Retinal angiographic blood flow is reduced in the ocular ischaemic syndrome

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INTRODUCTION: The aim of this study was to examine the use of quantitative fluorescein angiographic analysis as a means of estimating rates of perfusion of the retina in eyes with a circulatory deficit secondary to carotid artery stenosis.

MATERIAL AND METHODS: The study included 21 eyes with ocular ischaemic syndrome (OIS) and 20 control eyes from subjects with carotid artery stenosis but without signs of ocular ischaemia. Analyses of video fluorescein angiograms extracting time intervals for the time delay between specific phases of the angiogram were performed. Time delay was compared between groups and in relation to degree of carotid artery stenosis and ocular systolic blood pressure.

RESULTS: Among the three flow indices of retinal perfusion (arteriovenous passage time 1 (AVP1), arteriovenous passage time 2 (AVP2) and venous filling time (VP)), those including the venous filling phase were significantly prolonged in the OIS group. Furthermore, AVP2 was delayed by three seconds in OIS eyes (16.6 sec. versus 13.6 sec. in controls). VP was 2.4 seconds longer in OIS eyes (11.5 sec. versus 9.1 sec.). We found a significant correlation between AVP2 and ocular perfusion pressure, but no correlation between the degree of carotid artery stenosis and any of the flow indices.

CONCLUSION: In a patient population spanning a wide ocular systolic blood pressure range, angiography-based quantitative flowmetry demonstrated a difference between carotid artery stenosis patients with and without OIS and a correlation between flow and ocular perfusion pressure. While angiographic flowmetry proved effective in discriminating between groups of individuals, it can only be used to support the diagnosis of the ocular ischaemic syndrome in patients with extreme flow reduction.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Objective assessment of retinal perfusion is not only of scientific interest; it is also important in clinical conditions such as diabetic retinopathy, the study of the response of the intact retinal circulation to metabolic challenges such as hypoxia, and in conditions where reduced ocular perfusion is suspected of being the primary cause of visual dysfunction. Carotid artery stenosis of a sufficient magnitude can induce the ocular ischaemic syndrome [1], a characteristic clinical entity that was used in this study to serve as a paradigm for severe ocular hypoperfusion of extraocular origin. The reduction in ocular perfusion pressure that may follow due to carotid artery stenosis can be objectively quantitated by ocular pneumoplethysmography, a technique that measures the ocular systolic blood pressure [2]. The clinical manifestations of the ocular ischaemic syndrome are characteristic of chronic retinal hypoxia. They include mild to very severe reduction of best-corrected visual acuity, glare in bright light and ocular angina [3]. Common clinical findings are iris neovascularisation, mid-peripheral retinal haemorrhages, generalized dilation of retinal veins and diffuse fluorescein angiographic leakage from staining of the retinal vessels, of which haemorrhages and staining were required to make the diagnosis of the ocular ischaemic syndrome. A reduced ocular perfusion pressure supported the diagnosis. The exclusion criteria were retinal vasculopathy of other causes, including retinal vein occlusion and diabetic retinopathy.

No validated therapy is available. Carotid endarterectomy can normalize the ocular perfusion pressure but it is not obvious that it benefits visual function, either immediately or prospectively [3]. Methods for objectively measuring retinal perfusion are unavailable in routine clinical practice which makes the study of the ocular ischaemic syndrome difficult. In this study, we examined the utility of quantitative fluorescein angiographic analysis to estimate the rates of perfusion of the retina in eyes with ocular ischaemic syndrome secondary to carotid artery stenosis and in a control group of patients with carotid artery stenosis but without ocular ischaemic syndrome.

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The study was a post hoc analysis of video fluorescein angiograms from patients enrolled prospectively in an observational study of carotid artery stenosis. The study population consisted of two groups of patients: 1) patients with documented or suspected ocular ischaemic syndrome in at least one eye; these patients were identified during routine clinical practice in an ophthalmological clinic; and 2) patients with uni- or bilateral carotid

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Clinical characteristics of ocular ischaemic syndrome eyes and asymptomatic eyes in patients with carotid artery stenosis.

