Prague opening remarks

B Boles Carenini
University of Turin, Italy

In 2001, for the first time in its life, the AISG is holding its Annual Meeting far away from its traditional venue, i.e. Rapallo. The explanation for this decision on the part of its Directive Council, approved, moreover, enthusiastically, by the great majority of its members, lies, in my opinion, in two good reasons:

1. the concomitant IGS with the weight of its programme and the number of participants, as well as the outstanding names present;
2. the attractive beauty of this famous city of Prague, so full of history and charming spots.

Our idea has been very much appreciated by our Greek colleagues, who have decided to join us in this initiative, which, on the other hand, has been supported right from the beginning as well by the organizers of IGS, Prof Melamed and Prof Schumann. To both of them go our sincere thanks for their welcome and collaboration.

Let us think of it this way, however, that a third good reason for joining our forces may lie in the desire not only to exchange ideas and knowledge, but to meet friends who, for many reasons of life, we see all too rarely and with whom it is so nice to spend some time in a pleasant atmosphere speaking of many topics not necessarily only of ophthalmology.

Also for this reason, let us succeed in respecting the times of the programme so as to have more time for enjoying ourselves.
Normal tension glaucoma

M. Roy Wilson, M. S. Creighton
University School of Medicine, Omaha, NB, USA

Partly as a result of my participation as moderator in the 1999 American Academy of Ophthalmology Glaucoma Subspecialty Day Symposium on Normal Tension Glaucoma, I have been requested to present an overview on this topic. Having made liberal use of materials provided by each of the speakers in the symposium, I wish to thank Drs Brian Lee, David Greenfield and Roger Hitchings and acknowledge their contributions. This presentation will be divided into the following four sections:

I. The misnomer of normal tension glaucoma (NTG).
II. Potentially contributing factors in the pathogenesis of glaucoma and their relevance to normal tension glaucoma.
III. Potentially differentiating characteristics between glaucoma with normal IOP and glaucoma with elevated intraocular pressure (IOP).
IV. Lessons learned from the Normal Tension Glaucoma Study.

I. The misnomer of normal tension glaucoma (NTG)

There is considerable controversy on whether normal tension glaucoma represents a distinct entity or is simply primary open-angle glaucoma (POAG) with IOP within the normal range. Because IOP is a continuous variable with no definite dividing line between normal and abnormal, many authorities are questioning whether the term normal tension glaucoma should be abandoned.

Normal tension glaucoma is typically defined as a glaucomatous optic neuropathy despite IOP consistently below 21 mmHg. The question must therefore be asked, ‘What’s so special about 21 mmHg?’ Answering that question requires a review of Leydhecker’s landmark investigation of 1958 wherein the IOPs of 20,000 eyes were obtained with Schiotz tonometry (Leydhecker et al. 1959). The mean IOP was found to be 15.5 mmHg with a standard deviation (SD) of 2.57 mmHg. Thus, two standard deviations and three standard deviations above the mean would be 20.6 mmHg and 23.2 mmHg, respectively. Assuming a normal Gaussian distribution, only 2.5% of IOPs would be expected to be above 20.5 mmHg. An inference was thus made that IOPs of 21 mmHg and above were abnormal and most likely represented glaucoma, while those above 24 mmHg most assuredly represented glaucoma.

However, population-based studies have demonstrated repeatedly that IOP is not normally distributed but is, in fact, skewed to the right towards higher pressures (Armaly 1965). Thus, normal Gaussian statistics do not apply and an IOP of 21 mmHg does not represent the upper level under which 97.5% of IOPs would be expected to be included. None the less, IOPs of 21 mmHg and higher became operationally synonymous to glaucoma in the minds of many clinicians.

The link between 21 mmHg and glaucoma was so strong that occurrences of obvious glaucomatous damage despite ‘normal’ intraocular pressures and of elevated intraocular pressures without accompanying evidence for glaucoma were considered as inconsistencies and seemed to mandate separate terminology and pathogenic mechanisms. Eyes with intraocular pressures of 21 mmHg and higher, but unaccompanied by signs of optic disc damage or visual field loss, were labelled as ‘low’ or ‘normal’ tension glaucoma.

With respect to normal tension glaucoma, there is no such disease entity – distinct from primary open-angle glaucoma – and it serves no useful purpose to continue to perpetuate this term. We know that an IOP consistently under 21 mmHg in an eye with glaucoma is not an oddity and is, in fact, quite common. There are clearly cases of POAG that seem to be independent of IOP since glaucomatous damage may continue to progress despite a lowering of IOP. However, these cases do not occur exclusively at the low end of the IOP distribution, but across the full spectrum of IOP. The term ‘normal tension glaucoma’ thus obfuscates the causal mechanism of glaucoma, particularly as it relates to the role of IOP.

II. Potentially contributing factors in the pathogenesis of glaucoma and their relevance to normal tension glaucoma

Cross-sectional surveys have consistently demonstrated that up to 50% of subjects discovered to have glaucoma have IOPs below 21 mmHg. Data from the Baltimore Eye Survey indicate that over 92% of the population have IOPs less than or equal to 21 mmHg (Sommer et al. 1991). Because of the huge size of this at-risk population, a considerable number of subjects with glaucoma will have IOPs that fall within this lower range. On the other hand, a lower proportion of persons with IOPs below 21 mmHg, and a higher proportion of people with higher IOPs, will have glaucoma. An analysis comparing the IOP distribution in the Baltimore Eye Survey with the proportion of total glaucoma contributed by various IOP levels reveals that, while only 1.2% of eyes with IOP ≤ 21 mmHg had glaucoma, the proportion with glaucoma in eyes with higher IOPs (≥ 22 mmHg) was 8.6 times that of eyes with lower IOPs (≤ 21 mmHg).

The role of IOP as a risk factor for glaucoma is almost uniformly accepted. Sceptics claim that the hypothesis ‘pressure causes glaucomatous damage’ can be refuted by considering (1) examples of eyes with high pressure and no glaucomatous damage and (2) examples of eyes with low pressure and definite glaucomatous damage. However, the lack of a one-to-one relation between elevated pressure and glaucomatous damage simply indicates that other factors are contributory in the pathogenesis of glaucoma.

Although other factors are most certainly contributory, data supporting their role in the pathogenesis of glaucoma are typically poor and often contradictory. Likely candidates include systemic immunology, systemic circulation and ocular/optic nerve blood flow.

Some published data suggest that immunological factors may play a role in the pathogenesis of normal tension glaucoma. Patients with NTG have a higher occurrence of serum monoclonal proteins and autoantibodies to extractable nuclear antigens than patients with POAG (Wax et al. 1994). Additionally, serum taken from patients with HTG, when compared to serum from patients with POAG, have increased reactivity to glycosaminoglycans, a critical component of the optic nerve extracellular matrix (Tezel et al. 1999).

Studies examining systemic circulation have provided data suggesting that (1) capillary blood cell velocity in the fingertips is significantly slower in patients with NTG (Gasser and Flammer 1999), (2) higher systemic blood pressure and frank hypertension are associated with POAG, but not NTG (Dielemans et al. 1995) and (3) patients with HTG have lower mean minimum nocturnal diastolic blood pressure than patients with POAG (Hayreh et al. 1994). However, each
of these assertions have been refuted by data from other studies (Carter et al. 1990) (Graham et al. 1995). Thus, studies regarding systemic circulation and normal tension glaucoma have generated contradictory conclusions. The greater extent of cerebral infarcts and corpus callosum atrophy found by magnetic resonance imaging in brains of NTG patients compared with POAG suggests increased neuronal degeneration, possibly on an ischemic basis, in normal tension glaucoma (Stroman et al. 1995).

Eyes with progressive HTG have been found to have a lower blood flow velocity and a higher resistive index in the central retinal artery and in the short posterior ciliary arteries than eyes with stable NTG, while no such changes were present between eyes with progressive POAG and stable POAG (Yamazaki and Drance 1997). Other studies suggest, however, that there are both a similar magnitude of decrease in the end diastolic blood velocity and similar magnitude of increase in the mean resistive index in the ophthalmic artery, the central retinal artery, and short posterior ciliary arteries in both NTG and POAG compared to normal eyes (Rankin et al. 1995; Kaiser et al. 1997).

A disc haemorrhage is a manifestation of vascular insult to the optic nerve and is more prevalent in NTG than in POAG (Kitazawa et al. 1996). This would suggest a stronger role for vascular factors in the pathogenesis of NTG. However, the response to the development of a disc haemorrhage is likely similar in both NTG and POAG. A disc haemorrhage is a prognostic indicator of subsequent progressive damage regardless of whether the eye has NTG or POAG.

