Acta Neurol. Belg., 2011, **111**, 111-115

Reduction of flow velocities in patients with ischemic events in the middle cerebral artery – long-term follow-up with ultrasound

Christine KREMER[1] and Kasim ABUL-KASIM[2]

[1]Department of Neurology and [2]Diagnostic Centre for Imaging and Functional Medicine, Skåne University Hospital - Malmö, Lund University, Sweden

Abstract

Data concerning the persistent reduction of flow velocities measured by transcranial color-coded sonography (TCCS) in relation to the clinical and radiological outcome among patients with ischemic events in middle cerebral artery (MCA) territory is scarce. Patients with ≥ 50% reduction of peak systolic velocities (PSV-MCA) as compared to the contralateral MCA were prospectively included in follow-up by TCCS (mean 404 days). Out of 849 patients with stroke admitted to our stroke unit, 25 patients showed reduced PSV-MCA and included in the analyses of this study. Ten (40%) survivors showed persistent reduction of PSV-MCA. None of the patients with normalized PSV-MCA suffered an ischemic event compared with three patients with persistent reduction of PSV-MCA (all had ipsilateral occlusion of the internal carotid artery caused by dissection). Patients with persistently reduced PSV-MCA exhibited significantly (Mann-Whitney test, p = 0.02) larger infarct volumes on CT (mean ± SD 38 ± 50 cm³) compared to those with normalized PSV-MCA (6 ± 7 cm³). The functional outcome were, however, similar in patients with normalized and those with persistently reduced PSV-MCA. We found that a relatively high percentage (40%) of patients suffered ischemic event in the MCA territory with initial reduction of flow velocity on TCCS showed persistent reduction on long term follow-up.

Key words: Stroke; outcome; middle cerebral artery; transcranial colour coded sonography.

Background

Transcranial colour-coded sonography (TCCS) is a well established method for bedside monitoring of flow velocities of the middle cerebral artery (MCA). An increase peak systolic velocity in the MCA (PSV-MCA) would be expected in moderate atherosclerotic or embolic MCA stenosis. Reduction of PSV-MCA is usually seen in patients with high grade stenosis or near occlusion of the distal M1-segment, or as a sign of hemodynamic compromise in patients with high grade stenosis or occlusion of the extracranial internal carotid artery (ICA) and poorly developed collateral circulation (Zanette *et al*., 1989; Baumgartner *et al*., 1996; Baumgartner *et al*., 1999; Demchuk *et al*., 2001).

The long-term follow-up of patients showing a reduction of PSV-MCA as measured by TCCS has not been previously reported. A high percentage of patients usually show normalization of flow velocities of the MCA within days to weeks after stroke, indicating an embolic origin of their MCA obstruction (Molina *et al*., 2001).

The aim of this prospective study was to assess the evolution of a reduced PSV-MCA and its impact on stroke outcome.

Methods

A total of 849 consecutive patients with stroke or TIA in the territory of the MCA admitted to our stroke unit and examined by TCCS within 24 hours (Philips, Hewlett Packard, HP Sonos 5500, 7500). Out of 849 patients, 473 showed evidence of ischemia in the MCA territory and 112 showed anterior circulation transient ischemic attack (TIA). Stroke in the MCA territory was diagnosed clinically by stroke neurologist according to National Institutes of Health Stroke Scale (NIHSS). All patients underwent plain computed tomography (CT) of the brain upon arrival to hospital. TCCS studies of the basal cerebral arteries were performed using sector transducers (2.0-4.0 MHz). The transtemporal approach was used for insonation of the terminal (C1) ICA, MCA, anterior cerebral artery (ACA), precommunicating and postcommunicating posterior cerebral arteries, anterior communicating artery (ACoA) and

posterior communicating artery (PCoA). The contralateral MCA was insonated at nearly the same depth. Contrast agent (SONOVUE) was administered in case of insufficient temporal bone window. Intracranial arteries were investigated for the presence of stenoses, occlusions, and cross-flow through the ACoA and PCoA according to previously published criteria (Baumgartner *et al*., 1997; Baumgartner *et al*., 1999). All patients underwent extracranial colour-coded sonography with the same equipment using a linear probe (5-8 MHz). Systolic, diastolic and mean flow velocities were recorded for each artery. No angle correction was used. Carotid stenoses were quantified according to a local protocol (Hansen *et al*., 1996).

All patients with a reduction of PSV-MCA of in the proximal MCA (M1 segment, depth 50-55 mm) exceeding 50% compared to contralateral PSV-MCA were included and planned for the follow-up. PSV were expressed in cm/s and PSV reduction in percent (≥ 50% or < 50%) compared to the contralateral side. All patients had clinical follow-up visits (9-18 months) with documentation of the possible ischemic events and assessment of the functional outcome according to modified Rankin scale (mRS). The follow-up visit included extracranial and transcranial examinations by TCCS performed by the same initial examiner (CK). Persistent flow reduction was defined as flow reduction at the long term follow-up. Patients with reduced PSV-MCA at follow-up were categorized into those with ≥ 50% and those with < 50% reduction of PSV-MCA compared to the contralateral MCA.