	Ocular ischaemic syndrome (n = 21)	carotid artery stenosis without ocular ischaemia (n = 20)	p-value
Age, years, mean ± SD	68.9 ± 6.8	68.5 ± 7.8	–
Women, n	10	3	–
Men, n	11	17	–
Best-corrected visual acuity, ETDRS letters, mean ± SD	74.2 ± 18.2	78.1 ± 9.2	0.40
Ocular systolic blood pressure, mmHg, mean ± SD	69 ± 11.3	98 ± 16.4	< 0.0001
Degree of carotid artery stenosis, grades 1-6, median (IQR)	5.1 (3.8-6)	5.1 (3.6-6)	–

ETDRS = Early Treatment of Diabetic Retinopathy Study, a standardized method of visual acuity measurement; IQR = interquartile range; SD = standard deviation.

artery stenosis (70% stenosis or greater) as assessed by Doppler ultrasonography; these patients were recruited from collaborating vascular surgery and stroke clinics, irrespective of whether they had any ocular or visual complaints or not. All eligible patients with ocular ischaemic syndrome (n = 24) and a matching number of randomly selected age-matched patients without ocular ischaemic syndrome (n = 25) were included in the sub-study. An additional inclusion criterion for the present sub-study was the presence of a complete filling-phase video of acceptable quality. After exclusion of cases in which the image quality was too poor, we were left with 21 eyes with ocular ischaemic syndrome and 20 non-ocular ischaemic syndrome eyes in patients with carotid artery stenosis (**t able 1**).

Study procedures included routine clinical examination, determination of ocular systolic pressure using ocular pneumoplethysmography, intravenous fluorescein angiography, and applanation tonometry.

Stenosis of the carotid artery was classified as grade 1 (0-14%), grade 2 (15-49%), grade 3 (50-69%), grade 4 (70-79%), grade 5 (80-99%) or grade 6 (100%) [4]. All OIS patients had unilateral OIS and the eye with OIS was chosen as the study eye. In the controls, the eye with the highest degree of stenosis was chosen as the study eye.

Fluorescein angiography was performed according to our institution's standard operating procedure. A bolus 2.5 ml fluorescein injection was given intravenously over 1-2 sec. through an indwelling catheter in an antecubital vein. Fundus fluorescence was imaged using a scanning laser ophthalmoscope (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) on a continuous video recording mode during the filling phase of the angiogram up to the late venous phase. Angiographic filling rates were determined by frame-by-frame inspection of the video. The timing of the following events was noted for the largest vessels of the upper and lower temporal vascular arcades within 0-1 disc diameter of the rim of the optic nerve head (**Figure 1**): T1: first appearance of fluorescein dye in retinal arteries, T2: first appearance of fluorescein dye in retinal veins, T3: completion of venous filling with fluorescein-stained blood with disappearance of the visibility of laminar blood flow. T1, T2 and T3 were registered manually by the same person (GH). Reported data are means of values from the upper and lower temporal vascular arcades. Statistical analysis was made using unpaired two-sampled t-test. Exploratory analyses using the non-parametric Wilcoxon test gave qualitatively identical results in all analyses. Linear regression analysis was used to study the correlation between continuous variables. Non-parametric correlations between continuous and categorical variables (degree of carotid artery stenosis) were measured with Spearman's rho test. The level of statistical significance was set to $p < 0.05$.

Trial registration: not relevant.

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The sub-study included 21 OIS patients and 20 controls; see Table 1. The two groups were highly comparable regarding the clinical characteristics listed in Table 1. The only parameter that differed significantly between the groups was ocular systolic blood pressure, which was lower in OIS eyes than in controls.

Of the three angiographic indices of retinal blood flow rate (AVP1, AVP2 and VP), the two that included the venous filling phase (AVP2 and VP) were significantly delayed in the group of ocular ischaemic syndrome eyes and showed the largest relative difference between ocular ischaemic syndrome eyes and control eyes (**t able 2**). AVP2 was delayed by three seconds in OIS eyes (16.6 sec.) compared with control eyes (13.6 sec.), and VP was prolonged by 2.4 seconds in the OIS group (11.5 sec.) compared with controls (9.1 sec.), although an overlap

between the two groups was observed. The observed difference in AVP1 between OIS and control eyes (0.3 sec.) was not statistically significant.

A significant correlation between the flow index and ocular systolic blood pressure was seen for AVP2 (p = 0.04; **Figure 2**), but not for AVP1 (p = 0.25) or VP (p = 0.11). This analysis excluded two OIS eyes and five control eyes for which data for ocular systolic blood pressure were missing.

No correlation was found between the degree of ultrasonographic carotid artery stenosis and AVP1 (p = 0.29), AVP2 (p = 0.65) or VP (p = 0.97) (data not tabulated).