III. Potentially differentiating characteristics between glaucoma with normal IOP and glaucoma with elevated IOP
There is considerable debate concerning patterns of optic disc dakage and visual field loss in normal tension glaucoma compared to high tension open-angle glaucoma. In eyes matched for total visual loss, the neoro retinal rim has been reported to be thinner, especially inferiorly and inferotemporally, in those with normal tension glaucoma (Caprioli & Spaeth 1985). Varied patterns of peripapillary atrophy may also be more common. The visual field defects in normal tension glaucoma have been described as more focal, deeper, and closer to fixation, especially early in the course of the disease, compared to what is seen commonly in high tension glaucoma (Caprioli & Spaeth 1984). However, the validity of many of the reports of purported differences between normal tension and high tension open-angle glaucoma has been disputed by other studies that have found no differences in these characteristics (Motolko et al. 1982).

The above two sections underscore the fact that no consensus seems to have been reached about the relationship between NTG and POAG. Because the optic nerve has a limited number of responses to insult, structural or functional manifestation of damage (structural–optic nerve cupping; functional–visual field defect) from widely varying mechanisms of insult can be similar. The open-angle glaucomas (high-tension and normal-tension) are essentially diagnoses based on stereotyped patterns of optic deterioration. Because the exact aetiology is unknown, some authorities have advocated for use of the term idiopathic open-angle glaucoma. I asked earlier whether NTG was fundamentally a different disease entity from POAG. To truly answer this question will require that glaucoma be characterized less by phenotype (level of IOP, appearance of optic nerve, etc.) and more by the underlying pathophysiological causes of damage at the molecular and biologic levels. Based on current knowledge, rather than dichotomizing on the basis of IOP, the consideration of glaucoma as a condition that lies across a continuum of IOP is more scientifically and clinically justifiable.

IV. Lessons learned from the Normal Tension Glaucoma Study (NTGS)
The NTGS was conducted to determine if intraocular pressure plays a part in the pathogenic process of normal tension glaucoma. One eye of each eligible subject with progressive normal tension glaucoma was randomized to be untreated as a control or to have IOP lowered by 30% from baseline. The primary paper analysed the effect of a 30% intraocular pressure on the subsequent course of the disease (CNTG Study Group 1998a). A companion paper reported an intent-to-treat analysis in which all randomly assigned patients were compared for time to progression during the course of follow-up from the initial baseline (CNTG Study Group 1998b). Endpoints were specifically defined criteria of glaucomatous optic disc progression or visual field loss.

The results of this study can be summarized as follows:

- With intent-to-treat analysis, cataract developing in the surgery group obscured the protective effect of IOP reduction.
- Correction for the cataract effect showed a survival of 80% in the treated eye and 40% in the no treatment eye.
- Lessons learned can be summarized as follows:
  - There is a beneficial effect of IOP reduction in progressive NTG. However, not all eyes respond to a 30% IOP reduction (1 in 5 did not do so) and ‘pressure independent’ factors are clearly predominant in some eyes.
  - Over a 5-year period, as much as 40% of NTG eyes may not show demonstrable progression. This fact needs to be remembered when deciding upon treatment options since aggressive lowering of IOP to levels below 8 mmHg results in appreciable risk of developing hypotony choroidopathy with its attendant visual problems.
  - There is a significant risk of hastening cataract formation with glaucoma surgery. It is therefore important to establish that progression is occurring, and to establish the rate of progression if possible, before embarking on treatment that can have a deleterious effect on vision.

The Normal Tension Glaucoma Study has confirmed that IOP reduction is an effective strategy for reducing the rate of optic nerve deterioration and visual field loss for a substantial proportion of patients with NTG. It has also shown that medical treatment may be sufficient to achieving the required IOP reduction goal in many patients.

This study has answered some important questions. However, there are lingering questions that remain. Most critical among these is ‘Which eyes will benefit from pressure lowering and which will probably not?’ An answer to this question will more precisely guide therapy for individual patients with glaucoma and its value, I suspect, will not be limited only to those with pressure in the normal range, but will also extend to those with elevated pressure.

References
Epidemiology of angle-closure glaucoma

L. Bonomi
Verona

Primary angle-closure glaucoma (PACG) is considered a fairly uncommon disease in Caucasian populations while, on the contrary, it is believed to be the most frequent form of glaucoma in the Mongolian-type populations of the world. Overall, it is considered the most widespread type of glaucoma worldwide. These conceptions are based largely on clinical impressions and on the study of hospital series, which entails a strong selection bias. A further difficulty stems from the fact that, in many studies, the definition of the disease is not clear. Some authors seem to have considered the forms characterized by acute episodes, whereas the chronic presentations may have passed unnoticed or have been classified in other categories.

It is, however, believed that the prevalence of PACG varies considerably in the different populations with its maximum among the Eskimos and its minimum in the European countries. The prevalence seems to be greater among females and in the higher age brackets (Table 1).

Table 1. Prevalences of angle-closure glaucoma in different populations (age > 40 years).

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wales, UK</td>
<td>0.09%</td>
</tr>
<tr>
<td>Bedford, UK</td>
<td>0.16%</td>
</tr>
<tr>
<td>Israel</td>
<td>0.5%</td>
</tr>
<tr>
<td>Eskimos–Canada</td>
<td>2.9%</td>
</tr>
<tr>
<td>Eskimos–Greenland</td>
<td>5.0%</td>
</tr>
<tr>
<td>Japan</td>
<td>0.31%</td>
</tr>
<tr>
<td>China</td>
<td>1.3%</td>
</tr>
<tr>
<td>South Africa</td>
<td>1.0%</td>
</tr>
<tr>
<td>Aborigines–Australia</td>
<td>0%</td>
</tr>
</tbody>
</table>

For a sound understanding of PACG epidemiology, a clear definition of its different clinical presentations is of the utmost importance. The acute attack is a very typical presentation. It may more or less regress completely spontaneously or, more commonly, as a result of treatment and normalization of eye pressure. In less favourable cases, it may evolve towards the chronicized form of angle-closure with extensive goniosynechiae and residual ocular hypertension. In the intermittent presentation, repeated self-limiting attacks occur leaving no significant goniosynechiae and IOP is normal between attacks. A chronic and progressive presentation also exists in which acute attacks never occur. In this insidious variant, symptomless goniosynechiae form gradually with silent and progressive IOP increase. This is called ’creeping angle-closure glaucoma’ and, in the absence of gonioscopy, may easily be wrongly diagnosed as open-angle glaucoma. It is believed widely that the prevalent presentation in the Caucasian race is acute PACG, while the chronic presentations predominate in Mongolian populations (Table 2).

The Egna-Neumarkt glaucoma study (Bonomi et al., 1998, 2000) was carried out on the total population over the age of 40 years in a rural area of South Tyrol. We examined 1882 men and 2415 women with...
Table 2. Clinical presentations of PACG (Bonomi 1995).

<table>
<thead>
<tr>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute attack of angle-closure glaucoma</td>
</tr>
<tr>
<td>Resolved acute attack of angle-closure glaucoma</td>
</tr>
<tr>
<td>Chronicized acute angle-closure glaucoma</td>
</tr>
<tr>
<td>Intermittent angle-closure glaucoma</td>
</tr>
<tr>
<td>Chronic progressive (creeping angle-closure glaucoma)</td>
</tr>
</tbody>
</table>

Table 3. Peripheral depth of the chamber angle according to Van Herick grading in the Egna-Neumarkt population.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>106</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>632</td>
<td>14.9</td>
</tr>
<tr>
<td>3</td>
<td>2818</td>
<td>66.7</td>
</tr>
<tr>
<td>4</td>
<td>660</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Fig. 1. The Egna-Neumarkt study: the percentage of anterior chamber angles with predisposition to occlusion (Van Herick grades 0, 1, 2) was clearly greater in women than in men.

Fig. 2. The Egna-Neumarkt study: the prevalence of occludable was increasing parallel with the age.

Table 4. Mean refraction (spherical equivalent) in relation to Van Herick grade.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number</th>
<th>Sphéquiv</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106</td>
<td>+0.74</td>
<td>±1.82</td>
</tr>
<tr>
<td>2</td>
<td>632</td>
<td>+0.61</td>
<td>±1.97</td>
</tr>
<tr>
<td>3</td>
<td>2784</td>
<td>+0.35</td>
<td>±1.93</td>
</tr>
<tr>
<td>4</td>
<td>653</td>
<td>-0.08</td>
<td>±2.37</td>
</tr>
</tbody>
</table>

Fig. 3. The Egna-Neumarkt study: prevalence of the different clinical presentations of angle-closure glaucoma. The chronic progressive type (creeping ACG) was the most frequent.

Table 5. Glaucoma prevalence in the Egna-Neumarkt study.

<table>
<thead>
<tr>
<th>Type</th>
<th>Male %</th>
<th>Female %</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACG</td>
<td>0.2</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>POAG</td>
<td>0.2</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Others</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 6. Percentage distribution of PACG according to age.

