Ultrasound and Clinical Predictors of Recurrent Ischemia in Symptomatic Internal Carotid Artery Occlusion

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Abstract: BACKGROUND AND PURPOSE Occlusion of the internal carotid artery puts patients at risk of recurrent ischemic events because of hemodynamic compromise. Our goal was to characterize clinical and duplex parameters indicating patients at risk of recurrent ischemia. METHODS We retrospectively identified patients with symptomatic internal carotid artery occlusion. Clinical characteristics and ultrasound parameters, including collateral networks, were analyzed. Predictors for recurrent ipsilateral ischemia were investigated by Cox regression analysis. RESULTS Of 68 patients, at least 1 recurrent ischemic event within the same vascular territory was observed in 14 patients (20.6%) within 2 to 92 days (median, 29.5 days). The median follow-up period was 6 months. Diabetes mellitus and previous transient ischemic attack were associated with recurrence, as was activation of the maximum number of collateral pathways on transcranial ultrasound (28.6% versus 5.6%; P=0.03). Furthermore, flow in the posterior cerebral arteries was higher in patients with recurrence in ipsilateral and contralateral posterior cerebral artery P2 segments (76 IQR 37.5 versus 59, IQR 22.5 cm/s and 68, IQR 35.6 versus 52, IQR 21 cm/s; P<0.01 and 0.02). CONCLUSIONS Flow increases in both posterior cerebral artery P2 segments suggest intensified compensatory efforts when other collaterals are insufficient. Together with the presence of diabetes mellitus and a history of transient ischemic attack, this duplex parameter indicates that patients with internal carotid artery are at particular risk of recurrent ischemia.

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SUPPLEMENTAL MATERIAL

Supplementary methods

Study design and cohort description

The study was approved by the local ethics committee. Internal carotid artery occlusion (ICAO) was diagnosed by duplex ultrasound imaging. Stroke physicians assessed mortality and functional outcome using the modified Rankin Scale (mRS) and recurrent cerebrovascular event either during an outpatient visit or by a follow-up telephone interview.

Symptomatic patients experienced a stroke, transient ischemic attack (TIA) or retinal artery ischemia ipsilateral to ICAO. Stroke was defined as any localized neurological deficit lasting >24 hours or a shorter lasting deficit with a corresponding lesion on computed tomography (CT) or magnetic resonance imaging (MRI), while TIA was defined as a transient episode of neurological dysfunction lasting 24 hours or less caused by focal brain ischemia without a corresponding lesion on brain imaging. Recurrence was defined as new ipsilateral clinical symptoms most likely arising from the ICAO. Patients with contralateral recurrent ischemic events were excluded. We did not exclude patients with contralateral stenosis or occlusion of the internal carotid artery. All patients were treated according to standard clinical practice, including risk factor management and secondary prophylaxis. Acute phase blood pressure targets were ≤ 170/100 and ≥ 100/60 mm Hg, except in cases of blood pressure dependent fluctuations of symptoms. For secondary prevention, recommended blood pressure targets were 130/85 mm Hg [1]. Median blood pressure values in the acute phase were not significantly different between patients without (145/81.5 mm Hg) or with recurrent ischemia (155/ 87 mmHg); neither were subacute blood pressure values on day 5 (range 3-7): 140/80 versus 148/86 mmHg for no recurrence versus recurrence. Diagnostic stroke work-up was performed to classify etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[2].

Of 104 patients initially identified, 8 were excluded due to asymptomatic ICAO, 5 died during the course of hospitalization, 17 did not receive a complete ultrasound exam within 1 months, 3 had distal ICAO and 2 experienced contralateral ischemic events (one due to a high grade contralateral ICA stenosis, one was considered a lacunar lesion).

Ultrasound methods

Ultrasound examinations including color coded intra- and extracranial, transorbital and transforaminal sonography were performed on an Accuson Siemens X2000 duplex scanner.