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Of three angiographic flow indices of retinal perfusion, those that included the venous filling phase (AVP2 and VP) were significantly prolonged in the OIS group. This shows that the venous phase makes the main contribution to the data pool of the present study. The venous perfusion time (VP) has not previously been described separately in OIS patients.

We found a significant correlation between one of the flow indices (AVP2) and ocular perfusion pressure, but no correlation between the degree of ultrasonographic carotid artery stenosis and any of the flow indices.

Among the various methods for quantitating retinal perfusion, Doppler velocimetry coupled with retinal vessel diameter measurement is best validated [5]. The instrumentation is not commercially available though, and the procedure requires considerable experience. Fluorescein angiography, on the contrary, is a routine method that is widely available. In a field of investigation where no gold-standard method exists, we chose to define as the better method the one that would best

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Fig URE 1

Fluorescein angiograms. The timing of the following events was noted for the largest vessels of the upper and lower temporal vascular arcades within 0-1 disc diameter of the rim of the optic nerve head: **a.** T1 first appearance of fluorescein dye in retinal arteries. **b.** T2 first appearance of fluorescein dye in retinal veins. **c.** T3 completion of venous filling with fluorescein-stained blood with disappearance of the visibility of laminar blood flow. T2–T1 = arteriovenous passage time 1 (AVP1); T3–T1 = arteriovenous passage time 2 (AVP2); T3–T2 = venous filling time (VP).
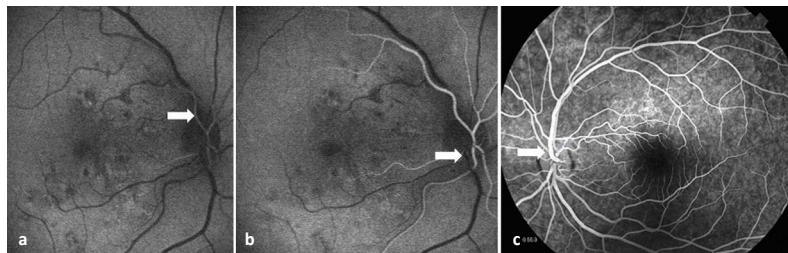
distinguish between the two categories of patients and show meaningful correlations with the physiological parameter that drives the ocular ischaemic syndrome, namely ocular perfusion pressure.

Our study used a well-defined clinical condition that imposes powerful external restraints on ocular perfusion, namely carotid artery stenosis, to evaluate three different retinal blood flow indices based on fluorescein angiography analysis. The best correlation was found for the time from the first appearance of fluorescein-stained blood in the eye to the end of the laminar flow phase in the retinal veins, AVP2.

The fact that the difference in AVP2 between the groups was significant when there was no significant difference in AVP1 may be associated with the longer vessel distance covered with AVP2 and the involvement of the delay between filling from capillaries close to the optic disc and filling from capillaries in the retinal periphery.

While the AVP2 flow rate index showed differences between groups and a significant correlation with the ocular perfusion pressure, the overlap between groups means that angiography-based quantitative flow measurement has limited clinical relevance as a method for distinguishing between carotid artery stenosis patients with and without the ocular ischaemic syndrome. The absence of a diagnostically useful strength of the relation between angiographic flowmetry and the ocular ischaemic syndrome may be related to methodological limitations including a relatively small study population or biological variation in the ability of the retina to tolerate poor perfusion. We have no data that can shed light on the latter hypothesis, but the highly variable distribution of vessels in the retina is likely to influence the delay between the beginning and the end of the laminar flow phase in the retinal veins. Specifically, a peripilary vein that receives blood from the far periphery of the

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Comparison of retinal fluorescein angiographic blood flow indices between ocular ischaemic syndrome eyes and asymptomatic eyes in patients with carotid artery stenosis. Data are presented as mean ± standard deviation.

	Ocular ischaemic syndrome	carotid artery stenosis without ocular ischaemia	p-value
AVP1, sec.	5.0 ± 1.78	4.7 ± 1.19	0.44
AVP2, sec.	16.6 ± 4.67	13.6 ± 2.64	0.025
VP, sec.	11.5 ± 3.88	9.1 ± 2.36	0.03

AVP1 = arteriovenous passage time 1: interval between first appearance of fluorescein-stained blood in temporal arcade retinal arteries and first appearance in comitant vein; APV2 = arteriovenous passage time 2: interval between first appearance in artery and end of laminar flow phase in vein; VP = venous filling time: interval between first appearance in vein and end of laminar phase.

