Management of carotid near-occlusion and acute carotid occlusion

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Abstract

As a stenosis becomes more severe, blood flow through it increases in velocity to maintain volume, flow and pressure. But there is a critical point beyond which further increase in stenosis no longer allows sufficient blood to pass through to maintain volumetric flow, and the carotid artery beyond the stenosis begins to decrease in diameter. This is the near occlusion. To maintain a sufficient blood flow in affected area, there is a progressive recruitment of collaterals followed by an activation of cerebral autoregulation with dilatation of resistance vessels. When this process fails to maintain normal CBF, oxygen extraction fraction of the affected brain tissue increases to maintain normal cerebral metabolism. Near occlusion has been described as involving 1 to 10% of all severe stenosis, but the potential for stroke from such critical stenosis is less than its appearance would suggest. The optimum management of near-occlusion therefore remains a matter of debate. Although endarterectomy for carotid stenosis of 70-99% was associated with an absolute risk reduction in any stroke or death of 16% in the original randomised trials, the benefit was less in patients with near-occlusion. In 2015, a meta-analysis focused on patients with near-occlusion confirmed only a small benefit of CEA or CAS compared to medical treatment in patients with near occlusion. In patients with near-occlusion and compromised haemodynamics, revascularization should improve cerebral blood flow and consequently prevent ischaemic stroke. Nevertheless the effect of improved cerebral haemodynamics after revascularization on prevention of ischaemic stroke is uncertain.

Introduction

Stroke is the second most common cause of mortality and the third most common cause of disability worldwide. The TOAST classification is commonly used to differentiate stroke etiology, but in this classification patients with near or total occlusion are not separately
identified, and most will be included within the category of large-artery atherosclerosis. This makes it difficult to estimate the prevalence of patients with near or total occlusion. Overall, 15-20% of strokes are related to an atherosclerotic stenosis of the internal carotid artery (ICA) and its prevalence increases with age and risk factors in western countries. It is generally assumed that a stenosis is considered a symptomatic stenosis when the ischaemic lesion causing the stroke is within an appropriate ipsilateral carotid artery distribution in the presence of a significant degree of stenosis, usually considered to be one that is >50% measured using the NASCET method. The prevalence of asymptomatic carotid artery stenosis >50% in the general population is estimated at 4.8% for men and 2.2% for women. The prevalence increases significantly after 70 years old. Low-grade internal carotid artery (ICA) stenosis (<50%) has a risk of 4 to 29% of progressing to a higher grade of stenosis and is then associated with an increasing risk of stroke. Indeed, some studies have suggested that the risk of stroke in low-grade stenosis starts at 7.8% and rises to 18.5% in high-grade stenosis in initially asymptomatic patients with a similar gradient in symptomatic patients from 18.7 to 27%. Nevertheless, there is a point towards occlusion where the risk of stroke begins to decline despite the severity of the stenosis, which is a feature of near-occlusion of the carotid artery (Figure 1).

The features of near-occlusion were drawn to attention by Lippman et al in 1970, using the descriptive term of the post-stenotic slim sign. Other appellations for the same phenomenon include pseudo-occlusion, the nearly-occluded carotid artery, string sign and carotid collapse. The prevalence has been described from 1 to 10% of all severe stenosis, but it is clear that the potential for stroke from such critical stenosis is less than its appearance would suggest. Moreover, although the management of severe carotid stenosis has been extensively studied, the optimum management of near-occlusion of the ICA still remains a matter of
debate. In this review, we discuss carotid artery near-occlusion from its identification to its management.

Pathophysiology

Atherosclerosis is as diffuse and degenerative disease of the arteries resulting in plaque and vessel narrowing and leading to ischaemic stroke or transient ischaemic attack (TIA). Plaques consist of necrotic cells, lipids and cholesterol crystals. The most frequent location of carotid atherosclerosis is the carotid bifurcation with extension into the proximal internal carotid artery. As a stenosis progressively becomes more severe, blood flow through it increases in velocity to maintain volume, flow and pressure. But there is a critical point beyond which further increase in stenosis no longer allow sufficient blood to pass through and the ICA beyond the stenosis begins to decrease in diameter. This defines ICA near-occlusion and in many cases, the stenosis will progress to complete occlusion. The hemispheric circulation is then supplied through inverted ophthalmic artery blood flow from the external carotid or by the contralateral ICA or vertebrobasilar circulation through the communicating arteries. Less commonly collaterals may come from the leptomeningial arteries or the cortical surface branches.

