CLINICAL INVESTIGATION

# Perimetric and retrobulbar blood flow changes following carotid endarterectomy

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**Abstract**

*Background* Carotid stenosis can produce visual changes. This study examines perimetric and retrobulbar blood flow changes following carotid endarterectomy (CEA) in patients without visual symptoms.

*Methods* Sixteen patients (13 male, three female) with bilateral carotid stenosis were included. Patients with a history of ophthalmic disease, including glaucoma, were excluded. Peak systolic velocity (PSV) in the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries (SPCAs) was measured preoperatively and 12 months following CEA with color Doppler imaging (CDI), using a 7.5 MHz probe, at both the side operated upon and its fellow side. Automated static perimetry (Octopus 500 perimeter, G1x program) was performed at the same intervals. Mean sensitivity (MS), mean defect (MD), loss variance (LV) and corrected loss variance (CLV) were recorded.

*Results* Preoperative PSV in the OA was significantly lower in the side operated on. Preoperative perimetric parameters were significantly compromised, compared with normative data, in both eyes. Postoperatively, PSV had significantly improved in all vessels examined in the carotid that was operated on, but only in the OA and SPCAs in the fellow side. MD had significantly improved postoperatively for both eyes, whereas improvement in the other perimetric parameters examined was not statistically significant.

*Conclusions* Perimetric changes occur in carotid stenosis. CEA results in the improvement of retrobulbar blood flow and perimetric parameters. Further research will be required to determine whether perimetric parameters may be used as additional indicators for carotid endarterectomy.

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## Introduction

Carotid endarterectomy (CEA) is a widely accepted method of treating patients with high-grade obstructive carotid artery disease (OCAD) [1, 2]. CEA is successful in preventing cerebral ischemic events, as shown by large trials, such as the prospective randomized North American Symptomatic Endarterectomy Trial (NASCET) [1] and the European Carotid Surgery Trial (ECST) [2]. In OCAD ocular blood flow is significantly reduced due to reduced or reversed ophthalmic artery (OA) flow in a fashion similar to that of subclavian steal syndrome [3–9]. Consequently, in the presence of OCAD, there is a significant risk of cerebral

and ocular transient ischemic attacks (TIAs), at a degree proportional to the carotid stenosis [1–3].

Color Doppler imaging (CDI) is a safe, non-invasive and reproducible method of evaluating orbital blood velocity, although reproducibility depends on the experience of the examiner [10–12]. Decreased blood flow velocities and increased resistivity indices at the OA, central retinal artery (CRA), and short posterior ciliary arteries (SPCAs) have been demonstrated with CDI in patients with OCAD associated with ophthalmic manifestations, including amaurosis fugax, ischemic ocular pain, iris or anterior chamber angle neovascularization and optic disc atrophy or edema [6, 13, 14]. Taking into account the importance of early OCAD diagnosis and appropriate management in the prevention of cerebral and ocular ischemic attacks, it would be interesting to explore possible retrobulbar hemodynamic changes in patients with OCAD without ocular manifestations. The possible correlation of such changes with perimetric findings could suggest a role for CDI and perimetry as additional indicators for CEA. This study employed CDI to evaluate retrobulbar blood flow in OCAD patients without ocular manifestations, before CEA, and 12 months postoperatively, and correlated the results with perimetric parameters recorded at the same intervals. Findings could provide evidence for the value of perimetry and retrobulbar CDI in the treatment of patients undergoing CEA in the future.

## Patients

This was a prospective, interventional, non-randomized study. All participants were recruited from the Department of Vascular Surgery of the University Hospital of Alexandroupolis, in Thrace, Greece. Bilateral OCAD sufferers without related ophthalmic symptoms or signs, such as amaurosis fugax, Hollenhorst plaques, retinal vascular abnormalities, optic disc atrophy or edema or neovascularization in the iris or anterior chamber angle, who were scheduled to undergo CEA were included. The indication for surgery was based on inclusion clinical criteria established by the Asymptomatic Carotid Atherosclerosis Study (ACAS) [15]. Internal carotid artery (ICA) stenosis was calculated by contrast angiography (applying the formula used in NASCET [1]) and/or by Doppler ultrasound. Angiographic or ultrasound findings in the diseased ICA prior to surgery were 70–79% stenosis in six cases, 80–89% stenosis in three cases, 90–95% stenosis in five cases and pre-occlusive stenosis (>95%) in two cases. For the fellow carotid, respective findings were 70–79% stenosis in nine cases, 80–89% stenosis in six cases, 90–95% stenosis in one case and pre-occlusive stenosis (>95%) in no case. Sixteen patients (13 male, 81.25%) were included. The age (mean ± SD, range) was 68.94±4.95

(range 57 to 76) years. There were ten CEAs on the right side and six CEAs on the left side.

