Hemodynamic Brain Ischemia in Patients with Symptomatic Total Carotid Occlusion; Transcranial Duplex and SPECT Study

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ABSTRACT

Objective: To identify the relation between cerebral collaterals (according to TCD based grading system) and cerebrovascular reserve (measured by SPECT) in patients with symptomatic chronic total carotid occlusion. In addition, to study the effect of vascular risk factors on both collaterals and cerebrovascular reserve.

Methods: Thirty-four patients with chronic total carotid occlusion diagnosed by ultrasound and had ischemic symptoms either stroke or TIA. Each was subjected to :

1- Clinical assessment. 2- Cerebrovascular reserve assessment with SPECT with dipyridamole stress. 3- Grading of cerebral collaterals using transcranial duplex and Doppler (TCD).then statistical analysis was applied using univariate and multivariate analysis methods.

Results: CVR showed significant positive correlation to collaterals grading with P value < 0.001 and Spearman correlation coefficient 0.686. Hypertension but not diabetes was predictor for poor collaterals with (p value 0.049 and 0.045, odds ratio 11.5 and 0.131 with 95% confidence interval 1.01 to 131.16 and 0.018 to 0.953 respectively). Smoking was related to poor cerebrovascular reserve capacity with P value 0.01. Smoking also was related to poor collaterals with P value 0.03 and CI (-2.14 to -.014).

Conclusion: cerebral collaterals has important role in the maintenance of cerebrovascular reserve in patients with total carotid occlusion. Furthermore, the proposed TCD-based collateral grading system showed good reliability indices when validated against some of the SPECT finding.

Key word

Carotid occlusion Transcanialduplex SPECT

Cerebral collaterals cerebrovascul ar reserve

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INTRODUCTION

Total carotid occlusion (TCO) is a real clinical challenge; it may be asymptomatic or present with fatal stroke. The risk of subsequent stroke in patients with symptomatic Carotid Artery Occlusion (CAO) is between 5% and 6% per year, but is estimated 10% in the presence of impaired cerebral blood flow, (Kappelle, et al., 2002) even with medical treatment, (Flaherty, et al., 2004).

Ischemic brain injury occurs in patients with total carotid occlusion either due to embolism to distal branches or due to hypoperfusion and inability of collateral circulation to maintain adequate flow leading to hemodynamic failure. (Thanvi & Robinson, 2007)

The carotid system has primary and secondary collaterals that open to maintain CBF in cases of carotid occlusion. Poor collateral circulation is associated with hemodynamic compromise and increased risk of stroke in patients with TCO. (Vernieri, et al., 2001)

Bypass surgery between external and internal carotid systems is a surgical procedure that has been invented in 1967 for treating patients with carotid occlusion that are not amenable to surgical correction by carotid endarterectomy surgery. It was widely practiced for this indication until 1986 where the international co-operative study of STA-MCA anastomosis had been able to show that such patients did not make benefit from surgery when compared to medical treatment alone. (Jeffree & Stoodley, 2009)

AIM OF THE WORK

To identify the relation between cerebral collaterals (according to TCD based grading system) and cerebrovascular reserve (measured by SPECT) in patients with symptomatic chronic total carotid occlusion. In addition, to study the effect of vascular risk factors on both collaterals and cerebrovascular reserve.

CONCEPT OF HEMODYNAMIC CEREBRAL ISCHEMIA

Cerebral circulation is a low-pressure high flow network of arteries that receives 15% of cardiac output to provide oxygen and glucose to the brain. Cerebral autoregulation keeps adequate blood flow despite changes in blood pressure. However, when limits of autoregulation are exceeded, hemodynamic failure occurs. Ischemic brain injury occurs in patients with large vessel occlusion either due to embolism to distal branches or due to hypoperfusion and inability of collateral circulation to maintain adequate flow leading to hemodynamic failure. (Thanvi & Robinson, 2007)

Cerebral Hemodynamic Physiology

Cerebral metabolism and cerebral blood flow:

