Varying Correlation Between $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography and Dynamic Contrast-Enhanced MRI in Carotid Atherosclerosis

Implications for Plaque Inflammation

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Background and Purpose—$^{18}$F-fluorodeoxyglucose positron emission tomography and dynamic contrast-enhanced MRI have been proposed to quantitatively assess plaque inflammation by probing macrophages and neovessels, respectively. We examined their correlation to study the in vivo relationship between macrophage and neovessel activities in atherogenesis.

Methods—Forty-one patients (34 men; aged 65±12 years) with a total of 68 carotid plaques (thickness ≥2 mm on ultrasound; 20 symptomatic) were assessed by both $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography and dynamic contrast-enhanced MRI within 2 weeks, measured as target-to-background ratio and transfer constant ($K_{\text{trans}}$), respectively.

Results—Overall, the correlation between target-to-background ratio and $K_{\text{trans}}$ was weak and marginal ($r=0.22; P=0.068$). They were correlated in the symptomatic plaques ($r=0.59; P=0.006$) but not in the asymptomatic plaques ($r=0.07; P=0.625; P=0.033$ for difference in $r$). Neither target-to-background ratio nor $K_{\text{trans}}$ was significantly higher in the symptomatic plaques, but both showed an inverse relationship with time since last neurological event ($r=-0.94$ and $-0.69$ for target-to-background ratio and $K_{\text{trans}}$, respectively).

Conclusions—The correlation between $^{18}$F-fluorodeoxyglucose positron emission tomography and dynamic contrast-enhanced MRI measurements varied with clinical conditions, pointing to a complex interplay between macrophages and neovessels under different pathophysiological conditions. The moderate correlation shown only in symptomatic plaques indicates the presence of acute plaque inflammation with increased metabolic activity and cytokine production by inflammatory cells. (Stroke. 2014;45:00-00.)

Key Words: atherosclerosis • carotid arteries • magnetic resonance imaging • positron emission tomography
artery within the past 4 months. The ipsilateral carotid plaque was considered the culprit based on clinical workup to rule out other common causes and defined as symptomatic.

**Dynamic Contrast-Enhanced MRI**
A previously published DCE-MRI protocol was used. Images were analyzed by 2 readers (X.Z. and H.C.) who followed a previously described approach to obtain plaque $K^{trans}$ while blinded to clinical information and PET/CT results (Figure 1).

**$^{18}$F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography**
PET/CT was performed on a dedicated PET/CT scanner (Biograph Truepoint, Siemens). Images were analyzed on a workstation (SynGo Somaris/5 software, Siemens) by 2 readers (Z.G. and C.L.) who were blinded to clinical information and DCE-MRI results. The approach described by Rudd et al was followed to obtain maximum TBR across slices that match MRI coverage (Figure 1).

**Statistical Analysis**
Spearman correlation coefficient ($r$) was used to assess correlation between variables. Correlation coefficients of mutually exclusive subgroups were compared using Fisher $z$ transformation. Mann–Whitney test was used to compare TBR and $K^{trans}$ between symptomatic and asymptomatic plaques.

**Results**
After excluding 5 subjects because of poor MR image quality, 41 subjects (34 men; aged 65±12 years) contributed 68 carotid arteries with atherosclerotic plaque (thickness >2 mm), of which 20 (29.4%) were symptomatic as a result of recent ischemic events (median: 29 days; range: 4–120 days).

The correlation between TBR and $K^{trans}$ was overall weak and marginal ($r=0.22$; $P=0.068$). Although no systemic condition modified their relationship, symptomatic status seemed to be a critical factor (Table). The 2 measurements were correlated in the symptomatic plaques but not in the asymptomatic plaques ($r=0.59$ versus $r=0.07$; $P=0.033$ for difference in $r$; Figure 2).