The presence of intracranial vascular disease was evaluated in all patients by a transcranial Doppler imaging study. No intracranial vessel disease was recorded in any patient. Anti-thrombotic medication was stopped in all patients 1 week before their admission to hospital and was reinstated unchanged on the first postoperative day. All other systemic medications were also not changed postoperatively. All surgical procedures were performed with the patient under general anesthesia. The standard operating technique was followed in all cases [16].

A history of systemic arterial hypertension was reported in six patients, diabetes mellitus in five patients, coronary artery disease in five patients, congestive heart failure in one patient, arrhythmia in one patient, smoking in seven patients, hypercholestermia in seven patients and obesity in four patients. Patients with a history of ophthalmic conditions, including glaucoma, age-related macular degeneration, congenital abnormalities of the anterior eye segments and ocular surgery or trauma, were excluded, to rule out vascular and visual field changes not related to carotid artery disease. Furthermore, only patients with best corrected visual acuity (BCVA) of 20/20 OU were included, to allow for accurate visual field testing. All participating patients signed a written informed consent form for this clinical study, in accordance with the tenets of the Declaration of Helsinki.

## Methods

All participants underwent a comprehensive clinical ophthalmic examination. Visual fields were examined in both eyes with the Octopus 500 EZ automated perimeter (Octopus, Interzeag, Switzerland), using the three-step G1x program and "peridata" analysis and was repeated at least three times before data were recorded, to allow patients to become familiar with the method. Only visual fields with a reliability factor less than 5% were included, to increase the diagnostic accuracy. Perimetric parameters recorded included the mean sensitivity (MS, measured in decibels), mean defect (MD), loss variance (LV) and corrected loss variance (CLV). Visual fields were tested preoperatively as well as at the 12-month postoperative interval.

All participants underwent bilateral CDI testing of the retrobulbar blood flow on both the side operated on and the fellow side with a 7.5 MHz linear array transducer (ATL-HDI 1500 ultrasound device, Phillips Medical Systems, Best, The Netherlands). CDI was performed in all cases by the same experienced examiner (A.A.A.) before the discontinuation of any anti-thrombotic medications. Preop-

**Table 1** Preoperative and 12-month postoperative PSV values (mean value ± SD) of examined vessels in the sides operated on and the fellow sides, and statistical significance of respective differences (one-way ANOVA)

| Vessel studied | Preoperatively | | | | Postoperatively (12-Month interval) | | | |
|---|---|---|---|---|---|---|---|---|
| | Side operated on | Fellow side | F | P | Side operated on | Fellow side | F | P |
| OA | 19.91±5.36 | 34.03±3.33 | 16.64 | 0.03 | 33.82±3.94 | 36.98±3.21 | 5.51 | 0.31 |
| CRA | 7.95±3.13 | 10.81±1.97 | 4.11 | 0.27 | 11.02±1.93 | 11.92±1.74 | 1.89 | 0.72 |
| SPCA | 10.79±3.05 | 12.54±1.90 | 3.92 | 0.19 | 14.28±3.43 | 14.95±2.14 | 1.55 | 0.25 |

eratively, the examiner was blind to the extent of carotid stenosis and to which side (right or left) was scheduled for surgery. For postoperative CDI examinations, the patient's neck was draped so that the examiner was again blind to the side to be operated upon (right or left). All examinations were carried out with the patient in the supine position with the eyes closed. Following the application of coupling gel an image of the optic nerve was first obtained to provide a landmark for the identification of the retrobulbar vessels. The OA was examined approximately 25 mm behind the globe in the nasal orbit, where it runs in a straight course, as described elsewhere [17]. The CRA was examined at approximately 10 mm behind the retrolaminar portion of the optic nerve, where it also exhibits a straight course, as described elsewhere [17]. The SPCAs begin as trunks approximately 10 mm to 20 mm behind the globe, before they form multiple branches surrounding the optic nerve in its retrobulbar portion. They were examined at this location, which enables the reliable assessment of the nasal and temporal SPCAs, as described elsewhere [17]. CDI examinations were performed preoperatively as well as at the 12-month postoperative interval. In each artery, peak systolic velocity (PSV) was measured from the spectrum analysis of the CDI signals. PSV was recorded as the highest blood velocity achieved during a systole and was measured from the frequency of the peak in the Doppler-shifted waveform.