CT-examinations of patients with reduction of PSV-MCA at admission were retrospectively evaluated for the occurrence of cerebral infarction and measurement of infarct volume. Infarct volume was estimated at the Leonardo work station (Siemens AG, Medical Solutions, Erlangen, Germany) using the "volume application".

Statistical analysis was performed using SPSS 17. Mann-Whitney U-test was performed to test the association between the infarct volume and the PSV-MCA reduction. Statistical significance was set to $p < 0.05$.

Results

Out of 849 acute stroke patients examined by TCCS, 25 (mean age 65 ± 15 years, 19 (76%) were males, mean NIHSS 12 ± 7) showed ≥ 50% reduction of PSV-MCA at baseline (Fig. 1, flow diagram). Twelve (48%) were admitted with major stroke (NIHSS ≥ 16), 5 with moderate stroke (NIHSS 8-15), 6 with minor stroke (NIHSS ≤ 7) and 2 patients with a TIA (patients whose stroke symptom resolved within 24 hours and with normal CT). Five patients with major stroke died during the follow-up; in four cases the cause of death was not directly related to stroke. One patient has moved to another country and therefore was lost to the long term follow-up. Nine patients showed normalized PSV-MCA at follow-up. The remaining ten patients showed persistent reduction of PSV-MCA, Table 1. Mean follow-up time was 404 days (range 289-553).

Three patients with persistent reduction of PSV-MCA had ipsilateral ICA occlusion caused by ICA dissection. All three patients suffered recurrent ischemic events during follow-up: (1) Patient no 5 with ≥ 50% persistent reduction of PSV-MCA suffered a left side cerebellar stroke 106 days after the initial event. No other embolic source could be found by echocardiography or Holter ECG. (2) During treatment of a severe pneumonia, patient no 8 suffered a recurrent minor stroke in the territory of the symptomatic MCA 111 days after the initial event. She had 80% stenosis of ipsilateral cervical ICA at the follow-up. CT showed a watershed infarction between the territory of the MCA and ACA. A haemodynmaic mechanism was assumed. (3) Patient no 9

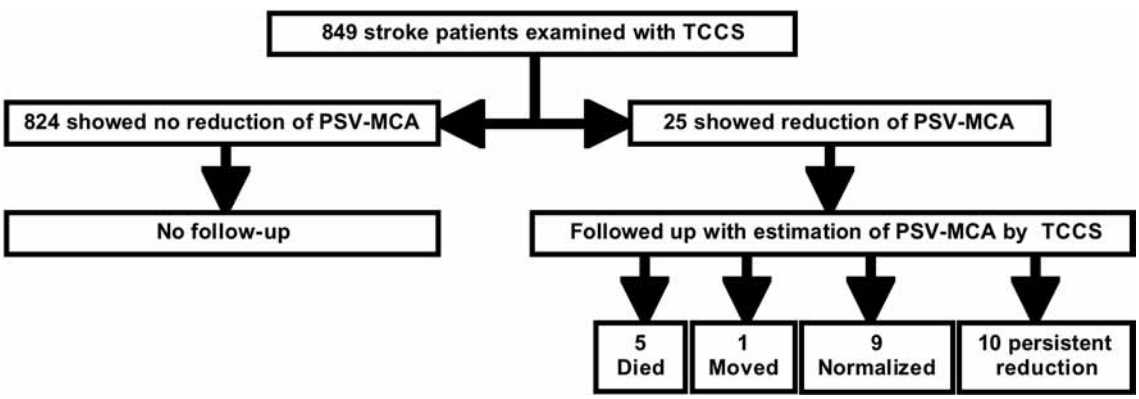

FIG. 1. — Flow diagram showing the schematic selection of patients included in this study

Table 1

Showing the findings at the follow-up of 10 Patients with persistent decrease of PSV in the symptomatic MCA