**Table. Correlation Between TBR and $K^{trans}$ Under Different Clinical Conditions**

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>$r$</th>
<th>$P$ Value</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=14)</td>
<td>0.18</td>
<td>0.53</td>
<td>0.80</td>
</tr>
<tr>
<td>Male (n=54)</td>
<td>0.26</td>
<td>0.06</td>
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</tr>
<tr>
<td>Symptomatic</td>
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<td></td>
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<tr>
<td>+ (n=20)</td>
<td>0.59</td>
<td>0.006</td>
<td>0.033</td>
</tr>
<tr>
<td>− (n=48)</td>
<td>0.07</td>
<td>0.625</td>
<td></td>
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<tr>
<td>Coronary artery disease</td>
<td></td>
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<tr>
<td>+ (n=39)</td>
<td>0.31</td>
<td>0.054</td>
<td>0.90</td>
</tr>
<tr>
<td>− (n=29)</td>
<td>0.08</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+ (n=17)</td>
<td>0.04</td>
<td>0.87</td>
<td>0.38</td>
</tr>
<tr>
<td>− (n=51)</td>
<td>0.24</td>
<td>0.08</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<tr>
<td>+ (n=52)</td>
<td>0.17</td>
<td>0.24</td>
<td>0.50</td>
</tr>
<tr>
<td>− (n=16)</td>
<td>0.42</td>
<td>0.10</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>+ (n=18)</td>
<td>0.20</td>
<td>0.43</td>
<td>0.80</td>
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<tr>
<td>− (n=50)</td>
<td>0.27</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
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<td></td>
<td></td>
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<tr>
<td>+ (n=35)</td>
<td>0.23</td>
<td>0.19</td>
<td>0.35</td>
</tr>
<tr>
<td>− (n=33)</td>
<td>0.20</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of correlation coefficients between 2 mutually exclusive subgroups.*

**Figure 1. Image analysis for measuring target-to-background ratio (TBR) and $K^{trans}$.**
A, A region of interest (ROI) around carotid artery is drawn to obtain maximum standard uptake value, which is then corrected for blood pool activity (jugular vein) to obtain TBR. B, Two ROIs are drawn coincident with lumen and outer wall enhancement on parametric vasa vasorum images generated from dynamic contrast enhanced MRI series to define wall area. Pixels within wall area and ≥1 mm away from lumen are averaged to obtain $K^{trans}$. 
Neither TBR nor $K^{\text{trans}}$ was significantly higher in the symptomatic plaques compared with the asymptomatic ones. Nonetheless, both showed an inverse relationship with time since last ischemic event ($r=-0.94$ and $-0.69$ for TBR and $K^{\text{trans}}$, respectively) in the symptomatic group.

**Discussion**

There is generally a hypothesized link between plaque macrophages and neovascularization. However, the nature and strength of their relationship are vague. Neovessels serve as a major entry route for inflammatory cells, and activated macrophages in turn may promote angiogenesis by secreting vascular endothelial growth factor and others alike. Such a relationship is complicated by the identification of macrophage subpopulations with diverse phenotypes and functions in atherogenesis. Although M1 macrophages may outnumber M2 macrophages in established lesions, it is suggested that the latter is involved more in angiogenesis. It is also equivocal whether improved perfusion via angiogenesis enhances (bringing more tracers) or suppresses (alleviating hypoxia) FDG uptake. The weak and marginal correlation between TBR and $K^{\text{trans}}$ reflects the many influential factors on macrophages and neovessels, as well as their imaging read-outs, which implies that the correlation could vary under different pathophysiological conditions.

A moderate correlation was noted in symptomatic plaques but not in asymptomatic ones. A prominent phenomenon in symptomatic plaques is the exacerbation of plaque inflammation, especially in the acute phase. The recruitment and activation of inflammatory cells lead to a parallel increase in proinflammatory cytokines that may have mediated the correlation between $^{18}$F-FDG PET and DCE-MRI signals seen in symptomatic plaques. We attribute the correlation to cytokines that influence microvascular permeability rather than microvessel density because the postevent decrease of $K^{\text{trans}}$ was rapid and paralleled the decrease in TBR, which could not be easily explained by regression in neovascularization.

In contrast to the traditional view of atherosclerosis as a chronic inflammatory process, our findings add in vivo evidence to the presence of acute plaque inflammation concurrently with clinical events, which was characterized by increased metabolic activity and cytokine production by inflammatory cells. Whether it is responsible for or just a consequence of clinical events remains to be investigated.

**Conclusions**

Our data from a heterogeneous population showed that the correlation between $^{18}$F-FDG PET and DCE-MRI measurements varied with clinical conditions, pointing to a complex interplay between macrophages and neovessels under different pathophysiological conditions. The moderate correlation shown only in symptomatic plaques indicates the presence of acute plaque inflammation and its clinical relevance.

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**Disclosures**

Dr Yuan has been a consultant for Philips Healthcare. The other authors report no conflicts.

**References**


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