Results were statistically analyzed with SPSS 8.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was set at 0.05. The pattern of the distribution in the variables included was compared with a theoretical normal distribution with the one-sample Kolmogorov–Smirnov test (K-S test) which yielded not statistically significant results

($P>0.05$) for all parameters examined (implying a normal distribution of values in all parameters). Differences between the side operated on and its fellow side with regard to intraocular pressure (IOP) and hemodynamic and perimetric parameters, as well as respective differences between the preoperative and postoperative intervals, were examined with one-way analysis of variance (ANOVA) and Bonferroni's adjustment for multiple comparisons. Correlations between hemodynamic and perimetric results were examined with Pearson's bivariate correlation coefficient. The power of the study was assessed with the G*Power statistical package http://www.psychologie.uni-tries.de:8000/projects/gpower.html), assuming significance level (alpha)=0.05 and an effect size of d=0.5. According to these assumptions a post-hoc analysis yielded a power of 0.78 for ANOVA (two groups) and 0.77 for Pearson's bivariate correlation coefficient.

## Results

The degree of preoperative carotid stenosis (mean ± SD, range) was 85±10% (65–99%) and 64±11% (50–95%) at the sides operated on and their fellow sides, respectively. At the 12-month postoperative interval, the degree of carotid stenosis was 10±4% (0–35%) and 66±12% (52–96%) in the sides operated on and the fellow sides, respectively. The difference between preoperative and postoperative degree of obstruction at the fellow carotid was not statistically significant (one-way ANOVA). The preoperative IOP was 15±2 (11–18) mmHg and 14±1 (12–17) mmHg in the eyes ipsilateral and contralateral to the carotids operated on,

**Table 2** PSV values (mean value ± SD) of examined vessels in the sides operated on and in the fellow sides, preoperatively and at the 12-month postoperative interval, and statistical significance of respective differences (one-way ANOVA)

| Vessel studied | Side operated on | | | | Fellow side | | | |
|---|---|---|---|---|---|---|---|---|
| | Preoperatively | Postoperatively (12-month interval) | F | P | Preoperatively | Postoperatively (12-month interval) | F | P |
| OA | 19.91±5.36 | 33.82±3.94 | 29.32 | ≈0.00 | 34.03±3.33 | 36.98±3.21 | 23.64 | 0.02 |
| CRA | 7.95±3.13 | 11.02±1.93 | 25.88 | ≈0.00 | 10.81±1.97 | 11.92±1.74 | 3.15 | 0.70 |
| SPCA | 10.79±3.05 | 14.28±3.43 | 24.01 | 0.01 | 12.54±1.90 | 14.95±2.14 | 25.01 | 0.02 |

**Table 3** Perimetric parameters (mean value ± SD) in the eye operated on and the fellow eye, and statistical significance of respective differences (one-way ANOVA)

| Perimetric parameter | Preoperatively | | | | Postoperatively (12-month interval) | | | |
|---|---|---|---|---|---|---|---|---|
| | Side operated on | Fellow side | F | P | Side operated on | Fellow side | F | P |
| MS | 14.42±5.35 | 15.11±5.62 | 3.15 | 0.59 | 13.88±5.84 | 15.73±6.36 | 2.51 | 0.52 |
| MD | 11.87±5.21 | 9.53±5.11 | 1.99 | 0.78 | 7.07±3.72 | 7.68±3.80 | 1.09 | 0.88 |
| LV | 31.51±26.47 | 29.50±26.93 | 2.14 | 0.63 | 28.16±30.13 | 26.26±30.50 | 1.24 | 0.80 |
| CLV | 27.57±31.62 | 21.18±20.50 | 1.02 | 0.86 | 26.21±35.57 | 17.33±20.61 | 2.57 | 0.71 |

respectively, without the use of any anti-glaucomatous medication. The IOP at the 12-month postoperative interval was 15±2(12–18) mmHg and 15±2 (12–18) mmHg in the eyes ipsilateral and contralateral to the carotids operated on, respectively, without the use of any anti-glaucomatous medication. Differences in IOP between the eyes operated on and the fellow eyes were not statistically significant at both preoperative and postoperative intervals (one-way ANOVA). Furthermore, differences in IOP between postoperative and preoperative intervals were not statistically significant for both the eyes operated on and their fellow eyes (one-way ANOVA).

