Prolonged Multifocal Electroretinographic Implicit Times in the Ocular Ischemic Syndrome

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Purpose. To examine retinal function in chronic ocular ischemia using multifocal electroretinography (mfERG).

Methods. Thirteen patients with unilateral ocular ischemic syndrome (OIS) underwent assessment of ophthalmic systolic blood pressure by ocular pneumoplethysmography, carotid artery patency by ultrasonography, intraocular pressure (IOP) by applanation tonometry, retinal perfusion by fluorescein angiography, and retinal function by mfERG.

Results. Ophthalmic systolic blood pressure was 67.0 ± 11.6 mm Hg in eyes with OIS and 106.1 ± 18.0 mm Hg in fellow eyes, whereas IOP was 13.8 ± 3.2 and 14.4 ± 1.7 mm Hg, respectively. Summed mfERG implicit times (N1, P1, N2) were prolonged in eyes with OIS, by 7.6%, 6.2%, and 7.5%, respectively, compared with fellow eyes ($P \leq 0.0048$). The retardation of retinal function was significant outside the macula, whereas the assessment of responses from the central retina was limited by high variance. Second-order kernel (first slice) summed implicit times (N1, P1, N2) were also prolonged in OIS, by 6.6%, 7.3%, and 6.8%, respectively ($P \leq 0.0058$). Of the amplitudes, only the second-order N2 amplitude was significantly abnormal, being reduced by 23.2% in OIS ($P = 0.011$).

Conclusions. The function of the outer and middle layers of the retina was found to be suppressed in chronic ocular hypoperfusion. The moderate delay in retinal function does not appear to explain the prominent photopic symptom of diffuse glare in bright light, and the delay could be evidence of a functional adaptation that serves to maintain and optimize signaling under conditions of compromised perfusion. (ClinicalTrials.gov number, NCT00403195.) (*Invest Ophthalmol Vis Sci.* 2010;51:1806–1810) DOI:10.1167/iovs.09-4555

Ocular ischemic syndrome (OIS) was first recognized as a result of severe carotid artery obstruction in 1963.[1] Definite diagnostic criteria have not been established. The principal symptoms are mild to severe visual loss, ocular pain that can be relieved by lying down, and diffuse glare in bright light. Findings include aqueous flare, iris rubeosis, cataract, narrow retinal arteries, dilated nontortuous retinal veins, retinal hemorrhages, microaneurysms, cotton-wool spots, and preretinal neovascularization. Fluorescein angiography reveals delayed and patchy choroidal filling and diffuse leakage from the retinal vessels and the optic nerve head.[2]

OIS is relatively rare. The largest study so far included 52 eyes with OIS in 43 patients collected retrospectively from a background of 1.5 million outpatient visits.[3] Patients found to have OIS are often referred with a diagnosis of diabetic retinopathy, central retinal vein occlusion, or neovascular glaucoma, showing that OIS is underdiagnosed in general clinical practice.

There is no strict correlation between the degree of carotid artery stenosis and the presence or severity of ipsilateral OIS, probably because there is considerable variation in the capacity of collateral and retrograde filling of the ophthalmic artery from the external carotid artery and the contralateral internal carotid artery. Studies of dark adaptation and electroretinographic oscillatory potentials show that subclinical abnormalities in patients with carotid artery stenosis precede the OIS.[4,5]

OIS in humans is unique in that no experimental paradigm can reproduce the protracted onset and long duration of retinal hypoperfusion of this condition. Transient ocular ischemia of a duration of ~5 minutes leads to immediate conditioning of the retina and improved ischemia tolerance, but little is known about long-term conditioning in chronic ischemia where electroretinography has shown reduced amplitude of a-waves, b-waves,[2,6–8] and oscillatory potentials.[8] To study the effect of long-term conditioning to chronic hypoperfusion, we performed multifocal electroretinography (mfERG) in 13 subjects with unilateral OIS, using the subject's fellow eye as the control and an additional control group of eyes without detectable eye disease in age-matched subjects who also had systemic atherosclerosis.

