Effect of carotid endarterectomy on retinal function in asymptomatic patients with hemodynamically significant carotid artery stenosis

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KEY WORDS

asymptomatic significant carotid stenosis, carotid endarterectomy, electroretinogram, internal carotid artery stenosis, neuroretinal function

ABSTRACT

INTRODUCTION The corrective effect of carotid endarterectomy (CEA) on impaired ophthalmic artery flow in patients with significant internal carotid artery (ICA) stenosis presenting with ocular ischemic syndrome (ie, symptomatic patients) is well established. However, there is no clear evidence regarding the efficacy of CEA for improvement of neuroretinal function in patients without symptoms of ocular ischemic syndrome.

OBJECTIVES We aimed to determine the effects of CEA on retinal function in asymptomatic patients with hemodynamically significant ICA stenosis.

PATIENTS AND METHODS We enrolled 46 patients with ICA stenosis referred for CEA. Full-field electroretinogram (ERG), pattern ERG, and pattern visual evoked potentials, as well as optical coherence tomography and ophthalmologic examination of both eyes were performed 1 day before and 3 months after CEA. We analyzed eyes ipsilateral (EIE) and contralateral (ECE) to CEA.

RESULTS We observed an increase in several ERG wave parameters in both eye groups, compared with baseline values: rod b-wave amplitudes ($P < 0.00001$ for EIE and $P = 0.0001$ for ECE); rod-cone a-wave ($P = 0.02$ for EIE) and b-wave ($P = 0.001$ for EIE and $P = 0.01$ for ECE) amplitudes; cone single flash a-wave ($P = 0.05$ for EIE and $P = 0.004$ for ECE) and b-wave ($P < 0.0001$ for EIE and $P < 0.0001$ for ECE) amplitudes; cone 30-Hz flicker amplitudes ($P = 0.0003$ for EIE and $P < 0.0001$ for ECE); and oscillatory potential wave index amplitudes ($P < 0.00001$ for EIE).

CONCLUSIONS The amplitudes of the standard full-field ERG were significantly increased following CEA in EIE and, to a lesser extent, in ECE. Multimodality ERG may represent a unique tool for investigating the effects of carotid revascularization on neuroretinal function in asymptomatic patients with ICA stenosis.

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INTRODUCTION Atherosclerotic stenosis of the internal carotid artery (ICA) is the leading cause of cerebrovascular disease and is devastating for health.[1] Although carotid endarterectomy (CEA) is an effective treatment for severe ICA stenosis in symptomatic patients, the management of patients with asymptomatic ICA stenosis remains controversial.[2] At present, there is a need to risk-stratify patients with asymptomatic ICA stenosis to select those who would benefit from carotid artery intervention. Several criteria have been proposed, such as the presence of carotid plaque ulceration detected by 3-dimensional ultrasound, intraplaque hemorrhage on magnetic resonance imaging (MRI), plaque inflammation on positron emission tomography–computed tomography, reduced cerebral blood flow reserve on MRI or transcranial Doppler ultrasound, and embolus detection.[3] Other markers of increased risk include asymptomatic plaque progression, thrombus presence, asymptomatic ipsilateral cerebral embolization on computed tomography or MRI, or contralateral ICA occlusion.[4] Nevertheless, optimal imaging criteria to identify patients with asymptomatic ICA stenosis at risk of complications remain undetermined.

The positive effect of CEA on the disturbed ophthalmic artery flow in patients with ocular ischemic syndrome is well established.[5] However, there is no clear evidence regarding the efficacy of CEA for the improvement of bioelectrical retinal function in patients with clinically healthy eyes, that is, without symptoms of ocular ischemic syndrome. Thus, it is important to understand the pathophysiological changes in the retina and the optic nerve of patients with hemodynamically significant ICA stenosis before and after the CEA procedure. To determine the effect of CEA on retinal function in asymptomatic patients with hemodynamically significant carotid stenosis, we performed multimodality electrophysiological testing, such as full-field electroretinogram (ERG), pattern electroretinogram (PERG), and pattern visual evoked potential (PVEP) before and after CEA.

