Biomed. Papers 148(2), 119–122 (2004)

CAN WE IDENTIFY PATIENTS WITH CAROTID OCCLUSION WHO WOULD BENEFIT FROM EC/IC BYPASS? REVIEW

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Received: September 9, 2004; Accepted (with revisions): October 15, 2004

Key words: Brain infarction/Carotid occlusion/Recurrent stroke/Cerebral vasomotor reactivity/Motor cortex/Extra-intracranial bypass

Occlusion of the internal carotid artery (CAO) is associated with a high mortality rate and frequent disability in survivors. Even in patients with good clinical recovery there is a high risk of recurrent stroke, mainly in those with impaired cerebral vasomotor reactivity (CVR). Current evidence based therapeutic options for patients with symptomatic CAO include antithrombotic medication and control of vascular risk factors. For stenosis of the contralateral internal or ipsilateral external carotid artery, endarterectomy or percutaneous transluminal angioplasty may be considered. Ongoing symptoms may cease after tapering antihypertensive medications. Extracranial to intracranial (EC/IC) arterial bypass surgery has been used since 1967 in patients with CAO. However, the international randomized EC/IC Bypass Study (1985) failed to confirm the effectiveness of EC/IC bypass for preventing cerebral ischemia in patients with symptomatic CAO when compared to those assigned to the best medical care. Nevertheless, the conclusion of the EC/IC Bypass Study has several objections and downfalls. Since then, there has been a revival of interest in cerebral revascularization procedures owing to the substantial progression of surgical techniques and the use of more advanced diagnostic methods. Thus, it has recently been reported that EC/IC bypass surgery can be useful in preventing stroke in patients with hemodynamic compromise. The main problem is to identify the small subgroup of surgical candidates. Presently, single photon emission computed tomography (SPECT), positron emission tomography (PET), transcranial Doppler sonography (TCD), computed tomography (CT) with administration of ^{133}Xe, perfusion CT, near infrared spectroscopy (NIRS), and functional magnetic resonance imaging (fMRI) are being used for this purpose.

Cerebrovascular stroke is the third most common cause of death in the majority of developed countries[1], including in the Czech Republic (CR). Approximately 7,000 men and 10,000 women die of stroke each year in our country[2]. The incidence of cerebrovascular stroke in the CR is two times higher than in Western Europe. Occlusion of the internal carotid artery (ICA) is associated with a high mortality rate and frequent disability in survivors[3]. Even in patients with good clinical recovery there is a high risk of recurrent stroke; the annual risk of stroke in patients with symptomatic carotid artery occlusion (CAO) and impaired cerebral vasomotor reactivity (CVR) is approximately 10–14 % versus 4–6 % in those with preserved CVR[4, 5].

It has been shown that patients with an increased oxygen extraction fraction (OEF) measured by positron emission tomography (PET) with inhalation of ^{15}O-labeled gas and low cerebrovascular reactivity assessed by transcranial Doppler sonography[6, 7] have an increased risk of recurrent ischemic stroke. Current evidence based therapeutic options for patients with symptomatic CAO include antithrombotic medication and control of vascular risk factors. For stenosis of the contralateral internal or ipsilateral external carotid artery (ECA), endarterectomy or percutaneous transluminal angioplasty may be considered. Ongoing symptoms may cease after tapering of antihypertensive medication[8].

In 1967 the first extracranial to intracranial (EC/IC) arterial anastomosis was performed[9]. However, the international randomized EC/IC Bypass Study (1985) failed to confirm that EC/IC superficial temporal artery (STA) to middle cerebral artery (MCA) bypass is effective for preventing cerebral ischemia in patients with symptomatic CAO when compared to those assigned to the best medical care[10]. Since then, the operation has been largely abandoned worldwide. Nevertheless, several objections and downfalls have been identified in this study, such as inclusion of the wrong patients (included in the study regardless of their clinical state and cerebral blood flow, CBF)[11, 12]. During the last 10 years, there has

been a revival of interest in cerebral revascularization procedures owing to the significant progression of surgical techniques and the use of more advanced diagnostic methods[13]. Some reports show that EC/IC arterial bypass surgery can be useful in preventing stroke in patients with hemodynamic compromise. For example, recent papers have reported that the supplementary activation of cerebral hemodynamics with EC/IC bypass increases regional CBF and regional cerebral oxygen metabolism ($rCMRO_2$), maintaining adequate cerebral blood oxygenation (CBO)[14–19] and it can even alleviate impaired cognition in stroke patients[20]. Derdeyn et al. demonstrated the cost-effectiveness of EC/IC bypass in patients with symptomatic CAO with increased OEF[12].

Various kinds of reconstructive operation for both high-grade and low-grade EC/IC bypasses are available. While superficial temporal artery (STA) is the standard donor vessel in both cases, the distal part of the ICA or M_1 segment of the MCA in high-flow EC/IC bypass, or the 2nd or the 3rd degree MCA branches in low-flow EC/IC bypasses can serve as recipient arteries[15, 21]. High-flow EC/IC bypass can establish a larger (up to 3.7-times) increase of blood flow than the low-flow one[22]. Nevertheless, this type of bypass may be associated with a higher risk of cerebral hemorrhage.