Materials and Methods

Subjects

This study is part of a prospective observational study that has recruited patients with OIS since January 2007 from ophthalmic clinics and through a screening program at two vascular surgery clinics. The present report comprises patients who volunteered during the first 2 years of the study. The criteria for referral from the vascular surgery clinics were carotid artery stenosis >70% or carotid artery occlusion in one or both internal carotids. The diagnosis of OIS[2] required at least four of the following symptoms and signs: (1) visual loss, abrupt or gradual; (2) ocular pain; (3) iris rubeosis; (4) narrow retinal arteries; (5) dilated, nontortuous retinal veins; (6) midperipheral retinal hemorrhages; and (7) neovascularization of the optic disc in the posterior segment; and two or more of the following fluorescein angiographic signs: (1) patchy, delayed choroidal filling; (2) increased retinal arte-

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TABLE 1. Clinical Characteristics of Patients with Unilateral OIS and Control Group with Some Degree of Atherosclerosis

	OIS Eyes	Fellow Eyes	*P**	Control Eyes	*P*†
Sex, men/women	9/4			8/0	
Age, y	67.5 (5.7)			66.3 (7.9)	
MABP, mm Hg	104.0 (7.3)			97.5 (7.0)	
Carotid stenosis, %	96.2	37.0		71.8	
Visual acuity, *n* ETDRS letters	66.6 (29.1)	83.7 (6.2)	0.081	82.6 (5.9)	0.073
IOP, mm Hg	13.8 (3.2)	14.4 (1.7)	0.51	14.7 (3.6)	0.48
OSP in mm Hg	67.0 (11.6)	106.1 (18.0)	<0.0001	103.4 (10.5)	<0.0001
OPP_{OPG}, mm Hg	53.2 (11.4)	91.7 (17.8)	<0.0001	88.8 (10.5)	<0.0001

Data are expressed as the mean (SD) and all comparisons are with OIS eyes.
* Two-sided paired *t*-test,
† Two-sided Student's *t*-test.

riovenous transit time; and (3) late retinal artery staining. We screened 188 eyes in 94 patients and diagnosed OIS in 25 eyes in 24 patients. For the present analysis, we excluded one patient with bilateral OIS, one patient with diabetic retinopathy in the fellow eye, and nine patients who had mfERG performed in only one eye because of poor compliance secondary to fatigue or a poor general condition. Thus, the present study included 13 patients with unilateral OIS and a healthy fellow eye. All subjects were using medication to treat arterial hypertension, platelet aggregation, and hypercholesterolemia. Two subjects were using IOP-lowering eye drops and three had undergone panretinal photocoagulation treatment in the eye with OIS.

In addition to comparing eyes with OIS with the patients' contralateral eyes, we also compared them with 16 eyes in eight subjects without any detectable eye disease who also had systemic atherosclerosis but no hemodynamically significant carotid artery stenosis or OIS.

Informed consent was obtained from all participants after a full explanation of the nature and possible consequences of the study. The study was approved by the medical ethics committee of Copenhagen County, adhered to the tenets of the Declaration of Helsinki, and was prospectively registered as a clinical trial.