If collateralisation is not sufficient to maintain normal blood flow in affected areas, the flow can be maintain by dilatation of the resistance vessels. This is cerebral autoregulation or cerebral vasoreactivity (CVR). This process is diagnosed by reduced or absent cerebral blood flow (CBF) response to vasodilate stimuli such as hypercapnia in the cerebrovascular reactivity test. In ICA occlusion, this vasodilatative stimulus may not increase CBF if autoregulation has already caused maximal vasodilatation in response to the low cerebral perfusion pressure. This was shown by Oka et al in 2013 using SPECT to quantify resting CBF in near-occlusion compared to severe stenosis without near-occlusion.6 Resting CBF
and CVR were both significantly lower in the patients with near-occlusion, consistent with the hypothesis of compromised haemodynamics in these patients.

Finally, when this process fails to maintain normal CBF, oxygen extraction fraction of the affected brain tissue increases to maintain normal cerebral metabolism. This is a haemodynamic failure or misery perfusion. An increase oxygen extraction fraction is an independent risk factor for subsequent ischaemic strokes in patients with symptomatic ICA occlusion. The annual stroke risk in patients with impaired haemodynamic measurements of any severity was 12.5% for all strokes and 9.5% for ipsilateral strokes. This highlights the worse prognosis in patients with impaired cerebral perfusion than in those without. CVR is an alternative parameter for predicting long-term outcome but its validity is still controversial. In their study, Kuroda et al. determined that CVR to acetazolamide is a reliable predictor of subsequent ischaemic stroke in medically treated patients with occlusive carotid disease. The overall annual rate for total and ipsilateral stroke was 5.8% and 2.6% respectively. The study demonstrated the higher risk of ipsilateral stroke and total ischaemic stroke in patients with decreased CVR.

**Clinical presentation**

Cardiovascular events and deaths are more frequent in patients with near-occlusion than in those without. This is in line with the fact that patients with severe stenosis sufficient to cause carotid artery collapse may also suffer from severe atherosclerosis throughout the body. The clinical spectrum of ICA occlusion ranges from being completely asymptomatic to devastating stroke or death. ICA occlusion is also an independent predictor of neurological worsening in stroke.

Clinical presentation of a near-occluded or occluded ICA is very varied. If collateral flow is inadequate, stroke may result directly from the reduction in flow but more commonly stroke
associated with carotid occlusion is embolic. Embolic TIA or stroke presents with clinical features similar to those due to any other etiology. However, a haemodynamic condition that reduces cerebral perfusion, such as postprandial hypotension, fluid or blood loss, exercise or cardiac failure can lead to a stroke from haemodynamic mechanisms. A rare manifestation of haemodynamic compromise is limb shaking which could be misdiagnosed as partial seizures. Some patients develop headaches in chronic occlusion due to the development of collateral circulation. Collateral flow from the external carotid may also cause ipsilateral pulsation at the angle of the jaw, brow and cheek known as the ABC pulsation of Fisher.\(^9\) This is not seen when collaterals arise from circle of Willis. In 4-18% of patients with occlusion or severe stenosis of the ICA a syndrome of chronic ocular ischaemia may develop. Patients complain of progressive loss of visual acuity. Although, emboli arising from a clot within evolving occlusion is the commonest mechanism of stroke, Molloy and Markus showed that there is a significant reduction in the number of microemboli detected using transcranial Doppler when the degree of stenosis is higher than 90% and particularly in patients with post-stenotic narrowing and blood flow reduction.\(^{10}\) This is in keeping with the observation that the incidence of ischaemic stroke in medically treated patients with near-occlusion are lower than in patients with severe stenosis without near-occlusion.