Glucose uptake is high in brain tissue and the cerebral metabolic rate for glucose (CMRGl) is about 30mg/100g/min, which represents approximately 25% of the body's total glucose consumption. Whilst cerebral cells do contain glycogen, this (and all available glucose) is exhausted within 2 min if cerebral blood flow (CBF) ceases. (Taylor & Hirsch, 2010)

Cerebral metabolic rate for oxygen ($CRMO_2$) is 3ml/100g/min in grey matter and 1ml/100g/min in white matter. This is quite high. To supply this, the cerebral blood flow (CBF) in resting state is about 90ml/100g/min for grey matter and 20ml/100g/min for white matter. If CBF decrease by 50%, it causes ischemic symptoms. Below 16ml/100g

/min, all electrical activities cease. If CBF maintained below 10ml/100g/min, stroke occur after 3 hours.

Cerebral perfusion pressure (CPP) is the main determinant of CBF. It is the difference between arterial blood pressure and intracranial pressure. 70-80mmHg is the normal value.

Control of cerebral blood flow:

To maintain an adequate blood flow during changes of the systemic blood pressure, the cerebral circulation has an **autoregulation** system aimed to protect the brain from excessive changes in arterial pressure. Therefore, within the high and low autoregulatory limit of blood pressure, usually ranging from about 60 to 140 mm Hg, cerebral blood flow remains constant. (Folino, 2007)

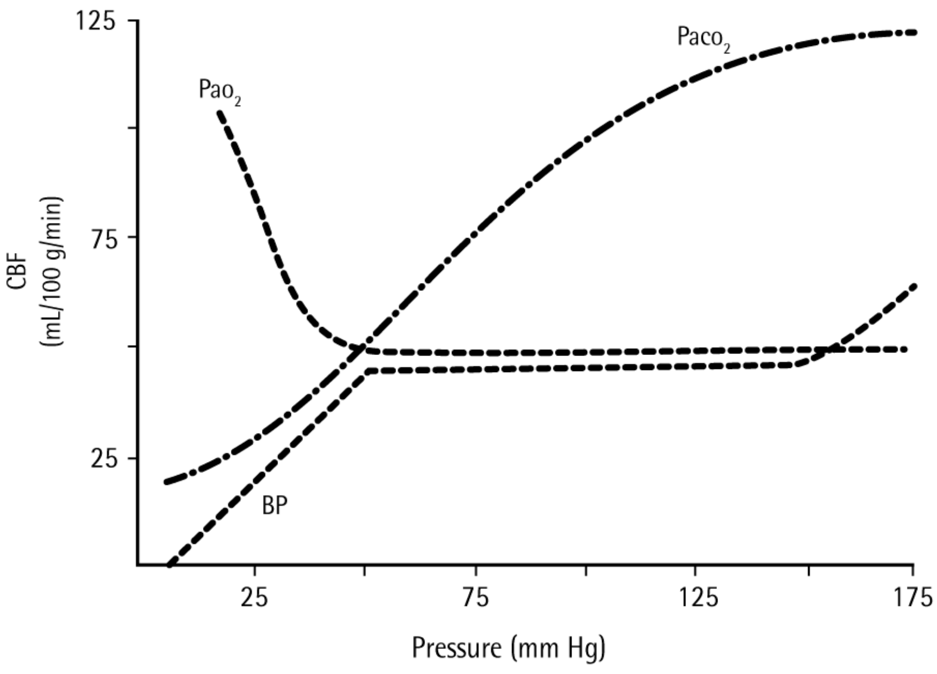


Figure 1 Cerebrovascular autoregulation in health and effect of blood gases on the CBF. Influence of alterations in arterial blood gases and blood pressure on cerebral blood flow. Acute hypoxia triggers dilation of cerebral microcirculation and increase in CBF. Hypercapnia causes marked dilation of cerebral arterioles and CBF elevation, whereas hypocapnia causes vasoconstriction and decrease in CBF. *(Bor-Seng-Shu, et al., 2012)***. CBF**: cerebral blood flow. **BP**: blood pressure.

Autoregulation occurs through myogenic, metabolic and neurogenic control mechanisms. ***Figure 1*** shows effect of changes in BP, PO_2, PCO_2 on cerebral blood flow. Note that cerebral autoregulation fails in very low and very high BP.