The preoperative PSV score in the OA was significantly lower in the side operated on than in the fellow side. In contrast, differences in preoperative PSV scores between the side operated on and the fellow side at the CRA and SPCAs were not statistically significant. Preoperative PSV values (mean value ± SD) of examined vessels in the sides operated upon and the fellow sides, and statistical significance of respective differences, are presented in Table 1. At the 12-month interval, differences in PSV scores between the side operated on and the fellow side were not statistically significant for all vessels examined (Table 1). At the 12-month postoperative interval, PSV was significantly improved in the OA, CRA and SPCAs at the side operated upon, whereas the improvement was statistically significant for the OA and SPCAs but not for the CRA in the fellow side (Table 2).

All perimetric parameters examined (MS, MD, LV and CLV) were preoperatively compromised in both the sides operated on and the fellow sides, compared with normative data, whereas differences in all preoperative and postoperative perimetric parameters examined between the sides operated on and the fellow sides were not statistically significant (Table 3). At the 12-month postoperative interval, all perimetric parameters had improved in both sides (more pronounced in the eye ipsilateral to the carotid that had ben operated on), although the improvement was statistically significant only for MD (Table 4). The results of the preoperative and postoperative (12-month interval) visual field tests of the eyes ipsilateral and contralateral to the side operated on of one of the patients studied are presented in Figs. 1 and 2, respectively.

The preoperative MD value at the eye ipsilateral to the side operated on was inversely correlated with PSV at the PCA (Pearson's bivariate correlation coefficient=−0.62, $P$=0.04) and at the CRA (Pearson's bivariate correlation coefficient=−0.61, $P$=0.04). No further statistically significant correlations could be found.
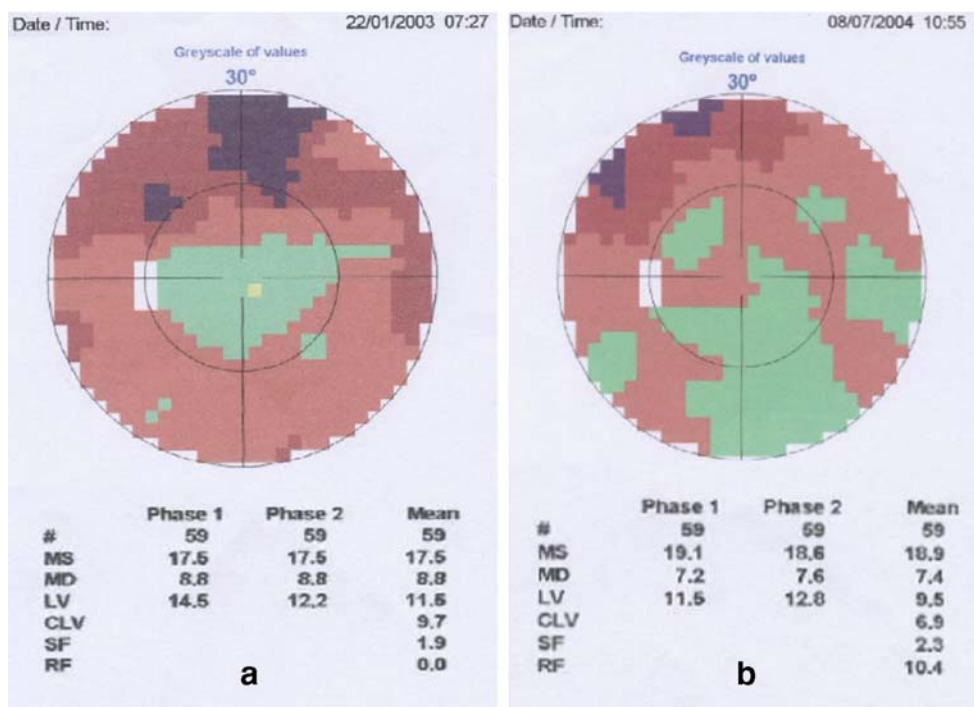
## Discussion

