The Ocular Pulse Amplitude as a Noninvasive Parameter for Carotid Artery Stenosis Screening: A Test Accuracy Study

Pascal B. Knecht, MD,1,* Moreno Menghini, MD,1,* Lucas M. Bachmann, MD, PhD,2 Ralf W. Baumgartner, MD,3 Klara Landau, MD1

Purpose: To investigate a potential correlation between the ocular pulse amplitude (OPA; i.e., the intraocular pressure difference between the systolic and diastolic phases of the heartbeat) and the severity of carotid artery stenosis (CAS) and to test its role as a screening parameter for CAS during routine ophthalmic examination.

Design: Test accuracy study.

Participants: Patients referred for color duplex ultrasound examination of the extra- and intracranial cerebral arteries were enrolled consecutively.

Methods: We measured OPA on both eyes by dynamic contour tonometry. Multivariate analyses were performed with risk factors for CAS (age, total cholesterol, low-density lipoprotein, and triglycerides) to compare the diagnostic value of OPA measurements with other non- or minimally invasive screening parameters.

Main Outcome Measures: The difference between OPA measurements in patients with no (<50%) and patients with severe CAS (>70%) as well as the value of OPA measurements to predict the severity of CAS taking further risk factors of CAS into consideration.

Results: One hundred thirty-four eyes of 67 patients (25 women, 42 men) with a mean age of 67±13 years (range, 25–87) were included. The means of the OPA values of those patients showing no CAS (<50%) differed significantly (P = 0.036) from those with a stenosis of ≥70%. The multivariate model produced a statistically significant odds ratio (0.46; P = 0.007) for CAS of ≥70%.

Conclusions: The results of the present study provide proof of principle that the OPA is reduced in patients with CAS and may be used as a noninvasive, inexpensive, readily available, and unconfounded screening parameter to detect CAS and possibly to reduce the incidence of stroke.

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Carotid artery stenosis (CAS) is a major risk factor for stroke, and early detection and treatment of CAS may reduce its incidence.1–3 Current diagnostic tools encompass color duplex ultrasound examinations, magnetic resonance angiography, computed tomographic angiography, and conventional angiography.1 These examinations are mostly used in symptomatic patients because they are costly and not readily available in a routine clinical setting.

The ocular pulse amplitude (OPA), representing the intracocular pressure difference between the systolic and diastolic phases of the heartbeat, has been mentioned as a potential screening parameter for CAS in earlier reports.4–12 The rationale behind this hypothesis is the assumption that the OPA is directly dependent on the filling of the choroidal vasculature during the systole, which is impaired in CAS. This would lead to a decrease in OPA. The proof of principle as well as the predictive value for CAS in a clinical context utilizing contemporary measurement methods has not been investigated as of yet.

With the increased availability and clinical use of dynamic contour tonometry (DCT) in ophthalmology, the OPA measurement is experiencing a renaissance as a diagnostic parameter for various diseases such as glaucoma, carotid cavernous sinus fistulas, and Grave’s disease.13–16 The main purpose of the DCT device is as an accurate and noninvasive measurement of intraocular pressure (IOP). More and more, DCT is being used during routine ophthalmic examinations because it is safe, inexpensive, and readily available.17–19

We performed a prospective, masked test accuracy study on patients examined at a tertiary neuroangiologic referral center for color duplex ultrasound examinations of the extra- and intracranial arteries.

Our study investigates a potential correlation between the OPA and the severity of CAS taking further risk factors of CAS into consideration and testing its role as a screening parameter for CAS during a routine ophthalmic examination.

Methods

This was a prospective, single-center, test accuracy study performed at the Department of Ophthalmology and the Department of Neurology at the University Hospital of Zurich. Informed consent was obtained from each subject, adhering to the tenets of the Declaration of Helsinki. The study protocol was approved by the
local ethics committee. Patients referred for color duplex ultrasound examination of the extra- and intracranial cerebral arteries were enrolled consecutively. Inclusion criteria were suspected CAS, informed consent for study participation, and an unremarkable ophthalmic examination. Exclusion criteria were a history of ocular surgery, fundoscopic impairment of choroidal vascularization (e.g., choroidal atrophy, scars, retinitis pigmentosa, etc), recent (<4 weeks) ocular disorder or inability to comply with repeated DCT measurements.

Ultrasound Examination

The severity of CAS was determined by color duplex ultrasound examinations during neuroangiology clinics. Ultrasound investigations were performed by experienced sonographers using identical equipment and diagnostic criteria. Color duplex and transorbital Doppler studies were stored on videotape. All ultrasound studies were reviewed by a core laboratory.

Extracranial color duplex sonography of the common, internal, and external carotid arteries were performed with linear 4- to 8-MHz transducers. Stenoses of the internal carotid artery were quantified by using criteria that were (1) published in peer-reviewed journals and (2) elaborated with the same ultrasound equipment that was used in the present study.20–24 When both common and internal carotid arteries showed a stenosis, the more severe degree of stenosis was used in the statistical analysis.

