Retrobulbar Ocular Blood Flow Changes after Orbital Decompression in Graves’ Ophthalmopathy Measured by Color Doppler Imaging

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PURPOSE. To evaluate if decompression surgery produces changes in retrobulbar blood flow parameters in Graves’ ophthalmopathy (GO).

METHODS. Retrobulbar blood vessels of 26 eyes (14 patients) that underwent orbital bone decompression between June 2009 and May 2010 were measured prospectively using color Doppler ultrasound before and after surgery. The disease was inactive in all patients enrolled according to the European Group on Graves’ Orbitopathy. Patients were classified with mild, moderate-to-severe, or sight-threatening disease. All patients underwent a full ophthalmic examination including intraocular pressure and Hertel measurement. An age-matched control group included 20 eyes of 20 healthy volunteers.

RESULTS. The resistance indexes (RIs) in the central retinal artery (CRA) and ophthalmic artery (OA) were significantly higher in patients with GO preoperatively than in the control group (P < 0.001, P = 0.001 respectively). After decompression surgery, a significant decrease in RIs occurred in the CRA (5%) and OA (6%) (P = 0.002, P < 0.001 respectively). Proptosis was decreased a median of 6 mm (range, 4–7). Three-wall decompression surgery resulted in a significantly greater reduction in exophthalmos (median 7 mm) compared with two-wall surgery (median 5 mm) and one-wall surgery (2.5 mm). Although no significant correlation was found, the RIs decreased more with major reductions in exophthalmos.

CONCLUSIONS. In inactive moderate-to-severe GO, the RIs of the CRA and OA are higher than in normal subjects. The authors hypothesized that increased RIs of inactive GO may be due to orbital extrinsic compression of vascular structures because decompression surgery leads to decreases in the RIs of both the CRA and OA. (Invest Ophthalmol Vis Sci. 2011;52: 5612–5617) DOI:10.1167/iovs.10-6907

Graves’ ophthalmopathy (GO), otherwise known as thyroid-related ophthalmopathy, is an autoimmune disease characterized by enlarged extraocular muscles and increased retrobulbar fat. Orbital fibroblasts are thought to play a crucial role in the pathogenesis of GO expressing the thyroid-stimulating hormone receptor, which acts as an antigen shared by thyroid cells and the orbital contents. GO results in infiltration of the extraocular muscles, connective tissue, and orbital fat with lymphocytes, immune complex, and mucopolysaccharides leading to edema and swelling and increased intraorbital volume and pressure.1,2 After an active inflammatory stage, in which immunosuppressive treatment is preferred, fibrotic changes develop in the retrobulbar tissues and rehabilitative surgery is indicated.1,3

Surgical decompression traditionally has been reserved for patients with compressive optic neuropathy, the most serious vision-threatening complication during the course of GO. Indications for surgery have widened as outcomes of decompressive procedures improved and include severe proptosis and related complications such as exposure keratopathy. More recently, as minimal invasive surgery techniques have been developed, cosmesis has become a new demanding indication.4–7 For all cases, decompressive orbitotomy resolves the intraorbital pressure caused by the discrepancy between increased extraocular volume and inextensible bony compartment by removing parts of the bony orbital wall.

Color Doppler imaging (CDI) has been used to study the ocular blood flow in patients with GO. Decreased superior ophthalmic vein blood flow velocity has been widely documented.8–12 Doppler ultrasound parameters of the retrobulbar arterial vascular structures have been related to the clinical activity score,9 suggesting increased arterial flow velocity in patients with active GO due to inflammation of the retro-orbital tissue.13 Otto et al.14 reported increased retrobulbar pressure in GO measured with a micropressure transducer catheter during bony orbital decompression and a substantial reduction in the intraorbital pressure at the end of surgery. However, to the best of our knowledge, no assessment has been published of CDI parameters of retro-orbital arterial vasculature in inactive moderate-to-severe GO and the changes after decompression surgery.

The aims of this study were to evaluate the hemodynamic parameters of retro-ocular arterial vascular structures in moderate-to-severe inactive GO, the changes after bony orbital decompression, and to determine a correlation with clinical findings and the surgical technique.