Methods

(mf)ERG was recorded in both eyes after maximum pupil dilation with topical 10% phenylephrine hydrochloride and topical 1% tropicamide. After topical anesthesia with 0.4% oxybuprocaine hydrochloride, a Burian-Allen bipolar contact lens electrode (Veris IR Illuminating Electrode; EDI Inc., San Mateo, CA) with built-in infrared light sources for fundus illumination was placed on the cornea using 1% carboxymethylcellulose to provide full electrical contract, together with a ground electrode attached to the forehead. The fellow eye was occluded during the procedure. Visual stimuli were displayed on a 1.5-in. white light stimulator/infrared fundus camera (Veris; EDI Inc.), permitting optimal correction of refraction without changing the size of the stimulus elements and ensuring fixation by providing the operator with a live screen display of the patient's fundus. An array of 103 eccentricity-scaled hexagons was displayed at a frame rate of 75 Hz. Responses were band-pass filtered outside of 10 to 300 Hz, amplified at gain 10^5, and sampled every 0.833 ms. A standard *m*-sequence length was used with $m = 15$, resulting in a total recording time of 7.17 minutes, divided into eight short segments for patient comfort. If loss of fixation or an artifact was observed, the affected segment was discarded and rerecorded. The luminance of the hexagonal stimulus fields was 200 cd/m^2 when on (white) versus 2 cd/m^2 or less when off (black). The surround luminance was set to 50% of the bright (white) test luminance (i.e., 100 cd/m^2). The examination was made in ambient room light. The recording protocol agreed with the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines for basic mfERG.[9] A single iteration of artifact rejection was applied to the raw data, whereas no spatial smoothing was applied before derivation of first- and second-order kernels, implicit times, and amplitudes of the mfERG components N1 (first negative), P1 (first positive), and N2 (second negative). The N1 response amplitude was measured from the starting baseline to the base of the N1 trough, the P1 response amplitude was measured from the N1 trough to the P1 peak, and the N2 response amplitude was measured from the P1 peak to the N2 trough. For data analysis, the hexagonal stimulus fields were grouped by eccentricity.

Ocular pneumoplethysmography (OPG) can be used to assess the ophthalmic systolic pressure (OSP) which is the systolic arterial blood pressure of the ophthalmic artery.[10] After topical anesthesia with 0.4%

TABLE 2. First-Order Summed Multifocal Electroretinography Amplitudes and Implicit Times in Eyes with OIS

	OIS Eyes Mean ± SD (*n* = 13)	Fellow Eyes Mean ± SD	Difference between OIS and Fellow Eyes				Control Eyes Mean ± SD (*n* = 16)	Difference between OIS and Control Eyes			
			Mean	CI_{95}	Δ%	*P**		Mean	CI_{95}	Δ%	*P*†
Implicit times, ms											
N1	17.9 ± 1.1	16.6 ± 0.8	1.28	0.83–1.72	7.6	<0.0001	16.7 ± 1.1	1.22	0.40–2.05	6.8	0.0053
P1	32.2 ± 1.2	30.3 ± 1.0	1.87	1.07–2.67	6.2	0.0003	30.2 ± 1.2	2.01	1.17–2.91	6.2	<0.0001
N2	48.0 ± 3.4	44.7 ± 1.1	3.34	1.23–5.44	7.5	0.0048	44.2 ± 1.2	3.85	1.98–5.73	8.0	0.0016
Amplitudes, nV/deg^2											
N1	−4.5 ± 2.3	−5.6 ± 1.5	1.10	−0.30–2.50	−19.5	0.11	−4.5 ± 1.8	−0.09	−1.62–1.45	2.0	0.91
P1	8.6 ± 3.9	10.7 ± 2.5	−2.12	−4.53–0.30	−19.9	0.081	8.9 ± 3.4	−0.33	−3.11–2.46	−3.9	0.81
N2	−6.7 ± 3.1	−8.2 ± 1.9	1.52	−0.22–3.26	−18.6	0.081	−7.0 ± 3.0	0.31	−2.01–2.63	−4.6	0.78

Absolute differences, relative percent differences (Δ%), and probabilities between eyes with OIS and their healthy fellow eyes and between eyes with OIS and control eyes without OIS.
* Two-sided paired *t*-test.
† Two-sided Student's *t*-test.

