Watershed Infarcts in Transient Ischemic Attack/Minor Stroke With ≥50% Carotid Stenosis

Hemodynamic or Embolic?

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Background and Purpose—Watershed ischemia is a significant cause of stroke in severe carotid disease, but its pathophysiology is unsettled. Although hemodynamic compromise has long been regarded as the main mechanism—particularly with deep watershed infarction—there is some contradictory evidence from clinical and pathological studies for a role of microembolism, thought to result from plaque inflammation. However, no study so far has directly addressed these conflicting scenarios.

Methods—In 16 consecutive patients with recent transient ischemic attack/minor stroke and ipsilateral 50% to 99% carotid stenosis, we prospectively obtained (1) plaque inflammation mapping with 18F fluorodeoxyglucose positron emission tomography; (2) brain MRI and perfusion MR; and (3) transcranial Doppler detection of microembolic signals (MES). Patients were excluded if on dual antiplatelets or with a potential cardiac source of emboli or contralateral MES.

Results—We found the expected significant relationship between (1) degree of stenosis and severity of distal hemodynamic impairment in the watershed areas; and (2) degree of in vivo plaque inflammation and rate of MES/hr. Deep watershed infarcts were present in 8 patients and MES in 8 (3 with both). There was no systematic association between the presence of deep watershed infarcts and either hemodynamic impairment or MES, but deep watershed infarcts were present only when either hemodynamic impairment or MES was present (P=0.01).

Conclusion—This pilot study supports the idea that in symptomatic carotid disease, deep watershed infarcts result either from hemodynamic impairment secondary to severe lumen stenosis or from microembolism secondary to plaque inflammation. There was no direct evidence that both mechanisms act in synergy. (Stroke. 2010;41:1410-1416.)

Key Words: carotid stenosis • CBF • PET • transcranial Doppler • watershed infarcts

Cerebral events distal to atherosclerotic carotid disease are thought to be mostly embolic1 and to originate from the unstable plaque as supported by a parallel time course of microembolic signals (MES) detected on transcranial Doppler (TCD).2,3 Plaque inflammation, a key component of this process,4 can now be assessed in vivo using 18F fluorodeoxyglucose positron emission tomography.5

Events distal to severe internal carotid artery (ICA) disease may also be due to hemodynamic impairment (HDI)6–8 and this is particularly relevant to the pathophysiology of watershed (WS) infarction, a significant cause of stroke in severe ICA disease.9 Historically, HDI was regarded as the sole determinant of cortical WS (CWS) infarction owing to the latter’s prevalence after severe systemic hypotension, and indeed HDI has been repeatedly demonstrated in association with CWS infarcts (reviewed by Momjian-Mayor and Baron6). However, some pathological reports also support a role for microemboli in CWS infarcts,8,10 and synergism between these 2 mechanisms has been proposed11 although not directly evidenced so far.

The second type of WS infarct found in carotid disease affects the white matter and is referred to as deep watershed (DWS).12 There is strong evidence that DWS infarcts are more strongly related to HDI than are CWS infarcts,8 but 2 perfusion studies13,14 found HDI not to be systematically associated with DWS infarcts and suggested microemboli may play a role here too, a notion supported by 1 pathological study.15

The present pilot study is the first to directly address these issues by assessing both the cerebral hemodynamics using...
perfusion-weighted MR (pMR) and the occurrence of MES by TCD in recent patients with transient ischemic attack (TIA)/minor stroke with $>50\%$ stenosis of the relevant carotid bifurcation, in whom the presence and distribution of WS infarcts was determined on structural MRI. In addition, carotid plaque inflammation as a potential source of MES was mapped in vivo with $^{18}$F Fluorodeoxyglucose positron emission tomography (FDG PET). Based on current understanding and literature reviews, we hypothesized that DWS infarcts would be related to the presence of HDI, whereas MES would be associated with the presence of plaque inflammation but not of DWS infarcts. Conversely, CWS infarcts would not be exclusively associated with either mechanism.

### Patients and Methods

#### Patients

Consecutive patients were prospectively recruited from Addenbrooke’s Hospital TIA clinic with the following clinical inclusion criteria: age $>40$ years; symptomatic within $<3$ months with amaurosis fugax, hemispheric TIA, or minor stroke clinically localized to the carotid territory; and $50\%$ to $99\%$ stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) of the clinically appropriate ICA on duplex ultrasonography. Exclusion criteria were: history of major stroke; anticoagulants or antiplatelet therapy; history of amaurosis fugax, hemispheric TIA, or minor stroke clinically localized to the carotid territory; and $50\%$ to $99\%$ stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) of the clinically appropriate ICA on duplex ultrasonography. Patients with bilateral MES were excluded for suspected noncarotid source. MES were recorded as present or absent and their rate expressed as MES/hr.

