No evidence that severity of stroke in internal carotid occlusion is related to collateral arteries

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People who occlude their internal carotid artery (ICA) may do so asymptomatically, or may experience neurological effects ranging from transient ischaemic attack (TIA) to major disabling stroke. The reason for such variation is uncertain, but one possible explanation is that severe strokes occur in patients whose potential collateral pathways were poor because of disease in, or developmental absence of, other extra or intracranial arteries supplying the brain.

Although there are several studies on ICA occlusion and type of symptoms, few have tried to determine why some patients present with severe symptoms and others do not. The few previous studies that do relate symptoms to intracranial flow were small, or only included TIA or minor stroke, not all stroke severities. Two found an association between symptoms and collateral flow in mild stroke and two did not.

Other studies were biased because they only included dead patients or those undergoing angiography. One study related the extent of cerebral infarction on brain imaging (but not symptoms) to collateral flow. Some studies investigated the risk of recurrent stroke in longstanding ICA occlusion. One of these studies found that recurrent stroke distal to a symptomatic ICA occlusion was associated with increased volume flow in collaterals (contralateral ICA), counterintuitive to the hypothesis that better collateral flow is protective.

Previous studies mainly examined intracranial collateral pathways and only two looked at collateral potential in the extracranial arteries.

The failure of previous studies to find any consistent association between collaterals and symptoms may be because they generally included patients with only mild symptoms. Therefore, our aim was to explore the influence of the collateral pathways on the nature and severity of symptoms in a large, consecutive, hospital based series of patients presenting with ICA occlusion and new cerebral or ocular ischaemic symptoms. We hypothesised that patients with ICA occlusion at presentation with severe stroke symptoms were more likely to have disease in other extra or intracranial arteries, impairing their function as collaterals.

METHODS
From November 1994 to April 1999, we prospectively identified all patients (including first and recurrent events) presenting to our stroke service with acute stroke, cerebral transient ischaemic attack (TIA), amaurosis fugax (AFx), and retinal artery occlusion (RAO). We recorded whether there was a history of prior stroke or TIA.

A stroke physician examined the patient as soon as possible following onset of symptoms. Those with acute stroke were classified clinically according to the Oxfordshire Community Stroke Project (OCSP). Cerebral TIAs were categorised as posterior circulation or anterior circulation, then the anterior circulation TIAs were further divided into lacunar or cortical TIAs according to the presence or absence of cortical symptoms. RAO was defined as monocular visual loss, partial or complete, lasting more than 24 hours likely to be due to vascular disease of the retina. Brain imaging (CT or magnetic resonance imaging) was not required for diagnosis.

Abbreviations: ACA, anterior cerebral artery; ACoA, anterior communicating artery; AFx, amaurosis fugax; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; LACI, lacunar infarct; MCA, middle cerebral artery; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarct; PCoA, posterior communication artery; POCI, posterior circulation infarct; RAO, retinal artery occlusion; TACI, total anterior circulation infarct; TIA, transient ischaemic attack.
Complete ICA occlusion was diagnosed if proportion of patients with ipsilateral or contralateral ICA tests for trend. We tests or Mead, Wardlaw, Lewis, et al.

Retrograde and velocity in the vertebral arteries was also detectable Doppler signal. Flow direction (orthograde or there was no colour flow in the lumen of the vessel and no occluded vertebral arteries were diagnosed when a clear view of the vertebral canal was obtained but no flow was detected.

The intracranial vessels: A1 segment of the anterior cerebral artery (ACA), anterior communicating artery (ACoA), posterior communicating artery (PCoA), middle cerebral artery (MCA), P1 and P2 segments of posterior cerebral artery, ophthalmic artery, intracranial portion of the ICAs and basilar artery, were examined using colour power transcranial Doppler by the same ultrasonographer at the time of carotid imaging, in as many patients as possible. A 2 MHz probe was used for the trans-temporal and subcortical approaches and a 7 MHz for the transorbital approach. The ultrasonographer made a diagnosis of “normal”, “reduced but still detectable flow”, “occlusion”, “hyperaemia”, or “focal stenosis” using previously reported criteria.

