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## 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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# **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 (ICAO) puts patients at risk of recurrent ischemic events due to hemodynamic compromise. Our goal was to characterize clinical and duplex parameters indicating patients at risk.

**Methods:** We retrospectively identified patients with symptomatic ICAO. 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 one recurrent ischemic event within the same vascular territory was observed in 14 (20.6 %) within 2 - 92 days (median 29.5 days). The median follow-up period was 6 months. Diabetes and previous TIA were associated with recurrence, as was activation of the maximum number of collateral pathways on transcranial ultrasound (28.6 vs. 5.6 %,  $p = 0.03$ ). Furthermore, flow in the posterior cerebral arteries (PCA) was higher in patients with recurrence in ipsi- and contralateral PCA- P2 segments (76 IQR 37.5 vs. 59 IQR 22.5 and 68 IQR 35.6 vs.  $52 \pm 21$  cm/s;  $p < 0.01$  and 0.02).

**Conclusions:** Flow increases in both PCA-P2 suggest intensified compensatory efforts when other collaterals are insufficient. Together with the presence of diabetes and a history of TIA, this duplex parameter indicates ICAO patients at particular risk of recurrent ischemia.

## **Introduction**

Patients with symptomatic ICAO are at an increased risk of recurrent stroke, which has been estimated between 5.5-10% per year<sup>1-5</sup>. The risk is likely increased if collateral supply is insufficient resulting in hemodynamic compromise<sup>6-8</sup>. Collateral pathways activated in response to ICAO have been categorized as either primary or secondary. Primary collateral pathways involve the circle of Willis, either through cross flow from the anterior communicating artery (ACoA) or the posterior communicating artery (PCoA). Reversed flow through the ophthalmic artery (OA) or enhanced flow within leptomeningeal collaterals (LPM) are considered secondary collateral pathways<sup>9</sup>. Secondary collaterals may have a limited capacity, and activation of secondary collaterals has been linked to impaired cerebral vasoreactivity<sup>10, 11</sup>. There are, however, studies suggesting that the type of collateral network does not impact cerebrovascular reserve, but that the activation of more collateral pathways indicates a higher risk of stroke recurrence in ICAO<sup>12,13</sup>. The current study aimed to define clinical and ultrasound predictors for recurrent ipsilateral ischemia or early vascular death in patients with symptomatic ICAO.

## **Methods**

### **Study design and cohort description**

In this retrospective analysis, patients with symptomatic proximal ICAO treated at the University Hospital Zurich Department of Neurology between 2009 and 2014 were included if they had received an extra- and intracranial duplex investigation at our site within 30 days and a clinical follow up of at least 1 month (see supplementary methods). Patient demographics, stroke severity on the National Institute of Health Stroke Scale (NIHSS) and medical history prior to stroke were obtained.

### **Statistical analyses**

Analyses were performed using non- and semiparametric methods. Group comparisons were performed using Fisher's exact test (categorical measurements) and 2-tailed Mann-Whitney U-test (continuous measurements) both yielding conservative p-values by ignoring the censoring. Predictors for recurrent ischemia were investigated using a univariate Cox regression model. Multiple testing corrections were omitted.

## Results

68 patients with symptomatic ICAO were included in the study (Table 1). At least one recurrent ischemic event within the same vascular territory was observed in 14 (20.6 %) patients at a median time of 29.5 days (IQR 8 – 89) during the median follow up of 6 months (IQR 4 – 24). In the group with an observed recurrent ischemic event, there were significantly more patients with diabetes and previous TIA as well as statin and antiplatelet use in their medical history. First duplex ultrasound was performed within a median time of 1 day (IQR 0.25 – 3) after the ischemic event (Figure 1). In patients with a recurrent event, activation of all four collateral pathways (ACoA, PCoA, LM, OA) was more frequently detected by TCD, but the type of pathway (type I or II) was not different between groups. Higher flow values within both PCA-P2 segments were observed in patients with recurrence (Supplementary Figure 1, supplementary Tables I and II).

According to univariate Cox regression analysis (Supplementary Table III), diabetes and previous TIA with the use of platelet inhibitors and/or statins as well as the presence of four activated collateral pathways were univariately associated with a recurrent ischemic event. Flow in the posterior cerebral arteries was higher in patients who experienced a recurrent event. All other investigated duplex parameters were not significantly different between patient groups.

## **Discussion**

Our data indicate that after symptomatic ICAO, the risk of a recurrent ipsilateral ischemic event is high, particularly in the early phase. We found that the activation of all four TCD-assessable collateral systems (ACoA, OA, PCoA and LPM) and increased flow in both PCA-P2 segments were more common in patients with a recurrent event. This suggests that recruitment of more collateral systems, particularly the vertebrobasilar vessels, implies impaired collateral capacity. MCA flow velocities were not predictive of ischemia recurrence

14.

