of the sample had no vascular abnormalities, one-third had stenoses of <50%, and the remainder had stenoses ≥50% or occlusions. Six subjects (2%) had aortic aneurysms. In subjects without evident vascular disease, 26% had significant vascular abnormalities.

Conclusions—Whole-body magnetic resonance angiography performed with a clinical scanner can be used for quantifying atherosclerosis in different vascular territories in a single examination in an elderly population. (Arterioscler Thromb Vasc Biol. 2007;27:649-654.)

Key Words: atherosclerosis | cardiovascular diseases | epidemiology | MRI | population

In epidemiological studies with evaluation of atherosclerosis in different vascular territories, mixtures of different imaging and other methods have been used, which has limited the possibility of direct comparison of atherosclerosis-induced stenosis in different arteries.1 Magnetic resonance angiography (MRA) has advantages over conventional angiography in that it lacks ionizing radiation, there are no risks otherwise associated with arterial cannulation, and there is less nephrotoxicity than with iodinated contrast agents on the account of the smaller volumes of contrast agents administered in MRA. Recently the concept of imaging of the whole arterial system, except the coronary arteries, with one intravenous injection of gadolinium contrast and a moving table, ie, whole-body magnetic resonance angiography (WBMRA),2 has been introduced. By this means the prevalence of stenosis in different arterial territories can be evaluated with minimal invasiveness at the same time with one single method.

It has previously been shown, using digital subtraction angiography (DSA) as the gold standard, that WBMRA has a high sensitivity and specificity for estimating the extent of atherosclerosis in patients with peripheral vascular disease.3–6 WBMRA of other vascular territories, however, has not been compared with the standard imaging techniques. The prevalence of atherosclerosis based on a sample from a general population of elderly citizens has never to our knowledge been established previously with the use of WBMRA.

The principal aim of the present study was to explore the feasibility of using WBMRA in a clinical scanner to assess atherosclerosis in different vascular territories in a cohort of elderly subjects (the Prospective Investigation of the Vasculature in Uppsala Seniors [PIVUS] study).7 Secondary aims were to estimate the prevalence and distribution of atherosclerotic abnormalities in this free-living population of 70-year-old subjects and to determine whether the degrees of atherosclerosis in different vascular territories are related to one another.

Materials and Methods

Subjects

The study was approved by the Ethics Committee of the University of Uppsala and the participants gave written informed consent. Over a 3-year period (November 2002 to November 2005), 307 subjects (145 women, 162 men) were randomly recruited from the population-based cohort study (PIVUS study, www.medsci.uu.se/ pivus) comprising 1016 participants. The primary aim of PIVUS was to evaluate the predictive power of 3 different tests of endothelium-dependent vasodilation to predict future cardiovascular events.
Eligible for that study were all subjects aged 70 living in the municipality of Uppsala, Sweden. The subjects for the PIVUS study were chosen from the Population Register of the municipality and were invited in randomized order within 2 months from their 70th birthday. Of the 2025 subjects invited, 1016 subjects were investigated. As the participation rate was only 50.1%, we performed an evaluation of the cardiovascular status and medications in 100 consecutive persons who were invited to participate in the PIVUS study, but declined, to see if there was any bias in the selection. A comparison was also made in these respects between the total PIVUS sample and the WBMRAsubsample. Exclusion criteria for the WBMRAscans were pacemaker, valvular prostheses, intracranial clips, and claustrophobia.

In a subanalysis, the subjects in the WBMRAsub sample were divided in 2 groups, either without or with known vascular disease, defined as myocardial infarction, stroke, angina pectoris, diabetes, cardiac heart failure, or coronary revascularization. These 2 groups were categorized according to the most severe atherosclerotic abnormality in any vascular segment into 3 groups; normal, only <50% stenosis, or ≥50% stenosis including occlusion.

