Reproducibility, Partial Volume Correction, and Correlation Between Methods

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Background and Purpose—Inflammation is a major risk factor for atherosclerotic plaque rupture and clinical events. Previous studies have shown that plaque [18F]fluorodeoxyglucose (FDG) uptake correlates with macrophage content. In this study we examined the reproducibility of 3 methods of quantifying plaque FDG uptake in the carotid arteries using positron emission tomography (PET). The correlation between 2 simplified uptake parameters (standardized uptake value [SUV], vessel wall-to-blood ratio [VBR]) and a gold standard technique (influx rate \([K_i]\)) was also determined. We used MRI to correct carotid plaque FDG uptake for partial volume error.

Methods—Seven patients with a recent carotid territory transient ischemic attack underwent imaging twice within 8 days using MR and FDG-PET. MR coregistered to PET was used to delineate regions of interest, and to facilitate partial volume correction (PVC).

Results—SUV was the most reproducible parameter irrespective of whether it was normalized by body surface area (BSA), lean body mass, or weight (intraclass correlation coefficient \( r = 0.85, 0.88, \) and 0.90, respectively). VBR correlated better to \( K_i \) than SUV \(( r = 0.58, VBR, r = 0.46, SUVB)\). PVC improved these correlations to \( r = 0.81, VBR \) and \( r = 0.76, SUVB\), and only slightly degraded the reproducibility of SUV (intraclass correlation coefficient \( 0.83–0.85\).

Conclusions—MR-guided FDG-PET is a highly reproducible technique in the carotid artery and the excellent anatomic detail provided by MR facilitates PVC. Of the methods examined, SUVB\(_{PVC}\) appears to represent the best compromise between reproducible and accurate determination of FDG metabolism in carotid artery vessel wall. (Stroke. 2009;40:86-93.)

Key Words: atherosclerosis ■ magnetic resonance imaging ■ positron emission tomography ■ partial volume correction ■ reproducibility

Despite improvements in both primary and secondary prevention of atherosclerosis, the clinical syndromes it causes still account for one-third of all deaths. Rupture of an atherosclerotic plaque underlies most acute stroke either by thrombotic occlusion at the site of rupture or by distal embolization. The likelihood of plaque rupture is related to the inflammatory activity of the plaque rather than the degree of luminal obstruction it causes. Conventional imaging (x-ray angiography) fails as a predictive tool because it provides no information on plaque inflammation. Molecular imaging approaches to more accurately predict plaques at risk of rupture are therefore being investigated. One promising technique is to image the radiolabeled glucose analogue [18F]-fluorodeoxyglucose (FDG) using positron emission tomography (PET), which we have already shown to be capable of identifying inflamed plaques in stroke patients with carotid and vertebral disease. However, if FDG-PET is to be used to assess stroke patients with extracranial atherosclerotic disease, then further methodological validation needs to be performed.

First, it remains uncertain as to how best to quantify FDG uptake within arterial wall and plaque despite several studies confirming that FDG-PET can differentiate atherosclerotic lesions according to their degree of inflammation. Vessel wall-to-blood ratio (VBR), whole vessel-to-blood ratio, differential uptake ratio, blood pool ratio, and standard-
ized uptake value (SUV)\textsuperscript{14,15} have all been used. Although several studies have measured circulating FDG levels to normalize the plaque FDG uptake measurements,\textsuperscript{6,9,11} none of the published data has used Patlak analysis, a technique that calculates the rate at which FDG is transported into the cells and metabolized (K\textsubscript{i}) by graphical analysis of blood sampling and PET data.\textsuperscript{16} This study is the first to our knowledge to examine the feasibility of determining K\textsubscript{i} for plaque imaging and to compare it to other measures of plaque FDG uptake.