<table>
<thead>
<tr>
<th>Age</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>0.65</td>
</tr>
<tr>
<td>50–59</td>
<td>0.65</td>
</tr>
<tr>
<td>60–69</td>
<td>1.23</td>
</tr>
<tr>
<td>≥70</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 shows a clear trend towards a hyperopic shift in the classes with narrow angles. Table 5 shows the prevalence of the different types of glaucoma in the Egna-Neumarkt population over 40 years of age. The overall prevalence of glaucoma is 2.8% with a prevalence of angle-closure glaucoma of 0.6%. This prevalence is higher than those found during the study, 15 (58%) were the chronic progressive type (creeping angle-closure glaucoma), 5 were former acute attacks resolved by therapy, 3 were chronicized acute episodes and 3 were glaucomas of the intermittent type.

From the data obtained in this study, it is also evident that the theoretically occludable angles are much more frequent in the population than the cases of actual angle-closure glaucoma. The high-risk eyes (Van Herick 0–1) were 2.8% and the moderate-risk eyes were 14.9%, while actual PACG was only 0.6%.

From the Egna-Neumarkt glaucoma study we can draw the following conclusions:

1. The prevalence of primary angle-closure glaucoma is higher than usually believed, reaching to 0.6% of the population over 40 years of age.
2. Eyes biometrically predisposed to angle closure are rather frequent, but only a minimal number of them (3%) actually develop glaucoma.
3. The most frequent clinical presentation of PACG is the chronic progressive type (creeping angle-closure glaucoma). This insidious disease progresses silently without acute episodes and, in the absence of gonioscopy, may easily be wrongly diagnosed as POAG.

References

Bonomi, L., Marchini, G., Marraffa, M., et al. (2000): Epidemiology of angle-closure glaucoma. Prevalence, clinical types and association with...
Biometric data and pathogenesis of angle closure glaucoma

G. Marchini
Eye Clinic, Department of Neurological and Visual Sciences, University of Verona

Purpose
Seventy-one patients affected by various forms of angle closure glaucoma (ACG) – primary ACG, plateau iris glaucoma, malignant glaucoma and ACG secondary to uveal effusion – were submitted to a conventional echographic and ultrasound biomicroscopic (UBM) study to determine the anatomic-biometric characteristics and the pathogenetic mechanisms of the ACG. The results were compared with those obtained in a control group of 64 normal subjects.

Patients and Methods
The 71 ACG patients included 54 pupillary block PACG patients (of whom 32 were affected by the acute/intermittent form and 22 the chronic form), 9 with plateau iris glaucoma, 3 with malignant glaucoma and 5 with glaucoma secondary to uveal effusion.

The 64 normal controls were free of ocular anomalies, had a refractive error within ±1D of spherical equivalent and were comparable for sex (women 76% vs 74%) and age (64 ± 8 vs 57 ± 10 years). Only one eye was considered in each patient and subject. Each eye received:

- a conventional ultrasound biomicroscopic A-scan study with the measurement of 5 parameters: anterior chamber depth (ACD), lens thickness (LT), axial length (AL), relative lens position [RLP = (ACD + ½LT)/AL] and lens axial length factor (LAF = LT/AL) (Marchini et al. 1998), both parameters multiplied by 10;
- evaluation of the morphological characteristics of the anterior segment by UBM with recording of the anatomic relationships between the various angular and retro-iris structures;
- a UBM biometric study with measurement of the quantitative parameters described by Pavlin (Pavlin et al. 1992a). For this work, we considered: anterior chamber depth (ACD) without corneal thickness, angle opening distance at 500 µm from the scleral spur (AOD 500), trabecular–ciliary process distance (TCPD), scleral–ciliary process distance (SCP), iris–zonule distance (IZD) or posterior chamber depth.
- The biometric differences were evaluated by statistical variance analysis using the one-way analysis-of-variance (ANOVA) test with significance limit set at P < 0.05.

Results
Table 1 reports the conventional ultrasound biometry results in the 54 patients with PACG. Their differences from the normal controls were a deeper anterior chamber, a thicker lens in a more anterior position and a shorter axial length with a higher LAF. Within this group, all the parameters with the exception of axial length showed values that were statistically less in the acute/intermittent form than in the chronic form.

In these 54 patients with PACG, UBM biometry exhibited a markedly less deep anterior chamber, a thinner lens in a more anterior position and a shorter axial length than the normals. In this case, the ACD, AOD 500 and TCPD values were statistically lower in the acute/intermittent form than in the chronic form (Table 2).

The UBM morphological study showed in all 54 eyes with PACG a variable degree of anterior convexity of the iris profile of ‘bombé iris’, while the 9 eyes with plateau iris had the characteristics of a flat anterior iris profile with a sharp posterior deviation at the angle, ciliary processes forward and adherent to the iris and no ciliary sulcus.

In the 5 cases of malignant glaucoma, the ciliary processes appeared markedly rotated and thrust forward; in addition, the peripheral part of the lens was in contact with the posterior and medial wall of the ciliary processes. In the 5 eyes with ACG secondary to uveal effusion, there was a choroid–ciliary detachment which extended to the scleral

<table>
<thead>
<tr>
<th>Biometric parameter</th>
<th>Acute/intermittent PACG (n = 32)</th>
<th>Chronic PACG (n = 22)</th>
<th>Normal controls (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD (mm)</td>
<td>2.41 ± 0.25</td>
<td>2.77 ± 0.31</td>
<td>3.33 ± 0.31</td>
</tr>
<tr>
<td>LT (mm)</td>
<td>5.10 ± 0.33</td>
<td>4.92 ± 0.27</td>
<td>4.60 ± 0.53</td>
</tr>
<tr>
<td>AL (mm)</td>
<td>22.31 ± 0.83*</td>
<td>22.27 ± 0.94*</td>
<td>23.38 ± 1.23</td>
</tr>
<tr>
<td>RLP</td>
<td>2.22 ± 0.12</td>
<td>2.34 ± 0.16</td>
<td>2.41 ± 0.15</td>
</tr>
<tr>
<td>LAF</td>
<td>2.28 ± 0.12</td>
<td>2.20 ± 0.11</td>
<td>1.97 ± 0.12</td>
</tr>
</tbody>
</table>

ANOVA test for all differences: P < 0.01 to P < 0.0001 except between *. ACD, anterior chamber depth; LT, lens thickness; AL, axial length; RLP, relative lens position; LAF, lens axial length factor.
The UBM biometry results in these forms of ACG are reported in Table 3. With respect to the pupil block PACG in the plateau iris glaucoma, the TCPD was smaller and the narrowing of the anterior chamber is so marked as to produce a TCPD less than that of the PACG and a contact between ciliary processes and iris. This characteristic aspect has already been noted (Pavlin et al. 1992b) and explains the inefficacy of Ng-YAG iridotomy and surgical iridectomy in this form of ACG. In malignant glaucoma, the ciliary processes are rotated and ‘squeezed’ in front of the lens so as to reduce the TCPD to a value so small as to make unmeasurable the angle opening distance at 500 μm from the scleral spur (AOD 500). In this type of ACG, the anterior chamber and the posterior chamber (IZD) have produced the lowest depth values of our series.

Finally, in ACG secondary to uveitis effusion, the mechanism is different. In this form, all the ciliary body is rotated forward and not only the ciliary processes, with consequent and important diminution of the SCPA and TCPD values. The accumulation of liquid in the suprachoroidal space causes the forward rotation of the ciliary bodies with forward displacement of the zonule–lens–iris complex, reduction of the anterior chamber and closure of the angle.

References
Anatomical and functional damage to the optic nerve in angle-closure glaucoma

M. Marraffa
Eye Clinic, Department of Neurological and Visual Sciences, University of Verona

Purpose
It is evident from various studies that the anatomic and functional damage to the optic nerve in primary open angle glaucoma differs according to the severity of the disease. A modest cupping with a moderate retinal nerve fiber loss and a little-compromised visual field are more typical of an initial form. On the contrary, the more advanced phases of the disease exhibit more marked alterations. Little is known, however, about damage to the optic nerve and perimetrics in angle closure glaucoma. Very probably this is because angle closure glaucoma (ACG) can have different clinical pictures, from the acute to the more typically chronic. To identify the morpho-functional aspects of the optic nerve, a prospective study has been carried out in patients affected by the various clinical forms of ACG.

Patients and Methods
The 629 ACG-affected eyes of 629 patients were examined. Both eyes were taken into consideration because the disease often presented differently from a clinical point of view in the two eyes of the same subject.