Method of WBMRAscans

The WBMRAscans were performed with the standard quadrature body coil in a 1.5-T Gyroscan Intera scanner (gradients: amplitude 30 mT/m, rise time 200 μs; slew rate 150 mT/m/ms), using standard MobiTrak software (Philips Medical System, Best, The Netherlands). The subject was placed in the supine position head first on the table, to which an extension of the table top was attached, allowing for larger coverage. The arms were placed over the patient’s head to avoid foldover. A 2-ml test bolus of Gadodiamide was used with a coronal dynamic acquisition. From these images the time taken from injection of the contrast agent into the antecubital vein to its arrival in the proximal descending aorta could be measured.

The WBMRAscans were divided into 4 stations. The first station included the supra-aortic arteries and the thoracic aorta. The second station contained the abdominal aorta, including the renal arteries, and the third station started at the external iliac arteries and continued to the popliteal arteries. The fourth and last station continued for a varying distance below the ankle. An overlap of 3 cm between each station gave a maximum total length of coverage of 171 cm. Breath-holding was performed only for the second station.

A 3-dimensional RF-spoiled T1-weighted gradient echo acquisition was performed at these 4 stations, beginning with the fourth station, before the injection. The scan time for each station was 17 seconds. The table top was moved automatically with the table. The scan time for the noncontrast-enhanced images was 87 seconds, including instructions for breath-holding and table movement, which took 4 seconds each for the three movements. Thereafter, 40 mL of gadodiamide (Omniscan; GE Healthcare, Oslo, Norway) was injected intravenously with an automated injector (MR Spectris; Medrad, Pittsburgh, Pa) at a rate of 0.6 mL/second in 67 seconds and flushed with 20 mL of saline solution. The scan was set to start after the time defined following the test bolus examination. The stations were scanned in reversed order during the contrast administration, with the first station first. Another 87 seconds is acquired for the following acquisitions for the 4 stations including table top movement.

The sequence parameters were: TR/TE/Trip angle 2.5 ms/0.94 ms/30°; bandwidth 781.3 Hz/pixel; matrix size 256×256; FOV/no. of slices×thickness 450 mm/60×4 mm; 80% scan percentage. The measured voxel size was 1.76×1.76×4.0 mm, and this was reconstructed by zero-filling to 0.88×0.88×2.0 mm, which gives a 1.54 mm³ volume of reconstructed voxel. Linear K-space sampling was used for the first station. For the other stations, a method of randomly segmented centric view order (Centra; Philips Medical System, Best, the Netherlands) was used.

WBMRDdata were postprocessed with subtraction of precontrast data from the postcontrast data, both in a 512×512 matrix. Maximum intensity projections were obtained from the subtracted series with a 512×512 matrix at 45° on each side from the coronal plane in a total of 9 images in every station. Seventy-five-axial multiplanar reconstruction (MPR) images over the renal arteries were acquired from the unsubtracted contrast-enhanced series with a slice thickness of 1.5 mm and zero gap in a 512 matrix. Source images, MPR and maximum intensity projection images were interpreted on an AGFA IMPAX workstation.

Image Evaluation

The arterial tree was divided into 26 vessel segments: internal carotid arteries, common carotid arteries including the brachiocephalic trunk on the right side, thoracic aorta, abdominal aorta, renal arteries, common iliac arteries, external iliac arteries, common femoral arteries, superficial femoral arteries, popliteal arteries, tibio-peroneal trunks, anterior tibial arteries, peroneal arteries, and posterior tibial arteries. The right and left sides were evaluated separately. Only the first 3 to 5 cm of the renal arteries and only the bulb of the internal carotid arteries were assessed.

If a segment could be evaluated, the finding in that segment was allocated to 1 of 5 groups: no stenosis, 1% to 49% reduction in lumen diameter, 50% to 99% reduction in lumen diameter, occlusion, or aneurysm. If a segment could not be evaluated, the reason for this was noted and categorized into 1 of 4 groups: venous overlap, motion artifacts, poor contrast filling, and other reasons (eg, susceptibility artifacts from knee prosthesis). Each segment was graded only according to the most severe stenosis. Significant atherosclerotic abnormality was defined as a reduction of the vessel diameter by 50% or more, or occlusion. Stenosis was measured in the narrowest part of the vessel and compared with the normal vessel diameter using both the source and maximum intensity projection images. Aneurysm was defined in the abdominal aorta as a lumen diameter of 3 cm or more, and elsewhere as a 50% dilation of the vessel diameter compared with the nearest apparently normal vessel. One radiologist (T.H.) evaluated all WBMRAscans blinded to other information. A consecutive series of 30 subjects were evaluated by another radiologist (H.A.) blinded to all other information. The radiologist who initially interpreted the images made a new evaluation of the same 30 subjects, blinded to the previous report and the other radiologists report.