**Imaging**

Nowadays, catheter-based cerebral angiography (DSA) has been almost completely removed from the standard assessment of carotid disease because of its invasive nature and risk. Current imaging methods for routine assessment include duplex ultrasound (DUS), computed tomography angiography (CTA) and magnetic resonance angiography (MRA). All three have a good sensitivity and specificity to estimate high-grade stenosis. DUS is used to detect focal increases in blood flow velocity indicative of high-grade stenosis, but is less precise in smaller stenosis and calcified arteries. It operator-dependency makes it also less
CTA provides an anatomic view of the carotid artery lumen, allows for evaluation of the intracranial and extracranial circulation and evaluation of adjacent soft tissue and bone structure. TOF-MRA is very sensitive in arterial stenosis but tends to overestimate stenosis. Contrast-enhanced MR has the advantage of not being limited by calcification (Figure 2). It was considered to be the most accurate non-invasive test for carotid artery stenosis by Chappell et al in 2009,\textsuperscript{11} but many would argue that CTA is now the more accurate modality, especially in the absence of calcification.

It becomes technically challenging to accurately visualise a near-total occlusion and to differentiate it from a total occlusion of the carotid using these non-invasive methods. The diagnosis of near-occlusion based on DSA uses 4 criteria: 1) delayed time of contrast arrival in the ICA compared to the filling of the ECA, 2) evidence of collaterals (anterior or posterior communicating arteries, external carotid collaterals (usually ophthalmic), 3) ICA-to-ICA comparison of diameter reduction and 4) ICA-to-ECA comparison of diameter reduction. The delayed of contrast arrival has the poorest sensitivity for diagnosing near-occlusion (37.5%) whereas ICA to ECA comparison of diameter reduction had the highest sensibility (84.4%).\textsuperscript{12}

A part from DSA, CT angiography can distinguish near-occlusion from total ICA occlusion with a high degree of accuracy but gives no information about blood flow velocity and directionality. With DUS, some symptomatic patients with near-occlusion stenosis are wrongly classified as having occlusion, because of the very low flow in the vessel\textsuperscript{13}. Newer techniques with contrast-enhanced agent or modified duplex protocol have shown to be effective in distinguishing between occlusion and pseudo-occlusion.\textsuperscript{13}

MR angiography is generally accurate in identifying total and near-occlusion from the ICA origin to the supraclinoid part (figure 2). However, the appearances can be disguised by the presence of collateral flow distal to the occlusion, without the ability on MRA to define the
flow direction or sequence of vessel filling. Gadolinium contrast-enhanced MR angiography (CEMRA) is better than the TOF angiography for depicting near-occlusion. In current practice the combination of CEMRA or CTA and CDUS is considered sufficient for identifying patients with carotid artery occlusion.

Perfusion imaging
The techniques mentioned above are able to identify a near-occlusion of the carotid but provide no consideration of the haemodynamic compromise. The evaluation of cerebral perfusion and blood supply can be assessed by SPECT, PET, functional MRI and perfusion or Xenon CT. Transcranial ultrasound (breath holding test) and quantitative MRA also evaluate cerebral vasoreactivity and PET quantifies the oxygen extraction fraction.

Treatment
The correct grading of the carotid stenosis is essential to guide the options for treatment. While carotid endarterectomy and endovascular treatment have been proved superior to best medical treatment (defined as treatment of risk factors, modification of lifestyle and medical treatment with aspirin or combination of aspirin and dipyridamole or clopidogrel) in high-grade stenosis, it remains a matter of debate whether the near-occluded carotid should be revascularised or not. In general, revascularisation is not an option for total carotid occlusion, unless perhaps in the hyperacute case, where the artery can be re-opened within a few hours of onset of the occlusion.

High-grade stenosis
Concerning high-grade carotid stenosis, two landmark large trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) showed a benefit of carotid endarterectomy (CEA) over medical treatment in
patients with more than 70% symptomatic internal carotid artery stenosis. Pooled analysis of these trials showed an absolute risk reduction in any stroke or death of 16% (p<0.001) and a number needed to treat of 6 in patients with a stenosis of 70-99%.\textsuperscript{15} Moreover, CEA within two weeks of a non-disabling stroke or TIA significantly lowered the stroke risk compared with later surgery. Carotid endarterectomy in asymptomatic patients with a stenosis greater than 60% also showed a benefit in the Asymptomatic Carotid Surgery Trial (ACST), although the benefit was much weaker.\textsuperscript{15} The net five-year risk for all strokes or perioperative death in the immediate CEA group was reduced by nearly half compared with the CEA deferral group (6.9 versus 10.9%; p=0.001).

