Multimodality Imaging of Carotid Artery Plaques

18F-Fluoro-2-Deoxyglucose Positron Emission Tomography, Computed Tomography, and Magnetic Resonance Imaging

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Background and Purpose—This study’s objective was to compare 18F-fluoro-2-deoxyglucose positron emission tomography (18F-FDG PET), CT, and MRI of carotid plaque assessment.

Materials and Methods—Fifty patients with symptomatic carotid atherosclerosis underwent 18F-FDG PET/CT and MRI. Correlations and agreement between imaging findings were assessed by Spearman and Pearson rank correlation tests, t tests, and Bland-Altman plots.

Results—Spearman ρ between plaque 18F-FDG standard uptake values and CT/MRI findings varied from −0.088 to 0.385. Maximum standard uptake value was significantly larger in plaques with intraplaque hemorrhage (1.56 vs 1.47; P=0.032). Standard uptake values did not significantly differ between plaques with an intact and thick fibrous cap and plaques with a thin or ruptured fibrous cap on MRI (1.21 vs 1.23; P=0.323; and 1.45 vs 1.54; P=0.727). Pearson ρ between CT and MRI measurements varied from 0.554 to 0.794 (P<0.001). For lipid-rich necrotic core volume, the CT–MRI correlation was stronger in mildly (≤10%) than in severely (>10%) calcified plaques (Pearson ρ 0.730 vs 0.475). Mean difference in measurement ±95% limits of agreement between CT and MRI for minimum lumen area, volumes of vessel wall, lipid-rich necrotic core, calcifications, and fibrous tissue were 0.4±18.1 mm² (P=0.744), −41.9±761.7 mm³ (P=0.450), 78.4±305.0 mm³ (P<0.001), 180.5±625.7 mm³ (P=0.001), and −296.0±415.8 mm³ (P<0.001), respectively.

Conclusions—Overall, correlations between 18F-FDG PET and CT/MRI findings are weak. Correlations between CT and MRI measurements are moderate to strong, but there is considerable variation in absolute differences. (Stroke. 2009; 40:3718-3724.)

Key Words: carotid atherosclerosis | computed tomography | 18F-FDG positron emission tomography | magnetic resonance imaging

Carotid atherosclerosis is an important cause of stroke. Because stroke results in considerable morbidity and mortality,1 prevention is pivotal. Currently, stenosis grade and symptomatology are the main grounds to perform carotid endarterectomy.2 However, for symptomatic patients with 70% to 99% stenosis, 6.3 patients need to undergo operation to prevent 1 patient who will experience ipsilateral ischemic stroke in 5 years. For symptomatic patients with 50% to 69% stenosis, this number is even as high as 22.2 Noninvasive imaging of carotid plaque characteristics may be used to improve patient selection for surgery.1 However, it still remains to be investigated which modality is most effective. 18F-fluoro-2-deoxyglucose positron emission tomography (18F-FDG PET),4,5 CT,6,7 and MRI8–10 are widely available and are among the most promising tools. Degree of plaque 18F-FDG uptake correlates well to histological degree of inflammation (Spearman ρ=0.85).4 CT measurements of calcifications and fibrous tissue also correlate well with histology (Pearson ρ=0.86 and 0.87, respectively). Lipid-rich necrotic core volume (LRNC) quantification by CT only...
correlates well with histology in mildly calcified plaques (Pearson ρ=0.88). In severely calcified plaques, the correlation is lower (Pearson ρ=0.48). Quantitative assessment of plaque components (LRNC, calcifications, hemorrhage, and fibrous tissue) by MRI has been shown to correlate well to histology (Pearson ρ: 0.70 to 0.84). Sensitivity and specificity for the detection of intraplaque hemorrhage (IPH) are good (82% and 77%, respectively). Besides having the potential to improve patient selection for surgery, each of the above-mentioned modalities may also be used to monitor the natural course of atherosclerosis and to assess the effect of drug therapy. Before applying 18F-FDG PET, CT, or MRI for plaque imaging, it is important to know whether they can be seen as independent imaging modalities, or whether their findings strongly correlate. To our knowledge, however, there are no published studies on this issue yet. Therefore, the purpose of this study was to compare 18F-FDG PET, CT, and MRI findings of carotid plaque assessment.