PATIENTS AND METHODS

Characteristics of the study population We analyzed 92 eyes in 46 patients who underwent CEA in the Department of Vascular Surgery at Pomeranian Medical University in Szczecin, Poland, as a result of hemodynamically significant ICA stenosis (≥70% of the ICA diameter reduction according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET], with a peak systolic velocity exceeding 230 cm/s) in neurologically asymptomatic patients. Those patients were defined as individuals who lacked chronic or transient ischemic symptoms typical for the carotid territory or transient ipsilateral blindness (amaurosis fugax) in the 6 months preceding the study recruitment. The degree of ICA stenosis in each patient was diagnosed by carotid color Doppler ultrasonography using a Voluson 730 PRO device (GE Medical Systems, Milwaukee, Wisconsin, United States), with a multi-frequency 7.5-MHz linear probe, in accordance with the guidelines recommended in the literature.[6,7] All examinations were performed in our institution by the same practitioner in accordance with the standard procedures for high reproducibility of stenosis calculations. We excluded patients with symptoms of ocular ischemic syndrome or evidence of concomitant chronic eye or systemic disease that potentially affects the retina and optic nerve (ie, glaucoma, intraocular inflammatory diseases, retinopathy, ocular surgery in the previous 3 months, advanced cataract, and collagen-related or neoplastic disease). Moreover, we excluded patients after CEA who were diagnosed with stroke in the postoperative period and those who might have suffered from transient ischemic attack or stroke during the follow-up period. All enrolled patients underwent a complete ophthalmic examination of both eyes, including distant best-corrected visual acuity and intraocular pressure measurements, anterior segment examination, dilated fundoscopy using a slit-lamp biomicroscopy, and optical coherence tomography. The ophthalmologic inclusion criteria were distant best-corrected visual acuity exceeding 0.8 (Snellen chart) and normal results of to a routine ophthalmologic examination.

For each patient, the medical history was recorded and physical examination was performed by physicians who participated in the study. Data regarding the medical history, current drug use, and smoking status were collected, with particular focus on cardiovascular conditions and preexisting arterial hypertension. The cumulative pack-years were calculated using the reported average number of cigarettes smoked per day and the number of years of smoking. Furthermore, the arterial blood pressure (BP) was directly measured prior to ophthalmic examination in all patients, using a noninvasive BP system with a manual aneroid manometer. The mean result from the 3 measurements obtained at 5-minute resting intervals was calculated. From the obtained BP data, the systemic mean arterial pressure (MAP) was calculated as follows: MAP = diastolic BP + 1/3 (systolic BP – diastolic BP). Furthermore, the following medical parameters were assessed in all patients: waist circumference, waist-to-hip ratio, and body mass index (BMI; weight [kg]/height [m^2]).

The study was conducted according to the Declaration of Helsinki and was approved by a local ethics committee. All patients provided their written informed consent to participate in the study.

