Role of Multimodal Evaluation of Cerebral Hemodynamics in Selecting Patients with Symptomatic Carotid or Middle Cerebral Artery Steno-occlusive Disease for Revascularization

Abstract

Background: The circle of Willis provides collateral pathways to perfuse the affected vascular territories in patients with severe steno-occlusive disease of major arteries. The collateral perfusion may become insufficient in certain physiological circumstances due to failed vasodilatory reserve and intracranial steal phenomenon, so-called 'Reversed-Robinhood syndrome'. We evaluated cerebral hemodynamics and vasodilatory reserve in patients with symptomatic distal internal carotid (ICA) or middle cerebral artery (MCA) severe steno-occlusive disease.

Methods: Diagnostic transcranial Doppler (TCD) and TCD-monitoring with voluntary breath-holding according to a standard scanning protocol were performed in patients with severe ICA or MCA steno-occlusive disease. The steal phenomenon was detected as transient, spontaneous, or vasodilatory stimuli-induced velocity reductions in affected arteries at the time of velocity increase in normal vessels. Patients with exhausted vasomotor reactivity and intracranial steal phenomenon during breath-holding were further evaluated by ^{99}technetium^{m}-hexamethyl propylene amine oxime single photon emission computed tomography (HMPAO-SPECT) with acetazolamide challenge.

Results: Sixteen patients (age 27-74 years, 11 men) fulfilled our TCD criteria for exhausted vasomotor reactivity and intracranial steal phenomenon during the standard vasomotor testing by breath holding. Acetazolamide-challenged HMPAO-SPECT demonstrated significant hypoperfusion in 12 patients in affected arterial territories, suggestive of failed vasodilatory reserve. A breath-holding index of ≤0.3 on TCD was associated with an abnormal HMPAO-SPECT with acetazolamide challenge. TCD findings of a breath holding index of ≤0.3 and intracranial steal during the procedure were determinants of a significant abnormality on HMPAO-SPECT with acetazolamide challenge.

Conclusion: Multimodal evaluation of cerebral hemodynamics in symptomatic patients with severe steno-occlusive disease of the ICA or MCA is helpful in the identification and quantification of failed vasodilatory reserve. This approach may be useful in selecting patients for possible revascularization procedures.

Keywords: Transcranial Doppler, cerebrovascular reserve, acetazolamide challenge, single photon emission computed tomography, revascularization

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Severe steno-occlusive lesions of the carotid and cerebral arteries increase the risk of cerebral ischemic events.[1,2] The two main mechanisms of ischemic stroke in these patients are thromboembolism and cerebral hemodynamic insufficiency.[3-6] Transcranial Doppler (TCD) monitoring can demonstrate thrombo-embolic phenomena by identifying the spontaneous microembolic signals in the appropriate branches distal to the steno-occlusive lesion[7-9] and thus help in planning the appropriate treatment.[10] However, assessment of dynamic cerebral hemodynamic insufficiency remains a complex issue.

Cerebral autoregulation is the ability of the vasculature of the brain to maintain adequate blood supply to meet metabolic demands by compensating for acute and chronic changes in cerebral perfusion pressure. It enables constant regional cerebral blood flow over a wide range of systemic blood pressure by adjusting the diameter of the intracranial arterioles.[11] The Circle of Willis provides collateral pathways to perfuse the affected vascular territories in patients with severe steno-occlusive disease of major arteries. Although, steno-occlusive lesions, and (in some cases) collateral pathways can be readily detected by digital subtraction cerebral angiography[12], computerized tomographic angiography (CTA)[13, 14], magnetic resonance angiography (MRA)[15]