Materials and Methods

Patients

Patients who had recent (<3 months) amaurosis fugax, TIA, or minor stroke and an ipsilateral carotid plaque causing <70% stenosis at duplex ultrasonography11 diagnosed by a neurologist were eligible for inclusion. Exclusion criteria were contraindications for MRI12 and a renal clearance <60 mL/min/1.73 m². This study was approved by our institutional review board and all patients gave written informed consent.

Imaging Parameters

18F-FDG PET/CT

Patients fasted overnight for ~12 hours. One hour after injection of 2.75 MBq/kg body weight of 18F-FDG, 3-dimensional PET scanning was performed on a PET/CT scanner (Gemini TF 64; Philips Healthcare). Low-dose CT scanning was used for attenuation correction. After PET scanning, contrast-enhanced CT images were obtained using 90 mL of iobitridol (Xenetix 350; Guerbet). Scanning parameters were collimation 64×0.625 mm, 120 kVp, 175 mAs, 0.5 seconds of tube rotation, and pitch 0.671. Field of view was 0.625 mm, 120 kVp, 175 mAs, 0.5

MRI

MRI examinations were performed on a 1.5-T scanner (Intera 11.1,4.3; Philips Healthcare). A dedicated 47-mm-diameter surface coil (Philips Healthcare) was fixed to the skin at the level of the carotid bifurcation at the symptomatic side. The plaque was imaged within 9 transverse slices. If the plaque was located symmetrically around the bifurcation (which was mostly the case), the analyzed slice package was also located symmetrically around the bifurcation. In other cases, the analyzed slice package was a little bit asymmetrical around the bifurcation (ie, more slices below than above the bifurcation, or vice versa). Five MR pulse sequences were acquired: (1) 3-dimensional T1-weighted turbo field echo (TFE), repetition time (TR)/inversion time (TI)/echo time (TE) 10.3/900/4.4 ms; flip angle, 15°; number of signal averager (NSA), 6; inversion prepulse, shot interval time, 3000 ms, TFE factor, 163; profile order, linear, slice thickness, 3.0 mm; (2) 3-dimensional time of flight (TOF), TR/TE 23/3.9 ms; flip angle, 25°, NSA, 4; slice thickness, 3.0 mm; (3) multislice T2-weighted turbo spin-echo (TSE), TR/TE 2 heartbeat/heart rate-dependent/18 ms; NSA, 2; echo train length, 9; profile order, linear, slice thickness/gap, 2.5/0.5 mm. The postcontrast T1-weighted TSE sequence was obtained 7 to 8 minutes after injection of 0.1 mmol/kg body weight of gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma AG). T1 was adjusted according to heart rate and postcontrast T1 relaxation time of blood. For all sequences, the field of view was 100×80 mm, with a matrix size of 256×205 (in-plane resolution, 0.39×0.39 mm), except for the T1-weighted TSE sequence (field of view, 100×80 mm; matrix size, 256×163; in-plane resolution, 0.39×0.49 mm).