Hemodynamic failure and hemodynamic cerebral ischemia

This refers to failure of autoregulation mechanisms to keep adequate cerebral blood flow to meet requirement of the brain. This occurs in a group of patients with total carotid occlusion with inadequate collateral circulation. When metabolic demands of the brain increases, collaterals cannot compensate and ischemic symptoms appear.

Pathophysiology of hemodynamic cerebral ischemia:

Patients with this disorder have been found generally to pass through two stages. Firstly, as the brain becomes ischemic the first defense mechanism that comes to play is vasodilatation in an attempt to increase cerebral blood flow to the ischemic brain tissue. This state is called the loss of cerebrovascular reserve capacity or **stage I hemodynamic failure**. Secondly, as the state of chronic ischemia persists and this mechanism fails

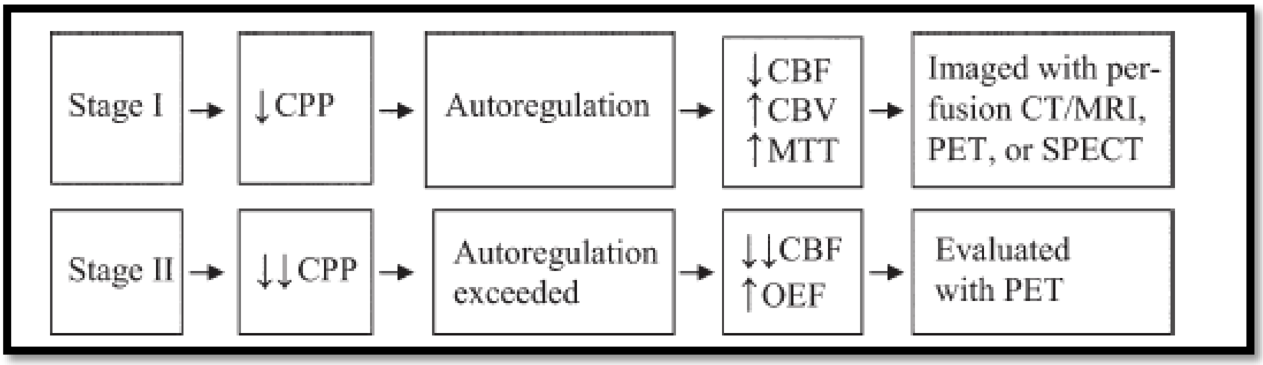


Figure 2 Diagram shows the effects of the early (stage I) and advanced (stage II) hemodynamic failure on cerebral perfusion parameters. CBF= cerebral blood flow, CBV= cerebral blood volume, CPP= cerebral perfusion pressure, MTT= mean transit time, OEF= oxygen extraction fraction.

to alleviate the state of ischemia that is presents then the brain starts to react by extracting more oxygen from the blood reaching the ischemic brain. This stage is called an increase in the cerebral metabolic rate of oxygen extraction ($CMRO_2$) or **stage II hemodynamic failure**. Figure 2 demonstrates changes in hemodynamic variables in each stage. (Derdeyn, et al., 2002)

Radiological assessment of hemodynamic state

Three basic strategies have been developed to assess regional cerebral hemodynamic status noninvasively. The first two strategies are used to identify stage 1 hemodynamic failure indirectly. The third relies on direct measurements of oxygen extraction (Stage 2). It is important to note that these approaches are accurate only with uninfarcted brain tissue (Derdeyn, et al., 1999)

The first strategy relies on paired blood flow measurements with the initial measurement obtained at rest and the second measurement obtained following a cerebral vasodilatory stimulus. Hypercapnia, acetazolamide, and physiologic tasks such as hand movement have been used as vasodilatory stimuli. Normally, each will result in a robust increase in CBF. If the CBF response is muted or absent, preexisting autoregulatory cerebral vasodilation due to reduced cerebral perfusion pressure is inferred. Three abnormal responses can occur; 1) Reduced augmentation (relative to the contralateral hemisphere or normal controls) 2) Absent augmentation (same value as baseline) 3) Paradoxical reduction in regional blood flow compared with baseline measurement (steal phenomenon). (Derdeyn, et al., 1999)