Electrophysiology Full-field ERGs (UTAS-E 2000, LKC Technologies, Gaithersburg, Maryland, United States), PERGs, and PVEPs (RetiPort System, Roland Consult Instr., Brandenburg, Germany) were recorded before and 3 months after CEA for each patient, according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocols.[8-10] For full-field ERG, the recordings were performed binocularly with the use of bipolar Burian–Allen electrodes (Hansen Ophthalmic Development Lab, Coralville, Iowa, United States) and with an ear clip electrode covered with gold, serving as a ground reference electrode (Natus Europe GmbH, Planegg, Germany) attached to the earlobe. The recording system parameters were as follows: amplifier sensitivity, 10–20–50 μV/div; filters, 0.3–500 Hz (for oscillatory potential [OP] extraction, 75–500 Hz); notch filters, off; time base, 5 ms/div; and artifact reject threshold, 0 μV. Prior to the recording, the pupils were maximally dilated (>6 mm) with eye drops containing 1% tropicamide and 10% phenylephrini hydrochloridum. A 30-minute dark adaptation (patients were sitting with the eyes closed and covered with special black goggles) preceded dark-adapted ERGs. After testing in dark conditions, background light (luminance, 32 cd/m^2) of the Ganzfeld bowl was turned on, and a 10-minute period of light adaptation preceded the light-adapted ERGs. Dark-adapted ERGs were obtained with single dim white flash of 0.012 cd·s·m^{-2} (primarily rod response; amplitude and peak time of the b-wave were analyzed) and strong flash of white light of 1.6 cd·s·m^{-2} (rod-cone response; amplitude and peak time of the a- and b-waves were analyzed). Dark-adapted oscillatory potentials were obtained with white flashes of 1.6 cd·s·m^{-2}. The second waveform was retained. The overall wave index of the OP amplitudes (O1+O2+O3) was measured. For light-adapted ERGs, primarily cone response was elicited with a white flash of 1.6 cd·s·m^{-2}, and the amplitude and peak time of the a- and b-waves were analyzed. Flicker ERG (cone response) was recorded with flickering flashes of 1.6 cd·s·m^{-2} presented at a rate of 30 stimuli per second (30 Hz). During the first 5 seconds of preadaptation, the waveforms were discarded to reach stable conditions. Next, the peak-to-trough amplitude and peak timing from the midpoint of the stimulus flash to the following peak were calculated automatically from 10 averaged recordings.

For PERG, monocular stimulation was used, in combination with an appropriate refractive error correction in relation to the eye-screen distance. The pupils were not dilated, and central fixation was used. The PERG stimulation parameters configuration consisted of the 21" cathode ray tube (CRT) monitor with a frame rate of 75 fps and a black and white reversing checkerboard (field of view, 30°), which was presented to the patient, with a check size equal to 1°2'; luminance for white elements, 120 cd/m^2; mean luminance of the stimulus screen for the white elements, 120 cd/m^2, with Michelson contrast set to 97%; and temporal frequency, 4.6 rps (2.3 Hz). A ground (gold disk) electrode (Roland Consult, Brandenburg, Germany) was placed on the forehead (Fpz; a position above the nasion in the middle of the forehead), a thread Dawson–Trick–Litzkow electrode (Diagnosys LLC, Lowell, Massachusetts, United States) was used as an active electrode, and a gold disk placed at the ipsilateral outer canthus was used as a reference. The recording system parameters were as follows: amplifier sensitivity, 20 μV/div; filters, 1–100 Hz; artifact reject threshold, 95% (for the amplifier range of ±100 μV); notch filters, off; averaging, 200 sweeps; and sweep time, 250 ms (time base, 25 ms/div). Two consecutive waveforms were recorded, and they were subsequently averaged and analyzed offline.

For PVEP, monocular stimulation was used without pupil dilation, and refraction correction was applied with respect to the eye-screen distance. Central fixation was used. A 21" CRT monitor with a frame rate equal to 75 fps was used for pattern stimulation; black and white reversing checkerboard was presented to the patient, with 2 check sizes equal to 1°4' and 0°16'; luminance for the white elements was equal to 120 cd/m^2, with Michelson contrast set to 97%; and temporal frequency was equal to 2 rev/s (1 Hz). An active-gold disk electrode (Roland Consult) was placed on the scalp over the visual cortex at occipital midline position (Oz) with a reference gold disk electrode placed at frontal midline position (Fz); a ground (gold disk) electrode was placed on the forehead at Fpz. The electrodes were placed relatively to bone landmarks according to the international 10/20 system. The parameters of the recording channel were as follows: amplifiers range, ±100 μV/div; filter frequency bandwidth, 1–100 Hz; and notch filters, off. The analysis duration (sweep time) was 300 ms. The artifact reject threshold was set to 95%, and 100 sweeps were averaged. For each eye and each check size, 2 consecutive PVEP waveforms were recorded and averaged offline for further analysis. The amplitude and time of the p100-wave with manual correction to the automatic cursor placement were also parsed. Every response in each performed electrophysiological testing was repeated in each time point to ensure reproducibility of the test. One of the reproducible waveforms was taken for final analysis in each patient. The flicker response was averaged at 10 sweeps.