Ophthalmic manifestations used as indicators for CEA in OCAD consist mainly of ipsilateral transient monocular visual loss (TMVL), retinal artery occlusion (RAO), asymptomatic Hollenhorst plaque and ocular ischemic syndrome (OIS) [18]. Ocular circulation is largely controlled by autoregulative mechanisms, which maintain a stable retinal and to a large extent choroidal and optic nerve blood supply [19]. In the case of carotid atherosclerosis and OCAD, chronic cerebral hypotension can induce a down-

**Table 4** Perimetric parameters (mean value ± SD) in the sides operated on and the fellow sides, preoperatively and at the 12-month postoperative interval, and statistical significance of respective differences (one-way ANOVA)

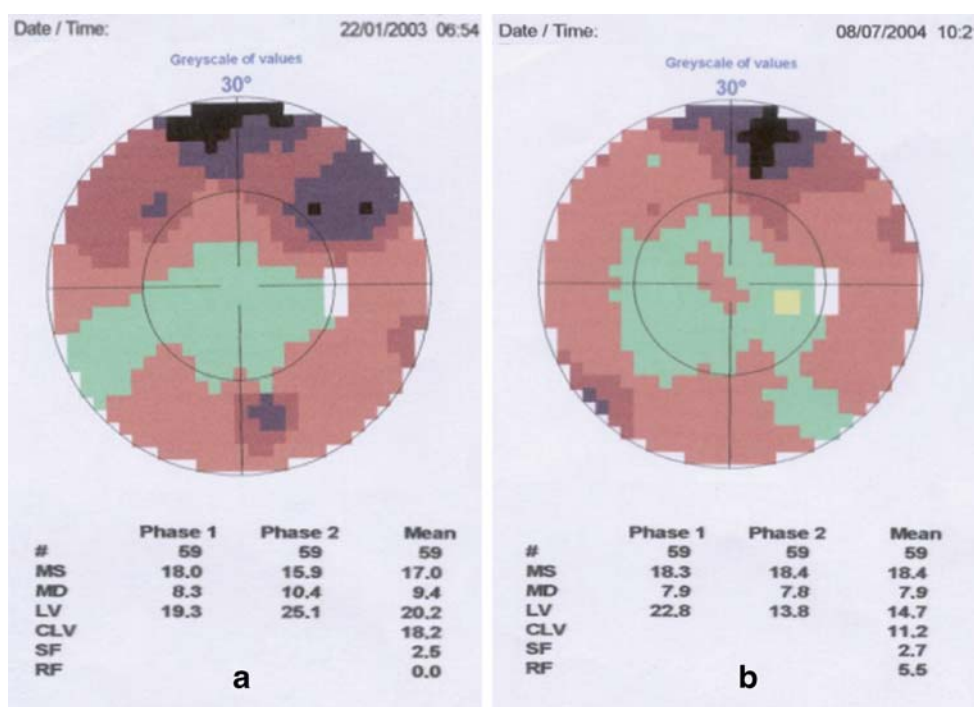| Perimetric parameter | Side operated on | | | | Fellow side | | | |
|---|---|---|---|---|---|---|---|---|
| | Preoperatively | Postoperatively (12-month interval) | F | P | Preoperatively | Postoperatively (12-month interval) | F | P |
| MS | 14.42±5.35 | 13.88±5.84 | 2.45 | 0.62 | 15.11±5.62 | 15.73±6.36 | 2.98 | 0.47 |
| MD | 11.87±5.21 | 7.07±3.72 | 25.88 | 0.01 | 9.53±5.11 | 7.68±3.80 | 27.49 | 0.01 |
| LV | 31.51±26.47 | 28.16±30.13 | 18.32 | 0.29 | 29.50±26.93 | 26.26±30.50 | 19.43 | 0.22 |
| CLV | 27.57±31.62 | 26.21±35.57 | 3.85 | 0.65 | 21.18±20.50 | 17.33±20.61 | 20.15 | 0.19 |

**Fig. 1** Preoperative (**a**) and 12-month postoperative (**b**) visual fields of the eye ipsilateral to the side operated upon



|  | Phase 1 | Phase 2 | Mean |
|---|---|---|---|
| # | 59 | 59 | 59 |
| MS | 17.5 | 17.5 | 17.5 |
| MD | 8.8 | 8.8 | 8.8 |
| LV | 14.5 | 12.2 | 11.6 |
| CLV |  |  | 9.7 |
| SF |  |  | 1.9 |
| RF |  |  | 0.0 |