The 26 vessel segments were categorized into 5 territories: (1) the carotids, including the internal carotid artery and common carotid artery; (2) the aorta, including both the thoracic and abdominal part; (3) the renal arteries; (4) the pelvic/upper limbs, including the common iliac artery, external iliac artery, common femoral artery, superficial femoral artery, and popliteal artery; and (5) the lower legs, including the tibio-peroneal trunk, anterior tibial artery, peroneal artery, and posterior tibial artery.

To obtain a comparable graded number reflecting the atherosclerosis in each territory, an atherosclerotic score was calculated for each territory. A normal vessel segment received null points, <50% stenosis was given 1 point and 50% reduction or more of the vessel diameter, including occlusions, was given 2 points. The points for the vessel segments in a territory were summarized. That sum was then divided by the maximum sum that would be achieved if all included segments had >50% stenosis or occlusion. The ratio was thereafter multiplied by 100. Hence, each territory could attain a maximum atherosclerotic score of 100. Vessel segments not possible to evaluate were excluded from the calculations.

Statistical Analysis

Differences between groups regarding nominal variables were evaluated by means of contingency tables and the χ² test. Relationships between pairs of variables were tested by means of Spearman correlation analysis. Two-tailed significance values are given, with P<0.05 regarded as significant. Inter- and intra-observer variability was quantified with kappa statistics. A k-value of <0.20 denotes poor agreement, 0.20 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and >0.80 denotes excellent agreement. The statistical program package StatView (SAS inc, NC) was used for calculations.
Results

Some characteristics of the total sample (PIVUS study) and of the WBMRA subjects are given in Table 1. No significant differences in the basic characteristics and major cardiovascular risk factors were found between the total PIVUS sample, the WBMRA subsample, and those not attending the basic investigation (Table 2). The mean length of time between the basic investigation and WBMRA was 16 months and ranged from 3 to 24 months. Some examples of WBMRA are given in Figure 1.

The examination could be performed in 306 of the 307 subjects. One subject had a vasovagal reaction before the contrast administration and the WBMRA could therefore not be completed. In total, 7956 vessel segments were evaluated with a success rate of 99.3%. Of these segments, 7186 were normal (90.9%). The results for the different vessel segments are presented in Table 3. The most frequent significant atherosclerotic abnormalities (<50% stenosis, occlusion) were found in the lower leg (72%), especially in the anterior and posterior tibial arteries. The most frequent segments, of all segments, that were not possible to evaluate were also located in the lower leg territory (67%). Luminal narrowing of 50% or more was present in 1.5% of the renal arteries and in 1.8% in the bulb of the internal carotid arteries. The numbers on individual level are presented in Figures 2 and 3. Two percent had an infrarenal abdominal aneurysm. In 27 subjects at least 1 segment was not possible to evaluate. The subjects (n=299) were divided in 2 groups according to the presence of evident vascular disease or not. In the group without evident vascular disease (n=230), the numbers were: normal (n=85), <50% (n=86), and ≥50% or occlusion (n=59). In the group with vascular disease (n=69), the numbers were: normal (n=14), <50% (n=22), and ≥50% or occlusion (n=33).