For patients with cortical brain events (that is, total anterior circulation infarcts, TACIs, partial anterior circulation infarcts, PACIs, and cortical TIAs) and an ipsilateral ICA occlusion, we compared the severity of the clinical syndrome with disease in the other extracranial arteries or patterns of flow in the intracranial circulation. We also sought any association between prior TIA or stroke and the severity of current symptoms using $\chi^2$ tests or $\chi^2$ tests for trend. We performed these analyses in two different ways: firstly, we included those patients with no brain imaging; and then we repeated the analyses after excluding patients with cerebral symptoms (that is, stroke and cortical TIA) and no brain imaging. Here we report results after the exclusion of patients with cerebral symptoms and no brain imaging.

**RESULTS**

**Patients**

Between November 1994 to April 1999, 2881 patients with stroke, cerebral TIA, RAO, or AFx were identified, of whom 2292 had CT or MR brain imaging (96% of strokes and 61% of cerebral TIAs). 148 patients with intracerebral haemorrhage and 336 patients with cerebral symptoms and no brain imaging were excluded. Of the remaining 2397 patients, there were 1713 ischaemic strokes, 401 cerebral TIAs, 193 AFx, and 90 RAO.

Of 2228 patients (93%) with carotid Doppler imaging, 195 (9%) had ICA occlusions (fig 1). Of the 195 patients with ICA occlusions, 146 (75%) had an occlusion ipsilateral to the brain or eye lesion only, 36 (18%) had a contralateral occlusion only, eight had bilateral occlusions; and a further

MRI) was done in patients with acute stroke, and when clinically indicated in patients with cerebral TIA, RAO, and AFx (for example, in patients with multiple or atypical attacks) immediately after medical assessment, in order to identify those with intracranial haemorrhage and stroke “mimics”. We classified infarct site and size using a validated stroke imaging scoring system.

**Table 1** Disease of the contralateral internal carotid artery, ipsilateral or contralateral external carotid arteries, and vertebral arteries in patients with cortical symptoms and an ipsilateral ICA occlusion

<table>
<thead>
<tr>
<th></th>
<th>TACI and ipsilateral ICA occlusion (n = 22)</th>
<th>PACI and ipsilateral ICA occlusion (n = 70)</th>
<th>Cortical TIA and ipsilateral ICA occlusion (n = 14)</th>
<th>Other patients with any ICA occlusion (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral ICA disease &gt;70% stenosis, n (%)</td>
<td>5 (23%)</td>
<td>20 (29%)</td>
<td>5 (36%)</td>
<td>47 (53%)</td>
</tr>
<tr>
<td>Any ipsilateral ECA stenosis, n (%)</td>
<td>10 (45%)</td>
<td>29 (41%)</td>
<td>5 (36%)</td>
<td>42 (47%)</td>
</tr>
<tr>
<td>Any contralateral ECA stenosis, n (%)</td>
<td>7 (32%)</td>
<td>18 (26%)</td>
<td>4 (29%)</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>Ipsilateral vertebral artery occluded or reduced flow, n (%)</td>
<td>1 (5%)</td>
<td>8 (11%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Contralateral vertebral artery occluded or reduced flow, n (%)</td>
<td>1 (5%)</td>
<td>7 (10%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; ECA, external carotid artery.

Ipsilateral vertebral artery is on the same side of the neck as the ipsilateral ICA.

“Other” includes the contralateral occlusions, and the RAO, AFx, LACI, lacunar TIA, POCI, and posterior circulation TIA with ipsilateral occlusions.
five occlusions were identified in patients with midline brain lesions or bilateral lesions.

Most of the 7% who did not have carotid imaging had had severe strokes and did not survive or were too ill to move for imaging. As expected, ipsilateral ICA occlusion was most common in patients with cortical and eye events and in those with more severe symptoms (fig 1).

There was a history of prior TIA or stroke in 7/22 TACIs (32%), 35/70 (50%) PACIs, and 8/14 (57%) cortical TIAs, but the difference was not significant ($\chi^2$ p = 0.33)

### Extracranial disease

Among patients with cortical symptoms (TACI, PACI, and cortical TIA) and ipsilateral ICA occlusion there was no significant difference in the prevalence of contralateral ICA disease ($\chi^2$ for trend p = 0.4), ipsilateral external carotid (ECA) disease ($\chi^2$ for trend p = 0.6), contralateral ECA disease ($\chi^2$ for trend p = 0.8), or contralateral or ipsilateral vertebral abnormalities between the three groups (table 1).

We repeated the analyses having excluded patients with previous stroke (that is, those whose ICA occlusion may have been symptomatic at some time in the past) but these data did not change the results (data available on request).