Second, the magnitude of the partial volume error (PVE) on measures of plaque FDG uptake and how these parameters are affected by partial volume correction (PVC) is currently unknown. PVE is the error that occurs as a result of limited spatial resolution,\textsuperscript{17} when quantifying regional tracer uptake with PET, the results are compromised by activity “spilling in” from adjacent regions and “spilling out” from the region of interest (ROI). In general, the smaller the ROI, the greater the PVE, although the relationship between size of ROI and degree of PVE is not straightforward because it also depends on the relative tracer uptake in the ROI to that in the surrounding tissues. PVE will lead to the overestimation of uptake in a region surrounded by higher uptake values and underestimation of uptake in a region surrounded by lower uptake values. In practice, it has been shown that PVE is minimal when the dimensions of a homogeneous uptake region are 2-3 times the spatial resolution of the scanner.\textsuperscript{18} The spatial resolution of most human PET scanners is \(\leq 6\) mm, and thus quantification of tracer uptake in atherosclerotic plaques (typical size \(<5\) mm)\textsuperscript{19} is likely to be significantly affected by PVE. The effect of PVE and correction for it has been studied extensively in brain PET.\textsuperscript{20–23} Following the general approach used most commonly in brain PET, we have used high-resolution magnetic resonance (HRMR) images coregistered to FDG-PET and the Rousset partial volume correction method\textsuperscript{21} to produce the first partial volume corrected results for atherosclerotic plaque imaging.

Very recently, the excellent test–retest reproducibility of FDG uptake in the carotid and aorta has been confirmed.\textsuperscript{11} However, results were only given for 1 FDG uptake parameter (whole vessel-to-blood ratio) and PVC was not applied. In this study the reproducibility of 3 measures of FDG uptake (VBR, SUV, K\textsubscript{i}) have been compared, both with and without PVC.

### Materials and Methods

#### Patient Recruitment

Seven patients (6 males and 1 female, aged 62 to 78 years; mean age\(\pm\)SD, 71.4\(\pm\)6.3) with recent carotid-territory TIA and evidence of ipsilateral carotid stenosis on Doppler ultrasound examination were recruited. All patients were assessed by experienced stroke physicians before entry into the study, and commenced on aspirin and statin medication. Antihypertensive medication was used at the physician’s discretion. Patients with standard contraindications to MR or PET imaging were excluded. The study was approved by the local ethics committee and the UK Administration of Radioactive Substances Advisory Committee. All patients gave written informed consent.

All patients underwent 2 FDG-PET scans within 8 days (mean\(\pm\)SD, 4\(\pm\)2 days) to enable reproducibility to be assessed. HRMR was performed for coregistration, resulting in a fused image with both anatomic information and the distribution of FDG.

Coregistered images were then used to determine plaque FDG uptake as described.

The PET and MR imaging protocols, together with the PET-MR coregistration method, have been described previously.\textsuperscript{7} Brief details are given.

#### PET Imaging

Data were acquired in 3-dimensional mode on a GE Advance PET scanner (General Electric Medical Systems) for 120 minutes (10\(\times\)5 sec, 7\(\times\)10 sec, 4\(\times\)15 sec, 6\(\times\)20 sec, 10\(\times\)30 sec, 5\(\times\)1 min, 5\(\times\)2 min, 19\(\times\)5 min) after an injection of 190 MBq FDG (191\(\pm\)16.3 MBq). An image was reconstructed for each timeframe using the PROMIS 3D filtered back-projection algorithm\textsuperscript{24} with corrections applied for attenuation, isotope decay, dead time, scatter, and random coincidences. A Hanning filter was applied transaxially to give a spatial resolution of \(\approx 6.8\) mm in all 3 directions at the center of the field of view. Blood samples were drawn at various time points (20, 40, 60, 80, 100, 120 sec, followed by 3, 4, 5, 7, 10, 15, 25, 35, 45, 55, 65, 75, 90, 105, and 120 min after injection) to allow measurement of plasma FDG concentration.

#### MR Imaging

HRMR images of voxel size 0.4\(\times\)0.4\(\times\)3 mm\textsuperscript{3} were acquired over a field of view of \(\approx 10\times10\times6\) cm around the carotid bifurcation using a T1-weighted sequence with fat saturation (TR=1\(\times\)R–R interval; TE=7.7 ms [Ef]; ETL=12, where TR indicates repetition time; R–R, time interval between successive R waves; TE, echo time; Ef, effective echo time; ETL, echo train length). To facilitate coregistration with PET, a large field of view T1-weighted MR (1\(\times\)1\(\times\)1 mm\textsuperscript{3} voxel size) was also acquired, covering approximately the same volume as the field of view of the PET scanner.

