Colour Doppler imaging of the orbital vasculature in Graves' disease with computed tomographic correlation

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***Aims*—To evaluate alterations in orbital blood flow parameters and their correlations with extraocular muscle enlargement, proptosis, and intraocular pressure in patients with Graves' disease.**

***Methods*—In this multicentre study blood flow parameters in the ophthalmic artery, superior ophthalmic vein, central retinal artery and vein were determined by colour Doppler imaging in 111 patients with Graves' disease in two groups (A and B) and 46 normal control subjects. Group A consisted of 42 patients with Graves' disease without ophthalmopathy; group B of 69 patients with Graves' disease with ophthalmopathy as detected by orbital computed tomographic scanning.**

***Results*—Peak systolic and end diastolic velocities in the ophthalmic artery, peak systolic velocity in the central retinal artery, and maximal and minimal velocities in the central retinal vein in patients in group B were statistically significantly higher than those in group A and the normal controls, whereas maximal and minimal velocities in the superior ophthalmic vein in patients in group B were statistically significantly lower than those in group A and the control subjects. Peak systolic and end diastolic velocities in the ophthalmic artery, peak systolic velocity in the central retinal artery, and maximal and minimal velocities in the central retinal vein also correlated with the sum of all extraocular muscle diameters in group B ($r \geq 0.31$, $p \leq 0.021$). Blood flow parameters had no consistent correlation with proptosis or intraocular pressure ($p > 0.05$). No statistically significant difference was found in resistivity indices between the groups ($p > 0.05$). Reversed blood flow was noted in nine (13%) superior ophthalmic veins in group B.**

***Conclusion*—Orbital blood flow velocities are altered in patients with Graves' ophthalmopathy and may be detected by colour Doppler imaging. Some of these changes also correlate with the enlargement of extraocular muscles. The increased blood flow velocities in arteries may be secondary to orbital inflammation.**

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Graves' disease is thought to be an autoimmune disorder and is the most common cause of unilateral and bilateral proptosis. The clinical and radiological findings of Graves' ophthalmopathy have been published widely. Although enlargement of the superior ophthalmic vein is a well known feature of Graves' ophthalmopathy,[1 2] possible alterations in orbital blood flow velocities have not been documented. In this study we aimed to evaluate alterations in orbital blood flow parameters and to examine their correlation with extraocular muscle enlargement, proptosis, and intraocular pressure in patients with Graves' disease using colour Doppler imaging and computed tomographic (CT) scanning.

Methods

A total of 111 patients (42 men, 69 women) with Graves' disease were examined in this prospective multicentre study. The mean age of the patients was 41.9 (SD 13.9) years. Diagnosis of Graves' disease was made by the department of endocrinology and/or by the department of ophthalmology from clinical and laboratory findings. Patients were divided into two groups according to the presence of ophthalmopathy determined by orbital CT scanning. Group A consisted of 42 patients (15 men, 27 women) with Graves' disease without ophthalmopathy and group B of 69 patients (27 men, 42 women) with Graves' disease with ophthalmopathy. Patients with ocular diseases other than Graves' ophthalmopathy or with a history of orbital surgery or radiation treatment were not included in this study. Blood pressures of all patients were within normal limits. The type of medication given to the patients to control hyperthyroidism was not a criterion for inclusion or exclusion. The patients had been free of local or systemic medication for the treatment of ophthalmopathy and were euthyroid at least 1 month before and during the study period.

Forty six healthy control subjects (16 men, 30 women) were examined to determine normative data for the blood flow velocities in the orbital vasculature. The mean age of the controls was 39.2 (SD 13.4) years. They were free from history of systemic or ocular diseases. Excluded were smokers or persons with pathological findings on routine ophthalmological examination. Informed consent was obtained from both the patients and the controls.

A Toshiba SSA-270A Scanner (Tokyo, Japan) was used to determine blood flow parameters. A 7.5 MHz linear transducer was used to measure blood flow velocities in the central retinal artery and central retinal vein while a 5 MHz pen transducer was used to

measure blood flow velocities in the ophthalmic artery and superior ophthalmic vein. All patients were examined in the supine position with the head tilted forward at an angle of about 30° after 10 minutes of rest. Patients were asked to maintain a forward gaze and gentle eye closure during the examination. The transducer was applied gently to the closed eyelid using a coupling gel, and care was taken to avoid applying any pressure to the eye. Mean values and standard deviations were calculated for peak systolic velocity, end diastolic velocity, and resistivity index in the arteries, and for maximal and minimal velocities in the veins. The resistivity index, also called the Pourcelot index, is used for assessment of arterial waveforms where there is no reverse flow component. This value is calculated as ([peak systolic velocity—end diastolic velocity]/peak systolic velocity) and has the advantage that the value is independent of beam/vessel angle.