Transorbital insonation of the ophthalmic arteries and carotid siphon were performed with 2-MHz pulsed-wave Doppler probes. Stenoses of the carotid siphon were identified according to criteria reported by Ley-Pozo and Ringelstein.25

Intraocular Pressure Measurement Technique/Procedure

All ophthalmic examinations were performed after assessment of the severity of CAS by color duplex ultrasound examination. Ophthalmologists were blinded to the results to prevent potential bias. A complete ophthalmic examination was performed. The IOP and OPA were both measured by a slit-lamp–mounted or handheld DCT device (Swiss Microtechnology AG, Port, Switzerland).17,19 It records the pulsatile pressure fluctuations of the eye and yields 2 readings with a single measurement procedure. Mean minimum values of the ocular pulse curve are indicated as “IOP” in millimeters of mercury, whereas “OPA” is defined as the difference between mean maximal and mean minimal values of the ocular pulse curve in millimeters of mercury (Fig 1). All measurements were performed on both eyes by the same 2 experienced ophthalmologists (P.B.K., M.M.) according to the manufacturer’s guidelines. Only readings with a quality index (“Q”) of 1 or 2 (range, 1–5, with higher numbers indicating lower measurement quality) were considered for analysis. This was accomplished by setting the quality threshold on the device to “2.” As a consequence, individ-
of available data. Considered them to be missing at random and imputed the means and triglycerides were missing in 32% of patients (n = 34). We considered them to be missing at random and imputed the means of available data.

To assess the discriminative capacity of each diagnostic model we calculated the area under the receiver operator characteristic curves (aROC). An aROC curve provides information of the entire range of test results. An aROC of 0.5 describes a noninformative test, whereas an aROC of 1.0 represents a test that discriminates perfectly between disease presence and absence. Finally, for each cutoff value of CAS, we compared the aROCs deriving from a model using the downstream OPA against the delta OPA.

To account for the fact that patients contributed with both eyes and thus data were not independent, we used the cluster option available in the Stata software package. This option corresponds with a mixed linear model using the subject variate as a random factor.

\( P < 0.05 \) was considered significant. Statistical analysis was performed using the programs GraphPad Prism (Version 4.06, GraphPad Software Inc, San Diego, CA) and the Stata 11.1 software package (StataCorp, LP, College Station, TX).

Results

A total of 72 patients were investigated during the study period, which lasted from October 2008 to February 2010. Five of these 72 patients were excluded, 4 because of incomplete data sets and 1 because of an inability to comply with repeated OPA measurements owing to blepharospasm. Thus, 134 eyes of 67 patients (42 men) with a mean age of 67 ± 13 years (range, 25–87) were included.

Mean downstream OPA measurements for patients with CAS <50% (n = 82) was 2.97 ± 1.22; for patients with a stenosis of ≥50% (n = 52), it was 2.53 ± 0.96; and for patients with a stenosis of ≥70% (n = 25), it was 2.35 ± 0.98 (Fig 2). The means of the downstream OPA values of those patients showing no CAS (<50%) to those with a stenosis of ≥70% differed significantly (\( P = 0.036 \)).

The univariate analysis showed a clear potential of the downstream OPA to predict a CAS of ≥70% (Table 1). The same analysis was not significant using a cutoff at degree of CAS of ≥60% and ≥50% (Table 1). Regarding the delta OPA, the univariate analysis was significant in all 3 cutoffs (Table 1). For the downstream OPA measurements, the multivariate model produced a statistically significant odds ratio for a CAS of ≥70% (Table 2). The delta OPA showed a significant potential to predict all 3 cutoffs in degree of CAS (Table 2).

Comparison of Diagnostic Models

The aROC for model 1 to predict a stenosis of ≥50% was 0.69 (95% confidence interval [CI], 0.60–0.79), to predict a stenosis of ≥60% was 0.65 (95% CI, 0.54–0.76), and to predict a stenosis of

<table>
<thead>
<tr>
<th>OPA Measurement</th>
<th>Degree of CAS (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downstream</td>
<td>≥50</td>
<td>0.780</td>
<td>0.544–1.118</td>
<td>0.446</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>0.854</td>
<td>0.570–1.280</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>0.577</td>
<td>0.336–0.990</td>
<td>0.046</td>
</tr>
<tr>
<td>Delta</td>
<td>≥50</td>
<td>3.687</td>
<td>1.381–9.835</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>3.679</td>
<td>1.687–8.024</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>5.023</td>
<td>2.047–12.327</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval.
stenosis and severe stenosis/occlusion of the carotid artery. A comparison of the aROC of both multivariate models shows an equal predictive value for CAS. Although the univariate approaches show a tendency for delta OPA measurements to be more dependent on CAS than the downstream OPA measurements, the comparison of the aROC values, we performed the same analyses with the corresponding IOP instead of the OPA measurements. We could not find any correlation between downstream IOP and CAS or delta IOP and delta CAS. Therefore, we suggest that the IOP plays no role in the screening for CAS and, based on these results, was not a confounding factor in our main analyses.