The following arterial segments were routinely analyzed according to standardized methods [3].: Distal common carotid (CCA), proximal external and internal carotid artery (ECA, ICA), vertebral artery (V0, V1, V2 and V4 segments), and basilar artery (BA). Transcranial duplex assessment (TCD) involved the middle cerebral artery (MCA) M1 and M2 segments, anterior cerebral artery (ACA) and posterior cerebral artery (PCA) P1 and P2 segments[4]. Peak systolic velocities (PSV), end diastolic velocities (EDV) and mean flow velocities (mean) were recorded for all extra - and intracranial vessels. Grading of a stenosis of the contralateral ICA was performed by duplex sonography according to the NASCET criteria[5]. Intracranial stenosis was graded according to published criteria[6]. The identification of the four main collateral pathways was done as follows[7, 8]:

1) ACoA: Reversed flow direction in the A1 segment of the ACA ipsilateral to the occluded ICA, usually accompanied by increased and turbulent flow in the contralateral ACoA or A1 segments due to functional stenosis. 2) PCoA: Direct visualization of the PCoA and/or cerebral blood flow increase of > 50 % in the ipsilateral P1 segment of the P1 Segment of the PCA compared with the contralateral side 3) Spontaneous leptomeningeal (LPM) collateral flow (LPM): Flow increase of > 30 % in the ipsilateral P2 segment compared with the

contralateral P2 segment and 4) OA: reversed flow in the periorbital arteries along with an internalized flow profile [8].

Statistical analyses

Statistics were calculated using *Stata Statistical Software: Release 13.1* (StataCorp LP, College Station, TX, 2011).

References

1. Powers WJ, Clarke WR, Grubb RL, Jr., Videen TO, Adams HP, Jr., Derdeyn CP, et al. Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia. *Neurology*. 2014;82:1027-1032
2. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke; a journal of cerebral circulation*. 1993;24:35-41
3. Reutern G-Mv, Kaps M, Büdingen HJ. *Ultraschalldiagnostik der hirnversorgenden arterien dopplersonographie und farbduplexsonographie der extra- und intrakraniellen arterien ; 39 tabellen*. Stuttgart u.a.: Thieme; 2000.
4. Baumgartner RW. Transcranial insonation. *Frontiers of neurology and neuroscience*. 2006;21:105-116
5. von Reutern GM, Goertler MW, Bornstein NM, Del Sette M, Evans DH, Hetzel A, et al. Grading carotid stenosis using ultrasonic methods. *Stroke; a journal of cerebral circulation*. 2012;43:916-921
6. Baumgartner RW. Intracranial stenoses and occlusions, and circle of willis collaterals. *Frontiers of neurology and neuroscience*. 2006;21:117-126
7. Baumgartner RW, Baumgartner I, Mattle HP, Schroth G. Transcranial color-coded duplex sonography in unilateral flow-restrictive extracranial carotid artery disease. *AJNR. American journal of neuroradiology*. 1996;17:777-783
8. Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Dynamic cerebral autoregulation and collateral flow patterns in patients with severe carotid stenosis or occlusion. *Ultrasound in medicine & biology*. 2003;29:1105-1113

Supplementary Table I:
Duplex assessment of PSV and EDV in extra- and intracranial arteries

Duplex parameter (in cm/s)	All N=68	No recurrent event observed N=54	Recurrent event observed N=14	p-value
Extracranial				
PSV CCA ipsi	61.5 (34.8)	63 (34.5)	52 (38.3)	0.52
EDV CCA ipsi	9 (7)	9 (7)	9 (7)	0.49
PSV CCA contra	80 (34.5)	81 (37)	74.5 (22)	0.35
EDV CCA contra	19 (11.75)	20.5 (12.3)	16.5 (10)	0.06
PSV ECA ipsi	108.5 (57.8)	101 (62.3)	132 (103.3)	0.12
EDV ECA ipsi	15 (9.5)	14.5 (10.8)	17 (12.5)	0.11
PSV ECA contra	102 (67.5)	100 (61.5)	135 (97.5)	0.80
EDV ECA contra	14 (10.5)	14 (10.5)	17 (13.5)	0.26
PSV ICA contra	73 (40)	76.5 (44.3)	67 (25.5)	0.051
EDV ICA contra	27 (16)	27.5 (14.5)	26 (11)	0.30
Intracranial				
PSV OA ipsi	30 (40.5)	26 (35)	45.5 (32.3)	0.07
EDV OA ipsi	13 (22.5)	8 (18)	20.5 (15.3)	0.10
PSV OA contra	34 (21)	34 (22.8)	35 (18)	0.62
EDV OA contra	8.5 (7)	9 (7)	6 (9)	0.41
PSV ACA ipsi	66.5 (38.5)	67 (39)	64 (31)	0.45
EDV ACA ips	30 (20)	29 (25.5)	32.5 (15.8)	0.83
PSV ACA contra	125 (73)	127.5 (73)	119.5 (103)	0.87
EDV ACA contra	51 (42.5)	51 (44)	53 (50.8)	0.62
PSV M1 ipsi	84.5 (39.3)	84.5 (41)	84.5 (36.8)	0.38
EDV M1 ipsi	42 (18)	42 (18.3)	38.5 (17.3)	0.92
PSV M1contra	112 (41)	112 (38.5)	110.5 (43.5)	0.75
EDV M1 contra	41 (14)	41 (15)	40.5 (16.5)	0.74
PSV P1 ipsi	84 (39.5)	82 (42)	90 (38)	0.16
EDV P1 ipsi	33 (18.5)	33 (17)	39.5 (19.3)	0.19
PSV P1 contra	69 (30.5)	69 (38)	69.5 (23)	0.90
EDV P1 contra	27 (15)	27 (17)	27 (9.8)	0.88
PSV P2 ipsi	63 (25)	59 (22.5)	76 (37.5)	<0.01*
EDV P2 ipsi	26 (13)	25 (9)	34 (21.5)	0.02*
PSV P2 contra	53 (23)	52 (21)	68 (35.6)	0.02*
EDV P2 contra	21 (11.8)	20 (11)	27 (15)	0.05*