**a**

|  | Phase 1 | Phase 2 | Mean |
|---|---|---|---|
| # | 59 | 59 | 59 |
| MS | 19.1 | 18.6 | 18.9 |
| MD | 7.2 | 7.6 | 7.4 |
| LV | 11.5 | 12.8 | 9.5 |
| CLV |  |  | 6.9 |
| SF |  |  | 2.3 |
| RF |  |  | 10.4 |

**b**

ward shift of the cerebral and ocular vascular autoregulation [20]. OIS occurs when perfusion pressure falls below the threshold of collateral vasculature and compensation of central autoregulation and manifests itself as chronic pain unrelated to increased IOP (ischemic pain), edema of the optic disc, and macula, neovascularization of the optic disc, retina and iris, uveitis-like syndrome and neovascular glaucoma (NVG) [18, 21]. Permanent visual loss, ranging from scotomas to complete blindness, occurs in up to 6.2%

of OCAD patients [8]. Previous studies evaluating retro-bulbar vessels with CDI have shown that CEA significantly improves ocular blood flow and corrects the reversal of flow through the ophthalmic artery [6, 13]. The significant improvement in PSV in all the vessels examined in the side operated upon in the present study is in agreement with such reports. PSV was the only hemodynamic parameter examined, since several previous studies have reported that it is more closely associated with the degree of carotid

**Fig. 2** Preoperative (**a**) and 12-month postoperative (**b**) visual fields of the eye contralateral to the side operated on (the same patient as presented in Fig. 1)



|  | Phase 1 | Phase 2 | Mean |
|---|---|---|---|
| # | 59 | 59 | 59 |
| MS | 18.0 | 15.9 | 17.0 |
| MD | 8.3 | 10.4 | 9.4 |
| LV | 19.3 | 25.1 | 20.2 |
| CLV |  |  | 18.2 |
| SF |  |  | 2.5 |
| RF |  |  | 0.0 |

**a**

|  | Phase 1 | Phase 2 | Mean |
|---|---|---|---|
| # | 59 | 59 | 59 |
| MS | 18.3 | 18.4 | 18.4 |
| MD | 7.9 | 7.8 | 7.9 |
| LV | 22.8 | 13.8 | 14.7 |
| CLV |  |  | 11.2 |
| SF |  |  | 2.7 |
| RF |  |  | 5.5 |

**b**

stenosis [21–23]. A system of staging of the degree of carotid stenosis has also been proposed, based on the levels of PSV in the ophthalmic artery [22]. Previous studies have reported blood flow redistribution phenomena through the circle of Willis following CEA in patients with severe ICA stenosis [24]. Therefore, the significant improvement in PSV in the OA and SPCAs in the fellow side may be attributed to the development of compensatory collateral hemodynamic changes.

It has previously been reported that, in cases of severe unilateral OCAD, orbital and ocular blood flow velocities before CEA have symmetrical patterns in both eyes and are generally reduced, compared with normative values [11]. This finding has been attributed to flow redistribution via the circle of Willis. which supplies several collateral pathways determining the balance of flow between the two cerebral hemispheres and between the anterior and the posterior cerebral circulation [11]. The external carotid artery via reversed flow through the OA, and leptomeningeal anastomoses, further contributes to the collateral circulation [24]. CEA affects the extent of collateral contribution from the contralateral side [24]. The principal factor determining the demand for collateral supply is the mean pressure reserve at the middle cerebral artery entrance [24]. It has been shown that collateral circulation and cerebrovascular reactivity become stable approximately 3 months after CEA, but it remains questionable whether redistribution of flow through the circle of Willis after CEA, and the consequent improvement in the hemodynamic condition, also affect the visual fields of both eyes. This possibility is supported by findings from the present study, such as the significantly improved MD, at the 12-month interval following CEA, in both eyes.