Blood flow velocities in the ophthalmic artery were measured at the proximal part of the artery before it crosses the optic nerve. Blood flow velocities in the central retinal artery and its accompanying vein, the central retinal vein, were measured within the optic nerve 2–3 mm behind the posterior margin of the globe. Blood flow velocities in the superior ophthalmic vein were measured at its distal part before it leaves the orbit. Velocities in each vessel were measured three times and only the highest values were used in the statistics. All the colour Doppler imaging measurements were performed by the same author (AO) in patients and in healthy controls. The effects of age and sex on blood flow parameters were also investigated.

CT examinations of all patients were performed with a high resolution scanner (Tomoscan SR 7000; Philips, Eindhoven, Netherlands). Both axial and direct coronal 3 mm thick non-overlapping contiguous sections were obtained in all patients with the method described previously.[3] The perpendicular distance between the interzygomatic line and the posterior margin of the globe at the mid globe section was used to measure the degree of proptosis. The scans of the patients were interpreted as normal or having ophthalmopathy according to the presence of proptosis and/or extraocular muscle enlargement based on the published normative CT data for orbital structures.[3] Patients in group B had enlargement of at least one extraocular muscle and/or proptosis as detected by orbital CT scanning. The presence of ophthalmopathy was also confirmed by an ophthalmologist unaware of the CT interpretation using the NOSPECS criterion.[4]

One eye of each control subject and of patients in group A was randomly selected to measure orbital blood flow velocities. In patients in group B, if both eyes had ophthalmopathy, selection of the eye to be examined was random, whereas if only one eye had ophthalmopathy the orbital blood flow velocities of the affected eye were measured. Since the selection of the eye for control subjects and patients in group A was random, we used blood flow parameters from the right and left orbits of control subjects for statistical analysis to examine the effect of sides on blood flow.

The muscle index was determined by adding the diameters of the following four extraocular muscles: medial rectus muscle, lateral rectus muscle, inferior rectus muscle, and superior rectus-levator palpebra superior group. We searched for correlations between the muscle index, proptosis, intraocular pressure, and the orbital blood flow parameters in patients with Graves' disease.

Means and standard deviations (SDs) of the measurements were calculated. The paired samples *t* test was used to compare data obtained from the right and left orbits. Analysis of variance (ANOVA) was used to compare the blood flow parameters of the groups. Tukey honestly significant difference test was used for multiple comparisons. We calculated correlations using Pearson's correlation. All statistics in this study were analysed using SPSS for Windows (SPSS Inc, Chicago, IL, USA).

Results

In control subjects blood flow parameters obtained from the right and left orbits were not significantly different ($p<0.001$, data not shown). All vessels could be examined successfully except for the superior ophthalmic vein in four patients with ophthalmopathy. Mean (SD) values of orbital blood flow parameters in control subjects and the patient groups are shown in Table 1. The mean ages of the controls and the patients were not significantly different. Neither age nor sex had a significant influence on blood flow parameters in any vessels in normal controls.

ANOVA showed statistically significant differences between groups for peak systolic velocity ($p<0.001$) and end diastolic velocity ($p<0.001$) in the ophthalmic artery, peak systolic velocity in the central retinal artery ($p=0.007$), maximal velocity ($p=0.011$), and minimal velocity ($p=0.049$) in the superior ophthalmic vein, maximal velocity ($p=0.001$) and minimal velocity ($p=0.01$) in the central retinal vein. The statistical comparison of normal controls and subjects in groups A and B is given in Table 2. Tukey honestly significant difference test showed that peak systolic and end diastolic velocities in the ophthalmic

Table 1 Blood flow parameters in orbital vessels in normal control subjects and in patients with Graves' disease

