Spontaneous Cerebral Embolisation in Asymptomatic and Recently Symptomatic Patients with TIA/Minor Stroke


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KEYWORDS
Carotid stenosis;
Microemboli;
Transcranial doppler;
Carotid endarterectomy

Abstract  Objectives: Spontaneous embolisation (SE) detected using Transcranial Doppler (TCD) after a Transient Ischaemic Attack (TIA)/Minor stroke is an independent predictor of recurrent stroke. There are, however limited data on the differential prevalence of SE in the first few days/weeks after onset of symptoms.
Method: 156 consecutive patients (symptomatic n = 123, asymptomatic n = 33) underwent Carotid Endarterectomy (CEA) during an 18 month period and had an accessible window permitting 30 min of pre-operative TCD monitoring. A prospective study was conducted with assessors blinded to clinical status.
Results: Spontaneous embolisation was detected in 31 symptomatic patients (25%) of which 1/1 (100%), 14/35 (40%), 8/37 (22%) and in 8/50 (16%) patients presented within 48 h, 3–7 days, 8–14 days and >14 days respectively from the index clinical event. SE occurred in only 6% of asymptomatic patients. Out of 31 symptomatic patients with SE, seven (22.6%) suffered recurrent cerebrovascular events following admission as opposed to 11/92 patients (11.9%) who had no evidence of spontaneous embolisation after admission (OR 2.2 (95% CI 0.8–6.1)) (P = 0.2)
Conclusion: Patients presenting for CEA in the hyperacute period after onset of TIA/Minor stroke have a high incidence of SE. Patients with SE had a 23% risk of recurrent cerebrovascular events. These data support the current drive towards expedited CEA in recently symptomatic patients.

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Introduction

Embolisation of atherothrombotic material from an extracranial carotid stenosis is responsible for up to one third of all strokes. Recent evidence suggests that the highest risk of recurrent stroke (after the index transient ischaemic attack (TIA) or minor stroke) is during the first seven days. This has been the impetus underlying the move towards expedited/emergency carotid endarterectomy (CEA).

The detection of emboli in the ipsilateral middle cerebral artery (MCA) using Transcranial Doppler (TCD) has been associated with a nine-fold increase in stroke risk. However, to date few large scale studies have evaluated the prevalence of spontaneous embolisation in the acute and hyperacute period after onset of a TIA or minor stroke and then correlated this with the risk of early recurrent cerebrovascular symptoms. Following a reconfiguration of vascular surgery and stroke medicine services in October 2008, a rapid access TIA service was established operating everyday of the year. Symptomatic patients found to have an ipsilateral stenosis >50% were transferred directly to the Vascular Unit for urgent CEA. This practice has ensured that 78% of Leicester patients coming through the new TIA clinic undergo CEA within 14 days of the index event, with 43% within 7 days.

The hypothesis underlying the current study was that TCD-detected spontaneous cerebral embolisation would be more prevalent in patients who were acutely symptomatic and that patients with spontaneous cerebral embolisation would have a higher rate of early recurrent cerebral ischaemic events. If true this would further support the drive towards expedited CEA in acutely symptomatic patients with carotid artery disease.

The aim of the study was to correlate patterns of spontaneous embolisation (SE) with the risk of suffering recurrent cerebral ischaemic events (new onset Stroke, TIA, or episode of Amaurosis Fugax).

Materials and Methods

The current study was authorised by the Leicestershire, Northamptonshire and Rutland Ethics Committee.

One hundred and seventy two patients undergoing CEA between August 2008 and March 2010 (including asymptomatic patients) were included in the study after giving informed consent. Sixteen patients were excluded (no temporal window for TCD) leaving 156 for inclusion in the study (symptomatic \(n = 123\), asymptomatic \(n = 33\)). Patients were included in the study if they were undergoing a carotid endarterectomy for a critical stenosis (>50% NASCET if symptomatic, >70% NASCET is asymptomatic) of the carotid artery during the study period. Patients were excluded if they were found to have any other probable cause of embolic cerebrovascular disease e.g. atrial fibrillation; or if there was not an accessible cranial window permitting transcranial Doppler (TCD) monitoring of the ipsilateral middle cerebral artery.