## **Summary**

Previous TIA and diabetes are clinical parameters associated with increased risk of recurrence after symptomatic ICAO. Presence of four activated collateral systems in transcranial ultrasound and increased flow in the PCA-P2 segments are further indicators of hemodynamic failure and risk of ischemia recurrence. Prospective validation in larger patient groups is needed. However, TCD has the potential to strengthen clinical prediction algorithms due to its unique capability to assess collateral flow pathways.

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## References

1. Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J. Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. *Stroke; a journal of cerebral circulation*. 1997;28:2084-2093
2. Bryan DS, Carson J, Hall H, He Q, Qato K, Lozanski L, et al. Natural history of carotid artery occlusion. *Annals of vascular surgery*. 2013;27:186-193
3. Powers WJ, Clarke WR, Grubb RL, Jr., Videen TO, Adams HP, Jr., Derdeyn CP, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: The carotid occlusion surgery study randomized trial. *Jama*. 2011;306:1983-1992
4. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD, Jr. Population-based study of symptomatic internal carotid artery occlusion: Incidence and long-term follow-up. *Stroke; a journal of cerebral circulation*. 2004;35:e349-352
5. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The ec/ic bypass study group. *The New England journal of medicine*. 1985;313:1191-1200
6. Reinhard M, Schwarzer G, Briel M, Altamura C, Palazzo P, King A, et al. Cerebrovascular reactivity predicts stroke in high-grade carotid artery disease. *Neurology*. 2014;83:1424-1431
7. Guler S, Utku U, Aynaci O. Early clinical signs, lesion localization, and prognostic factors in unilateral symptomatic internal carotid artery occlusion. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2014;23:1908-1914

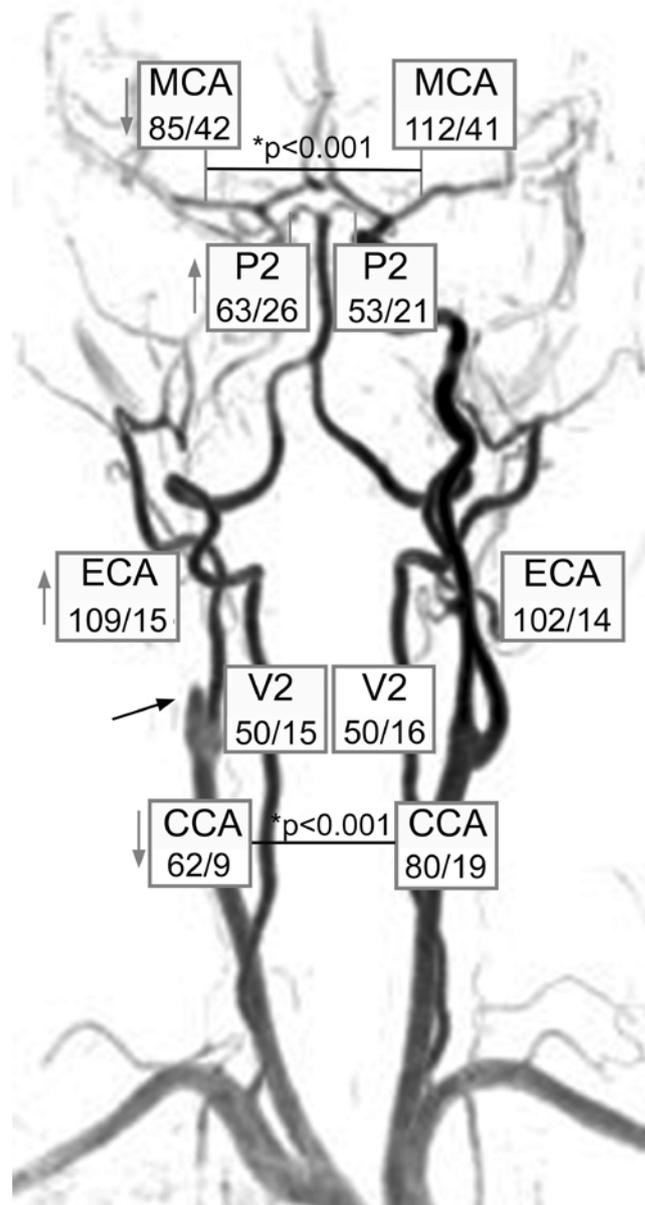
8. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *Jama*. 2000;283:2122-2127
9. Liebeskind DS. Collateral circulation. *Stroke; a journal of cerebral circulation*. 2003;34:2279-2284
10. Hofmeijer J, Klijn CJ, Kappelle LJ, Van Huffelen AC, Van Gijn J. Collateral circulation via the ophthalmic artery or leptomeningeal vessels is associated with impaired cerebral vasoreactivity in patients with symptomatic carotid artery occlusion. *Cerebrovascular diseases*. 2002;14:22-26
11. 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
12. van Everdingen KJ, Visser GH, Klijn CJ, Kappelle LJ, van der Grond J. Role of collateral flow on cerebral hemodynamics in patients with unilateral internal carotid artery occlusion. *Annals of neurology*. 1998;44:167-176
13. Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, Rossini PM, et al. Effect of collateral blood flow and cerebral vasomotor reactivity on the outcome of carotid artery occlusion. *Stroke; a journal of cerebral circulation*. 2001;32:1552-1558
14. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and tia risk in patients with carotid artery stenosis and occlusion. *Brain : a journal of neurology*. 2001;124:457-467