#### Structural Brain MRI

This was done within 2 days of PET and TCD on the same scanner described previously using fast spin echo T2-weighted (TE 100; TR 5800), fluid-attenuated inversion recovery (TE 121; TR 2181), and diffusion-weighted imaging (DWI; TE 66; TR 4925; 3 directions; b=1000; slice thickness 5 mm). The MR protocol purposely included DWI to maximize the detection and yield of watershed infarct. Hemispheric lesions in the population studied and hence optimally address our hypothesis.

To determine infarct presence and topography, the MRIs were anonymized and analyzed for the presence of supratentorial infarctions by 2 observers (R.R.M., J.-C.B.) on 2 separate occasions. Infarcts were classified as: (1) territorial: $\geq2$ subdivisions of the middle cerebral artery; (2) CWS: cortical border zone between middle cerebral artery and anterior cerebral artery or middle cerebral artery and posterior cerebral artery; (3) other cortical: nonwatershed nonterritorial cortical infarct; (4) DWS infarct: rosy-like, confluent, subcortical, or solitary located in the supra- or paraventricular areas (corona radiata or centrum semiovale), excluding immediately subcortical lesions; and (5) other deep: large striatocapsular lesions (>15 mm), single perforator (<15 mm). There was excellent intraobserver agreement ($k=0.9$ for the any lesion, $k=0.82$ for CWS lesion, and $k=0.75$ for DWS lesions; $P<0.01$) and interobserver agreement ($k=1$, $k=0.71$, and $k=0.8$, respectively; all $P<0.01$). Final adjudication was by consensus.

#### Transcranial Doppler

Detection of MES was done by simultaneous insonation of both middle cerebral arteries (Doppler box/multi-Doppler X4 with 2-MHz probe; DWL) at 2 depths for 1 hour on the same day as PET and, whenever feasible, repeated on separate days to account for MES variability. Identification of MES followed international consensus recommendations (unidirectional signals $<0.3$ seconds and intensity $>7$ dB over background) and was performed both on- and offline. Patients with bilateral MES were excluded for suspected noncarotid source. MES were recorded as present or absent and their rate expressed as MES/hr.

#### Perfuson-Weighted MR

pMR was acquired during the same session using spin echo echoplanar imaging (TE 65; TR 1500; field of view 220 mm; thickness 6 mm, interslice gap 1 mm; 14 slices). Gd-DTPA (0.1 mmol/kg) was injected as a bolus using a power injector and a total of 42 volumes acquired. The data were processed in nordicICE (NordicNeuroLab, Bergen, Norway), which involves automated estimation of the arterial input function and singular value decomposition with block-circulant deconvolution, which controls for tracer delay. Maps of relative cerebral blood volume, relative cerebral blood flow, time to peak, and mean transit time (MTT) were generated.

The pMR maps were visually analyzed for markers of HDI in the carotid territory of the symptomatic relative to contralateral hemisphere, namely a delay in MTT or time to peak or increase in cerebral blood volume and/or decrease in cerebral blood flow. Based on these criteria, a judgment was made as to whether HDI was absent, mild (limited abnormalities involving parts of the ICA territory), or significant (extensive and/or severe abnormalities). The analysis was carried out by the same 2 investigators and repeated on a separate session with scans presented in random order with very good intra- and interobserver agreement ($k=0.85$ and 0.78, respectively; $P<0.05$).

To substantiate the visual analysis as well as to focus on the WS areas more specifically, the MTT maps were also quantitatively analyzed by placing ROIs in 3 axial planes (spanning the body of the lateral ventricle) in the symptomatic hemisphere over the anterior CWS and posterior CWS (16-mm diameter circular ROIs) and DWS areas (20×5-mm radius ellipsoid ROIs) based on classic descriptions of the vascular anatomy. The ROIs were mirrored on the contralateral hemisphere and a symmetrical/contralateral hemisphere MTT ratio was calculated for each patient for the CWS and DWS areas.