We report here below the four clinical variants of ACG and their frequencies of appearance:
- Intermittent angle closure glaucoma (190 eyes): cases with repeated episodes of self-limiting angle closure, which resolved without leaving goniometsyses or residual hypertension in the intercises phases;
- Chronic angle closure glaucoma (320 eyes): cases which became chronic without ever having had an acute episode, but presented evident goniometsyses;
- Resolved acute attack of angle closure glaucoma (71 eyes): cases with evident hypertensive spikes and completely resolved with medical therapy or surgery;
- Chronicized acute angle closure glaucoma (48 eyes): cases which have had a typical acute episode followed by a residual hypertension notwithstanding therapy.

Examination was made of the visual field, the optic nerve head cup/disc ratio evaluated and nerve fibre thickness studied. The visual field was studied with the Humphrey 24–2 programme. The traditional perimetric indices were measured and considered pathologic in those defective points with a significance level of 5%. The perimetric damage was classified with the glaucoma Hemifield test. The topographic distribution of those points was found for each of the four concentric rings as proposed by Heijl. The cup/disc ratio was estimated ophthalmoscopically by an experienced operator.

Nerve fibre thickness was analysed with the instrument GDx-nerve fiber analyser. The parameter ‘the number’ was analysed, as was the presence of an asymmetry of the two principal fibre fasciculi and their diffused reduction.

Results
Tables 1–4 exhibit the results for the perimetric indices and the classification of the visual fields according to the glaucoma Hemifield test, for each clinical form of ACG. The topographical evaluation of the defect shows a greater interest of the third ring in the intermittent ACG form, with a mean of 4.1 compromised points. In the other clinical forms, however, there is a progressive extension of the damage, from the central area to the peripheral. Anatomical damage analysis shows a papilla significantly more cupped and a greater compromission of the nerve fibre layer in the chronicized forms of ACG (Tables 5 and 6).

Table 1. Intermittent angle closure glaucoma (190 eyes).

<table>
<thead>
<tr>
<th>Perimetric indices</th>
<th>Mean</th>
<th>SD</th>
<th>Classification according to GHT</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>8.8</td>
<td>±6.4</td>
<td>Within normal limits</td>
<td>61</td>
<td>32.1</td>
</tr>
<tr>
<td>CPSD</td>
<td>2.1</td>
<td>±1.9</td>
<td>Borderline</td>
<td>15</td>
<td>7.9</td>
</tr>
<tr>
<td>SF</td>
<td>2.1</td>
<td>±1.2</td>
<td>Outside normal limits</td>
<td>97</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>General reduction of sens.</td>
<td>17</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abnormally high sens.</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Chronic angle closure glaucoma (320 eyes).

<table>
<thead>
<tr>
<th>Perimetric indices</th>
<th>Mean</th>
<th>SD</th>
<th>Classification according to GHT</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>20.7</td>
<td>±7.1</td>
<td>Within normal limits</td>
<td>11</td>
<td>3.4</td>
</tr>
<tr>
<td>CPSD</td>
<td>7.4</td>
<td>±5.4</td>
<td>Borderline</td>
<td>27</td>
<td>8.4</td>
</tr>
<tr>
<td>SF</td>
<td>2.6</td>
<td>±1.3</td>
<td>Outside normal limits</td>
<td>235</td>
<td>73.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>General reduction of sens.</td>
<td>47</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abnormally high sens.</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Resolved acute attack of ACG (71 eyes).

<table>
<thead>
<tr>
<th>Perimetric indices</th>
<th>Mean</th>
<th>SD</th>
<th>Classification according to GHT</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>5.3</td>
<td>±4.8</td>
<td>Within normal limits</td>
<td>39</td>
<td>54.9</td>
</tr>
<tr>
<td>CPSD</td>
<td>3.4</td>
<td>±2.9</td>
<td>Borderline</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>SF</td>
<td>2.1</td>
<td>±1.1</td>
<td>Outside normal limits</td>
<td>28</td>
<td>39.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>General reduction of sens.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abnormally high sens.</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Primary angle closure glaucoma (PACG) is determined by the apposition of iris tissue on the angular region, which, in turn, causes a sudden increase of intraocular pressure (IOP). This clinical situation is characterized by pain and a decrease in vision. The classical treatment for PACG is medical therapy, either topical or systemic, associated with peripheral iridotomy. The crucial part of PACG treatment is IOP reduction quickly, in order to avoid permanent damage to the optic nerve. PACG medical therapy includes pilocarpine, beta-blockers, hyperosmotic agents and intravenous carbonic anhydrase inhibitors. All these systemic hypotensive drugs can have serious side-effects or be contraindicated in patients suffering from renal or hepatic failures, or congestive heart failure. Their use, in consequence, should be limited in hospitalized patients. In spite of the use of systemic and topical drugs, IOP can remain elevated and difficulties encountered in performing peripheral iridotomy. In these cases, it is important to try to open the iris with argon laser iridoplasty as primary treatment for acute angle closure glaucoma: a prospective clinical study

L. Quaranta, S. Bettelli, S. De Cillà, E. Gandolfo
Glaucoma Centre, Eye Clinic, University of Brescia

Introduction
Primary angle closure glaucoma (PACG) is determined by the apposition of iris tissue on the angular region, which, in turn, causes a sudden increase of intraocular pressure (IOP). This clinical situation is characterized by pain and a decrease in vision. The classical treatment for PACG is medical therapy, either topical or systemic, associated with peripheral iridotomy. The crucial part of PACG treatment is IOP reduction quickly, in order to avoid permanent damage to the optic nerve. PACG medical therapy includes pilocarpine, beta-blockers, hyperosmotic agents and intravenous carbonic anhydrase inhibitors. All these systemic hypotensive drugs can have serious side-effects or be contraindicated in patients suffering from renal or hepatic failures, or congestive heart failure. Their use, in consequence, should be limited in hospitalized patients. In spite of the use of systemic and topical drugs, IOP can remain elevated and difficulties encountered in performing peripheral iridotomy. In these cases, it is important to try to open the iris with argon laser iridoplasty as primary treatment for acute angle closure glaucoma: a prospective clinical study

L. Quaranta, S. Bettelli, S. De Cillà, E. Gandolfo
Glaucoma Centre, Eye Clinic, University of Brescia

Discussion
In acute ACG forms, the visual field may be normal with a percentage from 32% of the intermittent forms to 55% of the resolved acute ACG. When perimetric damage is present, this can be variable in amount. In these forms, the damage is localized prevalently in the third ring. In the chronic forms (chronic ACG and chronicized acute ACG), the visual field is damaged in over 85% of cases. The structural damage of the optic disk and of the nerve fibre layer is also less evident in the acute forms of ACG, with the disk scarcely cupped (C/D ≤ 0.3) in the intermittent ACG (40%) and the resolved acute ACG (70%). On the other hand, in the chronic forms a cupping with C/D > 0.6 is found in over 40% of cases. It must also be added that, in the resolved acute forms of ACG, there is disk atrophy without evident cupping in 15% of cases (Table 5). The nerve fibre layer is also more compromised in the chronic forms of ACG than in the acute forms (Table 6). The greater importance of the anatomic and functional damage in the ACG forms with chronic progress would lead one to think that the optic nerve can better tolerate elevated ocular pressure values, but of brief duration than more moderate but lasting ocular pressure values.

References
Iridocorneal angle mechanically. Argon laser peripheral iridoplasty (ALPI) has been proposed to try and ‘remove’ iris tissue from the angular region and thus try to restore normal levels of IOP in cases of acute PACG attack. The aim of this study was to determine if ALPI was an effective treatment for the relief of an acute PACG attack.

**Material and Methods**

Twenty-two consecutive patients were included in the study, with inclusion criteria: (a) first attack of PACG; (b) IOP ≥ 40 mmHg; (c) no previous ocular surgery; and (d) no previous administration of ocular hypotensive drugs before ALPI. ALPI was performed under topical anaesthesia with miotics. All the patients were examined by Goldmann applanation tonometry, before ALPI. IOP and corneal oedema were evaluated 1, 2 and 4 h after ALPI. On corneal clarity restoration, Nd:YAG iridotomy was carried out on all the eyes of the study.

**Results**

ALPI significantly reduced IOP within the first postoperative hour in all the eyes examined. Corneal oedema resolved in all the cases within 2 h of ALPI. In all cases, it was possible to perform Nd:YAG laser iridotomy without any difficulty or complications (Fig. 1). Gonioscopic evaluation of the angle after ALPI showed that, in 16 eyes, iridocorneal angle was visible only for small portions, even when IOP was normalized.

**Conclusion**

Our results suggest that ALPI seems to be a viable and safe procedure in the management of an acute PACG attack. This procedure is able to promptly reduce IOP and allow an optimal visualization of peripheral iris in order to perform peripheral iridotomy without complications in a short period of time.

**References**


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**Table 1.** Anterior chamber mean depth (±SD) in mm.