**Table 1: Patient clinical characteristics**

	All n = 68 (%)	No recurrent event observed n = 54 (%)	Recurrent event observed n = 14 (%)	p-value
<b>Demographic data</b>				
Age (Range)	65 (30-90)	64.7(30 – 88)	65.5 (47-90)	0.96
Male	47 (69)	38 (70.4)	9 (64.3)	0.75
<b>Type of event</b>				
TIA	5 (7.4)	4 (7.4)	1 (7.1)	0.6
Retinal ischemia	5 (7.4)	3 (5.6)	2 (14.3)	0.2
Stroke	58 (85.3)	47 (87)	11 (78.6)	0.2
<b>Medical history, n (%)</b>				
Smoking	29 (43)	20 (37)	9 (64.3)	0.21
Hypertension	49 (72)	37 (68.5)	12 (85.7)	0.32
Diabetes	13 (19)	7 (13.0)	6 (42.9)	0.02*
CAD	12 (17.6)	8 (14.8)	4 (28.6)	0.25
pAOD	12 (17.6)	9 (16.7)	3 (21)	0.68
Dyslipidemia	43 (63)	33 (61)	10 (71)	0.47
Atrial fibrillation	10 (14.7)	10 (18.9)	0	0.10
<b>Pre-Stroke Medication, n (%)</b>				
Platelet inhibitor	26 (38)	16 (29.6)	10 (71.4)	<0.01*
Statin	17 (25)	9 (16.7)	8 (57)	<0.01*
<b>Clinical scores, median (IQR)</b>				
NIHSS on admission	3 (9.5)	3.5 (11.8)	3 (5.2)	0.58
NIHSS at 3 months	0.5 (2.3)	0 (2)	1 (3.3)	0.38
mRS on admission	3 (4)	3 (4)	2.5 (2.5)	0.48
mRS at 3 months	1 (2.3)	1 (2.8)	1.5 (1.5)	0.42
<b>Past vascular events, n (%)</b>				
TIA	9 (13.2)	4 (7.41)	5 (35.7)	0.01*
Stroke	6 (8.8)	4 (7.41)	2 (14)	0.42
Retinal artery occlusion	3 (4.4)	2 (3.7)	1 (7.1)	0.58
<b>TOAST, subtype, n (%)</b>				
Large vessel disease	38 (56)	27 (50)	11 (78.6)	0.13
Cardio embolic	8 (11.8)	8 (14.8)	0	0.11
Small artery disease	0	0	0	-
Other causes	17 (25)	15 (27.8)	2 (14.3)	0.62
Undetermined	5 (7.4)	4 (7.41)	1 (7.1)	0.91

**Legend Table 1:** Clinical characteristics of all 68 patients (All) and patients groups without or with ipsilateral recurrent ischemic event. P values < 0.05 in Mann-Whitney U-test or Fisher Exact Test are marked with \*. CAD: coronary artery disease, pAOD: peripheral artery occlusive disease. Numbers (n) and percentage or median and interquartile range (IQR) are shown.

**Figure 1**



**Figure 1: Flow changes in extra- and intracranial arteries induced by ICAO**

Median values for PSV/EDV from all patients are superimposed upon characteristic MR angiography image of a patient with ICAO (black arrow). Differences between affected (ICAO) and contralateral side are supported by p-values resulting from Mann-Whitney U-test. Grey arrows illustrate typical flow changes observed ipsilateral to ICAO (direction of change in contrast to contralateral side). The MR angiography image was provided by the Department of Neuroradiology, University Hospital Zurich.