The intra-observer reproducibility was good (kappa value=0.73), with intra-observer agreement in 94% of the segments. Inter-observer reproducibility was excellent (kappa

<table>
<thead>
<tr>
<th>TABLE 1. Basic Characteristics and Major Cardiovascular Risk Factors in the Total and WBMRA Samples</th>
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<tr>
<td><strong>Total Sample</strong></td>
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<tr>
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<tr>
<td>Females, %</td>
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<td>Height, cm</td>
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<td>SBP, mm Hg</td>
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<td>DBP, mm Hg</td>
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<td>Heart rate, beats/min</td>
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<td>Serum cholesterol, mmol/L</td>
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<td>LDL cholesterol, mmol/L</td>
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<td>HDL cholesterol, mmol/L</td>
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<td>Serum triglycerides, mmol/L</td>
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<td>Fasting blood glucose, mmol/L</td>
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<td>Current smoking, %</td>
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No significant differences were found for any variables between the 2 sample sets. Means are given ±SD.

DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

<table>
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<th>TABLE 2. Self-Reported History of CV Disorders and Regular Drug Intake in the Investigated Sample in 100 Nonattendees and in the WBMRA Subjects</th>
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<tbody>
<tr>
<td><strong>Total Investigated Sample</strong></td>
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<td>N</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
</tr>
<tr>
<td>Stroke, %</td>
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<tr>
<td>Angina pectoris, %</td>
</tr>
<tr>
<td>CABG/PTCA, %</td>
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<tr>
<td>Congestive heart failure, %</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Any regular drug, %</td>
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<tr>
<td>Any CV drug, %</td>
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<tr>
<td>Any antihypertensive medication, %</td>
</tr>
</tbody>
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No significant differences in the basic characteristics and major cardiovascular risk factors were found between the total PIVUS sample, the WBMRA subsample, and those not attending the basic investigation. CABG/PTCA indicates coronary revascularization; CV, cardiovascular.
value=0.83) with inter-observer agreement in 77% of the segments. The atherosclerotic score for the different territories (means and ranges) was as follows: carotid territory 4.8 (0 to 50), aorta 7.0 (0 to 50), renal territory 4.3 (0 to 75), pelvic/upper leg territory 4.6 (0 to 45), and lower leg territory 7.3. (0 to 69). Then, when a correlation matrix was calculated for the atherosclerotic score in the 5 different vascular territories they were all found to be significantly interrelated (r=0.44 to 0.58, P<0.0001) for all comparisons (supplemental Table I, http://atvb.ahajournals.org).

**Discussion**

The present study showed that WBMRA can be performed and evaluated in an elderly population with use of a 1.5-T clinical scanner. Approximately one-third of the sample had no vascular abnormalities, one-third had stenoses of <50%, and the remainder showed stenoses with a luminal diameter reduction of at least 50% or occlusions. In addition, correlations between atherosclerotic abnormalities in different vascular territories were found for all territories, emphasizing that atherosclerosis is a systemic disease.

The prevalence of atherosclerotic abnormalities has been studied previously with WBMRA, but not in a large sample of elderly free-living citizens. In a study comprising 298 subjects after exclusion of subjects with stroke, myocardial infarction, and diabetes mellitus (mean age 50 years; range, 31 to 73), 12% had any vascular abnormality.8 In another study with 50 healthy subjects (mean age, 54 years; range, 41 to 63), only 1 abnormality was found, an occlusion of an anterior tibial artery.9 In these 2 studies only healthy subjects were included. The prevalence figure cannot therefore be compared with those in the present population-based study on 70-year-old subjects, 69% of whom showed manifest atherosclerosis.

In the present study, stenosis of at least 50% was found in the carotid arteries in 3.6% of the subjects. The prevalence of stenosis in these arteries has not been studied before with WBMRA in an elderly population in an epidemiological setting. In previous studies performed with ultrasound in elderly populations, the prevalence of stenoses of at least 50% in the carotid arteries ranged from 4 to 7.7%.10–12 Whereas the diagnosis of a at least 50% stenosis by WBMRA is based on

![Figure 2](image-url)

**Figure 2.** Distribution of subjects by maximum degree of atherosclerotic obstruction (of N=306). On an individual basis, 100 subjects showed no abnormalities and 112 subjects had a luminal reduction of <50%. Ninety-four subjects had significant atherosclerotic abnormalities, including ≥50% luminal reduction and occlusions.