#### PET and MR Coregistration

For this study the large field of view MR and the HRMR were automatically coregistered using the rigid normalized mutual information algorithm implemented in the VTK CIGS Registration Toolkit (Computational Imaging Science Group, King’s College). For each PET scan, a mean PET image was coregistered (rigid transformation) to the large field of view MR using the software package MIPITool (Max-Planck-Institut Für Neurologische Forschung) using anatomic landmarks present on both scans, such as spinal cord, submandibular glands, and soft tissue surrounding the skull and mandible. Fine manual adjustment was performed if needed to improve the coregistration of the PET image to the HRMR image. All PET images were then sliced again to the HRMR using the coregistration translations and rotations. Based on the position of the artery lumens in the HRMR and the coregistered PET images, we found that the coregistration accuracy in the region around the carotid artery is \(\approx 1.2\) mm.

#### ROI Delineation

For each patient, 3-dimensional ROIs were manually drawn on contiguous transaxial planes of the HRMR using commercially available software (Analyze; AnalyzeDirect). For each carotid artery, separate ROIs were drawn for the vessel wall and lumen. In addition, ROIs were drawn around all anatomic structures within a 20-mm radius (3\(\times\)full width at half maximum of the scanner resolution) of each carotid artery to give a total number of 15 ROIs to allow for PVC (Figure 1). Each ROI set was then transferred onto the corresponding coregistered PET images to allow for calculation of vessel wall FDG uptake.

#### FDG Uptake Parameters

For each PET study, the following measures of vessel wall FDG uptake were calculated: SUV, VBR, and the influx rate (K\textsubscript{i}). PVC was performed for each carotid vessel, giving the following measures of FDG uptake: SUV\textsubscript{VPC}, VBR\textsubscript{VPC}, and K\textsubscript{i, VPC}.
Patlak analysis is a graphical method that, for Calculation of \( \text{Ki} \) by way of Patlak analysis has been described in detail elsewhere.\(^{16} \) Patlak analysis is a graphical method that, for

\[ \text{FDG scan:} \]

\[ \text{derive VBR from an averaged image of the last 30 minutes of the circulating FDG concentration. The following equation was used to} \]

\[ \text{In contrast to SUV, VBR normalizes vessel wall FDG uptake to the} \]

\[ \text{VBR, KiPVC and SUVPVC, and KiPVC and VBRPVC were assessed using} \]

\[ \text{The mean difference, mean absolute difference, and SDs were then} \]

\[ \text{Comparison of Quantification Methods} \]

\[ \text{Ki was taken as the gold standard measurement of plaque FDG metabolism. The strength of correlation between Ki and SUV, Ki and} \]

\[ \text{Comparison of Quantification Methods} \]

\[ \text{The geometric transfer matrix MR-based method, first described by Rouset et al.}^{21} \text{ was used to correct the PVE of uptake into the carotid artery wall for each time frame. An in-house implementation of the Rouset algorithm used the ROIs defined on the HRMR, coregistered PET images, and the PET scanner resolution to calculate the contribution of tracer activity from each region to its surrounding regions, thus enabling partial volume-corrected FDG concentration to be estimated for each carotid vessel wall.} \]

\[ \text{The difference between partial volume corrected and uncorrected FDG uptake was calculated for SUV, VBR, and Ki for each carotid vessel in each scan. To allow for comparison between quantification methods, the difference (DPVC) was expressed as a percentage of the uncorrected FDG uptake value as follows:} \]

\[ \text{VBR, KiPVC and SUVPVC, and KiPVC and VBRPVC were assessed using} \]

\[ \text{Reproducibility} \]

\[ \text{To allow the reproducibility of the different quantification parameters to be compared, the percentage difference in FDG uptake between the 2 scans (DR) was calculated as follows:} \]

\[ \text{Reproducibility} \]

\[ \text{Comparison of Quantification Methods} \]

\[ \text{Figure 2 shows the correlation between Ki and SUV}^{\text{B}_{\text{BSA}}}, \text{ VBR (Figure 2a) and } K_{\text{PVC}} \text{ and both SUV}^{\text{B}_{\text{BSA}}} \text{ and VBR}_{\text{PVC}} \text{ (Figure 2b). The correlation between Ki and VBR } (r=0.58, \text{ } P<0.001) \text{ was stronger than between Ki and SUV}^{\text{B}_{\text{BSA}}} \text{ (} r=0.46; \text{ } P=0.014). \text{ Partial volume correction improved the correlations } (K_{\text{PVC}} \text{ and VBR}_{\text{PVC}}: \text{ } r=0.81, \text{ } P<0.001; K_{\text{PVC}} \text{ and} \]
PVC degraded the reproducibility of all the uptake parameters, with SUVPVC being the least affected.