PATIENTS AND METHODS

We prospectively evaluated 26 eyes of 14 patients (10 women, 4 men) with GO in whom surgical decompression was planned between June 1, 2009, and May 31, 2010, according to the inclusion criteria. The median patient age was 50.5 years (interquartile range [IQR], 34–66.3).

GO was diagnosed in the Department of Endocrinology and/or the Department of Ophthalmology based on the clinical and laboratory findings. According to the European Group on Graves’ Orbitopathy (EUGOGO), the enrolled patients were classified as having mild, moderate, or severe orbital disease. Mild disease was defined as minimal

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soft tissue swelling, minor lid retraction (<2 mm), exophthalmos <3 mm above normal for race and gender, no or intermittent diplopia, and corneal exposure responsive to lubricants. Moderate-to-severe GO was defined as marked soft tissue swelling, and/or exophthalmos of 3 mm or more above normal for race and gender, and/or lid retraction of 2 mm or more, and/or intermittent or constant diplopia but no optic nerve involvement. Sight-threatening eye disease was defined as optic nerve involvement (dysthyroid optic neuropathy) and/or corneal breakdown. If no alternative causes of visual impairment were identified, patients with the following conditions were considered to have dysthyroid optic neuropathy characterized by abnormal visual acuity (VA) associated with changes in the visual field examination compatible with optic neuropathy, a relative afferent pupillary defect, and/or impaired color vision. The presence of apical crowding on coronal computed tomography (CT) scans supported this diagnosis. Disease activity was evaluated using the clinical activity score. Patients with a clinical activity score of 3 or higher initially can expect beneficial effects from nonsurgical therapy and were not included in this study. Patients who had had an oculary surgery, had been treated with iodine 131, or had received steroid treatment during the last 6 months were also excluded. Orbits included were further subdivided into two groups: one with predominantly lipogenic disease and one with predominantly myogenic disease, corresponding respectively to type I and type II orbitopathy in Nunery’s classification. Basic clinical data including age, gender, smoking habit, disease duration, and history of steroid treatment and/or radiotherapy were recorded. A full ophthalmic examination including pupillary responses, best-corrected VA (BCVA), biomicroscopic evaluation of the anterior and posterior poles, Goldmann applanation tonometry, standard automated perimetry with the Swedish Interactive Threshold Algorithm 24 to 4 strategy, and optical coherence tomography (OCT) scanning of the optic nerve head were performed preoperatively and one month postoperatively. Axial proptosis was measured using Hertel exophthalmometry, and the presence of diplopia was recorded and measured with the alternate prism and-cover test preoperatively and postoperatively. CT examinations of all patients were performed preoperatively with a high-resolution scanner (multidetector CT; Philips and Samsung, Madrid, Spain), and muscle enlargement was measured and interpreted based on the published normative CT data for orbital structures. Muscle index determined by adding the diameters of medial rectus muscle, lateral rectus muscle, inferior rectus muscle and superior rectus-levator palpebra superior group was calculated.

All participants provided informed consent according to the Declaration of Helsinki. All cases had been euthyroid for at least 6 months before decompression in both clinical and laboratory examinations (free T3 and free T4 were within the normal range; thyroid stimulating hormone was low or within the normal range). The type of medication given to the patients to control hyperthyroidism was not a criterion for inclusion or exclusion. All cases had controlled systemic blood pressure (systolic pressure, ≤140 mm Hg; diastolic pressure, ≤90 mm Hg) and intraocular pressure (IOP) values with or without treatment ranged from 14 to 20 mm Hg. Twenty eyes of 20 healthy subjects (12 women, 8 men) with no history of systemic or ocular disease served as controls to determine normative data for the blood flow velocities in the orbital vasculature (median age 46.5 years). The age of control group was matched to the study group.

Surgical Technique

One author (MSS) performed all the orbital decompression techniques, i.e., one-wall procedures (medial through a transcunricular approach), two-wall procedures (medial and inferior through a transcaruncular-transconjunctival approach), and three-wall procedures (medial, inferior, and lateral through a transcaruncular-transconjunctival-lateral canthal approach).

