Combined $^{18}$F-FDG PET-CT and DCE-MRI to Assess Inflammation and Microvascularization in Atherosclerotic Plaques

Martine T.B. Truijman, MD; Robert M. Kwee, MD, PhD; Raf H.M. van Hoof, MSc; Evelien Hermeling, MSc, PhD; Robert J. van Oostenbrugge, MD, PhD; Werner H. Mess, MD, PhD; Walter H. Backes, PhD; Mat J. Daemen, MD, PhD; Jan Bucerius, MD, PhD; Joachim E. Wildberger, MD, PhD; Marianne Eline Kooi, PhD

Background and Purpose—Hallmarks of vulnerable atherosclerotic plaques are inflammation that can be assessed with $^{18}$fluorine-fluorodeoxyglucose positron emission tomography/computed tomography, and increased neovascularization that can be evaluated by dynamic contrast–enhanced-MRI. It remains unclear whether these parameters are correlated or represent independent imaging parameters. This study determines whether there is a correlation between inflammation and neovascularization in atherosclerotic carotid plaques.

Methods—A total of 58 patients with transient ischemic attack or minor stroke in the carotid territory and ipsilateral carotid artery stenosis of 30% to 69% were included. All patients underwent positron emission tomography/computed tomography and dynamic contrast–enhanced-MRI of the carotid plaque. $^{18}$Fluorine-fluorodeoxyglucose standard uptake values with target/background ratio were determined. Neovascularization was quantified by the mean (leakage) volume transfer constant $K_{\text{trans}}$. Spearman rank correlation coefficients between target/background ratio and $K_{\text{trans}}$ were calculated.

Results—Images suitable for further analysis were obtained in 49 patients. A weak but significant positive correlation between target/background ratio and mean $K_{\text{trans}}$ (Spearman $\rho=0.30$ [$P=0.035$]) and 75th percentile $K_{\text{trans}}$ (Spearman $\rho=0.29$ [$P=0.041$]) was found.

Conclusions—There is a weak but significant positive correlation between inflammation on positron emission tomography/computed tomography and neovascularization as assessed with dynamic contrast–enhanced-MRI. Future studies should investigate which imaging modality has the highest predictive value for recurrent stroke, as these are not interchangeable.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00451529.

Key Words: atherosclerosis ◼ imaging ◼ inflammation ◼ magnetic resonance imaging ◼ neovascularization ◼ plaque, atherosclerotic ◼ positron-emission tomography ◼ vascular diseases
Methods

Patients

Patients with recent (<3 months) amaurosis fugax, transient ischemic attack or minor stroke in the carotid territory and ipsilateral carotid plaque causing a mild to moderate (30%–69%) stenosis at Doppler ultrasonography, were eligible for inclusion. Cardiovascular risk factors and the use of medication were assessed by a questionnaire. The study was approved by the institutional Medical Ethical Committee. All patients gave written informed consent.

Imaging

PET-CT examination and the multisequence MRI have in detail been described previously. Parameters of the DCE-MRI protocol have been published as well.

Image Analysis

The analysis of the PET-CT images was performed using a dedicated workstation. To determine the target/background ratio (TBR), the standard uptake values were normalized to blood 18F-FDG activity by dividing them by the mean standard uptake value of blood as measured in the internal jugular vein (Figure). TBR is considered to be a reflection of arterial FDG uptake and reflective of underlying macrophage activity.

Plaque morphology was manually assessed using dedicated vessel wall analysis software (VesselMASS; LUMC, The Netherlands). The operator was blinded for the PET-CT results. Quantification of neovascularization was done using a custom-made Matlab program (Matlab version 7.5; The Mathworks, Natick, MA), using the Patlak model and a generalized vascular input function. The mean Ktrans per patient was determined. In addition, histogram analysis was performed to determine the 75th percentile Ktrans, which is more reflective for hot spots with high Ktrans values (Figure).

Statistical Analysis

To correlate TBR with Ktrans, Spearman rank correlation coefficient was calculated using SPSS version 20 (SPSS Inc, Chicago, IL). Relation between clinical characteristics, TBR and Ktrans, was explored by univariate linear regression analysis. A P value of <0.05 was considered statistically significant.

Results

In total 58 patients were included. Nine of them had to be excluded, because of poor DCE-MRI quality. Patients underwent PET-CT 36.7±19.4 days and DCE-MRI 33.7±19.6 days after their last neurological symptoms. Mean time interval between both examinations was 2.9±5.5 days.

For the 49 patients analyzed, clinical characteristics and their relation between Ktrans and 18F-FDG are displayed in Table 1. The mean TBR was calculated as 1.45±0.26. The morphological parameters of the plaque as determined with MRI are given in Table 2. The mean and 75th percentile Ktrans were determined as 0.11±0.03 and 0.15±0.04 min⁻¹, respectively. A positive weak correlation between TBR and Ktrans was found.

Table 1. Cardiovascular Risk Factors of the 49 Analyzed Patients and the Results of the Univariate Linear Regression Analysis With TBR and Mean Ktrans

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TBR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Mean Ktrans</th>
<th>Standardized Coefficient β</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.13</td>
<td>-0.08 to 0.22</td>
<td>0.87</td>
<td>0.12</td>
<td>-0.01 to 0.02</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>65.3±8.8</td>
<td>-0.02</td>
<td>0.91</td>
<td>-0.19</td>
<td>-0.00 to 0.00</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>-0.11</td>
<td>-0.24 to 0.11</td>
<td>0.44</td>
<td>0.05</td>
<td>-0.02 to 0.02</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>12 (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>20 (41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (86)</td>
<td>-0.03</td>
<td>0.72</td>
<td>-0.16</td>
<td>-0.03 to 0.01</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (22)</td>
<td>-0.16</td>
<td>0.26</td>
<td>-0.13</td>
<td>-0.03 to 0.01</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>8 (16)</td>
<td>-0.23</td>
<td>0.12</td>
<td>-0.09</td>
<td>-0.03 to 0.02</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Use of statins before event</td>
<td>18 (37)</td>
<td>-0.20</td>
<td>0.17</td>
<td>0.02</td>
<td>-0.02 to 0.02</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Use of statins after event</td>
<td>46 (94)</td>
<td>-0.22</td>
<td>0.12</td>
<td>0.10</td>
<td>-0.02 to 0.04</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and TBR, target/background ratio.