Table 1. PVC of FDG Uptake Values in the Carotid Artery Wall

<table>
<thead>
<tr>
<th>FDG Uptake Parameter</th>
<th>Mean Uncorrected FDG Uptake, Mean±SD</th>
<th>Mean PVC FDG Uptake, mean±SD</th>
<th>Mean Difference, ΔPVC, Mean±SD</th>
<th>Mean % Difference, ΔPVC, Mean±SD (range %)</th>
<th>Mean Absolute % Difference, Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV_{BSA}</td>
<td>0.63±0.09</td>
<td>0.68±0.16</td>
<td>0.05±0.11 (P=0.02)</td>
<td>5.7±16.4 (−39 to +33)</td>
<td>13.2±11.0</td>
</tr>
<tr>
<td>VBR</td>
<td>1.23±0.10</td>
<td>1.25±0.33</td>
<td>0.03±0.26 (P=0.60)</td>
<td>1.3±19.7 (−38 to +58)</td>
<td>14.8±12.7</td>
</tr>
<tr>
<td>K_i (×10^3)</td>
<td>4.95±0.99</td>
<td>5.22±1.92</td>
<td>0.27±1.36 (P=0.31)</td>
<td>4.1±26.1 (−53 to +53)</td>
<td>20.5±16.3</td>
</tr>
</tbody>
</table>

SU{_V_{BSA}}—standardized uptake value normalized by BSA.

$K_i$—influx rate (min$^{-1}$).

Figure 2. Correlations between (a) $K_i$ and both SUV_{BSA} and VBR and (b) $K_i^{PVC}$ and both SUV_{BSA}^{PVC} and VBR_{PVC}.

SUV_{BSA}: $r=0.76$, $P<0.001)$. SUV_{BSA} correlated better with $K_i$ than both SUV_{W} ($r=0.35$; $P=0.07$) and SUV_{LRM} ($r=0.43$; $P=0.022$). SUV_{BSA}^{PVC} also correlated better with $K_i^{PVC}$ than both SUV_{W}^{PVC} ($r=0.67$; $P<0.001$) and SUV_{LRM}^{PVC} ($r=0.73$; $P<0.001$).

PVC

The results are summarized in Table 1. Note that results are not given for SUV_{LRM} and SUV_{W} because the percentage changes will be the same as for SUV_{BSA}. After applying PVC, the mean SUV increased statistically significantly by 0.05 (SD, 0.11). PVC did not result in a significant change in the mean of the other 2 parameters (VBR, $K_i$). The mean absolute percentage differences are higher than the corresponding mean percentage differences because of the bidirectional effect of PVC, which is illustrated in Figure 3 for 1 of the parameters (VBR); for a threshold uncorrected VBR value of 1.25, all 5 of the values above this threshold increase with PVC and 7 of the 9 values below it decrease with PVC. The range values in Table 1 show that PVC increased or decreased some uptake values by >50%.

Reproducibility

The reproducibility results are summarized in Table 2 and Figure 4. SUV showed superior reproducibility to both VBR and $K_i$, PVC degraded the reproducibility of all the uptake parameters, with SUV_{PVC} being the least affected.

Discussion

This study reports on important areas of quantification that have not been addressed in previously published studies that have used FDG-PET to image inflammation in atherosclerotic vessels. First, this is the only study to our knowledge to correct FDG uptake in the arterial wall for PVE. The need for PVC to improve quantification of tracer concentration in small regions is well-established,17,18,21,22 and its application is highly relevant to FDG imaging of atherosclerotic plaques given their small size and proximity to FDG signal from the arterial lumen. In this study, PVC led to only a small increase in mean FDG uptake of 1% to 6%, depending on the quantification measurement used. However, this statistic hides the fact that high uptake values are increased with PVC but low uptake values usually decrease (Figure 3). Thus, the mean percentage change statistic is rather deceptive. It is better to express the effect of PVC in absolute percentage terms, in which case the change in uptake value was between 13% and 21%, depending on the quantification parameter used. Even this statistic does not clearly reveal that some values increased or decreased by >50% after PVC (Table 1). PVC also improved the correlation between influx rate ($K_i$) and the simplified methods SUV and VBR (Figure 2). These results suggest that PVC may significantly improve the quantification of inflammatory activity in individual plaques, but whether this will translate into a clinically meaningful difference remains to be seen.