Reduction of PSV MCA	Nr/Sex/Age	ICA ipsi	ICA contra	Possible mechanism, initial ischemic event and risk factors	Latency follow-up (d)	Therapy Follow-up	mRS
≥ 50%	1/F/69	occlusion	< 60%	Hemodynamic. Large vessel. HT, HC, CAD	431	Clopidogrel Statin	1
	2/M/78	< 60%	< 60%	Embolic atherosclerotic HT, DM	417	Aspirin Statin	2
	3/M/67	occlusion	< 60%	Hemodynamic. Large vessel. HT, HC, CAD	289	Asiprin, Statin	0
	4/M/73	< 60%	< 60%	Embolic atherosclerotic AF	553	Aspirin Statin	3
	5/F/37	occlusion	< 60%	ICA dissection CS, HC	423	Aspirin Statin	1
< 50%	6/F/76	< 60%	< 60%	Embolic atherosclerotic CS, HT, HC	419	Aspirin Statin	4
	7/M/58	occlusion	65%	Large vessel CS, DM, HC	445	Aspirin Statin	3
	8/F/50	> 80% cICA	< 60%	ICA dissection (multiple) HT	301	Aspirin	4
	9/M/21	occlusion	< 60%	ICA dissection DM	399	Aspirin	4
	10/M/78	occlusion	60%	Large vessel HT, DM, HC, CAD, MI	265	Aspirin, Statin	1

MCA: middle cerebral artery. ICA: internal carotid artery. cICA:cervical part ICA. ICA ipsi: internal carotid artery ipsilateral to symptomatic MCA. ICA contra: internal carotid artery contralateral to the symptomatic MCA.

PSV: peak systolic velocity. mRS: modified Rankin scale.

CS: cigarette smoking. HT: arterial hypertension. DM: diabetes mellitus Type II. HC: hypercholesterolemia. AF: artrial fibrillation. CAD: coronary artery disease. MI: history of myocardial infarction.

showed a recurrent stroke in MCA territory 205 days after the initial event. At the time of the event, the PSV-MCA was < 50%, which subsequently normalized. CT showed a watershed infarction between the territory of the MCA and ACA, Table 1. Three patients with persistent flow reduction (patient no. 2, 4, and 6) had a possible embolic origin of stroke. The remaining 4 patients (patient no 1, 3, 7, and 10) had large vessel occlusion, Table 1. Four patients showed watershed infarctions at baseline, all had ICA occlusions. All survivors with major stroke showed persistent reduction of PSV-MCA.

Patients with persistently reduced PSV-MCA showed significantly (Mann-Whitney test, $p = 0.02$) larger stroke volumes on CT (mean ± SD: 38 ± 50 cm^3) compared to those with normalized and symmetric PSV-MCA (mean ± SD: 6 ± 7 cm^3). There was no correlation between age and reduced PSV-MCA but a slight tendency ($p = 0.09$). Analysis of covariance showed that the association between the persistently reduced PSV-MCA and large infarct volume was independent of age ($p = 0.107$).

The functional outcome according to the mRS was similar in patients with persistently reduced PSV-MCA and in those with normalized and symmetric PSV-MCA (mean mRS 2.2 and 2.3, respectively).

Discussion

Our study showed that about 40% of the stroke survivors with initial decrease of flow velocities in the MCA exhibit persistent pathological peak systolic velocity in MCA at long term follow-up. The causes of MCA flow reduction are heterogeneous. The dynamic course of flow reduction in the symptomatic MCA in the acute phase reflects the development of sufficient collateral flow and/or recanalization of an embolic obstruction. Patients with high grade stenosis or occlusion of the ICA and reduced flow in the MCA with compromised cerebrovascular reactivity have a higher stroke risk (Markus *et al*., 2001). In one serial ultrasound study on chronic stroke patients, an association between

lower mean flow velocity in the MCA and stroke recurrence was found (Zbornikova *et al*., 2006). On the other hand, clinical outcome data of patients with bilateral occlusions of the ICA suggest that those patients have low risk of recurrent stroke during a follow-up of 7.5 years (Persoon *et al*., 2009). Patients with ICA occlusions and concomitant MCA stenosis have a different infarct patterns and a combination of different factors likely influence the stroke evolution (Mezzapesa *et al*., 2006). In our cohort, all recurrent ischemic events among patients with persistent reduction of PSV-MCA occurred in patients with ICA occlusions caused by ICA dissection. The occurrence of watershed infarctions in two of these three patients suggests that hemodynamic compromise played a central role in the recurrence of ischemic events. However, Benninger et al suggested that thromboembolism, not hemodynamic infarction, was the essential stroke mechanism in patients with ICA dissection (Benninger *et al*., 2004). Despite low stroke recurrency among patients with permanent carotid stenosis or occlusion after ICA dissection with annual rates of 0.7% for ipsilateral carotid territory stroke and of 1.4% for any stroke in a large series (Kremer *et al*., 2003), the patients of our small cohort may represent a high risk-group that need to be monitored closely.

