EBioMedicine 3 (2016) 2–3

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

In Focus

From Ultrasonography to High Resolution Magnetic Resonance Imaging: Towards an Optimal Management Strategy for Vulnerable Carotid Atherosclerotic Plaques

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Stroke remains a major cause of death and disability worldwide, with approximately one-third of ischaemic strokes being a consequence of carotid atherosclerotic plaque rupture. Thus, diagnostic strategies that could identify those patients at highest risk of events are of critical importance.

Severity of carotid luminal stenosis, as characterized by ultrasonography, continues to be the major determinant for assessing stroke risk, based on the results of historical trials. Here, ultrasound was used to quantify the degree of carotid stenosis, as it was one of few non-invasive imaging options available when these studies were designed and conducted. Furthermore, carotid ultrasound is relatively reproducible in quantifying the severity of luminal stenosis in experienced hands and remains relatively inexpensive when compared with contemporary cross-sectional imaging options. Based on measurements derived from ultrasound, studies showed that surgery only benefitted patients with severe luminal stenosis (≥70%; North American Symptomatic Carotid Endarterectomy Trial (NASCET) (Anon., 1991a) defined). However, the majority of patients who sustain strokes have carotid luminal stenosis ≤50% (NASCET-defined), suggesting severe luminal stenosis alone is insufficient to predict risk. Indeed, histopathological studies indicate that plaque stability is not simply due to luminal stenosis, but also dependent on necrotic core size, active inflammation and overlying fibrous cap (FC) thickness. Emerging imaging technologies, including high-resolution magnetic resonance imaging (MRI) and molecular imaging, have far surpassed luminal assessment and allow visualisation of plaque structure and the underlying biological process in far greater detail than ultrasonography (Underhill et al., 2010). This has led to suggestions that specific features on plaque imaging should be used as selection criteria, in addition to systemic risk factors, for future clinical studies in the hope of improving patient care.

Soon after carotid endarterectomy (CEA) was introduced for the prevention of ischemic stroke, enthusiasm for the procedure increased. However, CEA carries a 2–3% risk of causing death or a disabling stroke (Anon., 1991a, 1991b) and, as such, the operation can only be justified if the future net benefit is clearly larger than the immediate risk.

Two multicentre randomised trials, European Carotid Surgery Trial (ECST) and NASCET, were designed to answer this fundamental question in symptomatic patients. Interim results from ECST demonstrated that for patients with severe stenosis (70–99%; ECST-defined) total risk of surgical death and any stroke was 12.3% for surgery and 21.9% for control (Anon., 1991b). CEA conferred no benefit in patients with moderate stenosis (30–69%; ECST-defined) (Anon., 1996) and any 3-year benefit of surgery for patient with mild stenosis (0–29%; ECST-defined) was outweighed by procedural risk (Anon., 1991b). 6-year ECST follow-up reported that for patients with ≥80% luminal stenosis, the frequency of a major stroke or death at 3 years was 26.5% for control and 14.9% for CEA (absolute benefit 11.6%) (Anon., 1998). NASCET reported that CEA conferred an absolute risk reduction of 10.6% in preventing major stroke and death in patients with luminal stenosis ≥70% (NASCET-defined) (Anon., 1991a). However, CEA only yielded marginal risk reduction (6.5%; $p = 0.045$) in preventing ipsilateral stroke at 5-years for patients with moderate luminal stenosis (50–69%) (Barnett et al., 1998).

The potential of CEA for stroke reduction in patients with asymptomatic carotid atherosclerosis has also been studied. Here, the benefit of CEA was unclear until the publication of two landmark randomised trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS) (Anon., 1995) and the Asymptomatic Carotid Surgery Trial (ACST) (Halliday et al., 2004). Both trials reported similar findings, showing a 50% relative risk reduction in 5-year risk of stroke from 11–12% to 5–6% from CEA in patient with luminal stenosis ≥60% (NASCET-defined)/70% (ECST-defined).

The results of trials in patients with symptomatic and asymptomatic lesions are therefore in general agreement. Surgery only benefits symptomatic patients with severe luminal stenosis (≥80% ECST-defined or ≥70% NASCET-defined) at 3 years. Despite this, around 85–90% of procedures may not yield clear clinical benefit and the utility of CEA for symptomatic patients with mild/moderate luminal stenosis or in asymptomatic patients is questionable. As the majority of symptomatic patients do not have severe luminal stenosis, this leaves clinicians with a significant challenge. Although CEA may confer benefit in specifically selected patient subgroups, the majority of clinical events cannot be predicted by the degree of stenosis alone. Accordingly, screening asymptomatic patients using ultrasonography in the general population for carotid stenosis is not recommended (LeFevre and Force, 2014).

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http://dx.doi.org/10.1016/j.ebiom.2016.01.001

Histological analysis of CEA specimens from symptomatic patients has suggested that 'vulnerable plaque' is associated with specific characteristics, including FC rupture, intraplaque hemorrhage (IPH), large lipid-rich necrotic cores, erosions with overlying mural thrombus, neovasculature and inflammatory cell infiltration. Recent developments in MR imaging have enabled us to identify these components quantitatively (Underhill et al., 2010). MRI-identified IPH and FC defects are associated with clinical presentation and subsequent ischaemic cerebrovascular events. In a prospective study of asymptomatic patients with moderate luminal stenosis, investigators found a significant association between the presence of thin or ruptured fibrous cap at baseline and the subsequent development of an ipsilateral ischemic event (Hazard ratio (HR) = 17.0) (Underhill et al., 2010). The presence of IPH was associated with an increased risk for subsequent ischemic events (HR ranges from 3.6 to 9.8) (Underhill et al., 2010).

These findings suggest that larger prospective studies with long-term follow-up are required to fully quantify the annual risk of stroke related to plaque morphological/compositional features, especially, IPH. Additionally, high mechanical loading due to blood pressure may be useful in identifying those lesions at highest risk of stroke (Sadat et al., 2010), as FC rupture is likely to occur when such loading exceeds cap strength. Clinical trials are now required to quantify the benefit of such combined plaque-specific approaches, so that modern advanced imaging techniques may eventually benefit individuals with symptomatic and asymptomatic carotid atherosclerotic diseases.

Disclosure

Authors do not have any conflict of interest to declare.

Acknowledgment

This work is supported by Heart Research UK (RG2638/14/16).

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