Image Review

Analyses of 18F-FDG PET/CT and MRI images were confined to the same longitudinal scan section of the carotid artery, using the flow divider as reference. For CT, a total of 39 slices were analyzed, comprising a total thickness of 39×0.7=27.3 mm. For MRI, a total of 9 slices were analyzed, comprising a total thickness of 9×3.0=27.0 mm (only 1% difference between CT and MRI). One investigator with 2 years of experience in plaque analysis (R.M.K.) evaluated 18F-FDG PET and CT images of the symptomatic side, blinded to MRI results. Stenosis grade was assessed on the CT images, using the NASCET method.13 Plaque was identified as presence of calcification or thickening of the vessel wall on the CT images. Regions of interest were manually drawn encompassing the plaque. Each region of interest was transferred onto the coregistered PET images (Figure 1). Dedicated fusion software (Syntegra; Philips Medical Systems) was used to calculate mean and maximum 18F-FDG standard uptake values (SUV) of the plaque, which were normalized for blood 18F-FDG activity by dividing them through the mean blood SUV. A polymeasure plug-in for the software package ImageJ (Rasband, National Institute of Mental Health) was used to semi-automatically quantify different plaque components at the CT images, as described previously.6 Different Hounsfield value ranges were considered to represent different plaque components; calcification >130 HU, fibrous tissue 60 to 130 HU, and LRNC (including possible IPH) <60 HU. The cut-off value between atherosclerotic plaque and lumen was adjusted for each patient and based on the full-width half-maximum principle (mean lumen mean fibrous tissue attenuation [88 HU] /2). To compensate for partial volume effects, related to high lumen attenuation at the plaque–lumen border, pixels around the lumen with a Hounsfield value between 130 HU and the adjusted cut-off value were considered to be fibrous tissue.6,7 Figure 2 shows an example of the drawn contours on CT images. The software calculated minimum lumen area, and volumes of vessel wall, LRNC, calcifications, and fibrous tissue. Overall, this CT-based method of plaque analysis has good interobserver reproducibility (for lumen area, vessel wall volume, volume of LRNC, calcifications, and fibrous tissue: intraclass correlation coefficient=0.84, 0.79, 0.70, 0.96, and 0.70, respectively) and very good intraobserver reproducibility (intraclass correlation coefficient=1.00, 0.97, 0.94, 0.99, and 0.98, respectively).7 MR images were evaluated by 1 investigator with 2 years of experience in plaque analysis (R.M.K.), blinded to 18F-FDG PET/CT results. MR images were evaluated using dedicated vessel wall analysis software (VesselMass, Department of Radiology, Leiden University Medical Center).14 Regions of interest
were drawn around identified plaque components (Figure 3) using previously published criteria.9,10,15 First, calcifications were identified as areas with hypointense signals (relative to signal of adjacent sternocleidoid muscle) on T1-weighted MRI weightings.9 Second, on the T1-weighted TFE image, LRNC (including possible IPH) was defined as an area of high signal intensity in the bulk of the plaque, using signal intensity of the adjacent sternocleidoid muscle as reference.9 With the precontrast T1-weighted TSE image as a reference, LRNC was identified on the postcontrast T1-weighted TSE image as an area in the bulk of the plaque with no or slight contrast enhancement compared to surrounding, more strongly enhanced fibrous tissues.10 When on the T1-weighted TFE or on postcontrast T1-weighted TSE images LRNC was identified, LRNC was scored as present. TOF images were used to identify the vessel lumen (bright signal) and to distinguish it from potential juxtaluminal calcifications (hypointense signal). When a hyperintense signal within the LRNC was observed on TOF images, IPH was scored as present (Figure 3). The software calculated minimum lumen area, and volumes of vessel wall, LRNC, calcifications, and fibrous tissue. Fibrous cap (FC) status was also assessed when a continuous high signal between LRNC and the lumen was identified on postcontrast images; FC status was classified as “intact and thick.” Alternatively, it was classified as “thin and/or ruptured” (Figure 3). The plaque area that was analyzed was predefined (9 slices per plaque). On a per-plaque basis, FC status was considered “thin and/or ruptured” when the FC on at least 1 slice was scored as “thin and/or ruptured;” otherwise, it was considered “intact and thick.”15 A second investigator with 9 years of experience in plaque analysis (M.E.K.) and the first investigator (R.M.K) also (re)analyzed MR images of 15 consecutive patients independently. Overall interobserver reproducibility was good (for lumen area, vessel wall volume, volumes of LRNC, calcifications, and fibrous tissue: intraclass correlation coefficient =0.82, 0.71, 0.92, 0.77, and 0.64, respectively), whereas intraobserver reproducibility was very good (intraclass correlation coefficients of 0.98, 0.85, 0.87, 0.97, and 0.83 respectively). Interobserver and intraobserver reproducibility for the detection of IPH were very good (kappa coefficient=0.86 and 1.00, respectively). Interobserver reproducibility of FC status assessment was good (kappa coefficient=0.60 to 0.71), whereas intraobserver reproducibility was very good (kappa coefficient=0.97).15