Surgical procedure of carotid endarterectomy The patients were preoperatively treated with oral acetylsalicylic acid at a dose of 75 mg/d for at least 10 days prior to CEA. In all patients, CEA was performed under local anesthesia. Speech control monitoring and contralateral hand function were assessed throughout the procedure. The common, internal, and external carotid vessels were identified in all cases. Intravenous unfractionated heparin (3000–5000 IU) was administered 5 minutes before cross-clamping of all major vessels. After cross-clamping, shunting was selectively performed at the discretion of the operating surgeon if loss of consciousness was observed. The maximum carotid artery clamp time was 30 minutes. Endarterectomy without patch angioplasty was performed in a standard fashion with an optical power magnification of 2.5× and Prolene 6/0 (Ethicon Inc., Johnson & Johnson Company, Norderstedt, Germany) continuous sutures.

Statistical analysis The Wilcoxon signed-rank test was used to assess whether the differences in parameters measured between the time points were significant. The strength of the association between quantitative variables was measured with the Spearman rank correlation coefficient (*Rs*). A *P* value of less than 0.05 was considered significant.

TABLE 1 Optical coherence tomography parameters in the retinas of eyes ipsilateral to carotid endarterectomy (EIE group) and eyes contralateral to carotid endarterectomy (ECE group)

Parameter	EIE group			ECE group		
	Before CEA	After CEA	*P* value	Before CEA	After CEA	*P* value
CST, µm	266.17 (22.95)	265.80 (21.47)	0.71	275.56 (50.23)	275.15 (51.49)	0.93
CV, mm^3	9.90 (0.46)	9.98 (0.50)	0.17	10.00 (0.74)	10.01 (0.79)	0.33
CAT, µm	277.36 (12.90)	279.56 (14.20)	0.15	280.19 (21.00)	280.45 (22.18)	0.32
RNFL thickness, µm	91.39 (8.02)	91.56 (8.69)	0.46	91.36 (9.83)	92.63 (8.65)	0.17

Data are presented as mean (SD).

Abbreviations: CAT, cube average thickness; CEA, carotid endarterectomy; CST, central subfield thickness; CV, cube volume; RNFL, retinal nerve fiber layer

TABLE 2 Pattern electroretinogram and pattern visual evoked potential amplitudes and peak times in the retinas of eyes ipsilateral to carotid endarterectomy (EIE group) and eyes contralateral to carotid endarterectomy (ECE)

Parameter	EIE group			ECE group		
	Before CEA	After CEA	*P* value	Before CEA	After CEA	*P* value
PERG						
N35-P50 amplitude, µV	2.61 (1.66)	3.07 (1.70)	0.14	2.35 (1.80)	2.88 (1.70)	0.06
P50 peak time, ms	53.13 (4.26)	53.87 (3.77)	0.14	52.71 (3.92)	53.55 (3.91)	0.17
P50-N95 amplitude, µV	4.03 (2.90)	4.40 (2.71)	0.41	3.39 (2.58)	4.24 (2.52)	0.10
PVEP						
P100 amplitude, µV (1°4′)	7.70 (4.13)	7.27 (3.35)	0.64	7.68 (4.10)	7.39 (3.17)	0.87
P100 amplitude, µV (0°8′)	9.29 (5.70)	8.34 (4.46)	0.21	8.62 (5.04)	8.03 (4.57)	0.43
P100 peak time, ms (1°4′)	112.73 (10.36)	112.22 (8.72)	0.73	116.04 (9.57)	113.92 (7.60)	0.24
P100 peak time, ms (0°8′)	120.62 (11.73)	121.97 (11.18)	0.84	121.54 (13.87)	122.65 (9.16)	0.80

Data are presented as mean (SD).