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or TCD[16], none of these diagnostic modalities provides any information about cerebral perfusion or the cerebral blood flow vasodilatory reserve. The hemodynamic effect of a severe steno-occlusive lesion can be categorized into three stages: stage 0, normal cerebral hemodynamics; stage 1, autoregulatory vasodilatation; and stage 2, increased oxygen extraction.[17] The last stage is often called "misery perfusion".[18] Various imaging techniques currently used to measure perfusion include positron emission tomography (PET)[19], dynamic first-pass perfusion CT[20], xenon-enhanced CT[21], perfusion weighted MR imaging[22], and single-photon emission CT (SPECT).[23] Cerebral perfusion in regions distal to the steno-occlusive lesion may be normal at rest. However, it may become insufficient in certain physiological circumstances due to a failed vasodilatory reserve and intracranial steal phenomenon. We have previously described the intracranial steal phenomenon as 'Reversed-Robinhood syndrome' in acute ischemic stroke patients with persisting intracranial steno-occlusive lesions.[24]

Intracranial steno-occlusive disease is fairly common in Asian patients, especially of Chinese ethnicity.[25] In this pilot non-randomized study, we studied the cerebral hemodynamic status and vasodilatory reserve in patients with chronic and symptomatic severe steno-occlusive disease of the internal carotid artery (ICA) or middle cerebral artery (MCA) with continuous TCD-monitoring during voluntary breath-holding and HMPAO-SPECT with acetazolamide challenge. We aimed to establish the relationship between breath holding index by TCD and cerebral vasodilatory reserve by SPECT with acetazolamide challenge. Additionally, we evaluated the ability of combined TCD and SPECT with acetazolamide challenge to identify patients at risk of ischemic events. Some patients with impaired vasodilatory reserve underwent various cerebral revascularization procedures. Changes in their cerebral hemodynamic patterns and vasodilatory reserves after these revascularization procedures are also described.

Methods

Consecutive patients (age 18-80 years) with severe and symptomatic steno-occlusive disease of distal (high cervical) ICA or MCA who were treated by the stroke service at our tertiary care university hospital between April 2007 and March 2008 were prospectively included in this study. We included only the patients with good functional status prior to the event (modified Rankin scale 0-2) or who presented with transient or mild focal neurological deficits at baseline presentation (NIH Stroke Scale Score<10 points). We defined 'symptomatic' steno-occlusive disease as the identification of a severe stenosis or occlusion of the index artery (by TCD and contrast angiography-by CT angiography or digital subtraction angiography) in patients who presented with ischemic symptoms corresponding to the territory supplied by that particular artery. Severe carotid steno-occlusive disease was defined as more than 70% stenosis or occlusion of the distal ICA, beyond the 'surgical limits' in the neck. Severe stenosis of the MCA was defined as an underlying stenosis or occlusion by TCD and contrast angiography exceeding 70% according to the established and previously described diagnostic criteria.[16] Patients in whom a long stenotic segment involved both terminal ICA and proximal MCA were classified as having a steno-occlusive disease of terminal ICA. Our neurovascular laboratory used the diagnostic criteria validated against CT angiography.[26, 27] Patients with severe stenosis of the ICA in its cervical segment and amenable to the routinely performed carotid endarterectomy or stent placement were excluded from the study, since they do not require these extensive investigations for risk-stratification or therapeutic decision-making.

Data were collected regarding the demographic characteristics, underlying risk factors, and the relevant associated diseases. All the patients underwent a non-contrast enhanced CT scan of head. Additional relevant imaging studies to diagnose the underlying pathogenic mechanism were performed according to the discretion of the attending stroke neurologist.

All eligible patients underwent diagnostic TCD for assessment of collateral flow as well as monitoring for spontaneous emboli, with Nicolet –Viasys machine- Companion-III. Bilateral TCD monitoring was performed during voluntary breath-holding according to a standard scanning protocol to evaluate the dynamic changes in blood flow velocities as well as any intracranial steal phenomenon. Cerebral vasomotor reactivity (VMR) was assessed by breath-holding index (BHI) according to the method described by Markus et al.[28] Briefly, following identification of TCD baseline signals, patients were asked to voluntarily stop breathing. A gasp, deep inhalation, or sigh were not allowed. Similarly, at the point of restarting breathing, patients were instructed to start without a violent inspiratory gasp or sigh. A breath-holding period of ≥30 seconds was considered as appropriate. Patients unable to hold their breath for the required period were assessed by performing re-breathing in