Color Doppler Imaging Measurements

The same masked radiologist (CGG) performed the orbital CDI studies preoperatively and between one and two months postoperatively using an ultrasound scanner (S5A-770A; Toshiba, Madrid, Spain) and the 7.5 MHz linear-array transducer. The eyes were imaged with patients in the supine position, with the head tilted forward at about a 30° angle, eyes closed, and gaze directed toward the ceiling. The transducer was applied gently to the closed upper eyelid using a thick layer of acoustic gel, and the examiner’s hand rested on the orbital rim to avoid any pressure on the globe. The ophthalmic artery (OA) and the central retinal artery (CRA) were examined and the peak systolic velocities, end diastolic velocities, and resistance indexes (RIs) were measured. To measure the OA blood flow velocities, the Doppler sample gate was set 15 to 20 mm posterior to the globe, where the signal is stronger. The CRA was identified within the optic nerve shadow, 2 to 3 mm behind the surface of the optic nerve. All parameters were recorded three times during the same session and the mean values were used in the statistical analyses. The RI, also called Pecourlet’s index, is calculated as [(peak systolic velocity–end diastolic velocity)/peak systolic velocity] and is advantageous in that its value is independent of the beam/vessel angle. The RI is the most reproducible parameter of orbital blood flow measurements using CDI.

Application of orbital CDI to patients with GO has difficulties related to orbital anatomy and proptosis. Keeping the angle between the sound beam and the blood flow direction under 40 to 60° may be difficult, and the velocity values measured may be unreliable. Thus, although the CDI apparatus automatically calculated the systolic and diastolic flow velocities, RI was considered the main hemodynamic study parameter.

Statistical Analyses

Statistical analyses were performed (SPSS software, version 16.0; SPP Inc., Chicago, IL). The calculated power of the study was 90% when designed. Given the small sample size, the nonparametric test was used. The median values and IQR (P25–P75) were calculated for the RIs of the OA and CRA preoperatively and postoperatively. Comparisons of the preoperative and postoperative values were evaluated using the Wilcoxon signed-rank test; the level of significance was P < 0.05. We calculated correlations using Spearman’s correlation test. For statistical analysis of the surgical parameters and the outcomes, patients were divided into two groups: the one- and two-wall decompression surgery procedures and the three-wall decompression procedure. When differences among the surgical groups were evaluated, the Kruskal-Wallis test and Mann-Whitney U test were used. The Bonferroni correction was used to detect differences between one-, two-, and three-wall decompression surgeries to reduce exophthalmos.

RESULTS

Between June 2009 and May 2010, one surgeon (MSS) performed orbital decompression on 14 patients (26 eyes) with GO. The demographic and preoperative clinical patient characteristics, including age, the percentage of women, the severity of GO evaluated according to the EUGOGO, percentage of orbits with predominantly myogenic and lipogenic disease, and smoking habits are shown in Table 1. All patients had inactive disease and had been clinically stable for at least six months preoperatively. The indication for decompressive surgery was proptosis in 23 eyes and dysthyroid optic neuropathy in three eyes. Twelve patients (85.7%) underwent simultaneous bilateral decompression and two patients (14.3%) underwent unilateral surgery. The surgical techniques were one-wall decompression (medial wall, 4 orbits), two-wall decompression (medial and floor, 10 orbits), and three-wall decompression (medial, floor and lateral, 12 orbits) procedures. The RIs were measured successfully in all patients in the OA and CRA.
There was a significant ($P < 0.001$) median reduction in proptosis of 6 mm (range, 4–7). The median Hertel measurement preoperatively was 24 mm (range, 23–26) and postoperatively 18 mm (range, 17–21). Three-wall decompression surgery resulted in a significantly greater reduction in exophthalmos (median, 7 mm; range, 7–8) compared with the two-wall procedure (median, 5 mm; range, 4–6; $P = 0.003$) and the one-wall procedure (2.5 mm; range, 2–4.5; $P = 0.005$). No differences were found between the two-wall and one-wall procedures in exophthalmos reduction. Three-wall decompression surgery achieved a significantly greater reduction in exophthalmos than the one and two-wall decompression procedures (7 mm; range, 7 to 8 vs. 4.5; range, 3.8–6, respectively; $P < 0.001$) (Table 3). Proposis was not correlated with the RI of the retrobulbar arterial structures.