Functional ocular improvement following CEA has been documented by several previous studies examining various parameters, including visual acuity [25], macular photo-stress recovery time [23] and dark adaptation level [26]. The present study examined visual fields in the presence of hemodynamically significant OCAD in visually asymptomatic patients. The fact that the ophthalmic symptoms were absent in all patients included, whereas all perimetric parameters examined were compromised in both eyes, compared with normative data, implies that ocular function may be affected in patients with OCAD, even in the absence of visual symptoms, and it stresses the role of perimetry in the evaluation of the condition of such patients. The exact cause of visual field defects in OCAD cannot be determined, although it has been proposed that a crucial factor may be vascular deregulation (the so-called vasospastic syndrome), which eventually results in unstable ocular perfusion [27]. Reduction of ocular blood flow, resulting in the expression of glial fibrillary acidic protein in the retinal Muller cells, may also result in the

development of visual field defects in OCAD [28]. In the present study, the fact that the preoperative MD value in the eye ipsilateral to the side operated on was significantly inversely correlated with PSV at the PCA and at the CRA implies a relationship between visual fields defects and compromised ocular blood flow at the affected side. Thus, PSV in the SPCAs and the CRA may be a sensitive marker of ocular ischemia leading to visual fields defects. The respective preoperative correlation in the fellow side was not statistically significant, whereas, postoperatively, respective correlations were also not statistically significant in both the side operated on and the fellow side, implying that blood flow redistribution may occur primarily after CEA. The significant improvement in MD recorded at the 12-month postoperative interval for the eyes ipsilateral to the carotids operated on implies that the restoration of carotid artery blood flow (documented by the significant improvement in PSV at the OA, CRA and SPCAs at the 12-month interval) favorably affects visual function. The significant improvement in MD in the eyes contralateral to the carotid arteries operated on (although less pronounced than that in the eyes ipsilateral to the carotids operated on) may be explained by the development of generalized hemodynamic alterations in cerebral circulation following unilateral CEA, including increased blood flow across the midline and correction of blood shunt over the contralateral side [24, 29]. However, a "learning effect" in visual field performance has been reported, even for stable patients [26], and the possibility that this may have affected perimetric results in the present study cannot be ruled out, especially since the improvement in MD value was observed in both eyes [30].

The non-randomized nature of patients' recruitment, and the relatively small number of patients studied, limit the power of this study. On the other hand, the prospective consecutive recruitment of patients, and the fact that all CDI examinations were performed by the same examiner, who was blind to patient information, enhance the validity of the results. The fact that ocular ischemic stress caused by hemodynamically significant OCAD may be potentially reversible, as evidenced by the recorded improvement in MD, implies that perimetry may have a role in the decisions concerning the surgical management of OCAD.

## References

1. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD (1998) Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 339:1415–1425
2. Naylor AR, Rothwell PM, Bell PR (2003) Overview of the principal results and secondary analyses from the European and

North American randomised trials of endarterectomy for symptomatic carotid stenosis. Eur J Vasc Endovasc Surg 26:115–129

3. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ (2003) Carotid endarterectomy trialists' collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 11:107–116

4. Araki CT, Babikian VL, Cantelmo NL, Johnson WC (1991) Cerebrovascular hemodynamic changes associated with carotid endarterectomy. J Vasc Surg 13:854–859

5. Schneider PA, Rossman ME, Torem S, Otis SM, Dilley RB, Bernstein EF (1988) Transcranial Doppler in the management of extracranial cerebrovascular disease: implications in diagnosis and monitoring. J Vasc Surg 7:223–231

6. Costa VP, Kuzniec S, Molnar LJ, Cerri GG, Puech-Leao P, Carvalho CA (1999) The effects of carotid endarterectomy on the retrobulbar circulation of patients with severe occlusive carotid artery disease. An investigation by color Doppler imaging. Ophthalmology 106:306–310

7. Ho AC, Lieb WE, Flaharty PM, Sergott RC, Brown GC, Bosley TM, Savino PJ (1992) Color Doppler imaging of the ocular ischemic syndrome. Ophthalmology 99:1453–1462

8. Kirshner RL, Green RM, Searl SS, DeWeese JA (1985) Ocular manifestations of carotid artery atheroma. J Vasc Surg 2:850–853

9. Costa VP, Carvalho CA, Kuzniec S, Molnar LJ, Cerri GG, Puech-Leão P (1998) Collateral blood supply through the ophthalmic artery: a steal phenomenon analyzed by Color Doppler imaging. Ophthalmology 105:689–693

10. Nemeth J, Kovacs R, Harkanyi Z, Knezy K, Senyi K, Marsovszky I (2002) Observer experience improves reproducibility of color Doppler sonography of orbital blood vessels. J Clin Ultrasound 30:332–335