Table 1. Demographics, risk factors, and prevalence of atherosclerosis among the study patients (n=16)

Variable	Number (%)
Mean age in years	55
Male gender	11 (68.8)
Hypertension	13 (81.3)
Diabetes mellitus	6 (37.5)
Ischaemic heart disease	3 (18.8)
Hypercholesterolaemia	12 (75)
Atrial fibrillation	1 (6.3)
Internal Carotid Artery steno-occlusive disease	11 (68.8)
Middle Cerebral Artery steno-occlusive disease	5 (31.3)

Table 2. Cerebral hemodynamic patterns in patients with severe steno-occlusive disease of the distal internal carotid or middle cerebral artery.

Case	Age in years, gender	Artery involved	BHI	Intracranial steal	SPECT
1	56, M	Intracranial ICA	Exhausted	Yes	Abnormal
2	62, M	High cervical ICA	Exhausted	Yes	Abnormal
3	48, F	Intracranial ICA	0.2	Yes	Abnormal
4	62, M	High cervical ICA	0.6	No	NA
5	46, M	MCA	0.3	Yes	Abnormal
6	60, M	Intracranial ICA	0.5	No	NA
7	61, M	Intracranial ICA	Exhausted	Yes	Abnormal
8	42, M	MCA	0.2	Yes	Abnormal
9	57, F	Intracranial ICA	Exhausted	Yes	Abnormal
10	58, F	MCA	Exhausted	Yes	Abnormal
11	60, M	Intracranial ICA	Exhausted	Yes	Abnormal
12	36, F	Intracranial ICA	0.5	No	NA
13	57, M	MCA	0.2	Yes	Abnormal
14	63, F	Both MCAs	Exhausted on right side, 0.5 on left	Yes, on right side	Abnormal on right side
15	64, M	Intracranial ICA	Exhausted	Yes	Abnormal
16	55, M	Both MCAs	0.5 on right and 0.4 on left side	No	NA

Abbreviations used: M, male; F, female; ICA, internal carotid artery; MCA, middle cerebral artery; BHI, breath-holding index; SPECT, single photon emission computed tomography; NA, not available
Definitions used: exhausted breath-holding index, negative BHI; abnormal SPECT, failed vasodilatory reserve.

a paper bag, while monitoring the carbon-dioxide levels by a capnometer. For these cases we aimed at increasing the pCO2 by at least 1 mm Hg, if the procedure was well-tolerated by the patient. The assessments were performed at least 3 times to validate the results and we took into consideration the lowest BHI. None of the previous studies have reported a reliable cut-off value of BHI to represent an impaired VMR. We adopted a BHI value of less than 0.69 to represent an impaired VMR as described by Silvestrini et al[29] in patients with asymptomatic carotid artery stenosis. If the mean flow velocity (MFV) showed a paradoxical decrease, BHI showed a negative value. This was labeled as "exhausted VMR". Simultaneous monitoring of both MCAs and anterior cerebral arteries permitted us to diagnose intracranial steal. An intracranial steal was defined as an increase in MFV in an artery adjacent to the diseased artery, when the latter showed a paradoxical decrease in the MFV during voluntary breath holding. We have previously described this phenomenon as 'reversed Robinhood syndrome' in patients with acute ischemic stroke with persisting arterial occlusions.[24]
Patients with impaired VMR and intracranial steal phenomenon were further evaluated with acetazolamide-challenged HMPAO-SPECT. After the patient was kept in a dark and quiet area for 30 min, HMPAO SPECT and planar images were acquired with the intravenous injection of 732 MBq of 99mTc HMPAO. Scans were repeated within 3 to 7 days with acetazolamide challenge. Acetazolamide was injected intravenously (at a dose of 20mg/Kg body weight) and 20 minutes later, patient received 732 MBq of 99mTc HMPAO. SPECT as well planar images were acquired 20 minutes after the administration of HMPAO. Images were reconstructed in axial, sagittal as well as coronal planes after corrections for the attenuation using transmission maps. We constructed a 3-dimensional surface display of the brain. Comparisons were made between the images obtained with and without acetazolamide to assess the cerebral vasodilatory reserve.
All images were corrected for attenuation using Chang's method (uniform linear attenuation coefficient 0.12/cm).[30] Reconstructed images were displayed as standard sagittal, axial, and coronal sections.
All the patients were followed up for any cerebral ischemic events. Some patients underwent various cerebral revascularization procedures according to the recommendation of the stroke team consisting of an attending stroke neurologist, an attending vascular surgeon, and an attending neuroradiologist. These patients underwent repeat assessments with TCD and SPECT imaging to assess the effect of the interventions on cerebral hemodynamic status.