Figure 2. CT images of a transverse section of a carotid plaque. Region of interest encompassing the plaque and arterial lumen has been drawn on the CT image (A). To differentiate lumen area from the atherosclerotic plaque area and from calcified tissue, a second regions of interest should include the attenuated lumen area, but no calcifications. After the input of the cut-off values that differentiate the plaque components and the lumen, a pixel map based on Hounsfield unit values was obtained (green, arterial lumen; blue/white, calcifications; yellow, lipid; magenta/red, fibrous tissue) (C).

Figure 3. Coregistered T1-weighted TFE, TOF, T2-weighted TSE, and pre- and postcontrast T1-weighted TSE transversal images of carotid plaque. The right bottom panel displays the regions of interest (black, lumen; white, LRNC; dark grey, calcifications; light grey, fibrous tissue). Intraplaque hemorrhage was scored as being present (asterisk in TOF image) and the FC was designated as thin or ruptured (arrow in postcontrast T1-weighted TSE image).

Statistical Analysis
Statistical analysis was performed using SPSS version 11.5 (SPSS Inc), and MedCalc software (MedCalc). Correlations between SUV and CT/MRI-assessed parameters, which are not necessarily linear, were assessed by the Spearman rank correlation test, which measures whether one variable tends to take either a larger or smaller value, although not necessarily linearly, by increasing the value of the other variable. The correlation between SUV and MRI-assessed presence...
Results
Fifty patients (32 men; mean age, 68.1±9.6 years) were included. Mean time intervals between last symptoms and 18F-FDG-PET/CT and MRI examinations were 33.3±19.1 and 30.3±18.4 days. Mean time interval between 18F-FDG PET/CT and MRI was 5.7±3.7 days. Mean degree of stenosis at the symptomatic side on CT was 37±19%. Forty-three patients were using statin therapy (median duration of statin use at inclusion, 38 days; range, 5 days–20 years). There was a negative correlation between mean and maximum SUV and time after symptoms (Spearman ρ = −0.549 and −0.449, respectively; P<0.001).

18F-FDG PET vs CT and 18F-FDG PET vs MRI
There were no strong correlations between SUV and any of the CT/MRI-assessed parameters. There were some weak significant positive correlations as listed in Table 1. Mean SUV did not significantly differ between plaques with and without IPH (1.21 vs 1.22; P=0.059). Maximum SUV was significantly larger in plaques with IPH (1.56 vs 1.47; P=0.032). Mean and maximum SUV of plaques with an intact and thick FC did not significantly differ from those with a thin or ruptured FC (1.21 vs 1.23; P=0.323; and 1.45 vs 1.54; P=0.727, respectively).

CT vs MRI
Correlations between CT and MRI are listed in Table 2. Results of paired-samples t tests and Bland-Altman plots are displayed in Table 3 and Figure 4. Mean minimum lumen diameter and mean vessel wall volume on CT and MRI were not significantly different. Mean volume or LRNC and calcifications were significantly larger on CT, whereas mean volume of fibrous tissue was significantly larger on MRI. Mean difference in measurement ±95% limits of agreement between CT and MRI for minimum lumen area, volumes of vessel wall, LRNC, calcifications, and fibrous tissue were 0.4±18.1 mm², −41.9±761.7 mm³, 78.4±305.0 mm³, 180.5±625.7 mm³, and −296.0±415.8 mm³, respectively.