#### Statistical Analysis

Correlations were assessed using Spearman rho (Kendall $\tau$ in case of ties). Nonparametric tests were also used for comparing continuous variables (Wilcoxon signed ranks, Mann-Whitney $U$ test, and Kruskal-Wallis). Proportions were compared using corrected $\chi^2$. All values are presented as median and interquartile range unless otherwise specified, and 2-tailed $P<0.05$ was considered significant.

#### Results

**Patient Characteristics**

Clinical details are summarized in Table 1. Ten patients presented with a TIA, of which 6 were hemispheric and 4...
One had both a hemispheric TIA and amaurosis fugax. Six presented with a minor stroke. No patients reported precipitating events such as postural episodes or systemic hypotension; 9 of 16 patients were current or ex-smokers but none had chronic respiratory insufficiency.

Lumen stenosis in the index and contralateral carotid arteries was 69.8% (50% to 87.5%) and 0% (0% to 15%), respectively ($P<0.001$).

On brain MRI (Table 1), 10 of 16 patients had infarcts, all located in the WS except 1 of these patients also had a territorial parietal infarct. Five had infarcts in the DWS only, 2 had infarcts in the CWS only, and 3 had infarcts in both. Of the 8 patients who had DWS infarcts, 4 had a rosary-like pattern in the centrum semiovale.

pMR was marred by head movement in 1 patient (Patient 9). On visual analysis, HDI was present in 7 of 15 patients (HDI+) and absent in 8 (HDI−; Table 1). The MTT ratio was significantly higher in the DWS areas in patients with significant visually assessed pMR abnormalities ($n=4$) than in those with mild ($n=3$) or no abnormality (1.18 [1.0 to 1.3] versus 0.87 [0.68 to 0.9] versus 0.92 [0.81 to 0.98], respectively; $P=0.05$). Figure 1 illustrates 3 possible associations between HDI and DWS infarcts in 4 patients.

MES assessment was of inadequate quality in 1 patient (Patient 7). MES were present in 7 patients (MES+) and absent in 8 (MES−; Table 1).

### Lumen Stenosis Versus HDI and MES

The degree of ICA stenosis differed significantly between patients with different grades of HDI, being highest in those with significant HDI than in those with mild or absent HDI (91% [87.5% to 95%] versus 50% [50% to 75%] versus

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**Table 1. Summary of Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age, Years</th>
<th>Risk Factors</th>
<th>Clinical Presentation</th>
<th>Carotid Stenosis*</th>
<th>WS Infarcts†</th>
<th>TCD MES, N/hr</th>
<th>HDI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>71</td>
<td>Hypertension, hypercholesterolemia, exsmoker</td>
<td>L amaurosis fugax</td>
<td>L ICA 80–85%, R ICA 70–75%</td>
<td>None</td>
<td>No MES</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>57</td>
<td>IHD, previous CABG, hypertension, Hypercholesterolemia</td>
<td>L amaurosis fugax</td>
<td>L ICA 70–80%, R ICA 60–70%</td>
<td>None</td>
<td>MES (1/hr)</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>70</td>
<td>Hypertension, exsmoker</td>
<td>R hemiparesis, dysarthria</td>
<td>L ICA 70–90%</td>
<td>None</td>
<td>No MES</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>70</td>
<td>Hypertension, smoker, hypercholesterolemia</td>
<td>L amaurosis fugax</td>
<td>L ICA 80–95%, minor plaque in R carotid bulb</td>
<td>Multiple DWS infarcts</td>
<td>No MES</td>
<td>Significant</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>72</td>
<td>Hypertension, hypercholesterolemia, exsmoker</td>
<td>Recurrent transient R UL weakness</td>
<td>L ICA 50–60%</td>
<td>Multiple DWS and CWS infarcts</td>
<td>MES (2/hr)</td>
<td>Absent</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>74</td>
<td>None</td>
<td>L hemiparesis, neglect</td>
<td>R ICA 50%, L ICA &lt;30%</td>
<td>Multiple DWS infarcts</td>
<td>MES (1/hr)</td>
<td>Mild</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>63</td>
<td>Hypertension, smoker, hypercholesterolemia</td>
<td>L hemiparesis</td>
<td>L ICA 60–69%</td>
<td>Multiple DWS infarcts§</td>
<td>N/A</td>
<td>Absent</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>59</td>
<td>Hypertension, smoker</td>
<td>R amaurosis fugax</td>
<td>R ICA 50%</td>
<td>None</td>
<td>No MES</td>
<td>Absent</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>82</td>
<td>Hypercholesterolemia, smoker</td>
<td>Transient L UL weakness</td>
<td>R ICA 99%, minor plaque in L ICA</td>
<td>CWS infarcts¶</td>
<td>MES (1/hr)</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>77</td>
<td>Hypertension, mild aortic stenosis</td>
<td>R amaurosis fugax, several episodes of L UL tingling</td>
<td>R ICA 90–99%</td>
<td>Multiple DWS infarcts</td>
<td>No MES</td>
<td>Significant</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>56</td>
<td>Hypertension, diabetes, smoker</td>
<td>Transient dysphasia and R UL weakness</td>
<td>L ICA 95%, R ICA 50–60%</td>
<td>None</td>
<td>MES (2/hr)</td>
<td>Significant</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>73</td>
<td>Exsmoker</td>
<td>Dysphasia, recurrent R UL tingling and weakness</td>
<td>L ICA 50–70%</td>
<td>CWS infarcts¶</td>
<td>No MES</td>
<td>Absent</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>76</td>
<td>Hypertension, hypercholesterolemia</td>
<td>Dysphasia, hemianopia, R UL weakness</td>
<td>L ICA 50%</td>
<td>Multiple DWS and CWS infarcts§</td>
<td>No MES</td>
<td>Mild</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>75</td>
<td>None</td>
<td>Recurrent transient R UL and LL weakness and tingling</td>
<td>L ICA 50%</td>
<td>Multiple DWS and CWS infarcts§</td>
<td>MES (3/hr)</td>
<td>Absent</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>54</td>
<td>Hypertension, hypercholesterolemia, exsmoker</td>
<td>Transient R UL weakness and tingling</td>
<td>L ICA 50%</td>
<td>None</td>
<td>MES (2/hr)</td>
<td>Absent</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>54</td>
<td>Hypertension, exsmoker</td>
<td>Dysphasia, R UL weakness</td>
<td>L ICA 80–95% minor plaque in R ICA</td>
<td>Multiple DWS infarcts§**</td>
<td>No MES</td>
<td>Significant</td>
</tr>
</tbody>
</table>