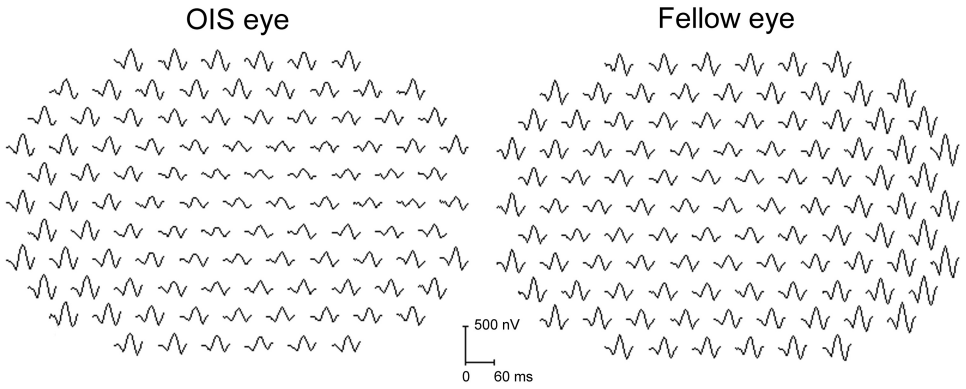

FIGURE 1. mfERG recording (field view) in a subject with OIS in the right eye and a healthy fellow eye.

oxybuprocaine hydrochloride, eye cups were placed bilaterally on the inferolateral quadrant of the eyeball, directly behind the corneal limbus. Vacuum suction at 300 mm Hg was applied via tubing connected to the eye cups and then gradually released over a period of 20 seconds with simultaneous measurement of pressure oscillations by a side port of the tube. The pressure at which the first pulse wave was noted was used in calculating the ophthalmic systolic blood pressure. The recording was done twice in each eye. If a pulse wave was noted immediately after vacuum induction, the suction pressure was raised to 500 mm Hg in a new recording.[10]

Ultrasonographic internal carotid artery studies were performed by experienced examiners. Stenosis was classified into intervals: 0% to 14%, 15% to 49%, 50% to 69%, 70% to 79%, 80% to 99%, or occlusion.[11] Furthermore, the examiner estimated the exact grade of stenosis with attempted double-digit accuracy.

Additional investigations included best corrected visual acuity (BCVA) according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, intraocular pressure (IOP), slit lamp biomicroscopy, ophthalmoscopy, fundus photography, fluorescein angiography, and optic coherence tomography (OCT). Mean arterial blood pressure (MABP) was calculated as $\text{Pressure}_{\text{diastolic}} + \frac{1}{3}(\text{Pressure}_{\text{systolic}} - \text{Pressure}_{\text{diastolic}})$ and the OPG-based ocular perfusion pressure (OPP_{OPG}) as OSP − IOP.

Data were analyzed by using the two-sided paired *t*-test for analyses between OIS eyes and fellow eyes and the two-sided Student's *t*-test for analyses between OIS eyes and eyes in the control group without eye disease. For all parameters, the observed differences between eyes were in agreement with a normal distribution. The level of statistical significance was set at $P < 0.05$. $P < 0.0083$ was considered significant after Bonferroni correction for multiple endpoints (analysis software: SAS 9.1; for Windows; SAS Institute Inc, Cary, NC).

RESULTS

The study population consisted of nine men and four women aged 67.5 ± 5.7 years (mean ± SD; Table 1). Mean arterial blood pressure was 104 ± 7.3 mm Hg. Best corrected visual acuity was 66.6 ± 29.1 ETDRS letters (corresponding to Snellen 0.4) in OIS eyes and 87.3 ± 6.2 ETDRS letters (corresponding to Snellen 1.0) in fellow eyes ($P = 0.081$). Intraocular pressure was comparable in OIS and fellow eyes (mean 13.8 vs. 14.4 mm Hg, $P = 0.51$; Table 1). The ultrasonographically measured carotid artery stenosis ipsilateral to the OIS eye was mean 96.2% (total occlusion in 10/13 cases) versus mean 37.0% (total occlusion in 2/13 cases) on the contralateral side. The pneumoplethysmographic OSP was 67.0 ± 11.6 (range, 48–92) mm Hg in OIS eyes and 106.1 ± 18.0 mm Hg (range, 76–143) in the healthy fellow eyes ($P < 0.0001$). After subtraction of the IOP, the OPP_{OPG} was 53.2 ± 11.4 mm Hg in OIS eyes and 91.7 ± 17.8 mm Hg in fellow eyes ($P < 0.0001$). Comparable differences were found between OIS eyes and eyes in the control group without OIS (Table 1).