Besides being informative, a screening parameter has to fulfill 3 main requirements: It has to be safe, cost effective, and readily available. We believe that measuring the OPA and IOP by DCT fits these criteria perfectly: The safety of DCT has been proven in many studies. The cost of the measurement is low because it is used during a routine ophthalmic examination. A metaanalysis regarding color duplex ultrasonography as the screening test and carotid endarterectomy as the treatment for asymptomatic CAS concluded that the actual stroke reduction from screening toward a probable CAS. To investigate this possible incremental diagnostic value of measuring delta OPA, we included further clinical parameters such as age, cholesterol, low-density lipoproteins, and triglyceride serum levels in multivariate analysis to assess the cumulative predictive value for CAS. Although the univariate approaches show a tendency for delta OPA measurements to be more dependent on CAS than the downstream OPA measurements, the comparison of the aROC values, we performed the same analyses with the corresponding IOP instead of the OPA measurements. We could not find any correlation between downstream IOP and CAS or delta IOP and delta CAS. Therefore, we suggest that the IOP plays no role in the screening for CAS and, based on these results, was not a confounding factor in our main analyses.

The OPA could be shown to decrease with high degrees of CAS in a clinical setting. Second, the difference between the OPA of both eyes was increasing with an increasing difference of both degrees of CAS. Finally, our data indicate that including OPA measurements as a general screening tool for CAS during a routine ophthalmic examination increases the probability of finding a clinically relevant CAS.

We followed earlier reports that investigated the ocular pulse and related ophthalmic parameters such as ophthalmic arterial pressure in patients with CAS by performing DCT measurements accordingly. Our outcome was similar to previous results, namely showing a significant decrease of our downstream OPA measurements with clinically significant degrees (≥70%) of CAS. The differences in downstream OPA measurements in patients with <50% CAS compared with ≥70% CAS were analogous to the differences in the mentioned parameters in patients with no stenosis and severe stenosis/occlusion of the carotid artery. We then went a step further and not only investigated the ipsilateral biometrical ophthalmologic parameters relating to CAS, but also examined the OPA difference between the right and left eyes (referred to as delta OPA), because asymptomatic CAS patients have been found to show an increased collateral blood flow. As reported by Kaufmann et al., normal OPA values vary greatly. It is possible for patients with a unilateral asymptomatic CAS to show normal OPA measurements and thus be missed by this proposed unilateral screening procedure. However, owing to the mentioned increase in contralateral cerebral blood flow, the OPA value of the fellow eye will most probably be increased. Thus, the resultant abnormally high delta OPA value would indicate the necessity of further investigations.

### Discussion

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The value of a screening parameter is significantly enhanced by a high specificity. In our setting, very few other disorders besides CAS are known to decrease a downstream OPA value or increase a delta OPA value between the 2 eyes. Such rare examples are arteritic anterior ischemic optic neuropathy,35 innominate steal syndrome,36 encircling buckle for retinal detachment,37 and Graves’ disease.38 All conditions can be easily diagnosed by history and routine ophthalmic examination. A metaanalysis regarding color duplex ultrasonography as the screening test and carotid endarterectomy as the treatment for asymptomatic CAS concluded that the actual stroke reduction from screening...
and treatment is unknown. However, performing OPA measurements may uncover an asymptomatic CAS, even in patients without any aggressive medical treatment, which remains the cornerstone of therapy, and may therefore lower the risk of stroke.

The limitations of our study are methodologic. The degree of CAS was determined by ultrasonography, not angiography, which is still the gold standard for determining the degree of CAS. However, because of the risk, inconvenience, and cost associated with angiography, we preferred color duplex ultrasonography as the reference for our study. Arterial blood pressure, as demonstrated by Polak et al in 2003, has a small but significant influence on choroidal blood flow. And because a decrease in choroidal blood flow should lead to a decrease in OPA, it is hence reasonable to assume that the OPA may depend on arterial blood pressure. However, in studies that addressed this issue, no dependence of OPA on arterial blood pressure was found. We therefore chose not to include the arterial blood pressure in our analyses.

In conclusion, the results of the present study confirm older hypotheses and provide proof of principle that the OPA measured by DCT is reduced in patients with CAS. Moreover, this study shows the equal predictive value of determining the difference between the OPA in both eyes. The OPA may be used as a noninvasive, inexpensive, readily available and unconfounded screening parameter to detect CAS and to reduce the incidence of stroke. Future studies are needed to determine normal values for everyday clinical use.

REFERENCES


Footnotes and Financial Disclosures

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