\textit{Near-occlusion}

In near-total occlusion the decision for or against revascularization still remains controversial. The decision should take into account the evidence that ICA occlusion will occur in approximately 40% of the patients within 12 months or in 100% within 34 months. Cerebrovascular or cardiac events are more frequent in patients with near-total ICA occlusion compared with patients with carotid artery stenosis. But, on the other hand, the reduction of blood flow across the stenosis may reduce the risk of brain embolization\textsuperscript{10}. Nowadays, data are limited since this group of patients were excluded from some of the biggest carotid trials, including CREST and ICSS. The available data originate from the post-hoc analyses of the large trials performed in the late 1990s (NASCET, ECST). In NASCET, the 3-years risk of ipsilateral stroke for surgically vs. medically treated patients was 11.4% vs 17.9% respectively. In ECST, the 3-year risk was 10.5% vs. 11.1% respectively.\textsuperscript{12} The difference between both studies was explained by the lower prevalence of some risk factors in the ECST trial. In 2005, Fox et al. merged the two trials ECST and NASCET and evaluated all patients with severe stenosis.\textsuperscript{12} The combined results of these studies showed a low risk of stroke in the medically treated patients with near-occlusion (Figure 3).\textsuperscript{15} This provided
again evidence that most strokes arising from a narrowed artery are embolic rather than haemodynamic. In 2015, a meta-analysis focused on patients with near-occlusion confirmed again the small benefit of CEA or carotid artery stenting (CAS) compared to medical treatment in these patients and balanced their results with the improvement of the medical therapy and lifestyle recommendation in the last 20 years. No difference was found between CEA and CAS concerning TIA or stroke risk, but a borderline significance was recorded concerning overall mortality favouring CEA compared to CAS (p=0.08) and restenosis favouring CAS compared to CEA (0.08).16

In patients with near-occlusion and compromised haemodynamics, revascularization should improve cerebral blood flow and consequently prevent ischaemic stroke. In 2013, Oka et al used SPECT imaging to investigate the haemodynamic effects of CAS in patients with near-occlusion in comparison with patient with stenosis without near-occlusion.6 After CAS, the mean resting CBF and CVR were both significantly increased in patients with near-occlusion. The study showed that cerebral haemodynamics were compromised in patients with near-occlusion and both CBF and CVR increased after revascularization. Nevertheless the effect of improved cerebral haemodynamics after revascularization on prevention of ischaemic stroke is uncertain. In another study comparing CEA and cognitive function, it appeared that cognitive changes are proportionally related to the metabolism in the cerebral hemisphere ipsilateral to CEA. Post CEA recovery of cerebral metabolism resulted in postoperative cognitive improvement and the inverse was also true.17

Carotid occlusion

In carotid occlusion, one has to consider acute and the chronic occlusion separately, because they are two different entities in terms of management. Acute occlusion of the carotid, if symptomatic often presents as a massive stroke with high NIHSS (national
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Institutes of Health Stroke Scale) related to profound neurological deficit. Acute ICA occlusion has a poor prognosis even with systemic thrombolysis, which is the first line of treatment in any acute ischaemic stroke. The second line of treatment of acute ICA occlusion involves mechanical thrombectomy. The third line of treatment involves surgery in some very rare and selected cases. Patients with mild or improving neurologic deficits, no evidence of haemorrhagic infarct on CT and a recent ICA thrombosis with a patent distal ICA could be considered as candidates for a surgical approach.

As mentioned above, some patients will evolve from a high-grade stenosis to a total occlusion and then have chronic occlusion, which can remain asymptomatic through life. One study established that the 2-year risk of ipsilateral ischaemic stroke following internal carotid artery occlusion in patients undergoing maximal medical therapy is 5-8% per year.\textsuperscript{18} In a recent retrospective study, the authors showed 0.3% rate of stroke related to progression to carotid occlusion in 316 carotid stenosis evaluated from 1990 to 2012.\textsuperscript{19} The authors concluded that preventing carotid occlusion should no longer be regarded as an indication for carotid revascularisation.