Summed mfERG implicit times from all 103 stimulus hexagons were significantly prolonged in eyes with OIS compared with healthy contralateral eyes. The delays amounted to 7.6% (1.28 ms, 95% confidence interval [CI_{95}] 0.83–1.72, $P < 0.0001$) for N1, 6.2% (1.87 ms, CI_{95} 1.07–2.67, $P = 0.0003$) for P1, and 7.5% (3.34 ms, CI_{95} 1.23–5.44, $P = 0.0048$) for N2. Comparable differences in implicit times were found between OIS eyes and eyes in the control group without eye disease ($P = 0.0053$, <0.0001, and 0.0016 for N1, P1, and N2, respectively). The summed peak amplitudes in eyes with OIS were nominally lower than in fellow eyes by 19.5% for N1 ($P = 0.11$), 19.9% ($P = 0.081$) for P1, and 18.6% ($P = 0.081$) for N2. Such a trend was not seen when comparing eyes with OIS with eyes in the control group without OIS (Table 2, Fig. 1). Exploratory analyses of amplitude differences between OIS eyes and fellow eyes were made by summation of rings 1 to 3 (center) and rings 4 to 6 (periphery). The trend toward lower amplitudes in eyes with OIS was entirely consistent but the difference reached statistical significance only for N1 in rings 1 to 3 ($P = 0.018$).

TABLE 3. First-Order P1 Implicit Times in Relation to Eccentricity in Eyes with IOS and Fellow Eyes

Rings	1	2	3	4	5	6
P1 Implicit time, mean ± SD						
OIS eyes, ms	31.4 ± 3.7	32.4 ± 2.3	31.8 ± 1.0	31.3 ± 1.4	31.7 ± 1.6	32.4 ± 1.0
Fellow eyes, ms	31.7 ± 2.1	31.4 ± 1.4	29.9 ± 1.1	29.6 ± 1.2	29.9 ± 1.4	30.6 ± 0.9
Difference						
Mean, ms	−0.4	1.0	1.8	1.5	1.5	1.7
CI_{95}	−3.1–2.2	−0.9–2.9	0.9–2.8	0.7–2.3	0.7–2.3	1.3–2.0
Δ %	−1.1	3.0	6.6	5.9	5.8	5.6
P	0.71	0.28	0.0013*	0.0018*	0.0019*	<0.0001*

Δ%, Relative percent differences between eyes with OIS and their healthy fellow eyes.
* $P < 0.0083$ was considered significant after Bonferroni correction.