Abbreviations: PERG, pattern electroretinogram; PVEP, pattern visual evoked potentials; others, see TABLE 1

RESULTS The study included 46 patients (27 men and 19 women who remained asymptomatic during the follow-up of 3 months and returned for repeated retinal function testing). A total of 92 eyes were analyzed. The mean (SD) age of the participants was 63.5 (6.1) years. The mean (SD) extent of ICA stenosis was 77% (12%). Smoking was reported for 91% of the participants. The number of pack-years of smoking varied from 4 to 150, with a mean value of 30. The mean BMI of the participants was 27.8 kg/m^2, and the mean waist-to-hip ratio was 0.93. Arterial hypertension was reported in 82.6% of the patients; ischemic heart disease, in 34.8%; stroke, in 28.3%; aortic aneurysm, in 13%, and peripheral artery disease, in 26%. The examined eyes were evaluated in 2 groups: the eyes ipsilateral to CEA (EIE, n = 46) and the eyes contralateral to CEA (ECE, n = 46). To estimate the restorative effects of endarterectomy on biological retinal function, we performed a quantitative analysis of retinal morphology and electrophysiological tests before and after CEA. A complete ophthalmologic examination, optical coherence tomography, and complex electrophysiological testing (ERG/PERG/PVEP) were performed 1 day before and 3 months after CEA. No significant changes were identified in the macular thickness and volume or the peripapillary retinal nerve fiber layer thickness after CEA either in the EIE or ECE compared with the baseline values on the day before CEA (TABLE 1). Similarly, the PERG and PVEP parameters of ERG revealed no significant changes in the EIE or ECE (TABLE 2).

Remarkably, significant differences were identified in the full-field ERG wave amplitudes measured before and 3 months after CEA in both groups. The results of the full-field ERG amplitude and peak-time changes in the EIE group are summarized in TABLE 3. We observed an increase in the rod b-wave amplitude after the CEA (P <0.0001) compared with the baseline values obtained before the surgical procedure. In contrast, the mean rod b-wave peak times remained unchanged during the 3-month follow-up. Furthermore, there were significant differences in the rod-cone b-wave amplitudes (P = 0.001). On the other hand, there were no differences in the peak times of these waves (P = 0.1). When the OP wave index was analyzed, an increase in the amplitude was identified exclusively in the EIE group (P <0.00001). Furthermore, we identified a significant change in the cone single flash a- and b-wave amplitudes and cone 30-Hz flicker amplitudes after 3 months of follow-up, whereas the mean peak times of these waves did not differ significantly compared with the baseline.

We also found (albeit to a lesser extent) an improvement in the ECE group. Especially this group

TABLE 3 Full-field electroretinogram amplitudes and peak times in the retinas of eyes ipsilateral to carotid endarterectomy

Parameter	Amplitude, μV			Peak time, ms		
	Before CEA	After CEA	*P* value	Before CEA	After CEA	*P* value
Rod b-wave	79.97 (35.32)	114.56 (34.56)	<0.0001	111.08 (9.68)	111.32 (7.71)	0.84
Rod-cone a-wave	159.04 (52.88)	170.77 (53.34)	0.1302	24.28 (1.09)	23.84 (0.87)	0.0036
Rod-cone b-wave	380.68 (84.85)	414.59 (83.49)	0.001	48.55 (2.51)	47.10 (5.97)	0.13
OP wave index	100.11 (29.34)	118.39 (34.06)	<0.0001	–	–	–
Cone a-wave single flash	26.92 (12.24)	32.87 (14.44)	0.05	16.20 (1.38)	16.05 (1.37)	0.39
Cone b-wave single flash	84.67 (27.57)	102.80 (31.89)	<0.0001	32.47 (1.78)	32.38 (1.64)	0.52
Cone b-wave 30-Hz flicker	71.48 (24.83)	82.89 (25.86)	0.0003	32.99 (0.70)	32.80 (1.04)	0.21

Data are presented as mean (SD).