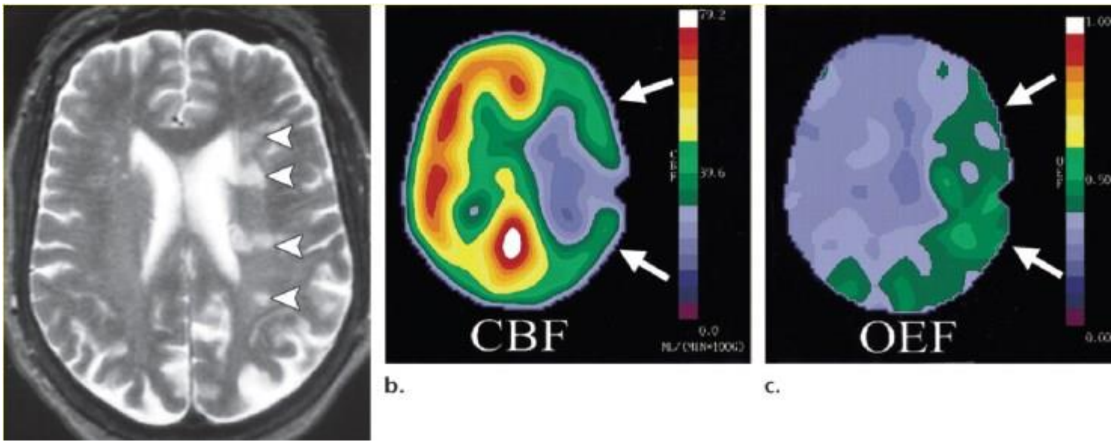
This has been measured with various methods, including xenon-enhanced CT, Doppler ultrasonography (US), perfusion CT, perfusion MR imaging, single photon emission computed tomography (SPECT), and PET. (Mangla, et al., 2011)

Stage I

-The second strategy (Stage **I** Hemodynamic Failure) uses either the measurement of rCBV alone or in combination with measurements of CBF in the resting brain to detect the presence of autoregulatory vasodilation. The CBV/CBF ratio (or, inversely, the CBF/CBV ratio), mathematically equivalent to the vascular mean transit time, may be more sensitive than CBV alone for the identification of Stage 1 hemodynamic compromise. However, it may be less specific. This can be assessed by SPECT, PET and CT perfusion. Figure 2. (Derdeyn, et al., 1999) (Eicker, et al., 2011)

Stage II

The third strategy relies on direct measurements of OEF to identify patients with increased oxygen extraction (Stage **II** Hemodynamic Failure). Regional measurements of OEF is made with PET using O-15 labeled radiotracers. **Figure *3*** .Both absolute values and side-to-side ratios of quantitative and relative OEF have been used for the determination of abnormal from normal. (Mangla, et al., 2011) MR spectroscopy with brain temperature measurement has recently been studied by Ishigaki *et al* and showed very good correlation to PET OEF results. (Ishigaki, et al., 2009)



a.

Figure 3 (a) Axial T2-weighted spin-echo MR image through the corona radiata shows several white matter infarcts (arrowheads) parallel to the long axis of the lateral ventricle. (b, c) Axial PET images show reduced cerebral blood flow (CBF) (arrows in b) and an increased oxygen extraction fraction (OEF) (arrows in c) in the hemisphere ipsilateral to the occluded carotid artery. *(Mangla, et al., 2011)*

Hemodynamic stroke

In patients with proximal major cerebral artery occlusion, infarction can occur either due to artery to artery embolism or due to hypoperfusion in the territory supplied by that artery. The latter type is called hemodynamic stroke.

Clinical characteristics:

Hemodynamic stroke is usually preceded acute cerebral hypoperfusion. **Bladin & Chambers** studied 300 consecutive patients with ischemic stroke. They found 29 patients with documented or presumed hypotension at stroke onset. Most of them (27/29) had watershed infarcts. Myocardial infarction, cardiac arrhythmias, and orthostatic changes in blood pressure related to diabetic dysautonomia and antihypertensive therapy were the predominant causes of hypotension. Ten patients had