Results

A total of 82 patients were found to have symptomatic steno-occlusive disease in the distal ICA or MCA. Sixteen patients (11 men, mean age 55 years) fulfilled our TCD criteria for an impaired VMR (BHI less than 0.69). Their baseline characteristics are shown in table 1. The steno-occlusive lesions involved ICA in 11 cases while MCA was affected in the remaining 5 cases. Two patients suffered from steno-occlusive disease of MCAs on both sides. Intracranial steal phenomenon by TCD during voluntary breath holding was observed in 12 patients.
When subjected to HMPAO-SPECT with acetazolamide challenge, 12 patients demonstrated significant hypoperfusion in the affected arterial territories, suggestive of failed vasodilatory reserve. All patients with an abnormal HMPAO-SPECT with acetazolamide challenge showed an impaired VMR (BHI less than 0.3 or exhausted) and in-

tracranial steal phenomenon during breath holding. Four patients with breath-holding indices of more than 0.3 demonstrated normal vasodilatory reserve on SPECT with acetazolamide challenge.

During the subsequent follow-up of these patients, cerebral ischemic events were noted in 3 cases. All these three cases had their breath-holding indices (on TCD) of less than 0.3 along with the failed vasodilatory reserve on HMPAO-SPECT with acetazolamide challenge. These three patients underwent successful revascularization procedures (carotid angioplasty in case 3, encephaloduralsynangiosis in case 8 and superficial temporal artery-MCA bypass in case 11) and all of them have remained asymptomatic (observation period of 3 months to 13 months). Two other patients (cases 7 and 10) with significant abnormalities of cerebral hemodynamics underwent an STA-MCA bypass procedure. Repeat assessments in these patients, by various modalities, showed considerable improvements in clinical and hemodynamic parameters. One such example is shown in figure 1. One patient (case 15) suffered a fatal stroke just before the planned revascularaization. Cases 1 and 5 with an exhausted VMR and failed vasodilatory reserve were found to have severe obstructive sleep apnea. They did not agree to undergo any interventions. However, they have been on nocturnal assisted ventilation and remained asymptomatic for 7 months.