![Figure 3](image-url)

**Figure 3.** Distribution of subjects by segments with significant (≥50%, occlusion) luminal obstruction (of N=306); 41 subjects had only 1 segment with a significant atherosclerotic abnormality, 31 showed 2, whereas 22 had ≥2 significant atherosclerotic abnormalities.
measurements of the luminal diameter, the clinical estimation of the degree of stenosis by ultrasound is based on Doppler blood velocity measurements.1

The prevalence of the renal artery stenosis in the present study was 3%. This is the first time to our knowledge that this prevalence has been reported in a free-living population sample. In a previous autopsy study, this figure ranged from 4.3% to 12%.13 In autopsy studies, however, bias toward patients with more severe disease is likely. In other studies, reporting higher prevalences ranging from 14% to 42%, either patients with risk factors for atherosclerotic renal artery stenosis, eg, hypertension, or renal insufficiency, or patients who had been referred for coronary angiograms or abdominal aortography before the renal angiography, was selected.14,15

All aortic aneurysms observed in this study (2%) were located in the infrarenal abdominal aorta. This is in line with previous prevalence estimations by ultrasound, which have ranged from 1 to 2% in the general population.16 In patient-based studies, the reported prevalence has varied between 4.3 and 6.8%.16,17

Atherosclerotic plaque in the femoral vessels has previously been evaluated by ultrasound in elderly British citizens (56 to 77 years). Plaques were defined as a localized wall thickening >1.2 mm and the prevalence in the common femoral artery was 64%. The prevalence of concomitant cardiovascular disease (previous ischemic heart disease, angina, or stroke) was higher in the group with femoral plaque.18 These findings are not comparable with our results, because such small vessel irregularities will not be visualized with WBMRA. In our study, 2% of the common femoral arteries were affected by atherosclerosis.

The prevalence of lower leg atherosclerosis has not previously been estimated in detail in the general elderly population. The relatively small diameter of the arteries in the lower leg can sometimes make the evaluation difficult. Therefore, the grade of uncertainty is probably higher for these vessels. In epidemiological research, a low ankle–brachial index (ABI) is often used as a substitute for a direct evaluation of lower leg atherosclerosis,1 but the relationship between ankle–brachial index <0.9 and lower limb atherosclerosis has not been evaluated in any population sample.

WBMRA allows all major arterial territories, except the coronary arteries, to be evaluated at the same time, with the same technique and with the same criteria. In the present study, relationships between the degrees of atherosclerosis in different territories were observed. Previously, atherosclerosis of the coronary arteries and of the vascular territories has been shown to be related,19,20 a finding that together with our results emphasizes that atherosclerosis is a generalized disease.

The intra- and inter-observer reproducibility in this study was good to excellent (kappa value 0.73, 0.83), indicating the robustness of the WBMRA method. Comparing a lower inter observer agreement (77%) than intra-observer agreement (94%), the resulting higher kappa value for inter-observer reproducibility seems paradoxical. The cause is that 1 observer (H.A.) consistently rated vessels as with more atherosclerotic abnormalities than the other observer (T.H.). The following lower inter-observer agreement, as compared with intra-observer agreement, causes a reduction in the statistical probability that a certain vessel segment by chance would receive the category normal or stenosis <50%. The 2 categories normal and stenosis <50% are by far the largest by numbers so they have the largest impact on the kappa value calculations. Then the fact that the observed distributions of the categories between the 2 observers were better than the expected resulted in a kappa value that was higher than the kappa value for intra-observer reproducibility. Previous WBMRA studies with inter observer reproducibility analysis obtained k-values of 0.90 to 0.93.9,21 In epidemiological studies, the fact that one minimally invasive, nonradiation technique, was feasible to perform in a large cohort of elderly citizens for quantifying atherosclerosis in different vascular territories makes WBMRA a safe and robust method.