Abbreviations: OP, oscillatory potential; others, see **TABLE 1**

showed an increase in the rod b-wave amplitude after the CEA (*P* = 0.0001) at 3 months compared with the baseline values (mean [SD], 110.16 [38.25] vs 85.48 [38.24]). Furthermore, there was a difference in the rod-cone b-wave amplitude (*P* = 0.01) after the follow-up period compared with the baseline (mean [SD], 407.51 [88.83] vs 374.08 [90.79]). Interestingly, only in the ECE group, the amplitudes of the rod-cone a-wave were increased (*P* = 0.02) at 3 months compared with the baseline (mean [SD], 164.92 [55.43] vs 142.82 [49.84]). This group also showed significant changes in the cone single flash a- and b-wave amplitudes and cone 30-Hz flicker amplitudes at 3 months compared with the baseline (mean [SD], 32.84 [15.15] vs 24.47 [11.56], *P* = 0.004; 98.36 [35.47] vs 81.78 [25.21], *P* <0.0001; and 81.90 [26.47] vs 66.24 [25.84], *P* <0.0001; respectively).

To characterize factors that may influence the results obtained from complex ERG testing, we evaluated the potential association between the changes in full-field ERG amplitudes and several systemic risk factors and metabolic conditions. Interestingly, the changes in the rod b-wave amplitudes in the EIE group were negatively correlated with the age of the participants (*Rs* = –0.33, *P* = 0.02 for EIE). This finding indicates that older patients showed less improvement in the rod--mediated response after CEA compared with their younger counterparts. Similarly, we identified a negative correlation between the changes in the rod b-wave amplitudes after CEA and the BMI values both in the EIE and ECE groups (*Rs* = –0.4, *P* = 0.006 and *Rs* = –0.33, *P* = 0.02, respectively) and the pack-years of smoking only in the EIE group (*Rs* = –0.31; *P* = 0.03). In the present study, we did not identify a correlation between the initial grade of ICA stenosis and the changes in the ERG amplitudes either in the EIE or ECE group after 3 months of follow-up.

DISCUSSION The principal finding of this study is that the amplitudes of several parameters of the standard full-field ERG were significantly increased following CEA in the ipsilateral eye and, to a lesser extent, in the contralateral eye. To our knowledge, this is the first report of the effect of carotid revascularization on retinal function in patients with asymptomatic carotid stenosis. Our previous study indicated temporal reproducibility of retinal function parameters over 3 to 12 months in individuals without carotid stenosis/intervention (Machalińska A.; unpublished data).

In the Caucasian population, the ICA is among the most common sites of atherosclerosis development that results in vessel stenosis.[11] Significant ICA stenosis is a well-established pathogenic factor for ischemic stroke and ocular ischemic syndrome, because it has a strong effect on the mass flow rate of the blood to the head and neck regions. Accordingly, carotid artery stenosis may reduce the blood flow to the eye and orbit, which significantly affects several parameters that describe the blood supply to the eye, such as the intraocular pressure, ocular systolic pressure, and ocular perfusion pressure.[12] It has been demonstrated that as the degree of ICA stenosis increases, the peak systolic velocity in the ophthalmic artery decreases.[13] In severe ICA stenosis, the flow in the ophthalmic artery cannot be detected or a reversed flow may be present, which may result in ocular ischemic syndrome.[5,14]

Several studies that have assessed the retrobulbar vessels in patients with severe ocular ischemic syndrome have demonstrated that CEA significantly improved the ocular blood flow and corrected the reversal of flow through the ophthalmic artery.[15,16] Consequently, ICA surgery for stenosis effectively improves hemodynamic parameters both in the central retinal artery and short posterior ciliary arteries in patients with acute and chronic forms of ocular ischemic syndrome in the postoperative period.[17,18] Therefore, CEA may reduce or prevent the progression of chronic ocular ischemia and improve hypotensive retinopathy, as well as remove the risk of plaque-related embolization. Functional ocular improvement following CEA has been documented by several previous studies that have examined various parameters, including visual acuity,[18] macular photostress recovery time,[19] dark adaptation level,[20] and visual field.[17] However, no comprehensive data are available regarding the retinal electrophysiological status following CEA, particularly in patients with clinically healthy eyes, that is, without the presence of abnormalities on ophthalmoscopy. Therefore, to the best of our knowledge, this is the first study to investigate the influence of CEA on the electrophysiological status of the retina.