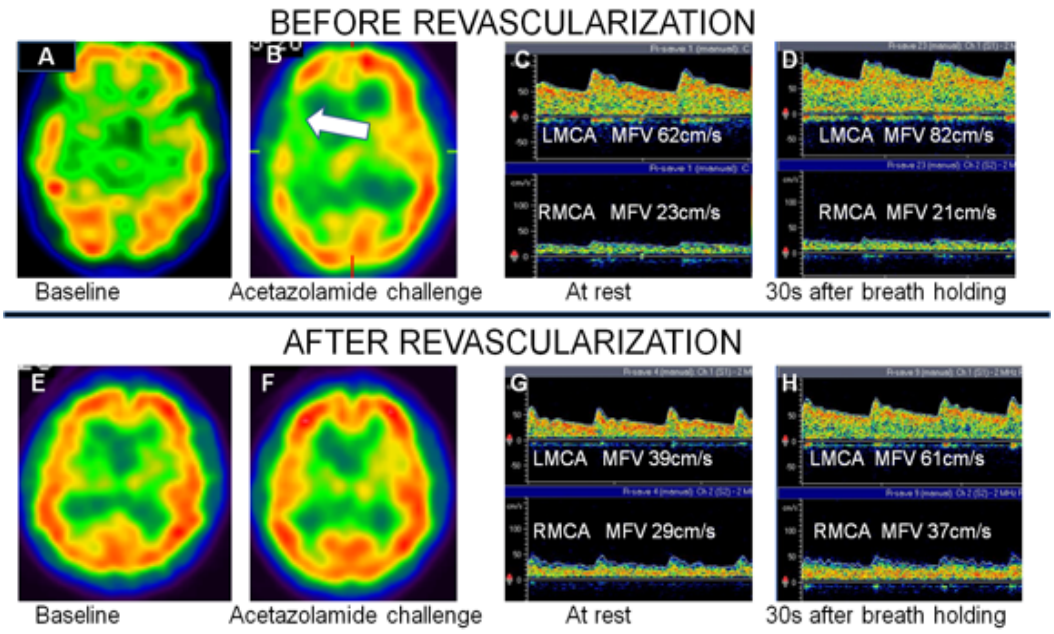

Figure 1. Hemodynamic consequences of a right internal carotid artery occlusive disease in Case 7. This 61 year-old man was having recurrent transient ischemic attacks referable to the right middle cerebral artery (MCA). Baseline HMPAO-SPECT (A) shows adequate perfusion in both cerebral hemispheres. SPECT images obtained after acetazolamide challenge (B) revealed markedly reduced perfusion in the right cerebral hemisphere, suggestive of a vasodilatory failure. Corresponding findings on transcranial Doppler vasomotor reactivity (VMR) by breath holding index (BHI) show a normal increase in mean flow velocity (MFV) in left MCA from 62cm/s at rest (C) to 82cm/s after 30 seconds of breath holding (D) with a BHI of 1.06. However, the paradoxical decrease in the MFV in right MCA from 23cm/s to 21cm/s during breath holding suggests an exhausted BHI.

Both acetazolamide-challenged HMPAO-SPECT (E, F) and TCD (G, H) were repeated 4 months after superficial temporal artery-MCA bypass shows a remarkable improvement in cerebral vasodilatory reserve. TCD assessment of VMR shows adequate BHI in both left and right MCAs (1.86 and 0.91, respectively). These improvements in the hemodynamic parameters were associated with clinical recovery and no further cerebral ischemic events occurred during 7-months of follow up.

Discussion

Our preliminary study shows the feasibility and potential applicability of multimodal evaluation of cerebral vasodilatory reserve in patients with severe steno-occlusive disease of ICA or MCA. We found that a breath-holding index of less than 0.3 (TCD) coupled with a failed vasodilatory reserve on SPECT imaging with acetazolamide challenge is predictive of subsequent cerebral ischemic events due to impaired cerebral hemodynamics.

Carotid endarterectomy and stent placement are recommended as standard procedures for the treatment of significant stenosis of the cervical ICA. However, there are no established treatments for the steno-occlusive disease involving the surgically inaccessible segments of the ICA and MCA. Inadequate vasodilatory reserve in these patients is considered a major risk factor for subsequent ischemic events.[32–34] The International Cooperative Study of Extracranial / Intracranial Arterial Anastomosis (EC/IC Bypass) study, with STA-MCA bypass surgery failed to demonstrate a reduction in the risk of subsequent ischemic stroke.[35-37] However, it did not rule out the possibility that bypass surgery could improve the hemodynamic status in selected patients.[34,38] STA-MCA bypass surgery however normalizes the cerebral oxygen extraction fraction (OEF) [39] and may be useful in patients with stage II hemodynamic failure.[40, 41] It has been suggested that the bypass surgery may benefit patients with impaired cerebral hemodynamic reserve.[34, 38] Identifying patients who are at increased risk for hemodynamic stroke is important, because they may benefit from various flow augmentation procedures.[12, 34, 42-46]