Legend Supplementary Table I:
Duplex assessment of flow (PSV/EDV) in extra- and intracranial arteries measured ipsi – or contralateral to ICAO ("ipsi" vs. "contra") in all 68 patients (All) and patients groups with or without recurrent ipsilateral ischemic event. P values < 0.05 in Mann-Whitney U test are marked with *. Median (IQR) is shown.

Supplementary Table II:
Ultrasound parameters, stratified by recurrent ischemic event

Duplex	**All n =68 (%)**	**No recurrent event observed n = 54 (%)**	**Recurrent event observed n = 14 (%)**	**p-value**
Number of collaterals, n (%)				
1	7 (10.3)	6 (11.1)	1 (7.1)	1.0
2	36 (52.9)	31 (57.4)	5 (35.7)	0.2
3	18 (26.5)	14 (25.9)	4 (28.6)	1.0
4	7 (10.3)	3 (5.6)	4 (28.6)	0.03*
Type of collaterals				
ACoA	54 (79.4)	41 (77.36)	13 (86.7)	0.52
PCoA	36 (53.7)	27 (59)	9 (64.3)	0.38
OA	49 (74)	38 (70.37)	11 (78.6)	0.68
LM	21 (31)	15 (27.8)	6 (42.9)	0.30
Primary collaterals (ACoA/PCoA)	64 (94.1)	50 (92.6)	14 (100)	1.0
Secondary collaterals (OA/LM)	56 (82.3)	44 (81.5)	12 (85.7)	1.0
Ipsilateral MCA occlusion	3 (4.4)	3 (5.6)	0	0.35
Contralateral ICA Stenosis				
Medium (50 - 60% NASCET)	5 (7.4)	5 (9.3)	0	0.6
High grade (≥ 70% NASCET)	4 (5.9)	3 (5.6)	1 (7.1)	1.0