	Mean (SD) velocity (cm/s)		
	Controls	*Group A*	*Group B*
Ophthalmic artery			
Peak systolic velocity	35.6 (9.8)	33.5 (8.9)	41.4 (12.4)
End diastolic velocity	9.7 (3.8)	8.8 (2.7)	11.9 (5.1)
Resistivity index	0.73 (0.06)	0.73 (0.06)	0.72 (0.07)
Central retinal artery			
Peak systolic velocity	9.9 (1.5)	10.0 (1.6)	11.1 (2.4)
End diastolic velocity	3.2 (0.7)	3.3 (0.9)	3.5 (0.9)
Resistivity index	0.68 (0.07)	0.67 (0.08)	0.68 (0.07)
Central retinal vein			
Maximal velocity	4.8 (0.7)	4.9 (0.9)	5.4 (1.1)
Minimal velocity	3.4 (0.7)	3.4 (0.6)	3.7 (0.6)
Superior ophthalmic vein			
Maximal velocity	10.1 (4.7)	10.7 (4.4)	8.0 (5.2)
Minimal velocity	4.1 (3.7)	4.3 (3.9)	2.2 (6.1)

Table 2 Statistical comparison of orbital blood flow parameters in normal control subjects and in patients with Graves' disease

	Compared groups		
	Control–A	*Control–B*	*A–B*
Ophthalmic artery			
Peak systolic velocity	NS	p=0.01	p<0.001
End diastolic velocity	NS	p=0.013	p<0.001
Resistivity index	NS	NS	NS
Central retinal artery			
Peak systolic velocity	NS	p=0.003	p=0.017
End diastolic velocity	NS	NS	NS
Resistivity index	NS	NS	NS
Central retinal vein			
Maximal velocity	NS	p=0.001	p=0.01
Minimal velocity	NS	p=0.009	p=0.012
Superior ophthalmic vein			
Maximal velocity	NS	p=0.033	p=0.007
Minimal velocity	NS	p=0.037	p=0.028

p Values for multiple comparison based on the Tukey honestly significant difference test.
NS = not statistically significant.

artery, peak systolic velocity in the central retinal artery, and maximal and minimal velocities in the central retinal vein calculated for patients in group B were significantly higher than for patients in group A and the normal controls, whereas maximal and minimal velocities in the superior ophthalmic vein calculated for patients in group B were significantly lower than those calculated for the patients in group A and the control subjects. However, no significant difference was noted in the resistivity index between normal subjects and patients in groups A and B. No significant difference was found in orbital blood flow parameters between normal controls and patients in group A in any vessels examined.

Pearson's correlation showed that the muscle index was significantly correlated with peak systolic velocity and end diastolic velocity in the ophthalmic artery (r=0.71, p<0.001 and r=0.80, p<0.001, respectively), peak systolic velocity in the central retinal artery (r=0.65, p<0.001), and maximal and minimal velocities in the central retinal vein (r=0.43, p=0.001 and r=0.31, p<0.021, respectively) in group B. In other words, blood flow velocities in these vessels tend to increase as the extraocular muscles enlarge in patients with Graves' ophthalmopathy.

We observed reversed blood flow in the superior ophthalmic vein in nine patients (13%) in group B. In two (3%) both the anteroposterior and posteroanterior direction of blood flow was noted. Blood flow velocities in the superior ophthalmic vein had no persistent correlation with the muscle index or the diameter of any extraocular muscle alone.

The degree of proptosis correlated well with the enlargement of the extraocular muscles in group B. The highest correlation was observed for the diameter of the inferior rectus muscle (r=0.64, p<0.001). The degree of proptosis did not have a persistent correlation with orbital blood flow parameters in any vessel in patients in group B.

The mean intraocular pressure in patients with Graves' disease was 15.8 (3.7) mm Hg. No significant difference was found between groups A and B (p=0.36). Intraocular pressure showed a significant correlation with proptosis (r=0.50, p=0.002) and with the muscle index (r=0.50, p=0.003) in group B. The blood flow parameters of any vessels had no significant correlation with intraocular pressure in group B.