Median muscle index was 22.21 (range 18.2–24.35). The Spearman’s rank correlation showed that the preoperative muscular index was significantly ($P < 0.001$) correlated with the RI of the OA ($r = 0.878$), indicating that the RI of the OA tends to increase as the extraocular muscles enlarge in patients with GO.

Two patients (3 eyes) who had open-angle glaucoma and four patients with ocular hypertension were using topical glaucoma medications at the time of surgery. All these cases had a preoperative IOP below 21 mm Hg. A significant reduction in IOP occurred after decompression surgery (Table 4).

The median preoperative BCVA (Snellen VA) was 0.8 (0.45–1) and postoperatively 0.9 (0.65–1) ($P = 0.02$) (Table 4). The percentage of patients with preoperative and postoperative diplopia in primary position is shown in Table 4. Resolution of diplopia postoperatively did not occur in any patient. New-onset postoperative diplopia developed in four patients, in two of them diplopia was intermittent, occurred only with extreme ocular movements, and resolved at 6 months follow-up. Squint surgery was performed in six patients postoperatively.

In six eyes (3 dysthyroid optic neuropathy and 3 glaucomatous eyes), abnormal thinning of the retinal nerve fiber layer seen on optical coherence tomography or a perimetric visual field defect were found. Higher RIs of the CRA and OA were found in these eyes (median RI of CRA, 0.77; median RI of OA, 0.82) compared with the eyes with unaffected optic nerves (median RI of CRA, 0.76; median RI of OA, 0.80) ($P = 0.83$ and $P = 0.344$ respectively).

No major complications developed in any patient. One patient had a unilateral retrobulbar hematoma 1 day postoperatively that resolved completely with local treatment without sequelae.

**Discussion**

Color Doppler imaging is a noninvasive ultrasound procedure that successfully shows changes in the orbital hemo-

### Table 2. Statistical Comparison of Ocular Blood Flow Resistance Index and Median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 20 Eyes)</th>
<th>Preoperative GO (n = 26 Eyes)</th>
<th>Postoperative GO (n = 26 Eyes)</th>
<th>$P^*$</th>
<th>$P^†$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RI CRA</td>
<td>0.65 (0.59–0.67)</td>
<td>0.762 (0.73–0.80)</td>
<td>0.715 (0.68–0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RI OA</td>
<td>0.73 (0.72–0.74)</td>
<td>0.805 (0.77–0.83)</td>
<td>0.745 (0.716–0.761)</td>
<td>&lt;0.001</td>
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$^*$ Preoperative Mann-Whitney $U$ test comparison of RIs between control group and patients with Graves’ orbitopathy.

$†$ Wilcoxon comparison of RIs preoperatively and postoperatively in patients with Graves’ orbitopathy.
dynamics associated with a variety of pathologies, including CRA and vein occlusions, glaucoma, cranial arteritis, nonarteritic ischemic optic neuropathy, and carotid disease.21,22 In patients with GO, however, few studies have evaluated the retrobulbar blood flow parameters and the changes after treatment.23

Orbital venous congestion and decreased flow velocity in the superior ophthalmic vein measured with CDI are well-documented findings in GO.8–12 Moreover, reversed flow in the superior ophthalmic vein, an indicator of more severely impaired orbital venous drainage, is related to the development of dysthyroid optic neuropathy.8,10–12 Despite no reports of CDI changes in venous stasis after treatment, previous studies have reported prompt improvement in congestive signs after decompression surgery.24 Therefore, if venous blood flow congestion is a contributory factor to the signs and symptoms in GO and they improved after decompression, surgery may help to release the intraorbital pressure and normalize venous blood flow parameters.25

Otto et al.14 measured the retrobulbar pressure in nine patients with GO before and during surgical decompression using an intraorbitally applied pressure transducer. The investigators found markedly elevated retrobulbar pressure in GO that decreased a mean of 10 mm Hg after surgery and higher retro-orbital pressures in patients with dysthyroid optic neuropathy. Riemann et al.26 also reported higher orbital tissue tension and lower orbital compartment compliance in patients with GO using direct orbital manometry. We used CDI, a noninvasive imaging technique, to evaluate the manner by which the retrobulbar blood flow changed with abnormally increased retro-orbital pressure in patients with inactive moderate-to-severe GO and to determine the hemodynamic changes that occurred after decompression surgery.