### Collateral flow patterns of intracranial vessels

We looked for trends in collateral flow patterns (table 2) across patients with cortical symptoms (TACI, PACI, and cortical TIA). There were no trends in the proportions of patients with abnormal flow in the intracranial or ophthalmic artery circulation across the three groups with cortical symptoms. The only hint of a difference was that the ipsilateral MCA flow was more often reduced among the TACI and PACI than the cortical TIA patients, as one would expect soon after stroke, consistent with an MCA occlusion rather than indicating collateral flow. Note that the commonest finding was for potential collateral channels, rather than indicating collateral flow. Note that the commonest finding was for potential collateral channels, rather than indicating collateral flow.
DISCUSSION
This large study of 2450 patients presenting with new neurological symptoms (ranging from transient symptoms to major disabling stroke) found that in those with ipsilateral ICA occlusion, there was no association between adequacy of potential collateral pathways and the severity of stroke symptoms. Although there is an extensive literature on ICA occlusion, few studies have investigated whether collaterals determine the severity and type of symptoms at the time of ICA occlusion, and most of these were either small and/or recruited patients with TIA or minor strokes. The strength of our study was that we prospectively studied a large cohort of patients presenting to a broad based hospital stroke service, involving a substantial number of patients with severe as well as mild strokes, TIs, and retinal symptoms. Almost all underwent carotid imaging, and of those with ipsilateral ICA occlusion, most had TCD performed, resulting in a complete data set in the majority of patients.

There were some limitations to our study. Our stroke registry did not include asymptomatic people with an ICA occlusion (who might be expected to have the best collateral flow if our original hypothesis was correct)—the registry only recorded patients with symptoms. Also, we could not reliably distinguish ICA occlusion occurring at the time of the patients presenting symptoms from those which may have occurred some time previously. However, even if the occlusion were longstanding, one might expect the severity of the presenting symptoms to relate to the adequacy of collaterals and therefore still have expected to observe a relationship between flow in collaterals and severity of symptoms. The group most likely to miss having carotid and transcranial Doppler studies (7% of 2397 patients) were the TACIs or POCIs who were more likely to die or be considered too ill for imaging. However, because we found no association between potential sources of intracranial collateral flow and the different patient groups, the exclusion of these few severe strokes probably did not influence our results. We used ultrasound rather than other imaging techniques because it is non-invasive, quick to perform, far more accessible than any other form of carotid imaging, and tolerated by the majority of patients, even those who are very ill. However, the intracranial vessels may be inaccessible in a substantial number of patients, and pathology in the intracranial internal carotid artery and basilar artery may be insufficiently evaluated by TCD. The accuracy of duplex Doppler compared with angiography is high for carotid disease, so even if we misclassified a few patients with severe ICA stenosis as ICA occlusion, this would not have affected the overall results. We did not examine cerebral perfusion patterns with PET or perfusion MR as it would not have been practical to perform these in such a large group of patients (including severe strokes) and would have restricted and biased our recruitment.

Therefore we still do not know why some patients with ICA occlusion develop severe stroke symptoms and others remain asymptomatic. The underlying cause of ICA occlusion (that is, cardioembolic or thrombus on atheroma) may influence the clinical effects of ICA occlusion by affecting the rate at which collateral vessels may develop. Old cannot be distinguished from new ICA occlusions reliably on Doppler imaging, but the few postmortem studies of patients dying from ischemic stroke show that the aetiology is generally fresh thrombus on pre-existing atheroma and sudden embolic occlusion in the neck of a previously normal ICA is unusual. There are some data to support the notion that prior stroke or TIA may protect against the effects of sudden ICA occlusion by “ischaemic pre-conditioning” and some that do not. Our data provide no conclusive evidence either way. However, if prior TIA and stroke are protective, this could relate to use of antiplatelet drugs rather than changes in cerebrovascular haemodynamics, because patients with previous TIA or minor stroke would be more likely to be taking aspirin at the time of their index stroke.

Further work is required to determine what causes some ICA occlusions to cause severe strokes, but our data suggest that it does not seem to be a simple “plumbing” problem. It might be helpful to develop a technique for distinguishing old from new occlusions. Comparison of symptoms in presumed atherosclerotic occlusion (progressive occlusion, with time to develop collaterals) with presumed cardioembolic occlusion might help to determine whether the collateral vessels are important in determining the clinical effects of occlusion.

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Competing interests: None.

Ethical approval (from Lothian Research Ethics Committee) was obtained for the study.

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