In addition to physically starting best medical therapy and risk factor control (anti-platelet, antihypertensive, antiarrhythmic, statin therapy etc) within the rapid access TIA clinic, patients found to have a 50–99% ipsilateral stenosis were then transferred immediately to the Vascular Surgery Unit at the Leicester Royal Infirmary for expedited CEA.

Patients were defined as being clinically symptomatic if they reported a stroke, TIA or Amaurosis Fugax in the territory of the ipsilateral stenosed internal carotid artery within the preceding 6 months. As soon as possible after admission (same day if admitted before 5pm or next day if admitted after 5pm) in symptomatic patients or at the time of pre-assessment for asymptomatic patients, a 30 min period of TCD monitoring was performed using a commercially available TCD machine (Sonara TCD System from Via- sys Healthcare) with the 2-MHz head probe held in place by an external fixation device. Insonation of the ipsilateral MCA was achieved via the temporal acoustic window at a depth of 50–60 mm using a 2-MHz pulsed Doppler transducer. The sample volume (generally 8–13 mm), power and gain were adjusted to ensure an optimal embolic signal to background signal relationship. Each embolic signal was recorded and categorised using the Consensus Committee Criteria to differentiate between true emboli and other high intensity transient signals (HITS), including artefacts. Patients were classed as having evidence of SE if one or more embolic signal found to be of a true emboli were detected in the 30 min monitoring period. Each TCD recording was made by a trained vascular technologist who was blinded to data regarding timing of the clinical event in symptomatic patients. Statistical analysis was performed using SPSS (v16). Statistical tests used included Fishers Exact test and student \(t\)-test to determine \(P\) values. Guidance was sought from the departmental medical statistician.

Following admission, all patients underwent a second Duplex assessment (in line with HTA guidelines). Patients with uncontrolled hypertension started treatment as soon as possible with the aim of getting the systolic BP below 160 mmHg wherever possible. It was the aim of the service to only delay CEA if the hypertension did not respond to treatment and remained excessively high (>190 mmHg systolic BP) and if there was no evidence of spontaneous embolisation on TCD.

The unit also aimed to offer expedited CEA to all patients who presented with a minor stroke provided they fulfilled the following criteria; (1) Rankin score \(0\)–\(2\), (2) no internal carotid artery (ICA) occlusion, (3) no evidence of haemorrhage on CT/MRI, (4) infarction <1/3 of the MCA territory, (5) patient not obtunded. Stroke patients with a Rankin score \(\geq 3\) only underwent urgent CEA if they had recurrent symptoms while in hospital and then only after discussion with the stroke physicians and anaesthetists.

The Vascular Surgery Unit maintains two half day operating lists (Tuesday/Friday) for performing expedited CEA. CEA procedures were performed by the consultant allocated to that particular list (i.e. this could be different to the consultant admitting the patient). The emergency theatre was only used if these lists were already filled or if the patient had evidence of spontaneous cerebral embolisation on TCD.

In the 33 asymptomatic patients, aspirin and statin therapy was started in the outpatient clinic. In the 123 recently symptomatic patients, aspirin and statin therapy was started as soon as possible after onset of symptoms. All patients physically received 300 mg aspirin and 40 mg simvastatin in the TIA clinic, in addition to other appropriate secondary prevention therapy, and these were then
continued throughout the pre-operative period, although the aspirin dose was reduced to 75 mg following transfer to the Vascular Surgery Unit. All patients received 75 mg clopidogrel the night before surgery in addition to their regular aspirin. Patients who were not referred through the Leicester TIA clinic (i.e.) from outside of Leicestershire, and who had not been started on aspirin and statin therapy from the referral centre (n = 7) were commenced on aspirin (75 mg) and simvastatin (40 mg) on admission to the vascular surgery unit.