Discussion
We found that overall correlations between 18F-FDG PET-assessed degree of plaque inflammation and CT/MRI-assessed morphological and anatomic plaque features were weak. However, maximum SUV was significantly larger in plaques with IPH, compared to those without. There were moderate-to-strong correlations between CT and MRI-assessed parameters. However, LRNC and calcification measurements were significantly larger on CT, whereas fibrous tissue volumes were significantly larger on MRI. There was considerable variation in absolute differences between all CT and MRI measurements.

Table 2. Correlations Between CT and MRI

<table>
<thead>
<tr>
<th>CT- and MRI-Assessed Parameter</th>
<th>Pearson ρ</th>
<th>P</th>
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<tbody>
<tr>
<td>Minimum lumen area</td>
<td>0.794</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel wall volume</td>
<td>0.773</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LRNC volume</td>
<td>0.591</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Only mildly (≤10%) calcified plaques</td>
<td>0.730</td>
<td>0.003</td>
</tr>
<tr>
<td>Only severely (&gt;10%) calcified plaques</td>
<td>0.475</td>
<td>0.003</td>
</tr>
<tr>
<td>Volume of calcifications</td>
<td>0.554</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume of fibrous tissue</td>
<td>0.727</td>
<td>&lt;0.001</td>
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Table 3. Comparisons Between CT and MRI

<table>
<thead>
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<th>Mean Value at CT ± SD</th>
<th>Mean Value at MRI ± SD</th>
<th>P</th>
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<tbody>
<tr>
<td>Minimum lumen area, mm²</td>
<td>18.7±14.9</td>
<td>18.2±9.9</td>
<td>0.744</td>
</tr>
<tr>
<td>Vessel wall volume, mm³</td>
<td>836.3±604.7</td>
<td>878.2±405.8</td>
<td>0.450</td>
</tr>
<tr>
<td>LRNC volume, mm³</td>
<td>169.1±187.5</td>
<td>90.8±147.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume of calcifications, mm³</td>
<td>246.3±356.6</td>
<td>65.8±80.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume of fibrous tissue, mm³</td>
<td>421.0±292.1</td>
<td>716.9±281.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

or absence of IPH and FC status were evaluated using independent-samples t tests. Correlations between CT-assessed and MRI-assessed parameters were analyzed by the Pearson rank correlation test (which measures the linear relationship between two variables), because we expected a linear relationship between CT-assessed and MRI-assessed parameters (both have the same units). Very weak, weak, moderate, strong, and very strong correlation were defined as 0 to 0.19, 0.20 to 0.39, 0.40 to 0.59, 0.60 to 0.79, and 0.80 to 1.00, respectively. Absolute agreement between CT-assessed and MRI-assessed parameters was analyzed by paired-samples t tests and by computing Bland-Altman plots. 17
little/no uptake was observed in other plaque areas. To our knowledge, there are no studies correlating plaque 18F-FDG uptake and lumen area, volumetric measurements of plaque components, or presence/absence of IPH. In the present study, we found weak correlations between maximum SUV and volumes of vessel wall, LRNC, and fibrous tissue, both for CT and MRI. All these correlations, except the correlation between maximum SUV and LRNC volume on MRI, were significant. We found no correlation between SUV and volume of calcifications. This is in accordance to the study by Dunphy et al,18 showing that vascular 18F-FDG uptake and calcification rarely overlap. We also found no correlation between SUV and minimum luminal area on CT and MRI. This is in accordance to the findings of Tang et al,19 who also found no correlation between degree of inflammation (assessed by ultra-small superparamagnetic particles of iron
oxide-enhanced MRI) and degree of luminal stenosis. In addition, we found that plaques with IPH had significantly larger maximum SUV. This observation is consistent to previous studies, showing that IPH is associated with excessive inflammation.\textsuperscript{20} Redgrave et al\textsuperscript{21} showed that plaque inflammation was strongly associated with FC rupture. However, we unexpectedly did not find a relation between plaque SUV and FC status on MRI. This may be declared by the fact that in the present study, 86\% of included patients were on statin therapy, whereas in the study by Redgrave et al\textsuperscript{21} only 16\% of patients were using statin therapy. It is known that statins attenuate plaque inflammation, as depicted on \textsuperscript{18}F-FDG PET.\textsuperscript{22} Because of the low number of patients not using statins (n=7), we could not perform a meaningful subgroup analysis for these patients.

