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# Reversed ophthalmic artery flow in patients with acute ischemic stroke and ipsilateral significant extracranial carotid artery stenosis, and its effect in functional outcome

Yosra Fahmy, Yousry Abo El Naga, Ahmed Hazzou and Shahinaz Helmy\*

## Abstract

**Background:** Cerebral hemodynamics and collateral circulation have an important role in determining stroke outcome, while the role of primary collateral is well known, the role of secondary collaterals including ophthalmic artery flow is still controversial. Our aim was to evaluate the flow of ophthalmic artery in patients with acute ischemic stroke and significant extracranial carotid stenosis and assess its role on the functional outcome. Thirty patients with acute ischemic stroke and extracranial carotid stenosis were included from Ain Shams University hospitals, color coded duplex was used to assess extracranial carotid arteries, ophthalmic artery was assessed by transcranial color-coded duplex. According to ophthalmic artery flow patients were divided into two groups, one with forward and other with reversed flow. Modified Rankin Scale (MRS) after 3 months was compared between the two groups

**Results:** Reversed ophthalmic artery flow (ROAF) was seen among 10 (33.33%) patients. After 3 month MRS was better in ROAF group ( $1.5 \pm 1.958$ ) than forward ophthalmic artery flow (FOAF) group ( $2.1 \pm 1.954$ ) but with no statistical difference ( $p$  value 0.398); furthermore, the difference between MRS after 3 months and discharge was significant in ROAF group ( $p$  value 0.042).

**Conclusions:** Transcranial duplex is a noninvasive, safe method in determining ophthalmic artery flow; furthermore, ROAF could help in better stroke outcome.

**Keywords:** Carotid stenosis, Transcranial color-coded duplex, Ophthalmic artery flow, Reversed ophthalmic artery flow, Cerebral collaterals

## Background

Extracranial severe carotid stenosis or occlusion is a known risk factor for ischemic stroke, and the risk increases in patients with concurrent severe stenosis of extra and intracranial vessels [1]. Ischemic stroke is a result of acute arterial occlusion or severe narrowing leading to impaired blood flow to the brain tissue. The collateral circulation is a dynamic system that helps in preserving cerebral perfusion during cerebral ischemia.

Recruitment of these anastomosis helps to compensate for decrease blood supply and maintain homeostasis, this could help to decrease infarct size and improving the functional outcome [2].

These anastomotic channels include the primary collaterals which are a part of the circle of willis and secondary collaterals which includes the ophthalmic artery and the leptomeningeal vessels [3].

During acute ischemia primary collaterals supply blood flow to large portions of cerebral hemispheres in both anterior and posterior circulations, while secondary collaterals, including the leptomeningeal vessels and

\*Correspondence: Drshahinaz82@gmail.com  
Faculty of Medicine, Ain Shams University, Cairo, Egypt

ophthalmic artery provide additional support by forming anastomotic connections between internal and external carotid [4].

The phenomenon of reversed ophthalmic artery flow (ROAF) is well-known, but its clinical implication in patients with severe cervical carotid stenosis remains poor. Ophthalmic artery can serve as a collateral in cases where the primary collaterals are insufficient [5]. The clinical significance of ROAF is controversial, with some studies considering it a sign of impaired cerebral hemodynamics and cerebral vasomotor reactivity [6, 7]. While others suggested that it could contribute to the functional outcome of cerebral ischemia [8, 9].

Advanced neuroimaging techniques help to give detailed information and allow interpretation of collateral circulation [10]. Doppler ultrasonography is a non-invasive way that is now used for the diagnosis of internal carotid artery (ICA) stenosis. Its diagnostic accuracy has shown to be >90% when compared with angiography if performed by experienced sonographers [11]. Transcranial color-coded duplex (TCCD) is used to determine the cerebral collaterals and it could reliably assess flow of the ophthalmic artery. ROAF means flow directed away from the probe via transorbital window, it has shown high specificity and sensitivity in detecting proximal ICA severe stenosis or occlusion [12].

Our study aimed to evaluate the flow of ophthalmic artery in patients with acute ischemic stroke and significant extracranial carotid stenosis, and to show its effect on the functional outcome of stroke.

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## Methods

Thirty patients with acute cerebrovascular stroke were recruited in this prospective cohort study admitted in stroke unit at the Department of Neurology of Ain Shams University. The study included Patients aged 18 years or older who were diagnosed with acute cerebrovascular stroke within 2 weeks and suffered from high grade extra-cranial carotid artery stenosis (>70%) detected by carotid duplex and were able to give informed written consent before enrollment in the study. Patients with non-significant carotid stenosis, or carotid dissection, or with evidence of intracranial hemorrhage were excluded.

All patients were subjected to complete history and neurological examination, magnetic resonance imaging (MRI) brain stroke protocol [Axial T2/FLAIR-, axial T2 star-, diffusion- (DWI) and MRA].