A recurrent cerebral ischaemic event was defined as any patient suffering a stroke, TIA or episode of amaurosis fugax between admission to the vascular surgery unit and time of surgery. All patients received a routine neurological examination at 30 days post-operatively by a consultant stroke physician. Any patient suspected of having suffered a pre/intra/post-procedural stroke underwent a repeat CT scan, extra-cranial Duplex ultrasound examination and intracranial transcranial Doppler ultrasound assessment as soon as possible after onset of symptoms and was reviewed by a stroke physician. All patients were seen by a consultant vascular surgeon prior to surgery on a daily basis to monitor for episodes of amaurosis fugax and TIAs, with a repeat neurological examination performed on patients suspected of having a recurrent cerebral ischaemic event.

Results

Between August 2008 and March 2010, 156 patients undergoing CEA with an accessible TCD window were entered prospectively into the study. One hundred and twenty three were recently symptomatic (stroke n = 29 (24%), TIA n = 73 (59%), amaurosis fugax n = 21 (17%). Thirty three were neurologically asymptomatic. Patient demographics are detailed in Table 1.

This study found that symptomatic patients had a significantly higher prevalence of SE than asymptomatic patients [31/123 (25%) vs. 2/33 (6%)] (OR 5.2 95% CI 1.2–23.1) (P = 0.02). This is consistent with the findings of other studies. In 31 symptomatic patients found to be spontaneously embolising 1/1 (100%), 14/35 (40%), 8/37 (22%) and 8/50 (16%) patients presented within 48 h, 3–7 days, 8–14 days and >14 days respectively from the index clinical event.

When analysed according to whether surgery was performed within <7 days vs. >14 days of the index event, the prevalence of SE was significantly higher in those treated within the earlier time frame [15/36 (42%) vs. 8/50 (16%) (OR 3.8 95% CI 1.4–10.2) (P = 0.01)]. Out of 31 patients found to be spontaneously embolising, seven (22.6%) reported recurrent cerebrovascular events following admission as opposed to 11/92 patients (11.9%) who had no evidence of spontaneous embolisation (OR 2.2 (95% CI 0.8–6.1)) (P = 0.2).

In 30 min of TCD monitoring, there was no significant difference in the mean rate of SE in the cohort that went on to have a recurrent cerebral ischaemic event (4.5/30 min monitoring) compared to the cohort that did not have a recurrent cerebral ischaemic event (3.3/30 min monitoring) (P = 0.376).

Table 2 details the degree of stenosis and rates of spontaneous embolisation in patients who were symptomatic and asymptomatic and also details the median delay from index symptom to CEA and the median delay from the most recent symptom to undergoing CEA. These data were then correlated with the risk of suffering a recurrent cerebral ischaemic event following admission but before undergoing surgery.

Overall, 18/123 symptomatic patients (14.6%) suffered recurrent cerebral ischaemic events between the time of admission and undergoing surgery, though none of these were strokes and on each occasion the secondary (recurrent) event was the same as the primary clinical event (Transient Ischaemic Attack = 14, Amaurosis Fugax = 4). Patients reported events occurring prior to, during and after TCD monitoring. Patient demographics are detailed in Table 3 for those recently symptomatic patients that had recurrent cerebral ischaemic events after transfer to the vascular surgery unit. Spontaneous embolisation was detected in 3/7 (43%) symptomatic patients who were commenced on aspirin and statin on admission but prior to TCD monitoring compared to 28/116 symptomatic patients (24%) who were on aspirin and statin therapy prior to admission (OR 2.3 (95% CI 0.5–11.1) (P = 0.4)). In the cohort of patients who were commenced on aspirin and statin following admission and found to have TCD evidence of SE, no recurrent cerebral ischaemic events occurred.