Second, this study compares different methods of quantifying FDG uptake in the vessel wall. Many different methods of quantifying tissue FDG uptake have been proposed.27,28 When FDG-PET is used for oncological purposes, SUV is the most commonly used parameter. It is quick to calculate and does not rely on drawing blood samples from the patient. In oncology its use has been validated against more sophisti-
cated “gold standard” methods of quantification such as K29–31. Because the use of FDG-PET for quantifying vascular wall inflammation is a relatively new concept, similar validation studies in patients with atherosclerosis until now have not been attempted. The results from this study show that normalizing SUV to BSA provides a better correlation with Ki than normalization using either LBM or body weight. The correlation of SUVBSA and Ki is not as strong as for another simplified method that normalizes vessel wall FDG uptake to the blood FDG concentration (VBR). As with calculation of SUV, estimation of VBR does not require blood sampling, but instead uses the scan data to determine the concentration of FDG in blood from an adjacent artery or vein, in this case the jugular vein. This normalization method is based on assuming that the jugular vein ROI value is proportional to the input function. The major weakness of this comparison of quantification methods is the lack of a histological “gold standard” measure of plaque inflammation to compare the quantification methods to. Unfortunately, human studies do not lend themselves toward this kind of study because of the difficulty in extracting tissue samples in a timely fashion. Therefore, an animal study would be the best way of examining this.

Last, this study reports on the reproducibility of combined MR and FDG-PET for quantifying vessel wall FDG uptake. The results are in broad agreement with the recently published study by Rudd et al,11 although there are a number of important methodological differences between the 2 studies: In this study all the patients had experienced recent strokes thought to be caused by the presence of carotid atheroma. Although Rudd et al reported on patients who had established but asymptomatic atherosclerosis, the uptake measure given by Rudd et al (whole vessel-to-blood ratio) differs from VBR used in this study. We used MR to provide anatomic coregistration, whereas Rudd et al used a combined PET/CT scanner. MR has several advantages over x-ray CT, including an absence of ionizing radiation exposure and, most importantly, clearer delineation of the vessel wall, allowing for plaque characterization, more accurate delineation of ROIs, and PVC. However, a combined PET/CT scanner provides

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean FDG Uptake (Scan 1), Mean±SD</th>
<th>Mean FDG Uptake (Scan 2), Mean±SD</th>
<th>Mean Difference, Mean±SD</th>
<th>Mean % Difference, Mean±SD</th>
<th>Mean Absolute % Difference, Mean±SD</th>
<th>ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVBSA</td>
<td>0.62±0.08</td>
<td>0.64±0.09</td>
<td>−0.02±0.05</td>
<td>−2.4±7.3</td>
<td>5.7±5.0</td>
<td>0.85 (0.61–0.95)</td>
</tr>
<tr>
<td>SUVLBM</td>
<td>1.88±0.29</td>
<td>1.92±0.31</td>
<td>−0.05±0.14</td>
<td>−2.4±7.3</td>
<td>5.7±5.0</td>
<td>0.88 (0.68–0.96)</td>
</tr>
<tr>
<td>SUVW</td>
<td>2.42±0.42</td>
<td>2.48±0.45</td>
<td>−0.06±0.19</td>
<td>−2.4±7.3</td>
<td>5.7±5.0</td>
<td>0.90 (0.73–0.97)</td>
</tr>
<tr>
<td>VBR</td>
<td>1.22±0.10</td>
<td>1.23±0.11</td>
<td>−0.02±0.10</td>
<td>−1.3±8.3</td>
<td>6.4±5.1</td>
<td>0.54 (0.48–0.82)</td>
</tr>
<tr>
<td>Ki (x105)</td>
<td>4.95±1.18</td>
<td>4.96±0.80</td>
<td>−0.01±0.94</td>
<td>−1.7±18.9</td>
<td>15.3±10.5</td>
<td>0.59 (0.12–0.84)</td>
</tr>
<tr>
<td>SUVBSAPVC</td>
<td>0.68±0.16</td>
<td>0.68±0.18</td>
<td>−0.002±0.10</td>
<td>0.4±15.9</td>
<td>10.5±11.6</td>
<td>0.83 (0.56–0.94)</td>
</tr>
<tr>
<td>SUVLBMPC</td>
<td>2.04±0.50</td>
<td>2.05±0.56</td>
<td>−0.008±0.31</td>
<td>0.4±15.9</td>
<td>10.5±11.6</td>
<td>0.85 (0.60–0.95)</td>
</tr>
<tr>
<td>SUVWPC</td>
<td>2.63±0.66</td>
<td>2.65±0.77</td>
<td>−0.02±0.41</td>
<td>0.4±15.9</td>
<td>10.5±11.6</td>
<td>0.84 (0.59–0.95)</td>
</tr>
<tr>
<td>VBRPC</td>
<td>1.24±0.28</td>
<td>1.27±0.38</td>
<td>−0.03±0.35</td>
<td>−1.2±25.6</td>
<td>19.8±15.4</td>
<td>0.48 (0.03–0.80)</td>
</tr>
<tr>
<td>Kipvc</td>
<td>5.52±1.94</td>
<td>4.91±1.91</td>
<td>0.61±2.03</td>
<td>10.8±43.3</td>
<td>29.7±32.5</td>
<td>0.43 (0.08–0.78)</td>
</tr>
</tbody>
</table>