Figure. Positron emission tomography/computed tomography (PET-CT; A) and dynamic contrast-enhanced (DCE) MRI (B–D) of a transverse section of the carotid plaque from a 64-year-old man. A, Fused PET-CT image. The lumen is delineated by the black line. The plaque is delineated by the dashed black line. B, Six minutes after contrast injection. C, T1-weighted Turbo Spin Echo MRI. D, Parametric Ktrans map overlaid on DCE-MRI. Voxel Ktrans values are color encoded from 0 to 0.2 min⁻¹. The lipid-rich necrotic core exhibits low Ktrans values at the center of the plaque. The highly vascularized adventitia (high Ktrans values) at the outer rim (arrow) is clearly visualized. ★, External carotid artery; and ▲, sternocleidoid muscle.
(mean $K^{trans}$, Spearman $\rho$ of 0.30 [$P=0.035$]; 75th percentile $K^{trans}$, Spearman $\rho$ of 0.29 [$P=0.041$]). No significant correlations between TBR and $K^{trans}$ in relation to the morphological parameters were observed.

**Discussion**

The purpose of this study was to investigate the relation between inflammation (PET-CT) and neovascularization (DCE-MRI) in carotid atherosclerotic plaques. We demonstrated that higher FDG uptake is weakly associated with increased microvasculature within the plaque. Cyran et al.\(^{15}\) also showed positive correlation between the mean TBR and the extraction fraction of DCE-MRI. Both imaging modalities provide information about hallmarks of plaque vulnerability, but it is unknown whether these imaging features are interchangeable or provide additive information. This study proves that, in symptomatic patients with mild to moderate (30%–69%) stenosis, PET-CT and DCE-MRI features of the plaque are related with each other, although the information provided is not interchangeable. This is expressed in the relative low correlation coefficient ($\rho$ of 0.30; $P<0.05$). However, we have not studied the use of these techniques for treatment decision making. Further studies should determine the clinical usage of inflammation and neovascularization for the individual patient’s management.

**Conclusions**

There is a weak but significant positive correlation between inflammation on PET-CT and neovascularization as assessed with DCE-MRI. Future studies should investigate that which imaging modality has the highest predictive value for recurrent stroke, as these are not interchangeable.

**Acknowledgments**

We thank B.J. Meems, MD, A.H.C.M.L. Schreuder, MD and N.P. van Orshoven, MD, PhD for their contribution in patient inclusion, F.M. Mottaghy, MD, PhD, S. Vöö, MD, and M.E. Gaens, MSc for their substantive contribution and R.J. van der Geest, MSc, MD for providing us the software (VesselMass) to analyze the data.

**Sources of Funding**

This research was performed within the framework of the Center for Translational Molecular Medicine (www.ctmm.nl), project PARISK (Plaque At RISK; grant 01C-202), and supported by the Dutch Heart Foundation.

**Table 2. Correlations Between TBR, mean $K^{trans}$, and Plaque Morphology as Assessed on MRI**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>TBR Spearman $\rho$</th>
<th>TBR $P$ Value</th>
<th>Mean $K^{trans}$ Spearman $\rho$</th>
<th>TBR $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lumen volume, mm$^3$</td>
<td>889.21±290.56</td>
<td>0.04</td>
<td>0.70</td>
<td>-0.03</td>
<td>0.82</td>
</tr>
<tr>
<td>Total wall volume, mm$^3$</td>
<td>979.84±333.31</td>
<td>0.05</td>
<td>0.73</td>
<td>-0.20</td>
<td>0.18</td>
</tr>
<tr>
<td>Total vessel volume, mm$^3$</td>
<td>1869.05±508.16</td>
<td>0.04</td>
<td>0.78</td>
<td>-0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean wall thickness, mm</td>
<td>1.46±0.42</td>
<td>0.04</td>
<td>0.79</td>
<td>-0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Max wall thickness, mm</td>
<td>3.99±1.43</td>
<td>0.26</td>
<td>0.07</td>
<td>0.05</td>
<td>0.73</td>
</tr>
<tr>
<td>Normalized wall thickness</td>
<td>0.52±0.09</td>
<td>0.13</td>
<td>0.37</td>
<td>-0.19</td>
<td>0.20</td>
</tr>
</tbody>
</table>

TBR indicates target/background ratio.

**Disclosures**

None.

**References**

Combined $^{18}$F-FDG PET-CT and DCE-MRI to Assess Inflammation and Microvascularization in Atherosclerotic Plaques
Martine T.B. Truijman, Robert M. Kwee, Raf H.M. van Hoof, Evelien Hermeling, Robert J. van Oostenbrugge, Werner H. Mess, Walter H. Backes, Mat J. Daemen, Jan Buceriuss, Joachim E. Wildberger and Marianne Eline Kooi

*Stroke*. 2013;44:3568-3570; originally published online October 10, 2013;
doi: 10.1161/STROKEAHA.113.003140

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/12/3568

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* 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 *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/