Differences between CT and MRI may be declared by differences in soft-tissue contrast. Poorer soft-tissue contrast makes it more difficult to delineate the outer vessel wall on CT, which may have lead to the misclassification of peri-arterial fat as being LRNC.\textsuperscript{7} Visual inspection of the Bland-Altman plot of LRNC volume (Figure 4C) supports this hypothesis, because many data points lay on a straight line. In these cases the LRNC volume on MRI was zero, whereas CT (probably falsely) detected LRNC. Additionally, LRNC quantification by CT has shown to be less accurate in severely calcified plaques: the blooming effect of calcifications may also explain why we found larger volumes of calcifications on CT and that, as volumes increased, calcification volumes tended to be larger on CT. Because of the blooming effect, CT may be more sensitive than MRI in detecting calcifications. This is also suggested by the Bland-Altman plot of calcifications, in which many data points lay in a straight line (Figure 4D), indicating that in these cases the volume on MRI was (probably incorrectly) zero, whereas CT detected calcifications. The blooming effect of calcifications may also explain that, at larger vessel wall volumes, measurements tended to be larger on CT (Figure 4B). Differences in slice thickness caused differences in partial volume effects, which may also have been a cause of differences between CT and MRI. Last, differences between CT and MRI may be declared by differences in image analysis; whereas CT images were analyzed semi-automatically, MR images were analyzed manually.

Our study has several limitations. First, we did not have histological confirmation, because the included patients were not operated (because the benefit of carotid endarterectomy was unclear). Future studies should compare the accuracy of \textsuperscript{18}F-FDG PET, CT, and MRI, using histology as reference. Second, degree of plaque inflammation, morphology, and composition may be time-dependent.\textsuperscript{23} We did find a negative correlation between SUV and time after symptoms. If imaging would have been performed sooner after symptoms, we might have found stronger correlations between \textsuperscript{18}F-FDG PET and CT/MRI. Third, 86\% of the included patients were on statin therapy. Besides their potential to attenuate plaque inflammation,\textsuperscript{22} statins may also decrease LRNC size.\textsuperscript{24} However, because carotid atherosclerosis is significantly associated with high cholesterol and triglycerides levels, it reflects normal clinical practice that most of the patients used statins. By keeping the time interval between \textsuperscript{18}F-FDG PET/CT and MRI as short as possible, we tried to avoid any possible discrepancies caused by change in plaque composition. Fourth, the time between \textsuperscript{18}F-FDG injection and PET imaging was 1 hour. By increasing this interval, higher lesion-to-background contrast could have been achieved.\textsuperscript{5} However, this was not possible because of too much patient discomfort. Last, this study only assessed morphological and compositional plaque features by MRI. Dynamic contrast-enhanced MRI and ultra-small superparamagnetic particles of iron oxide-enhanced MRI are 2 other promising techniques to evaluate inflammation in carotid atherosclerotic plaques.\textsuperscript{3} Future studies should investigate whether findings of these techniques correlate to \textsuperscript{18}F-FDG PET. The accuracy of (other) promising CT and MRI techniques, such as dual-energy CT or a motion-sensitized driven-equilibrium MRI sequence (which can improve blood suppression),\textsuperscript{25} should also be further explored.

In conclusion, the present study demonstrated that overall correlations between \textsuperscript{18}F-FDG PET and morphological and compositional CT/MRI findings are weak. Correlations between CT and MRI findings are moderate to strong, but measurements of LRNC and calcifications are significantly larger on CT, whereas measurements of fibrous tissue are significantly larger on MRI. There is also considerable variation in absolute differences between CT and MRI measurements, implying that CT and MRI are not interchangeable. Future prospective longitudinal studies should determine which imaging modality is most effective in improving patient selection for surgery.

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Disclosure

None.

References

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