It has previously been demonstrated that patients with ICA stenosis have thinner choroids compared with age-matched healthy individuals.[21] Choroidal hypoperfusion as a consequence of ICA obstruction resulted in multiple occlusions of the choriocapillaris and attenuated the choroidal vessels.[22] More importantly, CEA procedures on the carotid arteries have resulted in the recovery of choroidal thickness in all patients with hemodynamically significant ICA stenosis.[23] Thus, we speculate that improved retinal function is a result of increased choroidal blood flow in response to carotid surgery because the choroid vessels were merely controlled by autoregulative mechanisms.[24] In contrast, retinal circulation via the central retinal artery is highly dependent on the blood concentration of O_2 and CO_2 and the pH levels in the inner retina.[25] Retinal flux may be increased in hypoxia by up to 336%, which is not possible in the choroid.[25] It has been demonstrated that carotid artery revascularization improved the retinal circulation time in fluorescent angiography examinations.[26] Thus, we hypothesize that the CEA procedure improves retinal vascular autoregulation, which results in the recovery of outer retinal cell function. Importantly, we identified a significant increase in the amplitude of both the a- and b-waves in scotopic and photopic conditions, which indicates the functional improvement of both the outer and inner retinal layers.

Interestingly, no changes were identified in the implicit times of the ERG waves before and after the CEA. Similarly, in an animal model of retinal capillary closure, a significant reduction in the amplitudes of the scotopic b-wave, photopic a- and b-waves, and scotopic and photopic OPs of the full-field ERG were identified, whereas the mean implicit times were not increased compared with the control eyes.[27] These findings may indicate that more severe retinal hypoxia with clinical signs of ocular ischemic syndrome must be present prior to endarterectomy because it affects the ERG implicit times.

We noted a significant improvement in the ERG amplitudes also in the eyes contralateral to the operated stenosis of the carotid artery. Several studies have demonstrated the restoration of cerebral blood flow in ipsilateral cerebral hemisphere following CEA surgery in short- and long-term follow-ups[28,29]; however, recent studies have also reported a blood flow redistribution phenomena through the collateral circulation, that is, via the circle of Willis and ophthalmic arteries, following CEA.[30] Functional and efficient blood supply to the contralateral cerebral hemisphere via the circle of Willis leads to an improved cerebrovascular reserve in both cerebral hemispheres. Wang et al[31] demonstrated that the effects of CEA on cerebral blood flow and metabolism were similar in both cerebral hemispheres. In another study, Rijbroek et al[32] reported that blood flow and oxygen consumption are increased in the ipsilateral and contralateral hemispheres following CEA, with no significant postoperative difference in these parameters between the hemispheres. These findings may be explained by the effective collateral circulation in the brain. Our present findings, together with those of Wang et al[31] and Rijbroek et al,[32] suggest that unilateral surgery for significant carotid artery stenosis may improve the blood supply and metabolism not only in the ipsilateral eye but also in the contralateral eye.

The b-wave of the ERG is a particularly sensitive index of retinal ischemia as it has been demonstrated both in humans and experimental models of retinal ischemia.[33] In this study, the changes in the rod b-wave amplitudes in the full-field ERGs from the EIE group negatively correlated with the age of the participants. This finding may indicate the presence of atherosclerotic vascular lesions in the retinal bed in older patients, which are responsible for a weaker vascular response to increased blood inflow after CEA. With further data accumulation, ERG testing may become a part of the evaluation of patients with asymptomatic carotid stenosis in the context of interventional management.