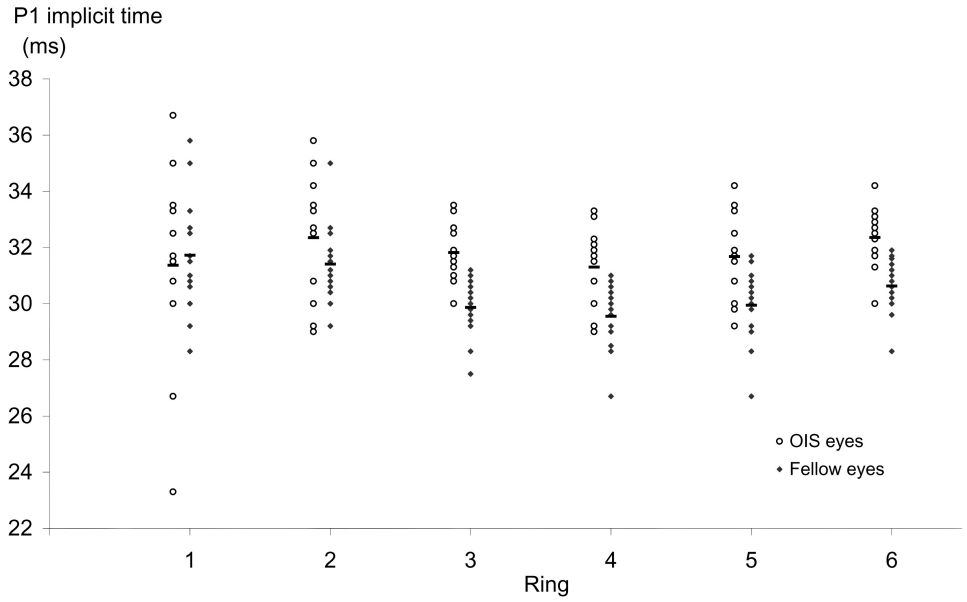

FIGURE 2. Distribution of first-order P1 implicit times by eccentricity in eyes with OIS and fellow eyes without OIS. *Horizontal bars*: average values. Differences were statistically significant for rings 3 to 6. Comparable patterns were observed for first-order N1 and N2 implicit times.

In relation to eccentricity, the implicit time delay in eyes with OIS was prominent outside the macula and smaller or absent in the macula. For P1, significant delays were 6.6% (1.8 ms, CI_{95} 0.9–2.8) at 5° to 9° (ring 3, $P = 0.0013$), 5.9% (1.5 ms, CI_{95} 0.7–2.3) at 9° to 13.5° (ring 4, $P = 0.0018$), 5.8% (1.5 ms, CI_{95} 0.7–2.3) at 13.5° to 19° (ring 5, $P = 0.0019$), and 5.6% (1.7 ms, CI_{95} 1.3–2.0) at 19° to 25° eccentricity (ring 6, $P < 0.0001$; Table 3, Fig. 2). In relation to eccentricity, a larger variation in P1 implicit times was seen in the central rings 1 and 2 than in the peripheral rings 3 to 6 where the number of sampled hexagons was much larger (Fig. 2).

Comparable patterns were seen for N1, with significant delays in OIS eyes for rings 4 to 6 only ($P \leq 0.0050$) and for N2, where significant delays were found for rings 3 to 6 only ($P \leq 0.0011$; data not shown).

Second-order kernel (first slice) summed responses were prolonged in OIS eyes, with the summed delays amounting to 9.9% (1.66 ms, CI_{95} 0.83–2.50, $P = 0.0012$) for N1, 6.6% (1.60 ms, CI_{95} 0.84–2.36, $P = 0.0009$) for P1, and 7.3% (2.27 ms, CI_{95} 1.13–3.41, $P = 0.0012$) for N2. Summed second-order kernel peak N2 amplitude was significantly decreased in eyes with OIS (−23.2%; $P = 0.011$; Table 4). Reliable subgroup analysis by eccentricity could not be made for the second-order kernel data, which are noisier than first-order signals.

The data did not demonstrate any effect of meridional orientation when analyzed by quadrant, and no correlation was found between mfERG abnormalities in OIS eyes and IOP, OSP, OPP_{OPG}, photocoagulation, or the degree of carotid artery stenosis.

DISCUSSION

This study on the use of mfERG in unilateral OIS secondary to carotid artery stenosis demonstrated significant delays of all first-order summed implicit times and a clear trend toward reduced amplitudes compared with the patients' healthy fellow eyes. In addition, eyes with OIS had prolonged second-order implicit times and reduced second order N2 amplitudes.

Human subjects exposed to acute hypoxia have reduced mfERG amplitudes, most prominently in the center of the macula, but N1 and P1 implicit times are unaffected.[12] In OIS, our most prominent finding was prolonged implicit times, perhaps reflecting the chronicity of the condition or that OIS involves not only chronic hypoxia but also reduced perfusion. Future studies should be conducted to determine whether it is the chronicity of OIS and secondary adaptive phenomena or merely the reduced perfusion that makes OIS different from acute hypoxia.