<table>
<thead>
<tr>
<th></th>
<th>PACG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperation</td>
<td>1.87 ± 0.25</td>
<td>2.85 ± 0.36</td>
</tr>
<tr>
<td>at 1 month</td>
<td>3.91 ± 0.28</td>
<td>4.26 ± 0.35</td>
</tr>
<tr>
<td>at 3 months</td>
<td>3.90 ± 0.33</td>
<td>4.24 ± 0.30</td>
</tr>
<tr>
<td>at 6 months</td>
<td>3.92 ± 0.30</td>
<td>4.21 ± 0.31</td>
</tr>
<tr>
<td>at 9 months</td>
<td>3.92 ± 0.31</td>
<td>4.22 ± 0.21</td>
</tr>
</tbody>
</table>

*P* < 0.001.

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**Phacoemulsification and intraocular lens implant in eyes with primary angle-closure glaucoma: our experience**

S. Di Staso, L. Sabetti, L. Taverniti, A. Aiello, I. Giuffrè, E. Balestrazzi

Department of Ophthalmology, 1University of L’Aquila, Institute of Ophthalmology 2University ‘La Sapienza’, Rome, Institute of Ophthalmology, University ‘Tor Vergata’, Rome, Italy

**Introduction**

Primary angle-closure glaucoma (PACG) is a pathology connected with anatomic alterations of the eye, especially the anterior segment. PACG eyes are characterized by a smaller corneal diameter, a less deep anterior chamber, a greater anteroposterior diameter lens, a more anterior lens position and a reduced axial length.

These particular conditions can lead to a pupillary block and iris deposition on the trabecular meshwork with peripheral synechiae formation and uncontrolled increase of intraocular pressure (IOP). A number of studies have shown evidence that PACG with pupillary block is more frequent in the 60–70 year age range and that in its pathogenesis the lens plays an important role. This study aims to verify the variations in the anatomical relationships between the anterior segment structures after phacoemulsification with IOL implant in the capsular sac and their influence on IOP.

**Patients and Methods**

We considered two groups of patients: one of 12 members (10 women and 2 men), aged between 67 and 78 years, affected with PACG and cataract (group A) and a control of 12 members (7 women and 5 men) aged between 69 and 71 years, with no ocular pathology but cataract (group B). All the patients had phacoemulsification of the cataract surgery with soft acrylic IOL implant in the capsular sac. All were carried out by the same surgeon with access through clear cornea at the point equivalent to 12 h. All the patients were examined by the HUMPHREY model 840 50 MHz ultramicroscope and the 11 HIRES 20 MHz. Measurements were made of anterior chamber depth, chamber angle width and IOP by Goldmann applanation tonometry, before the operation and at 1 month, 3, 6 and 9 months afterwards. Also measured before the operation were the lens thickness and the eyeball axial length (Table 1).

**Results**

Before the operation, group A anterior chamber depth (AC) was 1.87 ± 0.25 mm and at 9 months after the operation it was 3.92 ± 0.31 mm (*P* < 0.001), the mean increase thus being approximately 2 mm. The group B measures were, before the operation, a mean AC depth of 2.85 ± 0.36 mm and at 9 months after, 4.22 ± 0.21 (*P* < 0.001), being a mean increase of
approximately 1.3 mm. Chamber angle widths were (at the same times) for group A 19.28±5.3° and in group B 23.18±5.3° (P < 0.001), a mean approximate increase of 16.8° while for group B they were 30.25±4.8° and 38.5±4.7° (P > 0.001), a mean approximate increase of 8°. Before the operation, group A’s mean IOP was 21.5±2.6 mmHg and at 9 months 15.3±2.1 mmHg without significant variation (P > 0.5). Lens thickness in group A was 5.08±0.31 mm, in group B, 4.52±0.33 (P < 0.001). Axial length in group A was 22.02±0.86 mm and in group B was 23.18±0.82 (P < 0.05) (Table 2).

**Table 2. Angle width in degrees.**

<table>
<thead>
<tr>
<th></th>
<th>PACG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperation</td>
<td>19.28±5.3</td>
<td>30.25±4.8</td>
</tr>
<tr>
<td>at 1 month</td>
<td>36.3±4.1</td>
<td>37.9±3.8</td>
</tr>
<tr>
<td>at 3 months</td>
<td>35.8±3.8</td>
<td>38.2±4.1</td>
</tr>
<tr>
<td>at 6 months</td>
<td>36.2±4.0</td>
<td>38.1±3.9</td>
</tr>
<tr>
<td>at 9 months</td>
<td>36.1±4.8</td>
<td>38.5±4.7</td>
</tr>
</tbody>
</table>

P < 0.001.

**Discussion**

On the results obtained, we can confirm that the presence of a larger lens in an eyeball where the relationships between the CA anatomic structures are different to normal has an importance which is not negligible. Removal of the lens and the implant of a considerably smaller-sized IOL will in part go some way towards harmonizing those relationships and bring the eyeball into a state nearer to that physiologically normal. The fact that the IOP decreases significantly after IOL implant in the capsular sac of eyes affected by PACG confirms the opinions of other authors that, in these eyes, it is important to perform the lens operation before planning glaucoma surgery, always and in any case after a careful study of the anterior segment (Table 3).

**References**


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**Critical analysis of the new perimetric techniques**

E. Gandolfo

Brescia

The whole validity of the traditional automated perimetry lies in its diagnostic purposes and it remains unreplaceable in the follow-up of many visual system disturbances. Nevertheless, the development of different diagnostic tests, such as retinal nerve fibre layer and optic disc analysis or assessment of the electrophysiological responses, has shown that the sensitivity of perimetry in detecting the early signs of visual system damage can be insufficient. In addition, traditional perimetry suffers from other drawbacks characteristic of all psycho-functional tests (fatigue, learning and demotivation effects, possible simulation, dissimulation or amplification of a defect). These phenomena can be magnified by the complexity and duration of threshold perimetric tests which are, however, mandatory for a correct diagnosis and for a rational follow-up. Therefore, the experts of perimetry are working on three different research lines:

- simplification of the strategies for detecting the threshold (in order to shorten the tests and to reduce their complexity);
- elaboration of new techniques (more sensitive in detecting early perimetric damage);
- separation of the recorded visual responses from the influence of the cooperation and psychophysical state of the patients.
Fast threshold perimetric strategies
P. Capris

Department of Neurological Sciences and Vision (DNSV), Section of Ophthalmology B, University of Genoa, Italy

Automated standard perimetry is nowadays one of the most important means in glaucoma diagnosis and follow-up. Numerous attempts have been made to improve sensitivity, specificity and speed in data acquisition.

The standard ‘full threshold’ bracketing strategy to measure light sensitivity by means of a staircase algorithm with an initial threshold crossing of 4 dB increments and a final crossing of 2 dB decrements provides good reliability but is too time-consuming, with unavoidable fatigue effects. In the last 5 years new threshold algorithms, commonly defined ‘fast threshold strategies’, have been designed to reduce test time in standard clinical perimetry:

- **Dynamic strategy** (Weber 1900) (Octopus perimeter): the luminance steps in the staircase strategy are adapted to the sensitivity of the tested points (wide steps in low sensitivity points) according to the physiological threshold width in low sensitivity areas.
- **FASTPAC strategy** (Humphrey field analyser): single threshold crossing with 3 dB luminance step increases.
- **TOP strategy** (tendency orientated perimetry) (Gonzales de la Rosa 1997) (Octopus perimeter): every point of the pattern is tested only once, but each point is affected by the responses of the surrounding points to reach a final threshold approximation. A mathematical interpolation continuously adjusts the responses obtained in 4 intermingled grids of test points.
- **SITA standard** (Swedish interactive thresholding algorithm) (Humphrey field analyser): the algorithm works by the continuous estimation of measurement errors of threshold values with interruption of the staircase procedures when mathematical and statistical evaluations reach predetermined error levels. The continuous adaptation of the visual field model, starting from a previously defined one, allows further time-saving by reducing the number of presentations. The elimination of false-positive catch trials and improvement in time-pacing during the examination are other sources of reduced test duration.
- **SITAFAST**: the same expedients of the algorithm SITA for the standard strategy are applied to the FASTPAC strategy with a further time-saving.

The fast threshold strategies may be used in the standard patterns as the ‘central 24–2’, ‘30–2’ HFA or the 32, G1 and G2 Octopus with the same printout, graphical and statistical analysis that need no further experience for the evaluation of the results by the examiner.

The examination time is consistently shorter (about 50% for dynamic strategy and SITA standard, 3–5 min test time for TOP and SITAFAST) while the accuracy and the reproducibility of the fast threshold strategies are almost comparable to those of the ‘full threshold’. The examination time saving often allows better performances because of the markedly reduced ‘fatigue effect’, which is of particular importance in severely damaged visual fields.