*On Duplex ultrasonography.†Visual analysis of structural MR.‡Visual analysis of brain perfusion MR.§Rosary-like pattern of infarcts.¶Found on both DWI and T2/fluid-attenuated inversion recovery.**Small parietal cortical infarct was also found on structural MR.

M indicates male; F, female; IHD, ischemic heart disease; CABG, coronary artery bypass graft; L, left; R, right; UL, upper limb; LL, lower limb; N/A, not available.
57.5% [50% to 76%], respectively; \(P=0.01\). There was also a positive correlation between percent stenosis in the index carotid and the MTT ratio in the DWS (\(\rho=0.51; P=0.05\)) but not in the CWS. The degree of stenosis was not significantly different in MES+ and MES− patients (55% [50% to 90%] versus 81.3% [52.5 to 87.5%], respectively; \(P>0.05\)). There was minimal or no HDI in the 3 patients who presented with amaurosis fugax only (Table 1).

### Plaque Inflammation Versus MES and HDI

There was a very significant positive correlation between the rate of MES/hr and the index/contralateral partial volume effect-corrected SUV ratio (\(\tau=0.64, P=0.003\); Figure 2). The time interval from symptom onset to PET scanning was not different in MES+ and MES− patients (56 [21 to 70] days versus 30.5 [9.5 to 80.5] days, respectively; \(P=0.68\)). There was no difference in index/contralateral partial volume effect-corrected SUV ratio between patients with significant HDI on pMR and those with mild or absent pMR abnormalities (76 [0.53 to 1.18] versus 1.01 [0.62 to 1.14] versus 0.99 [0.86 to 1.29], respectively; \(P=0.5\)).

### WS Infarction Versus HDI and Microembolism

On visual analysis, DWS infarcts were present in 5 of 7 HDI+ and 3 of 8 HDI− patients (\(P>0.05\)). Consistent with this visual analysis, there was no difference in MTT ratio between patients who did and those who did not have DWS infarcts on MRI (\(P>0.05\) for all ROIs). Similarly, the presence of a rosary-like pattern on MRI was not associated with a different MTT ratio in either the CWS or the DWS areas (\(P>0.05\) for both). Regarding MES, DWS infarcts were present in 4 of 8 MES− patients but also in 3 of 7 MES+ patients (\(P>0.05\)).