We employed TCD to evaluate the cerebral hemodynamics, estimate vasodilatory reserve with subsequent risk stratification. A decreased VMR suggests failure of collateral flow to adapt to the arterial stenosis. Furthermore, in patients with persisting severe steno-occlusive lesions, hypercapnia can paradoxically decrease the residual flow velocity in the affected vessel at the expected time of normal brain vasodilation. We have described previously this phenomenon as "reversed Robin Hood" for analogy with "rob the poor to feed the rich".[24]

We compared our TCD assessments with brain perfusion imaging at rest and after a vasodilatory challenge. Positron emis-

sion tomography (PET) has been considered the gold standard for estimating cerebral vasodilatory reserve. However, PET cannot be used routinely in stroke patients because it is expensive and not widely available. Blood flow reserve as assessed by brain SPECT correlates well with the oxygen extraction rates measured by PET. Therefore SPECT can be employed reliably for evaluating brain perfusion and blood flow reserve. Acetazolamide is a potent cerebral vasodilator and is increasingly being used to assess the haemodynamic reserve in the brain.[47,48] Intravenously administered acetazolamide induces marked dilatation of cerebral vessels, thus increasing both cerebral blood flow and cerebral blood volume. Brain SPECT with acetazolamide challenge can reveal patients with reduced vasodilatory capacity. Hirano et al[49] reported that patients with reduced acetazolamide reactivity had significantly lower cerebral blood flow values and higher cerebral blood volume/ cerebral blood flow ratios compared to patients with normal acetazolamide reactivity. Reduced acetazolamide reactivity corresponded to enhanced OEF and these results indicated that a reduction in acetazolamide reactivity represents a stage II haemodynamic failure as demonstrated in PET studies.

Decreased reactivity to acetazolamide represents a reduced cerebral vascular reserve secondary to vasodilation in the resting state, as a compensatory measure for proximal steno-occlusive disease. Vascular reserve can be assessed by comparing brain perfusion by HMPAO-SPECT before and after injection of acetazolamide. Cerebral blood flow measurements before and after acetazolamide injection have been performed to assess cerebral perfusion reserve before EC-IC artery bypass surgery.[47, 48, 50] We found that a reduced or exhausted VMR on TCD, especially when associated with a detectable intracranial steal phenomenon, correlated with failed vasodilatory reserve on acetazolamide-challenged HMPAO-SPECT imaging.

Our study has some limitations. First, our observations on small number of patients may not be applicable to larger patient cohorts. We are currently recruiting more patients in our study to overcome this limitation. Second, PET is considered to be the gold-standard for the assessment of cerebral blood flow as well as flow reserve. Due to the non-availability of PET scanner at our center, we used actazolamide-challenged HMPAO-SPECT. The evaluation of baseline and acetazolamide brain perfusion SPECT images relies on visual and semi-quantitative analyses. It is used extensively in the pre- and post-operative assessment of patients with Moya-moya disease. Although the cerebral hemodynamic status as a result of vascular lesions may not differ on the basis of the underlying etiology, it may be difficult to compare our adult patients with primarily atherosclerotic disease with the pediatric patients with Moya-moya disease. SPECT with acetazolamide challenge may not be reliable in patients with bilateral steno-occlusive disease. While one patient (case 16) with impaired VMR in both MCAs had a normal SPECT study, the other patient (case 14) with distinct difference in BHI values revealed SPECT abnormality on the side of intracranial steal and exhausted VMR.

We believe that multimodal evaluation of the cerebral vasodilatory reserve in patients with severe steno-occlusive disease is feasible and may hold promise for providing a more scientific approach for selecting patients for various revascularization procedures. If our preliminary findings are replicated in a larger patient cohort, this approach of assessment of cerebral vasodilatory reserve may help in selecting suitable patients for various revascularization procedures to prevent further ischemic events.

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