The fast threshold strategies are useful means not only for perimetric screening for glaucoma, but are also a very reliable choice in the follow-up of the glaucomatous visual field damage, considering the short time consumption and the better acceptance by the patient, which permits more frequent examinations and, thus, a better follow-up.

Microperimetry and glaucoma
S. Miglior

Bicocca University of Milan

Glaucoma is defined as progressive optic nerve cupping and visual field damage which, ultimately, may determine loss of vision. An appropriate management of glaucoma includes the diagnosis of early changes both at the structural and functional levels.

Among the many imaging and functional techniques, microperimetry is peculiar because it allows retinal sensitivity while directly examining the fundus of the eye to be assessed. It consists in presenting the visual target in any retinal topographic region, depending on the area of interest.

In general terms, microperimetry is (and must be) a manual procedure depending on the direct interaction between the investigator and the real-time imaging of the fundus. For this reason, the clinical usefulness of this technique is limited to the evaluation of retinal sensitivity of localized retinal nerve fibre layer defects in patients with a normal standard visual field test, as its application in cases of diffuse nerve fibre layer defects or cases with established visual field changes does not add to the standard diagnostic techniques. With microperimetry, early loss of retinal sensitivity can be detected within localized nerve fibre defects, suggesting an early loss of visual function in eyes pronounced normal with standard visual field examination. Other applications in the field of glaucoma are unknown so far. Although custom automatic grid strategies have been developed with the aim of conducting an automatic threshold microperimetric examination, their clinical results have shown no advantages over standard techniques.
New techniques: frequency doubling technology perimetry, objective perimetry and flicker and motion perimetry

P. Brusini
S. Dona’ di Piave Hospital

Frequency Doubling Technology Perimetry
Frequency doubling technology perimetry (FDTP) is a new unconventional method of visual field testing which analyses selectively the My ganglionic cells, which have a very low redundancy. A small CRT monitor displays stimulus patterns of sinusoid gratings (alternate vertical black and white bars) with low spatial frequency (0.25 c/d) and high temporal frequency counterphase flicker (25 Hz). The threshold is the amount of contrast needed to perceive the stimulus and is measured in 17 visual field locations (four per visual field quadrant plus a central 5° stimulus). The central 20° visual field is tested. Test outcome appears both as a numerical table and as probability maps with five grey tones. A very swift screening programme is also available.

Objective Perimetry
A number of methods have been proposed in the last few years to obtain an objective visual field test, unlike automated perimetry, which is a psycho-physical subjective test:
- pupillo-perimetry, in which either the amplitude or the latency of pupillary responses to a bright stimulus are recorded by linking an automated perimeter to an infra-red electronic pupillometer;
- multifocal ERG, in which a number of areas (usually 103) within the central retina are stimulated by using white and black hexagonal stimuli presented on a CTR screen. The signals are recorded by a bipolar contact lens and responses are extracted from each stimulus element;
- multifocal VEP, in which pattern stimuli in a dashboard configuration are used. The recordings are collected by using two electrodes placed on the occipital scalp. Peak-to-trough amplitudes for each wave are determined.

Automated Flicker Perimetry
Automated flicker perimetry (AFP) is an unconventional testing method which measures the critical fusion frequency (the number of flickering stimuli/s at which the light does not appear to flash). AFP, like FDT, analyses selectively the magnicellular system. This technique should be more sensitive than standard automated perimetry in detecting early glaucomatous defects, but it is a lengthy and tiring test for patients. A special software has recently been created by Matsumoto to perform this technique with the Octopus 1-2-3 perimeter and will be included in the next generation of Octopus instruments (Octopus 301), together with new faster strategies. Medmont M700 automated perimeter has a programme that uses temporal modulation perimetry, where the flicker frequency is fixed and stimuli intensity increases up to perception.

Motion Perimetry
The capability to perceive movement is a particular visual ability mediated by the magnicellular system. A number of studies using different techniques have demonstrated that this ability is affected in the early stages of glaucoma. The main techniques which study the perception of movement are:
- Peripheral displacement threshold (Fitzke et al. 1990) in which two thin bars are moved from side to side above and below the blind spot up to perception;
- Motion perception perimetry (Silvermann et al. 1990; Bullimore et al. 1993; Trick et al. 1995), in which a number of stimuli have a coherent movement on a screen where random stimuli are moving;
- Random dot motion perimetry (Wall et al. 1995) in which, against a background of fixed dots, 50% of dots have a coherent movement within a circular area which is enlarged up to perception;
- Motion coherence perimetry and automated motion perimetry (Joffe et al. 1997; Bosworth et al. 1997; Brusini, 1999) in which an increasing percentage of coherent dots move within areas of various width and shape on a screen where similar dots have a random movement.

New techniques: blue/yellow perimetry – HRP(10˚)

G. Corallo
Department of Neurological and Visual Sciences (Ophthalmology Section R), University of Genoa

Short-wavelength Automated Perimetry
Colour perception has been a topic of research for many years but only recently, however, has a two-colour increment threshold technique been applied to automated perimetry for isolating the short-wavelength-sensitive mechanism. The name of the procedure was standardized to short-wavelength automated perimetry (SWAP).

The studies conducted to date indicate that SWAP is more sensitive than standard automated perimetry (SAP) for the detection of early glaucomatous visual field loss. And, moreover, SWAP also appears to be useful in detecting early or subtle visual loss in other optic neuropathies. It has been demonstrated that the S cones, which are sensitive to short-wavelength stimuli, are primarily affected by glaucomatous damage. SWAP analyses selectively this class of photoreceptors. The procedure utilizes the same
automated perimeters that are used in SAP. Also the strategies to reach thresholds are similar with the exception of the new fast strategies, which are not at present available but are in phase of development.

The main characteristics differentiating SWAP and SAP are:

- the luminance and colour of the background and
- the size and colour of the stimuli.

In SAP, the background is white and its luminance is 10 cd/m²; in SWAP, it is yellow and its luminance is 200 cd/m². In SAP, the stimuli are white and their size is Goldmann’s III; in SWAP, they are blue (500 nm) and their size is Goldmann’s V.

In addition, the maximum stimulus intensity is 10 000 cd for SAP and 16 000 cd for SWAP. The examination procedure is the same as for conventional perimeter, but some minutes are required for the patient’s adaptation to the luminance of the bowl. Some critical aspects are: the influence of lens yellowing with increasing age, which may affect SWAP sensitivity, the influence of the macular pigment, which selectively absorbs short-wavelength light (recent studies have demonstrated that this influence is not meaningful), a greater between-subjects variability and a longer ‘learning effect’ for SWAP than for SAP. However, the results for SWAP as an indicator of early glaucomatous damage are encouraging. Nowadays this technique has a widespread diffusion and the software required to apply it is now available for the majority of modern automated perimeters.

High-pass Resolution Perimetry

High-pass resolution perimetry (HRP), also named ‘ring perimetry’ because of the shape of the stimuli, was developed by Lars Friesen, from the University of Lund, Sweden. This original technique is a fully non-standard perimeter. Both the instrument and test conditions are quite different from SAP. The background is not represented by a bowl, but is a computer screen. The stimuli appearing on the screen are not bright spots changing their luminance, but are annular targets (‘rings’) changing their size. The smallest ring detected by the patient at any location defines the threshold. In other words, HRP thresholds are not differential light sensitivity thresholds, but contrast thresholds corresponding to the smallest detectable target size.

The targets are elaborated by the computer on the basis of a particular procedure named ‘high-pass spatial frequency filtering’. This procedure allows the targets to have the interesting characteristic that, at threshold level, each annular target is simply recognized as a ‘ring’ or is not detected at all. Therefore, two different thresholds coincide in time with perception: a simple ‘detection’ threshold and a more complex ‘resolution’ threshold. This property depends on the largest class (80%) of retinal ganglion cells, the parvocellular class. Parvocellular dependance might suggest that HRP could encounter major difficulties in diagnosing early stage glaucoma, where it is commonly held that magnocellular channels suffer most. Many independent investigators, however, have found HRP sensitivity at least equally as good as that of SAP, or even better. Major advantages of HRP are: short test duration (about 5 min per eye) and the possibility of estimating the rate of neural functional channels.

Five-stage glaucoma damage classification using FDT indices

P. Brusini
Department of Ophthalmology, Santa Maria della Misericordia Hospital, Udine

Introduction

Frequency doubling technology perimetry (FDT) is a new unconventional method of visual field testing, which analyses selectively the My ganglionic cells (Johnson & Samuels 1997). The test is quick and easy for the patients and results are well comparable with Standard Automated Perimetry (SAP) test results (Trible et al. 2000). However, FDT does not include any methods to calculated or stage the severity of damage, which may be of crucial interest in chronic glaucoma, both for research purposes and for day-to-day clinical practice.