One of the main problems for EC/IC bypass is to identify a small subgroup of patients with "hemodynamic" cerebral ischemia. Characteristically, these patients demonstrate a severely impaired cerebrovascular reserve capacity due to occlusive disease and an insufficient collateral blood supply. Besides PET, other methods such as computed tomography (CT) with administration of ^{133}Xe,[23] perfusion CT,[24] single photon emission computed tomography (SPECT) and near infrared spectroscopy (NIRS) are being used to assess CVR and thus identify patients who could benefit from EC/IC bypass surgery. For example, SPECT, ^{133}Xe inhalation, acetazolamide (ACT) administration[25], as well as the technique of benzodiazepine receptor SPECT (BZR- SPECT) with ^{123}I-iomazenil[26] have been useful in assessing possible candidate patients. In patients with occlusion of both ICAs, the same techniques may be used also for selection of the appropriate side suitable for the establishment of EC/IC bypass.

Transcranial Doppler sonography (TCD) has also become widely used in assessing CVR by providing information regarding cerebral autoregulation and collateral circulation. Cerebral vasomotor reactivity is defined as a shift between CBF or cerebral blood velocity before and after the administration of a potent vasodilatory stimulus test, such as the apnea test (dilatatory response of CBF to hypercapnia.) This breath-holding maneuver enables assessment of CVR by means of calculating the breath-holding index (BHI). The apnea test can be replaced by inhalation of 5 % CO_2. Breath-holding has the advantage that it is more rapid and better tolerated than CO_2 inhalation, but the reproducibility is lower with breath-holding. Intravenous (i.v.) ACT administration can be also used as a vasodilatory stimulus for TCD assessment of CVR. The main technical problem is the non-existence of a standardized examination procotol in both CO_2 inhalation and ACT administration (in the latter case, the route of administration using i.v. injection or infusion, the total dose dependent/non-dependent on body weight and monitoring interval are unclear). The breath-holding/hyperventilation test is a combined test being used for the assessment of CVR during hyper- and hypocapnia[27–32]. The assessment of CVR by combining TCD and provocative vasodilatory tests allows the intracranial hemodynamic status to be evaluated in patients with CAO. It is intended to predict the occurrence of ischemic brain events, compare intracranial hemodynamics before and after EC/IC bypass and autoregulation, measure collateral circulation in the different parts of the circle of Willis, and also predict dementia after stroke[33].

Used together in a complementary protocol, CVR testing with TCD and cortical assessment with PET can evaluate both the vasodynamics in major vessels, microvascular cortical perfusion, and OEF. The disadvantages of PET is that it is not widely available and theexamination carries a radiation load.

Alternative noninvasive hemodynamic imaging can be performed with functional magnetic resonance imaging (fMRI), a more recently developed method utilizing mostly blood oxygenation level dependent (BOLD) contrast. BOLD fMRI can be accomplished on a typical 1.5 Tesla scanner, available in all regional and university hospitals that perform neurovascular surgery. Functional MRI has been used worldwide to visualize the cortical networks participating in behavioral control and cognitive processing in healthy subjects as well as in patients with cerebrovascular and brain disease. It allows higher spatial resolution than PET and also permits longitudinal studies without a cumulative radiation load. Functional MRI studies in cerebrovascular diseases have typically mapped movement-activated areas in stroke patients recovering motor function by comparing them to motor activation patterns in healthy controls. These studies replicated and extended PET findings by demonstrating differences between patients and controls in multiple brain areas including cortical[34–43], subcortical, and cerebellar regions[41]. Longitudinal fMRI studies can also reveal motor system changes associated with successful motor recovery[40] and rehabilitation. Functional MRI has further been used to detect the cortical hemodynamic impact of large-vessel disease, such as asymptomatic carotid stenosis[44]. This study reported slowing and diminution of the cortical hemodynamic response in the hemisphere ipsilateral to carotid stenosis. The same technique was also recently used to assess the CVR in patients suffering from unilateral common carotid artery occlusion and with a patent ECA and ICA[45]. However, it is not known whether fMRI can replace PET in complementing CVR testing with TCD and ultimately help select patients who will benefit from surgical restoration of major vascular flow by EC/IC bypass.

In summary, it is believed that EC/IC bypass surgery can provide significant benefit to selected patients with

atherosclerotic arterial disease of the ICAs and MCAs. However, the selection of patients who would likely benefit from the procedure is still questionable. Several patient selection and procedural problems are evident and include the availability of PET examination, the radiation load involved in both SPECT and PET examinations, and acetazolamide availability (not available in some countries, e.g. in the Czech Republic.) Additionally, no standardized protocols exist for the TCD evaluation of CVR using ACT administration and CO_2 inhalation. Furthermore, the effectiveness of high- and low-flow EC/IC bypasses has not yet been sufficiently compared. Thus, further studies are needed both in the field of CVR testing and assessing the effects of EC/IC bypass.

ACKNOWLEDGEMENT

Supported by the IGA Ministry of Health CR grant number NR/7830-3/2004.

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