In the 1960s, it was common to believe that patients with carotid occlusion could be successfully treated by bypass surgery. In 1977, the first prospective randomized trial on extracranial-intracranial (EC-IC) bypass in conjunction with best medical therapy showed no statistical difference in outcomes between the 2 cohorts neither within 30 days nor in the long term. The rate of recurrent stroke in the bypass group was 31% vs 29% in the medical therapy alone group. Later the observational St Louis Carotid occlusion study (STLCOS) demonstrated that ipsilateral increased oxygen extraction fraction (OEF) is an independent risk factor for subsequent stroke in symptomatic patients (5.3% stroke risk in 42 patients with normal OEF and 26.5% in 39 patients with increased OEF; p=0.040). The authors suggested
that selection using PET should be considered as a preliminary to bypass surgery. In 2011 the carotid occlusion surgery study (COSS), showed that despite improved cerebral haemodynamics with reduced OEF on follow-up PET, there was no benefit to EC-IC bypass surgery and no difference in event rates between the medical and surgical groups was found. Nevertheless, it was suggested that a longer 5-year follow-up would have shown a benefit of surgery and that bypass should still be considered a viable option in a very select patient population (those with severe haemodynamic compromise whose symptoms are refractory, postural or blood pressure dependent).20

*Surgery complications*

Severely impaired autoregulatory mechanisms, as seen in near-occlusion, have been suggested as a risk factor for developing cerebral hyperperfusion syndrome. The same correlation is true with regard to the degree of stenosis. The presence of good ipsilateral and collateral circulation can help reduce the ischaemic damage. The hyperperfusion syndrome arises when blood is restored after intervention and altered starling forces promote oedema formation. Vessels are no longer able to constrict to reduce hydrostatic pressure and increased membrane permeability promotes oedema and haemorrhage. Free radicals will further damage cells and predispose to neuronal damage. Symptoms can be various including change in mental status, headaches, seizure and focal neurologic deficit. Symptoms generally occur within four to seven days after a carotid endarterectomy and can come earlier after stenting. Patients who developed the syndrome have by definition a pressure-dependent blood flow and management includes tight control of blood pressure.

**Conclusion**

Carotid stenosis is an important cause of stroke and the risk increases as the artery becomes more narrowed. This is true until a certain critical point, the point of near-occlusion
of the carotid. This is the point, just before occlusion, where the blood flow decreases and
the survival mechanisms may intervene to prevent ischaemia. These mechanisms include
formation of collaterals, vascular autoregulation with vasodilation and increment in the
oxygen extraction fraction by the tissue. Although carotid surgery and endovascular
treatment are the gold standard treatment for cases of severe symptomatic stenosis, the
optimum treatment of near-occlusion stenosis is still under debate. Considering the risk of
embolism, the evidence suggests that the surgical risk is higher than the carotid risk by itself,
although a prospective study using current treatment modalities is needed to confirm this
view. Regarding the haemodynamic point of view, surgery seems clearly logical to improve
cerebral blood flow in these patients. But how much this will improve the risk of stroke and
result in cognitive improvement remain controversial.
References

Figure 1: 5-year risks of ipsilateral stroke on the sides of the symptomatic and asymptomatic carotid stenosis treated medically in 1820 patients included in NASCET. Data extracted from Inzitari et al, 2000.
Figure 2: Contrast-enhanced magnetic resonance angiogram showing near occlusion of the internal carotid artery.
Figure 3: Absolute risk reduction (ARR) in the rate of ipsilateral ischaemic stroke and any operative stroke or operative death at 3, 5, and 8 years' follow-up associated with surgery at different degrees of stenosis (NASCET measurement) in an analysis of pooled data from ECST and NASCET. The box on the right hand side of the figure draws attention to lack of benefit in patients near-occlusion compared to patients with 90-99% stenosis without near-occlusion. Figure taken from Rothwell et al 2003\textsuperscript{15} with permission.