It is worth noting that the changes in the rod b-wave amplitudes in full-field ERGs were also negatively correlated with BMI in our study. This finding may indicate that obese patients showed less improvement in the rod-mediated response after CEA compared with their lean counterparts. Global data indicate that the risk of developing cardiovascular diseases, such as hypertension, diabetes mellitus, and dyslipidemia, increases with increasing BMI values,[34] and these vascular diseases may also affect the metabolic functioning of the retina. Moreover, the retinal function of patients with hyperlipidemia was significantly decreased compared with that of healthy controls, even before the occurrence of pathological changes in the fundus, and BMI values negatively correlated with the OP wave index.[35] Previous studies have demonstrated that an increased BMI was associated with narrower retinal arteriolar and wider venular calibers.[34,36,37] Moreover, overweight and obese people have thinner choroids compared both with normal-weight and underweight individuals.[38] Thus, we cannot exclude the possibility that obesity is associated with alterations in the microvasculature and a shift in the balance of vasoconstrictor- and vasodilator--related molecules in the choroid, which would be consistent with the negative correlation identified in the present study.

Several studies have demonstrated that cigarette smoking increases the risk of developing retinal diseases, including age-related macular degeneration (AMD), with heavier smokers exhibiting an increasingly greater risk of developing

AMD.[39,40] In contrast, smoking cessation reduces the risk of AMD and progression to neovascular AMD.[40] There are several mechanisms by which cigarette smoking negatively affects the retina: increased oxidative stress, lipid peroxidation, and platelet aggregation, as well as a reduction in the plasma high-density lipoprotein or antioxidant levels.[39,41] Cigarette smoking also causes inflammation by activating complement C3 and other inflammatory factors and by reducing the serum levels of complement factor H.[41] Finally, cigarette smoking may damage the choroidal vessels and diminish choroidal blood flow, thereby causing chronic vasoconstriction.[39] In view of these data, it may not be surprising that chronic smoking was also an important risk factor for electrophysiological dysfunction of the retina in our study.

Our study has several limitations. First, the lack of fluorescein angiographic findings precluded the diagnosis of macular ischemia and nonperfusion retinal areas, which might affect retinal bioelectrical function. Furthermore, we did not evaluate the time course of the retinal function improvement after carotid artery revascularization or its temporal stability over months or years of follow-up. Finally, due to a limited number of patients and the follow-up time points, the study failed to evaluate the duration of postoperative effects of CEA in the short-term (few days after CEA) and long-term (several months or years after CEA) follow-up. Future conclusive studies should address the above limitations for better evaluation of the short- and long-term outcomes. Finally, it remains to be established whether different modes of carotid revascularization[42] have similar effects on retinal function improvement in patients with asymptomatic carotid artery stenosis.

In conclusion, we found that CEA for asymptomatic carotid artery stenosis is reproducibly associated with improvement of retinal function in the ipsilateral eye and, to a lesser extent, in the contralateral eye. We expect that early detection of significant ICA stenosis and necessary surgical intervention in asymptomatic individuals may help protect neuroretinal function in these patients. While there is little doubt that patients with symptomatic carotid artery stenosis benefit from revascularization, risk stratification in asymptomatic cohorts remains challenging. Therefore, the optimal management of patients with asymptomatic ICA stenosis is still controversial.[4,43] Retinal function testing might be important for identifying patients with asymptomatic carotid artery stenosis who may benefit from revascularization before overt clinical symptoms develop (caused by brain damage), but evidence from larger studies is needed to confirm this. As a noninvasive examination, ERG may become increasingly used as the sole investigation for assessing the biological effects of carotid stenosis on the nervous tissue. We postulate here that widely accessible retinal full-field ERG testing should be included in future randomized controlled trials investigating the final biological outcomes of CEA in patients with different stages of carotid artery disease. Multimodal ERG examination may indeed represent a unique opportunity to investigate the effects of the CEA procedure on retinal function in asymptomatic patients with ICA stenosis, which can improve individual neurovascular risk assessment and optimize strategies aimed at preventing neurovascular complications in this specific group of patients.

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