Fig URE 2

Correlation between retinal blood flow index AVP2 (arteriovenous passage time 2: time from first appearance of fluorescein in temporal arcade artery to end of visible laminar flow in comitant vein) and ocular systolic blood pressure assessed by ocular pneumoplethysmography in 19 ocular ischaemia eyes in patients with carotid artery stenosis (diamonds) and 15 eyes in 15 patients with carotid artery stenosis without manifestations of ocular ischaemia (squares). Increasing perfusion pressure was associated with faster retinal perfusion (p = 0.04).
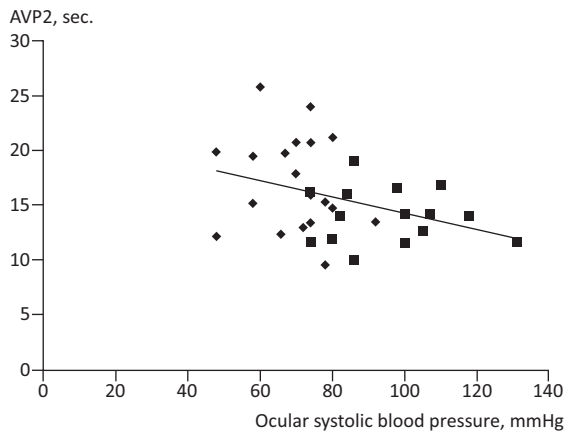
retina should have a longer delay than a vein that collects blood from a venous drainage area closer to the optic disc.

A source of bias in our study is that exclusion of cases due to poor image quality mainly involved those patients who had a more pronounced ocular ischaemic syndrome. In our clinical experience, corneal oedema and epithelial keratopathy are occasional causes of blurred fundus view in patients with ocular ischaemia, but the data from the study patients do not support a quantitative description of this phenomenon.

We did not check for intra- and interobserver variability, but the method applied in our study obviously involves some degree of subjectivity. We also did not examine intrapatient variability, which was approximately 10-14% in previousvideo fluorescein angiography studies of retinal haemodynamic parameters [6, 7]. This, again, should impart a conservative bias to the study.

The study included no healthy subjects and therefore provides no information about the ability of the method to distinguish between healthy subjects and either of the two conditions that characterized the study participants. In healthy subjects, AVP1 has been found by Jung et al to be 2.01 ± 0.65 sec. and 1.79 ± 0.48 sec. for the superior and inferior vascular arcades, respectively [8]; and later studies have shown similar values [6, 7, 9]. The mean circulation times in our two patient groups were approximately twice as long, which suggests that there could be value in producing normative data based upon our local implementation of the angiographic

method. A previous study by Brown & Magargal [1] of qualitative aspects of the fluorescein angiograms in the ocular ischaemic syndrome and control eyes found that AVP2 was prolonged in 95% of the OIS patients compared with the reference population of healthy subjects (the upper normal limit of AVP2 is 11 sec.) [1].

The lack of correlation between the ultrasonographic degree of carotid artery stenosis and the arteriovenous perfusion index is not unexpected given the indirect relation between stenosis and flow and the unmapped contribution of extracranial arteries to ocular perfusion in our patients. Previous studies found no clear correlation between the degree of stenosis and the presence or the degree of OIS [10, 11], which was probably due to varying capacity in collateral and retrograde filling of the ophthalmic artery from either the external carotid artery or the opposite internal carotid artery. Similarly, early studies of the accuracy of carotid stenosis in predicting the degree of haemodynamic compromise found that although reduction in perfusion pressure was only seen in cases in which stenosis exceeded a 75% area reduction, many cases with severe stenosis had a normal perfusion pressure owing to good collaterization. Also, flow reversal of the periorbital arteries and the ophthalmic arteries occurs when the perfusion pressure is reduced and this is only the case in some of the patients with carotid stenosis (poor collateral blood supply) [12]. This is in line with the fact that several control subjects had stenosis of degree 5-6, while some OIS patients had stenosis of degree six and few symptoms, while others had stenosis of degree five and severe OIS.

cOncl UsiOn

In conclusion, angiography-based quantitative retinal flow measurement demonstrated proof-of-concept correlations with the presence and clinical severity of a prototype condition with reduced perfusion and identified the superior one of the three flow indices. However, the method has limited clinical relevance in distinguishing between carotid artery stenosis patients with and without the ocular ischaemic syndrome. This study may provide a useful benchmark for future comparison with newer methods of retinal blood flow measurement.

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