SUVBSA=standardized uptake value normalized by body surface area (X=BSA), lean body mass (X=LBM), and body weight (X=W).
SUVLBM=partial volume corrected SUVW.
VBRPC=partial volume corrected VBR.
Kipvc=partial volume corrected Ki (min⁻¹).
ICC indicates intraclass correlation coefficient.
Figure 4. Bland-Altman plots for 3 uptake parameters both with and without PVC (a to f). Box and whiskers plot showing the interscan variability of the different methods in percentage terms (g). The boxes represent the outer limits of the 25th and 75th percentiles. The whiskers represent the minimum and maximum values. o = median value. For the box and whiskers plot SUV is given rather than individual SUV, because the results are independent of the normalization method.
anatomic and functional images in the same imaging session, which aids coregistration accuracy. The results from this study clearly show that the intertest reproducibility of FDG-PET for quantifying FDG uptake in the arterial wall depends on which quantification method is used. The data show that SUV is the most reproducible method for estimation of FDG uptake and the reproducibility of this parameter compares well with those obtained for other atherosclerosis imaging modalities such as MR, intravenous ultrasound, and CT. They also compare favorably to those from a reproducibility study of FDG uptake in tumors. VBR is less reproducible than SUV because of the extra variability introduced by normalizing to an image ROI value from the jugular vein. K is the least reproducible because it is obtained from the gradient of transformed data rather than the mean of multiple frames as in the case of SUV and VBR. Partial volume corrected parameters are less reproducible than their corresponding noncorrected measures. The accuracy of partial volume correction is known to be reduced by noise, inaccurate delineation of regions, and, in particular, inaccurate coregistration of PET and MR scans. The latter is likely to improve with the use of the combined PET/MR scanners that are currently in development. Nevertheless, SUV_{PVC} performs reasonably well in terms of reproducibility.

In summary, we have shown that MR-based PVC is both feasible and important when quantifying FDG uptake in atherosclerotic vessels. Of the methods tested, SUV is the most reproducible method for quantifying FDG uptake in carotid artery vessel wall, and its correlation with K, almost matches that of VBR. Of the simplified methods examined, it appears that SUV_{SSA}_{PVC} represents the best compromise between reproducible and accurate determination of FDG metabolism in carotid artery vessel wall. However, further studies are needed to confirm the accuracy of the different FDG parameters used in this study in quantifying inflammation. Ideally, such a study should look at both the relationship between the different parameters and the degree of plaque inflammation at a histological level and their accuracy in predicting future atherothrombotic events. If the results from such a study are positive, then FDG-PET could become a powerful clinical tool for both predicting stroke risk and guiding pharmacological and interventional therapy.

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