One limitation of the present study is the low spatial resolution of WBMRA. In the present study, the volume of the reconstructed voxels was 1.54 mm3 (0.88×0.88×2.0 mm) and the smaller vessels in the lower leg had a diameter of 2 to 3 mm, which means that a vessel could consist of just 2 to 3 voxels in the image. This could lead to lower certainty in assessment of the smaller arteries. A practical approach to handling the relatively low resolution of WBMRA is to add a dedicated coil and a second administration of contrast agent when performing a sequence with higher resolution when there is suspicion of relevant pathology. The contrast and signal to noise ratios are lower when compared with a more dedicated examination to a specific region, caused by the shorter scan time in WBMRA. The recent approval of a blood pool agent (MS-325) could also enable later scans with high resolution. Also higher field strength (3T) in combination with total imaging matrix coils which allows parallel imaging for higher resolution. WBMRA visualizes the lumen of the arteries, which could possibly lead to an underestimation of aneurysms. Other limitations are that the method is not capable of visualizing the coronary arteries because of motion artifacts and the relatively low resolution of the examination, and that the present sample is limited to whites aged 70. Thus caution should be observed in extrapolating the results to other ethnic and age groups. The present study had a moderate participation rate. However, an analysis of nonparticipants showed the present sample to be fairly representative of the total population regarding most cardiovascular disorders and drug intake.

Previously, MRA in several vascular territories has been shown to be a valid technique for assessing significant atherosclerotic disease in patients, using DSA as a gold standard. The validations of WBMRA in previous studies have shown a high sensitivity and specificity for the pelvic and lower limb arteries in comparison with DSA. For the renal, aortic, and carotid arteries, there exists no systematic validation using DSA. Instead various methods have been used for confirmation of vascular abnormalities found on WBMRA, such as ultrasound, dedicated MRA, or DSA with a reasonably high agreement.1–6,8,9,21,22 The lack of validation using DSA is caused by the ethical problems with whole-body ionizing radiation. The value of WBMRA both in clinical practice and in patient-based studies is yet to be established. However, the present study has shown that the
technique is feasible for assessing atherosclerosis in 70-year-old subjects and that significant atherosclerotic abnormality is present in subjects without evident vascular disease. Potentially it can be used in screening of risk groups for cardiovascular events. Screening is a controversial matter, and it is not proven that the cost to society of screening a population to detect asymptomatic disease and prevent future cardiovascular events in individual subjects is effective.

In conclusion, WBMRA can be performed and successfully interpreted in a random population sample of elderly subjects. Approximately one-third of the sample had no vascular abnormalities, one-third had stenoses of <50%, and the remainder had luminal reductions of at least 50% or occlusions. The study confirmed that WBMRA in a 1.5-T clinical scanner, a minimally invasive, nonradiation technique, can be used for quantifying atherosclerosis in different vascular territories in a single examination. This method could be useful as a tool for assessing atherosclerosis in an epidemiological setting.

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Disclosures

L. Johansson was previously employed by GE Healthcare and is now employed by AstraZeneca. L. Lind is employed by AstraZeneca. M.E.-S. has received honoraria from Edwards and Medtronic and is on the advisory board for Edwards.

References

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Table I

Spearman rank correlation coefficient between the atherosclerotic scores of the different territories.

<table>
<thead>
<tr>
<th></th>
<th>Carotid</th>
<th>Aorta</th>
<th>Renal</th>
<th>Pelvic/upper leg</th>
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<tbody>
<tr>
<td>Aorta</td>
<td>0.542</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>0.579</td>
<td>0.563</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic/upper leg</td>
<td>0.479</td>
<td>0.645</td>
<td>0.564</td>
<td></td>
</tr>
<tr>
<td>Lower leg</td>
<td>0.439</td>
<td>0.459</td>
<td>0.472</td>
<td>0.494</td>
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</tbody>
</table>

The AS is a sum of the vascular abnormalities for the five different vascular territories. A normal vessel segment received null points, < 50% stenosis one point and ≥ 50% stenosis and occlusion received two points. The sum for each territory was then divided by the maximum achievable sum for that territory. The ratio is multiplied by 100. p values for all correlations were <0.0001.