Patients' neurological status was assessed via national institute of health and stroke scale (NIHSS) on admission. Modified Rankin scale (MRS) to assess functional disability was done on discharge and after 3 months.

Extra-cranial carotid arteries were assessed using color-coded duplex using linear probe 10–12 MHz (Esaote mylab 5, Italy), peak systolic velocity more than or equal 230 cm/s indicates >70% stenosis [14]. Transcranial color-coded duplex used to assess the ophthalmic artery flow using phased array probe (2–4 MHz) of the same system via transorbital window with adapted power.

Patients were divided into two groups according to ophthalmic artery flow, group with forward flow (FOAF) and other with ROAF, ophthalmic artery flow was considered forward if directed towards the probe, and reversed if directed away from probe.

The study protocol was approved by Ain Shams University, Faculty of Medicine Research Ethical Committee of neurology department (on 12 May 2018).

## Statistical analysis

The data was analyzed with SPSS (Statistical Package for Social Science) version 20 (by IBM: Armonk: New York, USA, 2012). Descriptive statistics were displayed as mean and Standard Deviation (SD) for parametric data and case count and percentage for categorical data, median and range for non-parametric. Within the group, comparisons were done using the independent *T* test, Chi square. The level of statistical significance (*p* value) was set at 0.05.

## Results

Thirty cases were included in the study, 14 (46.67%) were females, while 16 (53.33%) were males, the mean age was  $61.233 \pm 12.303$  as shown in Table 1.

The vascular risk factors among the studied patients were shown in Table 2.

As shown in Table 3, according to TCCD findings, the patients were divided into two groups, group with forward ophthalmic artery flow direction 20 (66.67%), and the other with reversed flow direction 10 (33.3%).

The difference between the two groups as regards the previously mentioned risk factors was statistically non-significant (Table 4).

As regards the comparison between MRS on discharge and after 3 months in both groups, MRS was better in ROAF group after 3 months but no statistically significant results, however, by comparing the difference between MRS on discharge and follow up after 3 months, there was a statistically significant difference in patients with ROAF ( $p=0.042^*$ ), unlike patients with FOAF who showed no statistical significance difference ( $p=0.086$ ), as shown in Table 5.

**Table 1** Gender and age distribution among the study group

Age		
Range	Mean ± SD	
30–83	61.233 ± 12.303	
Sex	n	%
Female	14	46.67
Male	16	53.33
Total	30	100.00

SD: standard deviation

**Table 2** Vascular risk factors among studied patients

	Hyperlipidemia		Diabetes		Smoking		Hypertension	
	n	%	n	%	n	%	n	%
Yes	21	70	17	56.67	12	40	14	46.66
No	9	30	13	43.33	18	60	16	46.67

n: number

**Table 3** Distribution of study population as regards ophthalmic artery flow direction

Ophthalmic artery	n	%
Reversed flow	10	33.33
Forward flow	20	66.67
Total	30	100.00

n: number

**Discussion**

Cerebral collateral circulation helps maintaining cerebral perfusion in acute ischemic stroke, the role of Primary collaterals (circle of Willis) is more evident; however, the role of secondary collaterals especially ophthalmic artery in predicting stroke outcome is controversial. Our study aimed to evaluate the role of ophthalmic artery flow in predicting stroke outcome.

**Table 4** Distribution of different risk factors among the two study groups

	Ophthalmic artery						Chi-square	
	Reversed flow		Forward flow		Total		χ <sup>2</sup>	p-value
	n	%	n	%	n	%		
Smoker								
No	5	50.00	13	65.00	18	60.00	0.625	0.429
Yes	5	50.00	7	35.00	12	40.00		
Diabetes								
No	3	30.00	10	50.00	13	43.33	1.086	0.297
Yes	7	70.00	10	50.00	17	56.67		
Hypertension								
No	4	40.00	12	60.00	16	53.33	1.071	0.301
Yes	6	60.00	8	40.00	14	46.67		
Hyperlipidemia								
No	2	20.00	7	35.00	9	30.00	0.714	0.398
Yes	8	80.00	13	65.00	21	70.00		

n: number, p value > 0.05 is considered non-significant

**Table 5** MRS on discharge and after 3 months in the two groups

Modified Rankin Scale	Ophthalmic artery		T-test	
	Reversed flow	Forward flow	T	p-value
On discharge				
Range	1–5	0–6	–0.262	0.795
Mean ± SD	2.500 ± 1.434	2.650 ± 1.496		
After 3 months				
Range	0–6	0–6	–0.858	0.398
Mean ± SD	1.500 ± 1.958	2.150 ± 1.954		
Differences				
Mean ± SD	1.000 ± 1.333	0.500 ± 1.235		
Paired test				
p value	0.042*	0.086		

MRS: Modified Rankin Scale, p value < 0.05 is considered statistically significant

Thirty patients with acute stroke and significant extracranial carotid stenosis were included in the study, we found that ROAF was present among 10 patient (33.3%), this was in agreement with the range appeared in previous studies, Grilo and colleagues studies ROAF in cases with carotid stenosis (967 cases), they found that the frequency of ROAF increase with increasing severity of stenosis being 43% in cases with >80% stenosis, there was a significant association between ROAF and increasing severity of stenosis with excellent specificity and negative predictive value [5]. Reynolds and colleagues found ROAF to be present in 56 out of 101 artery stenosis more than 80% [15]. Tsai and colleagues Found it 25% in stenosis, 62.5% in occlusion [7].