Table 4 correlates the prevalence of SE and its relationship with recurrent cerebral ischaemic events relative...
to delay surgery from the index event in recently symptomatic patients with a 50–99% stenosis and a 70–99% stenosis ($n=104$).

When all 123 recently symptomatic patients with a 50–99% stenosis are combined, the presence of SE was associated with a non-significant two-fold increase in the risk of recurrent cerebrovascular events {OR 2.2 (95% CI 0.8–6.1)} ($P = 0.2$ Fisher’s Exact test).

**Discussion**

This is one of the first studies to correlate the prevalence of SE in the hyperacute period after suffering a TIA or minor stroke and to then correlate patterns of SE with recurrent cerebral ischaemic events.

This study observed that symptomatic patients had a significantly higher prevalence of SE than asymptomatic patients ($P = 0.02$). In addition, this study observed that the prevalence of SE was closely related to the recency of both the index clinical symptom and the most recent clinical event. There was a significantly higher incidence of SE in patients treated within 7 days compared to those treated after 14 days from the index event ($P = 0.01$). It should be noted that patients found to have TCD evidence of SE were prioritised for urgent surgery either on the next available CEA list (twice weekly) or on the emergency list if space was not available on the CEA list; i.e. the detection of spontaneous embolisation did influence decision making relating to the planning of urgent surgery following admission.

The third finding of this study was the relationship between SE, delays to surgery and the risk of recurrent cerebral ischaemic events prior to CEA. Overall, 18/123 symptomatic patients (14.6%) suffered recurrent cerebral ischaemic events between the time of admission and undergoing surgery, though none of these were strokes (Transient Ischaemic Attack = 14, Amaurosis Fugax = 4). The prevalence of recurrent events was higher in patients with 70–99% stenoses {17/104 (16%)} than in those with 50–69% stenoses {1/19 (5.3%)} ($p = 0.3$).

Overall, the prevalence of recurrent cerebral ischaemic events was twice as high in patients with TCD evidence of SE {7/31 (23%)} than in those with no evidence of SE {11/92 (11.9%)} (OR 2.15 (95% CI 0.75–6.1) ($P = 0.2$)) but this did not reach statistical significance.

### Table 2  Relationship between degree of carotid stenosis determined by duplex ultrasound, presence of spontaneous emboli and timing of emboli to clinical event.

<table>
<thead>
<tr>
<th>Degree stenosis (NASCET)</th>
<th>Recently symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 104</td>
<td>19 (15%)</td>
<td>85 (85%)</td>
</tr>
<tr>
<td>Spontaneous embolisation</td>
<td>Yes 2/19 (11%)</td>
<td>No 17/19 (89%)</td>
</tr>
<tr>
<td>Median time from index</td>
<td>8 days (95% CI 1–48 days)</td>
<td>14 days (95% CI 5–12 days)</td>
</tr>
<tr>
<td>symptom to carotid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>endarterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time from most</td>
<td>8 days (95% CI 1–34 days)</td>
<td>12 days (95% CI 3–9 days)</td>
</tr>
<tr>
<td>recent symptom to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carotid endarterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with recurrent cerebral ischaemic events between TCD and CEA</td>
<td>0/2</td>
<td>1/17 (6%)</td>
</tr>
<tr>
<td>P value</td>
<td>1</td>
<td>0.23</td>
</tr>
</tbody>
</table>

### Table 3  Demographics for Symptomatic patients presenting with/without recurrent cerebral ischaemic events after admission to the vascular surgery unit.