These results did not support our hypothesis of a systematic association between DWS infarcts with HDI but not with MES. However, they suggested that DWS infarcts can be associated with either HDI or MES. Accordingly, we then tested this double association. The results are shown in Table 2. None of the 4 patients who did not have either HDI or MES had DWS infarcts, whereas 7 of 10 patients with HDI, MES, or both had DWS infarcts (\(P=0.01\)). Due to their small incidence (Table 1), no further analysis was considered regarding CWS infarcts.
In this pilot study on recently symptomatic patients with TIA/minor stroke with 50% ICA stenosis, we found significant relationships between degree of stenosis and severity of hemodynamic impairment in the WS and between degree of PET-based plaque inflammation and density of microembolic signals on TCD, both biologically expected. However, contrary to our hypothesis, there was no systematic association between the presence of DWS infarcts and HDI nor between their absence and MES. In other words, inconsistent with our hypothesis, DWS infarcts were observed in some but not all patients with HDI and conversely were present in some patients without it. This led us to test whether DWS infarcts would be associated with the presence of either HDI or MES but not when both are absent. The data, shown in Table 2, support this post hoc hypothesis. Overall, therefore, our results suggest that, in this sort of population, WS infarcts are not exclusive to either mechanism but appear to develop secondary to microembolism from plaque inflammation, HDI from plaque stenosis, or both in association (Figure 3).

Finally, due to the low occurrence of CWS infarcts, no meaningful conclusion about their pathophysiology could be reached.

Although there is ample evidence for the correlation of MES with carotid atherosclerotic disease, the precise mechanism underlying microemboli formation is not entirely clear. In 1 study, the presence of MES was associated with higher plaque macrophage inflammatory burden on carotid endarterectomy specimen. By showing in vivo a strong relationship between MES and PET-derived plaque inflammatory content, our present results corroborate these earlier findings.

The association found between HDI (especially in the DWS areas) and lumen stenosis was also expected. Cerebral HDI is largely determined by the degree of carotid stenosis. Conversely, lumen stenosis is known not to be directly associated with plaque inflammation, with plaques silently growing to cause lumen narrowing until inflammation sets in and causes them to become unstable and potentially symptomatic.

The incidence of WS infarcts in this study (10 of 16 patients) may seem high, but their detection was optimized by adding DWI to T2 and fluid-attenuated inversion recovery sequences (see Table 1). In addition, the population studied was selected a priori to represent patients with recent TIA or ministroke (ie, not leaving any deficit beyond 7 days) and a clinically appropriate ≥50% stenosis, carefully excluding patients with completed stroke or a potential proximal source of emboli. There is no previous study on the incidence of WS infarcts in a similar population using both standard and DWI sequences to compare with, but 1 previous similar study found WS infarcts, including DWS infarcts, in one third of patients with acute stroke with ≥50% carotid disease.

Regarding DWS infarcts first, the most salient finding from this investigation is that, contrary to our hypothesis, their prevalence was not different between the HDI+ and HDI− groups nor between the MES+ and MES− groups. The association of HDI to DWS infarction in carotid disease has been found in many studies using PET, single photon emis-
sion CT, pMR, or TCD (reviewed in Momjian-Mayor and Baron). Yet, 3 studies found inconsistent results\(^\text{13,14,25}\) and proposed that emboli may play a significant role in DWS infarcts. However, because none of these studies included detection of MES in their design, any role ascribed to embolic mechanisms was by inference only. Our results derived from directly assessing both MES and HDI in the same patients are the first to provide direct evidence that either HDI or microembolism may cause DWS infarction. Thus, probably because of their small size,\(^6\) some microemboli may enter cortical “distal field” arteries and from there medullary arteries, in turn causing centrum semiovale infarcts in the DWS territory.

Although HDI and MES may work separately to cause DWS infarcts, it is also plausible that they act synergistically. Thus, decreased perfusion may promote brain damage from otherwise innocuous microemboli entering vulnerable areas with an exhausted vascular reserve; reciprocally, by blocking end arteries, small emboli could further impair perfusion. Furthermore, reduced perfusion may facilitate local thrombosis and/or impede “clearance” of microembolic material.\(^1\) In our study, however, DWS infarcts were present in only 1 of 3 HDI+/MES+ patients, and conversely the coexistence of both mechanisms was not necessary for their occurrence. Our preliminary data do not therefore provide strong support to this hypothesis.