Discussion

Colour Doppler imaging is a sonographic imaging technique that permits non-invasive assessment of blood flow velocity in orbital vessels. Data on normal ocular circulation have been published in many references.[5–15] Although previously presented values in a normal population showed a large range, our results lie within the range of published data and are close to the largest data pool of normal values published so far.[16] This method has also been used in ophthalmology to investigate alteration of blood flow parameters in various disorders such as central retinal artery occlusion, central retinal vein occlusion, glaucoma, diabetes mellitus, ocular ischaemic syndrome, uveitis, and endophthalmitis.[7 10–14 17 18] To our knowledge, only two reports concerning colour Doppler imaging of the orbital vasculature in patients with Graves' disease have been published.[19 20]

Theoretically, several factors may cause alterations in orbital blood flow parameters in patients with Graves' disease. It is assumed that hyperthyroidism, increased systemic blood pressure, increased intraocular pressure and/or orbital inflammation may affect orbital blood flow. In this study there was no difference between normal controls and patients with Graves' disease with regard to their systemic blood pressure or thyroid state. Thus, neither the state of the thyroid nor systemic blood pressure could be responsible for the changes in orbital blood flow parameters reported in this study.

It is well known that intraocular pressure itself may influence ocular blood flow parameters.[14 21] Despite the fact that blood flow velocities calculated for patients in group B were significantly higher than those calculated for group A and the normal controls, there was no significant difference in intraocular pressure between groups A and B. This parameter is therefore unlikely to be responsible for changes in orbital blood flow parameters.

It has been suggested that ocular hypertension in patients with Graves' ophthalmopathy is caused, in part, by increased intraorbital pressure associated with proptosis.[22] We have also observed that the intraocular pressure was significantly correlated with proptosis and with the muscle index in patients with Graves' ophthalmopathy. This means that proptosis or extraocular muscle enlargement, or both, may result in an increased intraocular pressure in patients with Graves' ophthalmopathy. However, we have observed no significant difference in intraocular pressures between patients with Graves' disease, with or without ophthalmopathy. Further studies are warranted to clarify whether the presence of ocular hypertension may be an indicator for ophthalmopathy in patients with Graves' disease.

Since it has been clearly shown that retrobulbar fat and/or extraocular muscle volumes increase in Graves' ophthalmopathy as a result

of orbital inflammation,[1 2] the increased sum of all extraocular muscle diameters, a raised muscle index, may represent an increased volume of inflamed tissue in the orbit. We have found that there was a correlation between orbital blood flow velocities and the muscle index in patients with Graves' ophthalmopathy. Our results suggest that orbital inflammation in patients with Graves' ophthalmopathy may be responsible for alterations in ocular blood flow velocities. Furthermore, if an increase in peak systolic velocity in an artery results from extrinsic compression caused by raised intraorbital pressure, a decrease in end diastolic velocity resulting in an increased resistivity index would have been observed. However, we noted a proportional increase in both peak systolic velocity and end diastolic velocity in the ophthalmic artery which resulted in an unchanged resistivity index. This finding also leads us to the conclusion that changes in blood flow parameters may be secondary responses to orbital inflammation in Graves' ophthalmopathy.

We have observed a reduction in the blood flow velocity in the superior ophthalmic vein in patients with Graves' ophthalmopathy, which is consistent with well known venous stasis in the orbit of these patients. Moreover, reversed blood flow in the superior ophthalmic vein, an indicator of severe venous stasis, was also noted in some patients with Graves' ophthalmopathy. A similar finding has also been reported in the literature.[19 20] Although it has been postulated that enlarged extraocular muscles may induce venous stasis in patients with Graves' ophthalmopathy,[2] we have observed no consistent correlation between blood flow velocities in the superior ophthalmic vein and the muscle index. This finding suggests that there may be other factors affecting blood flow in the superior ophthalmic vein in patients with Graves' disease. We could not visualise the superior ophthalmic vein in four patients with ophthalmopathy but assumed that the blood flow velocity was near to zero and therefore could not be distinguished from the background noise.

In conclusion, our study has shown that at least some orbital blood flow parameters are significantly changed in patients with Graves' ophthalmopathy compared with patients with Graves' disease without ophthalmopathy and normal subjects. This means that alterations in blood flow parameters in the orbital vasculature in patients with Graves' disease may be due to Graves' ophthalmopathy rather than Graves' disease itself. Moreover, alterations in orbital arterial blood flow velocities seem to correlate with the degree of extraocular muscle enlargement. It is likely that orbital arterial blood flow velocities are increased in patients with Graves' ophthalmopathy as a result of orbital inflammation.

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