It has been shown that full-field a- and b-wave ERG amplitudes are subnormal in OIS compared with healthy eyes, which is in agreement with our finding that OIS compromises the function of

TABLE 4. Second-Order Summed mfERG Amplitudes and Implicit Times in Eyes with OIS and Fellow Eyes

	OIS Eyes Mean ± SD	Fellow Eyes Mean ± SD	Difference between OIS and Fellow Eyes			
			Mean	CI_{95}	Δ%	*P*
Implicit times (ms)						
N1	18.4 ± 1.6	16.7 ± 1.1	1.66	0.83–2.50	9.9	0.0012
P1	26.0 ± 1.2	24.4 ± 1.0	1.60	0.84–2.36	6.6	0.0009
N2	33.3 ± 1.8	31.0 ± 1.3	2.27	1.13–3.41	7.3	0.0012
Amplitudes (nV/deg^2)						
N1	−0.6 ± 0.4	−0.6 ± 0.4	−0.04	−0.29–0.21	7.1	0.75
P1	1.1 ± 0.5	1.3 ± 0.5	−0.21	−0.57–0.15	−16.4	0.22
N2	−2.5 ± 0.7	−3.3 ± 0.9	0.76	0.21–1.31	−23.2	0.011

Absolute differences, relative percent differences (Δ%), and probabilities (paired *t*-test) between eyes with ocular ischemic syndrome (OIS) and their healthy fellow eyes.

both the outer and the middle layers of the retina.[2,6–8] This is consistent with the compromise of both retinal and choroidal perfusion by OIS. Abnormalities of ocular physiology can be found in the presence of carotid artery stenosis without OIS, which could lead one to expect marked, pervasive abnormalities of the mfERG in OIS.[4,5] On the contrary, we found selective abnormalities only, a finding that may be dispelled as evidence of lack of statistical power or conservative bias associated with using fellow eyes and patients with atherosclerosis as controls. Nevertheless, there are such marked retinal effects of acute systemic hypoxia that it is astonishing for chronic retinal hypoperfusion not to have more profound effect on electroretinographic function. We propose that the chronic nature and insidious onset of OIS leads to gradual habituation and adaptation of the retina, so that it can maintain its signaling at a level close to normal despite marked hypoperfusion.

The origin of the second-order kernel is believed to involve temporal adaptation processes with contributions from amacrine cells, ganglion cells, and ON- and OFF-bipolar cells.[13,14] The suppression of second-order mfERG responses in OIS has no parallel in acute hypoxia,[12] suggesting that the middle and inner layers of the retina are particularly involved in protracted responses to hypoxia.

The outer and middle layers of the healthy retina are physiologically hypoxic and appear to use glycolysis as a major source of energy production.[15–18] We suspect that the relative contribution of glycolysis to energy production in the retina is increased in OIS, but have found no clinically applicable method of testing this hypothesis, and no animal model of OIS is currently available.

The moderate delay of retinal function in OIS does not appear to explain the prominent photopic symptom of diffuse glare in bright light, and the delay may be evidence of a functional adaptation that serves to maintain and optimize signaling under conditions of compromised perfusion.

The higher variance of mfERG parameters in the central retina compared with the peripheral retina makes it difficult to make conclusions about the effect of eccentricity in OIS.

The strengths of this study include that the control eyes were closely matched to the systemic characteristics of the eyes with OIS. This similarity is particularly relevant, given that all patients used medication against arterial hypertension, platelet aggregation, and hypercholesterolemia. Limitations include the small sample size. It should be noted that the study was not intended to assess the utility of mfERG as a method of diagnosing OIS.