Evidence in favor of microembolism playing an important part is much stronger for CWS infarcts, both from hemodynamic studies\(^8\) and from pathological and experimental studies.\(^10,15,27,28\) Although their incidence (n=5) in the present study precluded formal statistical analysis, it is worth noting that MES were present in 3 of these patients—without HDI in 2—further strengthening the growing notion that CWS infarcts often result from microemboli alone.

This study has limitations. Due to the complexity of the protocol, we were able to recruit only a small sample so the results require replication before the conclusions are considered definitive. Because the investigations were not conducted immediately close in time to the symptoms, it is possible that either the MES would have subsequently cleared or that the HDI had subsided, although the latter tends to remain stable over short time spans.\(^24\) The possibility that the HDI was missed because it affected highly circumscribed WS areas that went on to infarct is unlikely, because previous evidence indicates that when present, HDI in carotid disease is quite extensive, spreading well beyond any WS infarcts.\(^6,14,23,24\)

Conclusions

The present study provides direct support to the idea that in symptomatic ICA disease, DWS infarcts may result from HDI through severe lumen stenosis, but also from microemboli alone through plaque inflammation. These results, although preliminary, imply that the finding of DWS infarcts on structural imaging in patients with severe carotid stenosis may be compatible with an underlying microembolic mechanism from plaque inflammation, which has management implications.

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Disclosures

None.

References


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Watershed Infarcts in Transient Ischemic Attack/Minor Stroke With ≥50% Carotid Stenosis: Hemodynamic or Embolic?

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Background and Purpose: In severe carotid disease, watershed zone ischemia is a major cause of stroke, but its pathophysiology is not well understood. Despite hemodynamic compromise (hemodynamic compromise) being generally considered the main mechanism, especially with deep watershed, some clinical and pathological studies support a source of embolic etiology. Although controversial, no direct studies have yet elucidated the role of both mechanisms.

Methods: We prospectively enrolled 16 new patients with a transient ischemic attack (TIA) or minor stroke with a carotid stenosis of ≥50% to 99%. We measured (1) the extent of plaque inflammation using [18F] fluorodeoxyglucose positron emission tomography (FDG PET); (2) cerebral magnetic resonance imaging (MRI) and MR perfusion imaging; and (3) microembolic signals (MES) detected by transcranial Doppler (TCD). We excluded patients on dual-antiplatelet therapy as well as patients with an obvious cardiac source of emboli or with MES on the contralateral hemisphere.

Results: The degree of stenosis correlated with the severity of hemodynamic compromise, and the prevalence of MES correlated with the extent of plaque inflammation. Of the 16 patients, 8 were diagnosed with deep watershed infarcts, 8 with MES, and 3 had both. There was no system relationship between deep watershed and hemodynamic compromise or MES, but only when both were present did deep watershed appear ($P=0.01$).

Conclusion: Our preliminary study suggests that in symptomatic carotid disease, deep watershed infarcts may be produced by hemodynamic compromise or plaque inflammation with embolic events, although no direct evidence has confirmed this hypothesis.

Keywords: carotid stenosis, cerebral blood flow, FDG PET, TCD, stroke.
子信号只与斑块炎症相关。与之不同的是皮层分水
岭梗塞不只与一种机制相关。

### 对象与方法

#### 对象

前瞻性连续纳入Addenbrooke’s医院TIA门诊
符合以下临床纳入标准的患者：年龄>40岁；发病
3个月内，伴随一过性黑朦，半球TIA症状，或
颈内动脉系统的小卒中；多普勒超声显示颈内动脉
狭窄50%-99%（北美症状性颈动脉内膜剥脱术[NA-
SCET]所用标准）。排除标准：既往卒中病史；抗凝
及双联抗血小板治疗（单一抗血小板治疗不会显著
降低MES的发生率[16]，患者可以入组）；TCD
颞窗不能探及；双侧MES（见后）；临床或常规检查显示
有潜在心源性栓子，包括超声心动图或TCD发泡实
验证实的卵圆孔未闭。

#### 经颅多普勒

MES探测使用双侧大脑中动脉同步超声（Dop-
pler box/multi-Doppler X4 with 2-Mz probe；DWL），
设置2个深度各检测1小时，另一天重复该操作，计
数MES变异性。MES的识别采用国际统一标准[17]
（单向信号<0.3秒，高于背景强度7dB以上），所
有操作都在线或线下状态完成。双侧微栓子信号
通常不是颈内动脉源性，此类患者需要排除。MES
将被记录为出现及未出现，出现率使用MES/hr描
述。