We found significantly higher RIs in the CRA and OA in patients with inactive moderate-to-severe GO compared with normal controls. After orbital bone decompression surgery, a significant reduction in the RI occurred in both CRA and OA (median, 5% and 6%, respectively). Although the RI reduction tended to increase with decompression of a greater number of bony orbital walls and a greater reduc-
tion of exophthalmos was achieved, the differences between the procedures did not reach significance. A low prevalence of surgical GO in Spain limited patient recruitment in the present study, and the study may not have been sufficiently strong to identify the statistical significance of these results.

In the present study, higher preoperative RIs were significantly associated with greater postoperative RI reductions. In fact, the median RI reduction was 0.02 larger after three-wall decompression surgery compared with the one and two-wall procedures. The role of preoperative RI as a clinical indicator of more aggressive surgery deserves more research.

We considered that the high preoperative RIs of the OA and CRA in the current patients with inactive moderate-to-severe GO may have been due to extrinsic compression of the orbital vessels caused by raised intraorbital pressure seen in GO. Moreover, a correlation between the muscular index and preoperative RI of the OA supports the idea that a greater retro-orbital space conflict occurs in inactive myogenic GO. Because decompression surgery resolves the orbital space conflict and decreases the orbital pressure in GO, the decreased RIs of both the OA and CRA after surgery in the present study may be consistent with resolved vascular extrinsic compression.

Yanik et al. tried to correlate disease activity, based on the clinical activity score, with CDI blood flow parameters and found higher arterial flow velocities and lower RIs of the OA of patients with a high clinical activity score. Orbital inflammatory activity was considered to be responsible for the blood flow alterations. Alp et al. found velocities in the OA and the CRA to be significantly higher in patients with GO than in patients without ophthalmopathy with Graves’ disease or in healthy controls. Because no change in the RIs was associated with increased arterial blood flow velocities, the notion of extrinsic compression was rejected and orbital inflammation was considered the cause of the hemodynamic modifications.

In the present study, no retrobulbar tissue inflammation could have modified the preoperative RIs because the patients enrolled for decompressive surgery had inactive disease (clinical activity score, <3) and were euthyroid. Moreover, when CDI was performed postoperatively, patients had discontinued corticosteroid treatment and had no signs or symptoms of orbital inflammation. Therefore, a compressive mechanism may be responsible for the abnormally elevated values before surgical procedure.

One of the limitations of the study was the small number of patients. Only subjects who required surgical decompression and had undergone no previous radiotherapy treatment were included. This represents a small portion of patients with GO. Both eyes of each GO subject who underwent bilateral surgery were used for the study. This could represent a bias in the study data. On the other hand, volumetric study of the extraocular muscles would have been a more accurate measurement method than coronal CT images. Despite these limitations, we believe that the prospective and controlled study design make our observations useful. We showed that the RI of the retrobulbar blood flow is higher in both the CRA and OA in patients with moderate-to-severe GO compared with healthy controls. Second, the increased RIs in patients with inactive GO may be due to extrinsic compression of the vascular structures because RIs decreased after surgical decompression. Third, resolution of the retro-orbital pressure after surgery resulted in normal RIs of the OA based on our control group and data published so far.

Based on these findings, we believe that the retrobulbar vascular supply is compressed in patients with moderate-to-severe GO, a situation that is reversible with decompression surgery. Further studies should evaluate if the impaired arterial vascularization of the orbit and the optic nerve in inactive GO justifies performing earlier decompression surgery to prevent optic neuropathy in these patients.

References