The present study demonstrated that the function of the outer and the middle layers of the retina is suppressed in chronic ocular hypoperfusion. Since OIS replicates some of the traits found in highly prevalent retinal diseases such as diabetic retinopathy,[19] the study of OIS may lead to generalizable insights into the retinal response to compromised metabolic conditions and their potential reversibility.

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References

1. Kearns TP, Hollenhorst RW. Venous-stasis retinopathy of occlusive disease of the carotid artery. *Proc Staff Meet Mayo Clin*. 1963;38:304–312.
2. Brown GC, Magargal LE. The ocular ischemic syndrome: clinical, fluorescein angiographic and carotid angiographic features. *Int Ophthalmol.* 1988;11:239–251.
3. Sivalingam A, Brown GC, Magargal LE. The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment. *Int Ophthalmol.* 1991;15:15–20.
4. Coleman K, Fitzgerald D, Eustace P, Bouchier-Hayes D. Electroretinography, retinal ischaemia and carotid artery disease. *Eur J Vasc Surg.* 1990;4:569–573.
5. Havelius U, Bergqvist D, Falke P, Hindfelt B, Krakau T. I. Impaired dark adaptation in symptomatic carotid artery disease. *Neurology.* 1997;49:1353–1359.
6. Kiser WD, Gonder J, Magargal LE, Sanborn GE, Simeone F. Recovery of vision following treatment of the ocular ischemic syndrome. *Ann Ophthalmol.* 1983;15:305–310.
7. Russell RW, Ikeda H. Clinical and electrophysiological observations in patients with low pressure retinopathy. *Br J Ophthalmol.* 1986;70:651–656.
8. Story JL, Held KS, Harrison JM, Cleland TP, Eubanks KD, Brown WE Jr. The ocular ischemic syndrome in carotid artery occlusive disease: ophthalmic color Doppler flow velocity and electroretinographic changes following carotid artery reconstruction. *Surg Neurol.* 1995;44:534–535.
9. Hood DC, Bach M, Brigell M, et al. ISCEV guidelines for clinical multifocal electroretinography (2007 edition). *Doc Ophthalmol.* 2008;116:1–11.
10. Gee W. Ocular pneumoplethysmography. *Surv Ophthalmol.* 1985;29:276–292.
11. Kofoed PK, Kofoed SC, Gronholdt ML, Sillesen HH. Interobserver variation in ultrasonographic scanning of carotid stenosis (in Danish). *Ugeskr Laeger.* 2003;165:2099–2101.
12. Klemp K, Lund-Andersen H, Sander B, Larsen M. The effect of acute hypoxia and hyperoxia on the slow multifocal electroretinogram in healthy subjects. *Invest Ophthalmol Vis Sci.* 2007;48:3405–3412.
13. Hare WA, Ton H. Effects of APB, PDA, and TTX on ERG responses recorded using both multifocal and conventional methods in monkey: effects of APB, PDA, and TTX on monkey ERG responses. *Doc Ophthalmol.* 2002;105:189–222.
14. Hood DC, Frishman LJ, Saszik S, Viswanathan S. Retinal origins of the primate multifocal ERG: implications for the human response. *Invest Ophthalmol Vis Sci.* 2002;43:1673–1685.
15. Birol G, Budzynski E, Wangsa-Wirawan ND, Linsenmeier RA. Retinal arterial occlusion leads to acidosis in the cat. *Exp Eye Res.* 2005;80:527–533.
16. Wang L, Tornquist P, Bill A. Glucose metabolism in pig outer retina in light and darkness. *Acta Physiol Scand.* 1997;160:75–81.
17. Wang L, Tornquist P, Bill A. Glucose metabolism of the inner retina in pigs in darkness and light. *Acta Physiol Scand.* 1997;160:71–74.
18. Wangsa-Wirawan ND, Linsenmeier RA. Retinal oxygen: fundamental and clinical aspects. *Arch Ophthalmol.* 2003;121:547–557.
19. DCCT Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *Ophthalmology*. 1995;102:647–661.