#### 18F脱氧葡萄糖正电子发射照相术

FDG斑块成像及相关的颈部及斑块MRI的方
法学详见文献[18]。简述之，本研究使用GE Advance
scanner（GE Medical Systems，Milwaukee，Wis）。在
注射185MBq18F-FDG后以三维模式动态扫描75分
钟。在FDG扫描衰减矫正之前先行透视扫描，获
取颈部MRI（1.5 T Signa Excite；GE Medical Systems）
配准PET图像与解剖结构以及颈动脉斑块高分辨率
MRI与颈动脉斑块FDG吸收量[18]。使用标准吸收
值（SUV）衡量斑块的摄取量[18,19]。高分辨率MRI所
示，所有患者健侧斑块明显小于患侧（P<0.001）。兴
趣区域（regions of interest，ROIs）在高分辨率MRI
上被转换到配准的平均55-75分钟时的PET图像上，
计算双侧颈动脉斑块ROIs平均SUV。部分容积效
应的校正不再详述[13]。计算患侧/健侧矫正的部分
容积效应SUV率以备分析使用。
后皮层分水岭区(围绕 ROIs 半径 16 mm 的圆形区域)及内分水岭梗塞区域(围绕 ROIs 半径 20×5 mm 椭圆区域)，将 ROIs 置于 3 轴平面定量分析 MTT 图像(旋转侧脑室体)，在对侧半球的相同部位进行相同的分析，然后计算每位患者 CWS 及 DWS 区患侧/健侧半球 MTT 比率。

数据分析
使用 Spearman 相关系数来分析相关性(假如秩次相同采用 Kendall τ)。使用非参数检验比较连续变量(Wilcoxon 秩和检验，Mann-Whitney U 检验，Kruskal-Wallis 检验)。校正的卡方检验进行率的比较。所有的数据，若未显示有统计学差异(双侧检验，P<0.05)，都以中位数及四分位数的形式描述。

结果
具体临床资料可见表 1。10 例患者表现为 TIA，
其中6例为半球症状，4例为视网膜症状。1例患者仅有半球TIA症状也有一过性黑朦。6例患者表现为小卒中。无患者出现例如体位性或全身低血压的突发事件；16例患者中的9例吸烟或者曾经吸烟，但都不存在慢性呼吸功能不全。患侧及对侧颈内动脉管腔狭窄的比率分别为69.8%(50%-87.5%)及0%(0%-15%)，P<0.001。脑MRI(表1)显示16例患者中的10例存在梗塞灶，梗塞的患者中除了1例患者伴有顶叶流域性梗塞外均发生在分水岭区。只有5例内分水岭梗塞，2例皮层分水岭梗塞，3例两者兼有。在8例内分水岭梗塞的患者中4例表现为半卵圆中心玫瑰花样的梗塞灶。1例患者由于头部晃动(患者9)，pWR效果欠佳。可视分析显示15例患者中的7例出现HDI(HDI+)，剩余8例无HDI(HDI-)，表1)。DWS患者中，可视化pMR中重度(n=4)患者MTT比率明显高于轻度(n=2)或无异常者(1.18[1.0-1.3] vs. 0.87[0.68-0.9] vs. 0.92[0.81-0.98]；P=0.05)。图1展示了4例患者HDI与DWS梗塞之间可能的3种关系。1例患者的微栓子检测质量欠佳(患者7)。7例患者检测到MES(MES+)，8例患者未检测到MES(MES-)（详见表1）。

### 管腔狭窄与HDI和MES

不同程度的HDI患者颈内动脉的狭窄程度是不同的，明显HDI与轻度或无HDI患者的血管狭窄程度差异很大(91%[87.5%-95%] vs. 50%[50%-75%] vs. 57.5%[50%-76%]；P<0.01)，DWS梗塞患者侧颈内动脉狭窄的百分比与MTT比率相关(r=0.15；P=0.05)，但在CWS梗塞中两者无相关性。在MES+及MES-患者中狭窄的程度无统计学意义(55%[50%-90%] vs. 81.3%[52.5%-87.5%]；P>0.05)，仅表现为一过性黑朦的3例患者无HDI或很轻微(表1)。

### 斑块炎症与MES和HDI

每小时MES的出现率与患者/健侧部分容积效应校正的SUV比率有明显的相关性(r=0.64，P=0.003；图2)。MES+及MES-患者从发病到检查时间无差异(分别为56[21-70]天，30.5[9.5-80.5]天；P=0.68)。pMR上显示明显HDI及轻度或无HDI患者的患/健侧校正的部分容积效应SUV比率无统计学差异(76[0.53-1.18] vs. 1.01[0.62-1.14] vs. 0.99[0.86-1.29]；P<0.5)。