Purpose

The purpose of our investigation was to investigate the possibility of using FDT, DM and DSM indices together to stage the severity of functional damage in a population of patients with chronic glaucoma.

Patients and Methods

Some 121 eyes of 77 patients affected by chronic open-angle glaucoma (mean age 61.3 ± 11.4 years; range 22–83 years) were assessed. All the patients had previously been tested with the Humphrey 30–2 (full threshold strategy) test. The stage of damage was classified on the glaucoma staging system (GSS; Brusini 1996). The distribution of the cases into GSS stages was as shown in Table 1. These patients were then tested using FDT perimetry (Welch-Allyn, Skaneateles Falls, NY & Zeiss-Humphrey Systems, Dublin, CA, USA; N-30 threshold test, which examines 17 areas in the 20° central visual field + 2 areas in the nasal periphery).

A new 2-axis diagram was created, inserting the DM and DSM indices, analogous to MD and PSD SAP indices, on the x and y axes, respectively. (Warning: DM and DSM indices normal limits are not the same as the MD and PSD limits used in the first FDT version.) To obtain this diagram, a further population of 200 glaucomatous patients was analysed previously.

The correlation between the two classification systems was studied using the gamma

| Table 1. FDT five-stages subdivision of defects in comparison with the GSS classification. |
|----------------------------------|-------------|-------------|-------------|-------------|-------------|
| Glaucoma Staging System Stages  | (no. of cases) |
| Stages                           | 0   | 1   | 2   | 3   | 4   | 5   |
| No. of cases                    | 34  | 36  | 15  | 17  | 13  | 6   |
| FDT stages                      | 0   | 30  | 5   | 0   | 0   | 0   |
| 1                               | 4   | 28  | 3   | 2   | 0   | 0   |
| 2                               | 0   | 3   | 7   | 6   | 2   | 0   |
| 3                               | 0   | 0   | 4   | 9   | 0   | 0   |
| 4                               | 0   | 0   | 1   | 0   | 9   | 0   |
| 5                               | 0   | 0   | 0   | 0   | 1   | 6   |


Different perimetric techniques to detect early glaucomatous defects

M. Iester1,2, M. Altieri1, P. Capris1, P. Vittone2, M. Zingirian1, C. E. Traverso1

1Department of Neurological and Visual Sciences, Ophthalmology B, University of Genoa, Genoa
2Division of Ophthalmology, G Gaslini Institute, Genoa

Introduction

Standard threshold perimetry is based on the detection by the patient of localized light spots shown on a homogeneously illuminated background. Many different techniques are used to assess visual field. High pass resolution perimetry (HRP) (Nikon-High Tech Vision, Malmö, Sweden) is based on resolution or acuity targets and has been proposed as an alternative to standard threshold perimetry in order to identify early visual field defects by detecting P cell loss (Frisén 1987; Frisén 1993). HRP showed a better reproducibility and also a strong capability of detection of early visual field disorganization in the perimetric glaucomatous damage.

Frequency doubling technology (FDT) (Welch Allyn, Skaneateles, NY; Zeiss Humphrey, San Leandro, CA, USA) is a perimetric technique recently introduced into the clinic. It is based on a different type of stimuli that are detected by retinal ganglion cells which have the larger mean axon diameter sizes associated with magnocellular cells (M cells) (Johnson & Demirel 1997; Quigley 1998).

The aim of this study is to evaluate the correlation between two different perimetric techniques, HRP and FDT, which theoretically detect the loss of different patterns of retinal ganglion cells: P-cells and M-cells, respectively.

Patients and Methods

Eighty-two eyes were consecutively included in the study. Patients were not excluded on the basis of media opacity, gender, age or race. Visual fields were assessed by a Humphrey Field Analyser 750 (HFA), 30-2 program, which tested the central 30’ of the visual field. Patient
refractive errors ranged from $-7$ to $+7$ dioptres. Only one eye per patient was randomly selected for data analysis.

Patients were classified as having POAG when they had a typical glaucomatous visual field, a typical abnormal ONH/RNFL, or both, open angle on gonioscopy and no clinically apparent secondary cause for their glaucoma (EGS 1998). Patients with ocular hypertension were identified if they had high intraocular pressure (>21 mmHg untreated), normal visual field and normal ONH and RNFL (EGS 1998). All the patients had their visual fields assessed by HRP and FDT.

In HRP, thresholds are determined by varying the size of the stimuli, which have fixed luminance characteristics. The stimulus is ring-shaped. Each ring is made up of a bright core with darker boundaries with a luminance of 25 cd/m², respectively. Stimuli below threshold are not visible because they vanish into the 20 cd/m² background. With this technique, as soon as the patient sees the stimulus, he also perceives its shape. In this technique, thresholds for perception (the identification of a stimulus without recognition) and for recognition (the identification of the form and margins of the stimulus) are calculated simultaneously.

Therefore, the perception of a stimulus coincides with the recognition of the stimulus, a function which involves the neuronal system sensitive to the high frequency levels of the parvocellular chain (Frisén 1989).

The FDT provides a rapid means for detecting glaucomatous and neurological visual field defects. The technique demonstrates high sensitivity and specificity and can quantify visual field loss accurately (Johnson & Samuels 1997; Iester 2000; Iester et al. 2000). The FDT presents stimuli on a black and white videomonitor with specialized control circuitry interfaced to a microprocessor. An optical system is used to display the stimulus at optical infinity, with an eye-piece adjustment provided to correct for spherical refraction errors up to 7 dioptres. During program C-20, full threshold, 17 tests are used for spherical refraction errors up to 7 dioptres. During program C-20, full threshold, 17 tests are used for spherical refraction errors up to 7 diopters. For all stimuli, the total exposure time is 2 s with a 1 s interval between trials. Test time ranges between 4.5 and 5 min. The location for each stimulus presentation is selected randomly and the contrast between black and white is modified according to the conventional ‘bracketing’ threshold strategy of the automated standard perimetry. The threshold value for each test location is defined by the minimal contrast of the pattern that is perceived.

All three functions are important in glaucoma for early diagnosis and a test exploring them is of strong clinical interest (Johnson & Demirel 1997; Johnson & Samuels 1997).

The HRP indices global deviation (GD) and local deviation (LD), and the FDT indices FDT–mean deviation (FDT-MD) and FDT–pattern standard deviation (FDT-PSD) were considered for analysis. All the data were analysed by Student’s $t$-test and Pearson’s $r$-coefficient when the distribution of the data was normal, and by Spearman coefficient correlation and Mann–Whitney test when the distribution of the data was not normal. $P < 0.005$ was considered statistically significant.

Results

Table 1 lists the demographic data of the patients considered. When the entire group was analysed, significant ($P < 0.001$) correlation was found between the HFA indices and those of HRP and FDT, as it also was when the glaucomatous group alone was considered. When the correlation between HRP and FDT indices was analysed, strong correlation was found between GD and FDT-MD ($r = 0.57$) and between LD and FDT-PSD (0.55) both for the entire group and for the glaucomatous group. Significant correlation was found in the ocular hypertensive group between LD and FDT-PSD.

Discussion

The correlation between standard threshold perimetry indices and the indices of the other perimetric techniques are of great interest in the studies concerning the early detection of glaucomatous visual field loss. It has been shown that the glaucomatous alterations of ONH and RNFL caused by nerve fibre loss precede the perimetric defect (Pederson & Anderson 1980). As it is clinically relevant to detect visual field glaucomatous damage at an early stage, an array of psychophysical tests is being investigated for this purpose. Furthermore, many new perimetric techniques are also available to detect very early visual field damage, including HRP, FDT, short-wave automatic perimetry, motion perimetry and flicker perimetry, each of which is based on a different theoretical concept (Wiesel & Hubel 1966; Breton & Drum 1996). Many studies have shown correlation between standard threshold perimetry and some of these new techniques. FDT was found to have very good sensitivity and specificity (Johnson & Samuels 1997), while a good correlation of sensitivity and specificity was demonstrated between Humphrey and FDT indices (Quigley 1998). A good correlation between FDT and Humphrey 30–2 perimetry results has been shown (Sponsel et al. 1998) and also a significant correlation between FDT and Octopus visual field (Iester et al. 2000).

A strong correlation exists between the indices of Octopus perimeter, program G14, and the indices of HRP program Ring (Dannheim et al. 1988/9) and between HFA and HRP indices (Chauhan et al. 1993). Also in this study, a significant correlation was found between FDT-MD and HRF-GD and between FDT-PSD and HRF-LD in glaucomatous patients. A further significant correlation was found between the indices FDT-PSD and HRF-LD, which showed localized damage of visual field in the ocular hypertensive group. The significant correlation suggests that early glaucomatous damage of the visual field generally starts with localized sensitivity depression.