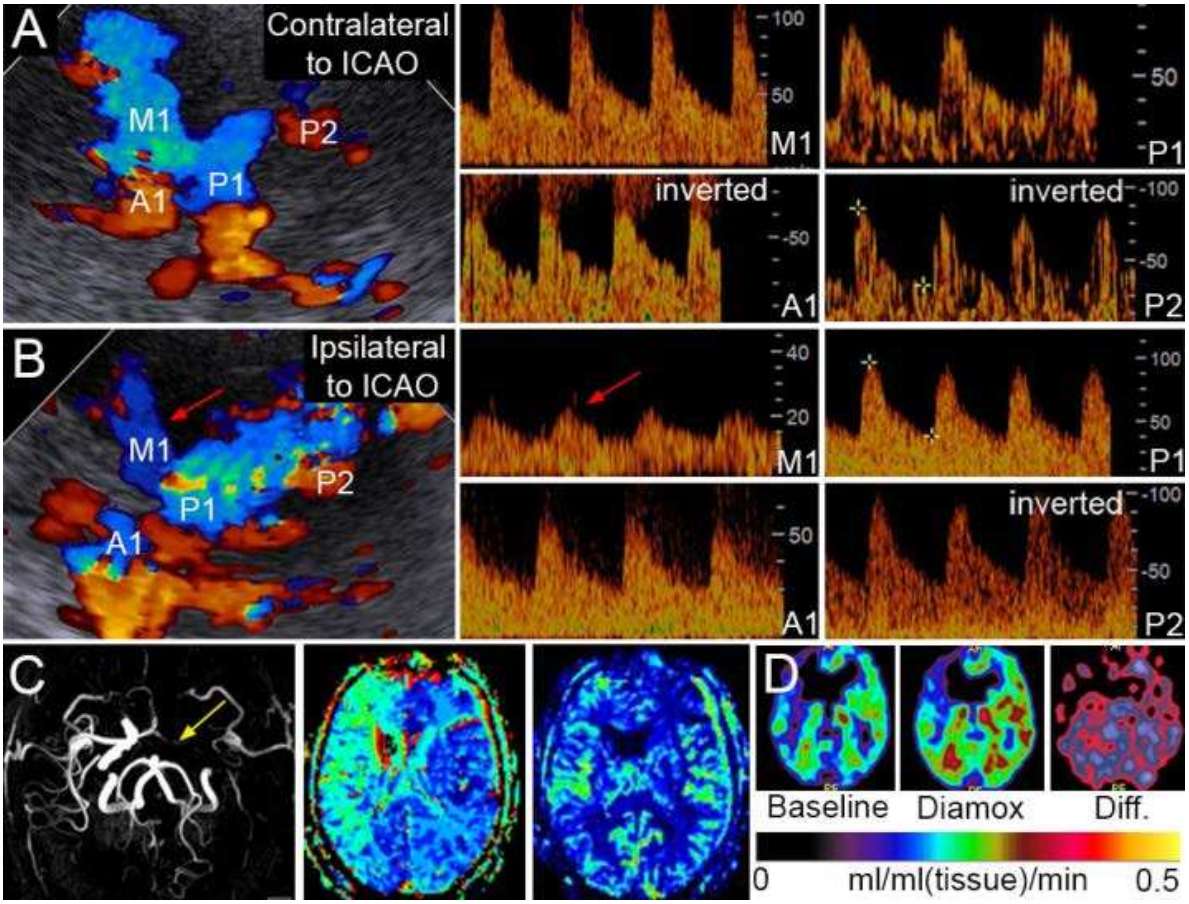
Legend Supplementary Table 2: Duplex assessment of collaterals and concurrent MCA and contralateral ICA stenosis in all 68 patients (All) and patients groups without or with ipsilateral recurrent ischemic event. P values < 0.05 are marked with *. Numbers (n) and percentage are given if not specified otherwise.

Supplementary Table III: Cox regression analysis

Predictors	HR	95% CI	p-value
Univariate cox regression analysis			
Diabetes mellitus	3.90	1.35 – 11.3	0.01
Antithrombotics	4.61	1.44 - 14.7	0.01
Statin	4.61	1.44 – 14.7	0.01
Previous TIA	6.97	2.4 – 20.22	< 0.001
Number of collaterals = 4	4.46	1.39 – 14.29	0.01
PSV P2 ipsi	1.01	1.00 – 1.02	0.02
PSV P2 contra	1.04	1.01 – 1.07	< 0.01
PDV P2 ipsi	1.03	1.0 – 1.05	0.03
PDV P2 contra	1.06	1.0 – 1.11	0.06

Legend Supplementary Table III: Results of the univariate cox regression analyses for recurrent ischemic event. HR: hazard ratio, 95% CI: 95 % confidence intervals. HR refers to a 1-unit increase in the explanatory variable. “ipsi” and “contra” refers to side with respect to ICAO. PSV P2 = PSV within the P2 segment of the PCA.

Supplementary Figure I: TCD assessment in a patient with ICAO



A) TCD contralateral to ICAO. Arterial segments: M1: MCA-M1, A1: ACA-A1, P1: PCA-P1, P2: PCA-P2. The panel on the right displays the respective flow profiles.
B) TCD ipsilateral to ICAO. Same arterial segments and flow profiles as in A) on the affected side are shown. Note decreased PSV in M1 with post-stenotic flow profile (red arrow). Flow direction in A1 is reversed (AcoA collateral). Flow values in both PCA are high.
C) Left: MR angiogram of the patient demonstrating ICAO and low flow within the ipsilateral MCA (yellow arrow). Middle: Characteristic section of the Time-to-Peak (TTP) perfusion MRI indicating the region receiving collateral, i.e., delayed, blood supply. Right: cerebral blood flow (CBF) perfusion MRI of the same patient indicating no flow deficit at baseline. D) The H_2O-PET with Diamox challenge shows reduced baseline CBF (Baseline) within the ipsilateral infarct territory with an attenuated CBF increase in peri-infarct areas upon diamox challenge (Diamox). Diff: Difference image (Diamox – Baseline). Images 1C-E provided by the Department of Neuroradiology, University Hospital Zurich, images in 1F provided by the PET Center, Division of Nuclear Medicine, University Hospital, Zurich.