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Recurrent cerebral ischaemic event ($n=18$)</th>
<th>No recurrent cerebral ischaemic event ($n=105$)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (78%)</td>
<td>73 (70%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>4 (22%)</td>
<td>32 (30%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Age (median)</td>
<td>70 (52–87)</td>
<td>73 (37–94)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (72%)</td>
<td>71 (68%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>16 (89%)</td>
<td>83 (79%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (11%)</td>
<td>23 (22%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>7 (39%)</td>
<td>21 (20%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ex/current smoker</td>
<td>13 (72%)</td>
<td>77 (73%)</td>
<td>1</td>
</tr>
<tr>
<td>On anti-platelet therapy following admission</td>
<td>18 (100%)</td>
<td>105 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Anti-platelet therapy pre-admission</td>
<td>18 (100%)</td>
<td>98 (93%)</td>
<td>0.6</td>
</tr>
<tr>
<td>On statin therapy following admission</td>
<td>18 (100%)</td>
<td>105 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>On statin therapy pre-admission</td>
<td>18 (100%)</td>
<td>98 (93%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
So how should these results be interpreted? This study has shown a non-significant trend towards SE being predictive of recurrent cerebral ischaemic events, especially in patients with a 70–99% stenosis. It may be that a significant result might have become evident with greater numbers which is accepted to be one of the study limitations, but the fact that only 30 min of pre-operative TCD monitoring was performed may also have missed patients who were truly embolising (i.e. a type II error).

Reducing delays in admission and therefore surgery after the index clinical event remains an important benchmark for secondary stroke prevention. We have previously reported that following the introduction of a rapid access TIA clinic in October 2008, 43% of patients in our unit now underwent surgery within 7 days of their index clinical event. The findings and clinical impact of this study is limited by the delay in admission from index clinical event. Enhancing patient education, and improving links between primary care and secondary care, and between stroke physicians and vascular surgeons is ensuring that this delay is reduced.

Although no strokes occurred prior to surgery in this particular series, these findings are otherwise entirely consistent with natural history studies demonstrating the higher risk of recurrent stroke and TIA in the hyperacute period after suffering a TIA.\(^1,^9\) The impetus for undertaking more rapid intervention came from two recently published meta-analyses by Giles and Wu.\(^2,^13\) These meta-analyses showed that the risk of stroke after a TIA was highest in the first seven days. The meta-analyses by Giles and Wu\(^2,^13\) (which were based on natural history studies that utilised ‘face to face’ follow up of the entire population of TIA patients) demonstrated that at 48 h the risk of stroke increased to 6.7%, and was 10% at seven days. This represents a fourfold increase in the early risk of stroke after a patient presented with their index TIA when compared to conventional teaching. Analysis of the Carotid Endarterectomy Trialists Collaboration (CETC)\(^19\) data has also allowed researchers to model the number of strokes prevented per 1000 CEAs at 5 years in relation to the procedural risk and delay to surgery. The evidence from this analysis suggest that surgical intervention within 14 days with a procedural risk of 10% would still prevent more strokes at 5 years than if surgery was delayed by four or more weeks and then performed with a procedural risk of 0%.\(^15\)

For these reasons, there is a drive towards undertaking urgent/emergency treatment of TIA patients. While guidelines from the European Vascular Surgery Society\(^16\) and the UK National Institute for Clinical Excellence (NICE)\(^17\) now recommend that CEA should be performed within 14 days of onset of symptoms unless contra-indicated, the ultimate goal of the UK National Stroke Strategy\(^18\) is that CEA should be regarded as an emergency procedure and should be performed within 48 h of a TIA or minor stroke.

The use of pre-operative TCD monitoring and detection of SE allows for individualised patient management, in order to prioritise treatment and meet current guidelines. The study serves as a pilot study which can now lead to a powered study with the possibility to do two-time point
TCD measurements to determine intra-patient variation in rate of SE in time.

In summary, therefore, this study lends further support to natural history studies which suggest that the risk of recurrent cerebral ischaemic events is highest in the first few days after onset of symptoms and that the higher rates of SE detected during these time periods support on-going thrombo-embolisation (despite initiation of anti-platelet therapy) being the principle cause of these recurrent events. These data, therefore, support the move towards expedited CEA in patients who present with TIA or minor stroke.

Conflict of Interest/Funding

None.

References

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