### 分水岭梗塞与HDI和微栓子

可视分析中7例HDI+中的5例，8例HDI-患者的3例显示有DWS梗塞(P>0.05)。与此相一致的是MRI显示及未显示DWS梗塞的患者的MTT比率无明显差异（所有ROIs，P>0.05）。同样，攻击
瑰花样梗塞与 CWS 或 DWS 梗塞的 MTT 比率相关（两者的 $P>0.05$)。8 例 MES- 的患者中的 4 例，7 例 MES+ 中的 3 例患者出现 DWS 梗塞 ($P>0.05$)。

这些结果不支持最初关于 DWS 梗塞与 HDI 相关而与 MES 无关的设想，但是结果也显示 DWS 梗塞既与 HDI 相关也与 MES 相关。于是本研究对这种双重联系进行了验证，结果如表 2。4 例不存在 HDI 或者 MES 的患者无一出现 DWS 梗塞，然而 10 例存在 HDI、MES、或者两者并存的患者中有 7 例存在 DWS 梗塞 ($P=0.01$)。由于 CWS 梗塞的低发生率，未对其行进一步分析。

### 讨论

本研究显示，在新发的颈内动脉狭窄 >50% 的症状性 TIA/小卒中患者中，狭窄的程度与血流动力学障碍的严重程度相关；PET 显示的斑块炎症程度与 TCD 上的微栓子信号的密度密切相关，以上结果与从生物学上的推断相一致。但与之前的预测相反的是，内分水岭梗塞并不完全与 HDI 相关，而非内分水岭梗塞也不与 MES 相关。也就是说，DWS 出现在部分 HDI 患者而不是全部，也出现在部分无 HDI 的患者，这与先前的设想不一致。这一发现促使我们验证 DWS 可能与 HDI 或 MES 相关，但不会在两者都不存在的情况下出现。表 2 的数据支持这一假设。总之，我们的结果显示在新发的颈内动脉狭窄 >50% 的症状性 TIA/小卒中患者中，分水岭梗塞的产生并不只有单一的机制，可能发源于斑块炎症产生的微栓子，或由斑块所致的狭窄导致，或者是两者的协同作用（图 3）。由于 CWS 的发生率低，未得到有关其病理生理机制有意义的结论。

尽管有充足的证据显示 MES 与颈内动脉动脉硬性疾病相关，但是有关微栓子形成的确切机制尚不十分明了。一项有关颈内动脉剥脱术标本的研究表明，标本斑块中较高巨噬细胞炎症负荷且与 MES 出现相关 [22]。我们通过体内实验显示 MES 与 PET 获得的斑块炎症成分有强烈的相关性，与之前的发现一致。研究显示 HDI(尤其是内分水岭区)与管腔狭窄相关，这与预想的相一致。HDI 的程度多取决于管腔狭窄的程度 [23,24]。然而，通常认为管腔的狭窄并不直接与斑块炎症相关，斑块缓慢稳定的生长导致管腔狭窄，当炎症过程启动后，斑块变得不稳定，可出现临床症状 [4]。

本研究中分水岭梗塞的发生率看起来较高（16 例患者中有 10 例），但当在 FLAIR 序列的基础上再使用 DWI 时，分水岭梗塞的发生率更高（见表 1）。另外人群的选择着重于新近发生的 TIA 或小卒中（例如，7 天之内未遗留任何功能缺损），而且管腔狭窄
国外很少有关颈内动脉疾病中分水岭梗塞的预测和预防意义的研究，本研究正尝试利用MDCTA（多层螺旋CT血管成像）技术结合其他的影像学方法来探索颈内动脉疾病中分水岭梗塞的预测和预防意义。本文报道了1例分水岭梗塞的影像学特征及其与临床症状和诊断的关系。材料与方法：患者为1例58岁女性，有高血压病史。入院时神志清楚，无肢体乏力，但有头痛、恶心、呕吐、意识模糊等症状。CTA显示右侧颈内动脉管腔狭窄，其远端分支有血栓形成。通过进一步的影像学检查发现患者右顶叶有明显的低密度区，符合分水岭梗塞的特征。结论：分水岭梗塞的影像学特征及其与临床症状和诊断的关系需要进一步研究。