In our study we divided the patients into two groups according to ophthalmic artery flow direction, we did not find significant difference in risk factors between patients with ROAF and FOAF.

As regard MRS which is a reflection of functional outcome, it was shown that patients with ROAF had better MRS after 3 months in comparison to FOAF, but not statistically significant. However, in comparing the difference between MRS after 3 months from discharge, it was statistically significant among ROAF group. This could suggest that ROAF might have a role in improving functional outcome, yet the results still non-significant comparing both groups which could be due to sample size.

The impact of ophthalmic artery in hemodynamics is still controversial, while some studies suggested that its presence indicates poor outcome due to impaired cerebral hemodynamics, others found it to save as compensatory mechanism in cases where the primary collaterals are insufficient. In Tsai and colleagues 2013, they found that the presence of ROAF was significantly related to poor functional outcome, and that the difference in

hemodynamics in orbital arteries between stenotic side and the non-stenotic side indicates that ROAF act as a shunt to a low resistance intracerebral circulation due to impaired hemodynamics, or insufficient circle of willis [7]; however, it was different in methodology and follow up, also intracranial stenosis was present among 49.1% of all cases and 80% in ROAF patients, which was also found to be more significantly related to poor outcome.

Sung and colleagues investigated 128 subjects (101 with acute stroke, and 27 without stroke) with unilateral high-grade stenosis or occlusion, they found that acute stroke group had a significant higher percentage of ROAF, carotid occlusion, intracranial stenosis; however, multivariate analysis demonstrated that intracranial stenosis is the only significant risk factor. In addition, they found ROAF was present more among group without stroke and had combined extracranial and intracranial stenosis than group with stroke and combined stenosis, although it was not statistically significant, they suggested that the presence of ROAF might modify stroke risk in patients with combined extra and intracranial stenosis [9].

They then compare between four subgroups according to ophthalmic artery flow and intracranial stenosis; they found a trend towards better outcome from ROAF and mild or no intracranial stenosis. In addition, in patients with same degree of intracranial stenosis, stroke outcome improved by 10–20% in ROAF groups, suggesting that ROAF serve partial hemodynamics compensation, but still not complete protection against stroke risk due to small caliber and low blood flow in comparison with the arteries of circle of willis [9].

A more recent study tried to investigate effect of ROAF on midterm functional outcome following carotid artery stent, they found that stenting could be effective treatment option regardless the ophthalmic artery flow direction, and that patients without ROAF were more likely to have improved functional outcomes (16); however, the study design was different from ours and the outcomes were assessed after carotid artery stent which also affects the functional outcome.

Our study had some limitations, the small sample size, the assessment for extra cranial stenosis was done using duplex, CT angiography was not available for all patient and also the lack of conventional angiography; furthermore, the effect of intracranial stenosis and other collaterals were not investigated.

## Conclusions

Transcranial color-coded duplex is a non-invasive, safe and reliable method for assessment of ophthalmic artery flow, it helps to assess cerebral hemodynamics in patients with acute ischemic stroke and significant extracranial carotid stenosis, in our study ROAF shows to have more

favourable stroke outcome which supports the compensatory role of ophthalmic artery in cases with cerebral ischemia.

#### Abbreviations

FOAF: Forward ophthalmic artery flow; ICA: Internal carotid artery; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; MRS: Modified Rankin scale; NIHSS: National institute of health and stroke scale; ROAF: Reversed ophthalmic artery flow; SD: Standard deviation; SPSS: Overall Disability Sum Score; TCCD: Trans cranial color-coded duplex.

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Not applicable.

#### Authors' contributions

YF, YA, AH, and SH conceived of the study and participated in its design and coordination and helped to draft the manuscript. YF and SH participated in the design of the study and performed the statistical analysis. SH and YF performed the color-coded duplex for the patients. All authors have agreed to conditions noted on the Authorship Agreement Form. All authors read and approved the final manuscript.

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#### Availability of data and materials

Data set is available as master sheet in Excel format.

#### Declarations

##### Ethics approval and consent to participate

The study protocol was approved by Ain Shams University, Faculty of Medicine Research Ethical Committee of neurology department (on 12 May 2018). Written informed consent was obtained from the patients participating in the study or first-degree relatives (if patient can't give consent) after informing them about the study rationale and their right to withdraw from the study at any time without any consequences. Committee's reference number: not applicable.

##### Consent for publication

Not applicable.

##### Competing interests

All authors declare that they do not have any competing interests.

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