11. Quaranta L, Harris A, Donato F, Cassamali M, Semeraro F, Nascimbeni G, Gandolfi E, Quaranta CA (1997) Color Doppler imaging of ophthalmic artery blood flow velocity: a study of repeatability and agreement. Ophthalmology 104:653–658

12. Schmetterer L, Dallinger S, Findl O, Strenn K, Graselli U, Eichler HG, Wolzt M (1998) Noninvasive investigations of the normal ocular circulation in humans. Invest Ophthalmol Vis Sci 39:1210–1220

13. Ward JB, Hedges TR 3rd, Heggerick PA (1995) Reversible abnormalities in the ophthalmic arteries detected by color Doppler imaging. Ophthalmology 102:1606–1610

14. Costa VP, Kuzniec S, Molnar LJ, Cerri GG, Puech-Leao P, Carvalho CA (1997) Clinical findings and hemodynamic changes associated with severe occlusive carotid artery disease. Ophthalmology 104:1994–2002

15. Rothwell PM (2006) Symptomatic and asymptomatic carotid stenosis: how, when, and who to treat? Curr Atheroscler Rep 8:290–297

16. Loftus CM (1997) Carotid endarterectomy: how the operation is done. Clin Neurosurg 44:243–265

17. Matthiessen ET, Zeitz O, Richard G Klemm M (2004) Reproducibility of blood flow velocity measurements using colour decoded Doppler imaging. Eye 18:400–405

18. Wolnitz RJ (2005) Carotid endarterectomy for ophthalmic manifestations: is it ever indicated? J Neuroophthalmol 25:299–302

19. Vicent D, Ilany J, Kondo T, Naruse K, Fisher SJ, Kisanuki YY, Bursell S, Yanagisawa M, King GL, Kahn CR (2003) The role of endothelial insulin signaling in the regulation of vascular tone and insulin resistance. J Clin Invest 111:1373–1380

20. Keunen RW, Eikelboom BC, Stegeman DF, Ackerstaff RG (1994) Chronic cerebral hypotension induces a downward shift of the cerebral autoregulation: a hypothesis based on TCD and OPG-GEE studies in ambulatory patients with occlusive cerebrovascular disease. Neurol Res 16:413–416

21. Fujioka S, Karashima K, Nakagawa H, Saito Y, Nishikawa N (2006) Classification of ophthalmic artery flow in patients with occlusive carotid artery disease. Jpn J Ophthalmol 50:224–228

22. Fujioka S (2003) Use of orbital color Doppler imaging for detecting internal carotid artery stenosis in patients with amaurosis fugax. Jpn J Ophthalmol 47:276–280

23. Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J (1997) Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. Stroke 28:2084–2093

24. Vriens EM, Wieneke GH, Hillen B, Eikelboom BC, Van Huffelen AC, Visser GH (2001) Flow redistribution in the major cerebral arteries after carotid endarterectomy: a study with transcranial Doppler scan. J Vasc Surg 33:139–147

25. Geroulakos G, Botchway LT, Pai V, Wilkinson AR, Galloway JM (1996) Effect of carotid endarterectomy on the ocular circulation and on ocular symptoms unrelated to emboli. Eur J Vasc Endovasc Surg 11:359–363

26. Havelius U, Bergqvist D, Falke P, Hindfelt B, Krakau T (1997) Impaired dark adaptation in symptomatic carotid artery disease. Neurology 49:1353–1359

27. Gasser P, Flammer J, Guthauser U, Mahler F (1990) Do vasospasms provoke ocular diseases? Angiology 41:213–220

28. Osborne NN, Block F, Sontag KH (1991) Reduction of ocular blood flow results in glial fibrillary acidic protein (GFAP) expression in rat retinal Muller cells. Vis Neurosci 7:637–639

29. Schaser KD, Settmacher U, Puhl G, Zhang L, Mittlmeier T, Stover JF, Vollmar B, Menger MD, Neuhaus P, Haas NP (2003) Noninvasive analysis of conjunctival microcirculation during carotid artery surgery reveals microvascular evidence of collateral compensation and stenosis-dependent adaptation. J Vasc Surg 37:789–797

30. Heijl A, Bengtsson B (1996) The effect of perimetric experience in patients with glaucoma. Arch Ophthalmol 114:19–22