The occurrence of abnormal flow velocity and MCA stenosis among patients with anterior circulation stroke varies widely in the published reports. Reduced flow in MCA at the time of stroke event was found in 25 out of 849 patients (2.9%) included in our study. In a series of 2564 first ever TIA or stroke patients, 26 (1%) had (Arenillas *et al*., 2001) a severe MCA stenosis. Allendoerfer *et al*. showed that up to 66% of patients with moderate to severe anterior circulation stroke had pathological changes in MCA flow but only 2% had severe MCA stenosis (Allendoerfer *et al*., 2006). However, in selected cohorts such as patients with moderate to severe anterior circulation stroke treated with intravenous thrombolysis examined within 3 hours, occlusion or near occlusion was found in up to 73% of patients (Demchuk *et al*., 2001). Patients with persistent reduction of flow velocities in the MCA showed larger stroke volumes. Literature is scarce, but in parts a large stroke lesion can be responsible for the upstream down regulation of blood flow.

Limitations of this study are the low number of included patients and the heterogeneity of our patient population. The study design was to only include patients with reduced PSV-MCA at the time of stroke event. This resulted in a limited number of patients that subjected for the follow-up (25 out of 849 patients with stroke) and may have resulted in some selection bias.

In conclusion, our study showed that the reduction of flow velocity among patients with ischemic events in the MCA territory persists in a relatively high percentage of stroke patients (40%). This is particularly true for patients with ICA dissections and concomitant occlusion. These patients have a higher rate of recurrent ischemic events and a larger stroke volume on CT. Follow-up of these patients by TCCS may help to select high risk patients who might need intensified therapeutic measures.

REFERENCES

Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D. *et al*. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. Stroke. 1989;20(7): 899-903.

Baumgartner RW, Mattle HP, Schroth G. Assessment of >/ = 50% and < 50% intracranial stenoses by transcranial color-coded duplex sonography. Stroke. 1999;30(1):87-92.

Demchuk AM, Burgin WS, Christou I, Felberg RA, barber PA. *et al*. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. Stroke. 2001;32(1):89-93.

Baumgartner RW, Baumgartner I, Mattle HP, Schroth G. Transcranial color-coded duplex sonography in unilateral flow-restrictive extracranial carotid artery disease. AJNR Am J Neuroradiol. 1996;17(4):777-83.

Molina CA, Montaner I, Abilleira S, Arenillas JF, Ribo M. *et al*. Time course of tissue plasminogen activator-induced recanalization in acute cardioembolic stroke: a case-control study. Stroke. 2001;32(12): 2821-7.

Baumgartner RW, Baumgartner I, Mattle HP, Schroth G. Transcranial color-coded duplex sonography in the evaluation of collateral flow through the circle of Willis. AJNR Am J Neuroradiol. 1997;18(1): 127-33.

Hansen F, Bergqvist D, Lindblad B, Lindh M, Mätzsch T. *et al*. Accuracy of duplex sonography before carotid endarterectomy – a comparison with angiography. Eur J Vasc Endovasc Surg. 1996; 12(3):331-6.

Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain. 2001;124: 457-67.

Zbornikova V. Long term follow-up of unilateral occlusion of the internal carotid artery including repeated tests of vasomotor reactivity by transcranial Doppler. Neurol Res. 2006;28(2):220

Persoon S, Klijn CJ, Algra A, Kappelle LJ. Bilateral carotid artery occlusion with transient or moder-

ately disabling ischaemic stroke: clinical features and long-term outcome. J Neurol. 2009;256(10): 1728-35.

Mezzapesa DM, Petruzzellis DM, Cibaddo G, Prontera M, Tinelli A. *et al*. Multimodal MR examination in acute ischemic stroke. Neuroradiology. 2006; 48(4):238-46.

Benninger DH, Georgiadis D, Kremer C, Studer A, Nedeltchev K. *et al*. Mechanism of ischemic infarct in spontaneous carotid dissection. Stroke. 2004 Feb;35(2): 482-5.

Kremer C, Mosso M, Georgiadis D, Stöckli E, Benninger D. *et al*. Carotid dissection with permanent and transient occlusion or severe stenosis: Long-term outcome. Neurology. 2003 Jan 28;60(2):271-5.

Arenillas JF, Molina CA, Montaner J, Abilleira S, González-Sánchez MA. *et al*. Progression and clinical recurrence of symptomatic middle cerebral artery stenosis: a long-term follow-up transcranial Doppler ultrasound study. Stroke. 2001;32(12): 2898-904.

Allendoerfer J, Goertler M, von Reutern GM; Neurosonology in Acute Ischemic Stroke Study Group. Prognostic relevance of ultra-early doppler sonography in acute ischaemic stroke: a prospective multicentre study. Lancet Neurol. 2006;5(10): 835-40.

Christine Kremer, M.D.,
Department of Neurology,
University Hospital Skåne-Malmö,
Lund University,
Ing. 53,
SE-20502 Malmö (Sweden).
E-mail: christine.kremer@skane.se