In conclusion, these data suggest that both FDT and HRP are very useful for screening populations and detecting early glaucomatous visual field progression in early and moderate stages of the disease.
not very evident from these data are the different pathways used by the two techniques, but both new techniques seem to measure ganglion cell loss.

**References**


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**Frequency doubling perimetry in ocular hypertension and chronic open angle glaucoma**

M. Cellini, A. Torreggiani

Surgery, Resuscitation and Transplant Disciplines, Bologna

**Summary**

The authors have studied the reliability of frequency doubling perimetry (FDP) in screening glaucomatous disease and in ocular hypertension. The study was made on 30 patients affected by chronic simple open-angle glaucoma (COAG) and 30 patients with ocular hypertension. MD and PSD variations were evaluated after a W/W perimetry and after FDP. In the COAG patients, FDP confirmed the perimetric alterations found by the W/W method. In the ocular hypertensive patients, with FDP we found a significant PSD increase over that found by the W/W technique: 4.051 ± 0.822 against 2.501 ± 0.928 (P < 0.001). FDP can therefore be put forward as a valid instrument for screening even precocious perimetric defects.

**Key words:** frequency doubling perimetry – chronic simple open-angle glaucoma – ocular hypertension – white/white perimetry.

**Introduction**

Glaucomatous disease is characterized by a triad of symptoms: intraocular pressure increase, an optic neuropathy and visual field damage. The present most widespread method of evaluating visual field damage is automated white/white perimetry. Recently in optics, more sensitive investigational methods of revealing precocious neuronal suffering have been proposed, such as blue/yellow perimetry (Johnson et al. 1993) and perimetry with doubled frequency (FDP). This latter technique is based on the presentation to the patient of a low spatial frequency stimulus (less than 1 cycle/s) at high temporal frequency (over 15 Hz) in such a way as to give the optical illusion of a doubling of the number of black and white bars of the stimulus. With FDP, the functionality of the large axon ganglion cells or M cells are studied; that is, those cells which are first to feel any metabolic damage caused by ocular hypertension and/or vascular damage (Quigley et al. 1988). On the basis of these presumptions, we thought it interesting to evaluate the reliability of FDP in confirming full-blown visual field damage in chronic simple open-angle glaucoma and in pointing up initial variations of the perimetric indices in ocular hypertension.

**Material and Methods**

We studied two groups of patients. Group A included 30 patients (60 eyes) affected by ocular hypertension. Ocular hypertension was defined as an intraocular pressure (IOP) increase to above 21 mmHg without a glaucomatous optic neuropathy nor visual field alterations (Krupin 1993). Mean age was 52.6 ± 12.2 years and mean IOP was 23.8 ± 1.6 mmHg. None of these patients had any other ophthalmic or general pathologies in progress. Group B included 30 patients (60 eyes) affected by chronic simple open-angle glaucoma (COAG) with variable degrees of visual field defects. All the patients were in beta-blocking antiglaucomatous therapy. Mean age was 57.3 ± 12.06 years and mean IOP was 16.4 ± 2.1 mmHg. All the patients were examined by computed perimetry with the Humphrey 740 perimeter, programme 30.2 full-threshold and by frequency doubling perimetry with the Rapid Field Analysers (Welch Allyn Inc. Skaneateles Falls, NY, USA, distributed by Zeiss-Humphrey Co.) with full-threshold
N-30 program. All the patients had in the past experienced at least 5 conventional examinations, and with frequency doubling automated perimetric examinations. Statistical analysis took account of the mean deviation (MD) and pattern standard deviation (PSD) with the use of Student’s t-test for unpaired data and a significance P < 0.05.

**Results**

The results are exhibited in Tables 1 and 2 and in Fig. 1. The test mean time for FDP with program N-30 was 4.43 ± 1.07 min and for conventional white/white with program 30.2 full-threshold it was 10.04 ± 2.03 min. Group A (ocular hypertension) did not produce statistically significant differences in the MD, but in the PSD there was a significant increase of the index values with FDP (2.501 ± 0.928 for W/W against 4.015 ± 0.822 for FDP, P < 0.003) in 70% of the eyes examined. Group B (glaucomatous subjects) did not produce any statistically significant differences with the two methods either for MD values (P < 0.185) or for PSD values (P < 0.532).

### Table 1. Variation of the perimetric indices found by automated W/W perimetry and FDP in subjects with ocular hypertension.

<table>
<thead>
<tr>
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<th>W/W</th>
<th>FDP</th>
<th>P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>−2.154 ± 1.465</td>
<td>−1.166 ± 2.714</td>
<td>0.158</td>
</tr>
<tr>
<td>PSD</td>
<td>2.501 ± 0.928</td>
<td>4.015 ± 0.822</td>
<td>0.001</td>
</tr>
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</table>

### Table 2. Variation of the perimetric indices found by automated W/W perimetry and FDP in patients affected by COAG.

<table>
<thead>
<tr>
<th></th>
<th>W/W</th>
<th>FDP</th>
<th>P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>−6.517 ± 5.279</td>
<td>−5.590 ± 4.226</td>
<td>0.185</td>
</tr>
<tr>
<td>PSD</td>
<td>5.151 ± 3.325</td>
<td>5.474 ± 2.033</td>
<td>0.532</td>
</tr>
</tbody>
</table>

Fig. 1. Scatterplots of frequency doubling perimetry (FDP) and automatic perimetry white/white (W/W) pattern standard deviation (PSD) in ocular hypertension.

**Conclusions**

Our study showed that, in glaucoma patients, there are no statistically significant differences between the perimetric indices found by the classic white-on-white and the frequency doubling methods. In ocular hypertensive subjects, we found a statistically significant increase in the pattern standard deviation (PSD) with frequency doubling against that with automated white/white perimetry. These data confirm those of earlier studies (Brusini & Busatto 1998; Cello et al. 2000; Iester et al. 2000). We think that, by using the FDT method, the perimetric index of greater interest to evaluate, with regard to indicating precocious neurofunctional alterations, is the pattern standard deviation. The index allows us to individualize initial dishomogeneities of retinal sensitivity in the visual field compared to that of healthy subjects; that depression is caused by the loss of ganglionic large-axon M cells. With FDP, the study of ganglionic damage becomes more refined in that this method will evaluate the functionality of a subpopulation of M cells, with non-linear response, called My cells which constitute only 25% of all the magnocellular cells (Maddess & Henry 1992). FDP has shown itself very effective in revealing and/or confirming perimetric damage in glaucomatous subjects. As far as ocular hypertension subjects are concerned, FDP use in revealing preclinical, ganglionic cell anguish is to be confirmed by careful longitudinal monitoring of these patients with conventional perimetric methods. In conclusion, we consider that frequency doubling perimetry, given its speed and simplicity of execution as well as its ease of transport of instrumentation, can be regarded as a routine glaucoma screening examination.

**References**


Intraocular pressure and progression of visual field damage

B. Brogliatti, R. Rigault, L. Palanza, E. Savio, T. Rolle, A. Fea, S. Boggio Merlo
Eye Clinic, University of Turin

Summary
Contradicting results concerning IOP control and visual field deterioration are presented. Some of these inconsistencies may be due to the statistical method of analysis. Sixty POAG patients with a perimetric follow-up over 3 years were selected. Mean and maximum IOPs were considered during the same period. The patients were divided into two groups according to the IOP control (well controlled or poorly controlled). Visual field progression was defined as a reduction in sensitivity over the fifth percentile in more than four points. Mean IOPs were not significantly different in the group of patients with a visual field deterioration compared to the stable ones, but the percentage of patients with a visual field deterioration was significantly higher in patients with higher IOPs. This holds especially true if IOP below 16 mmHg (G) is considered the ‘target pressure’. IOP reduction seems to play an essential role in visual field progression. In glaucomatous patients, a strict (<16 mmHg (G)) might be necessary.

Introduction
The functional and morphological changes typical of glaucomatous neuropathy are put traditionally in relationship with intraocular pressure increase. However, the direct role of intraocular pressure increase in the aetiopathogenesis of glaucoma has recently been called into discussion. Some authors report, in fact, that from 30% to 50% of patients with typical perimetric changes do not present an intraocular pressure increase (Johnson 1993; Sample 1993) and that 90% of subjects with an intraocular pressure over and above the levels considered normal do not present a typical perimetric damage even 5 or 10 years after ocular hypertension finding (Johnson 1993; Kwon 1998). On the basis of these studies, it seems evident that intraocular pressure is not a unique determinant of the glaucomatous damage onset. There is a notable discordance of opinions concerning glaucomatous damage progression as a function of intraocular pressure control in patients with perimetric changes already demonstrated.

While some authors have reported a significant correlation between the value of intraocular pressure during treatment and the progression of perimetric deficit others, even recently, have shown that the mean pressure during a relatively long follow-up was, in patients with a damage progression, like that of those who were stable. We therefore evaluated through a retrospective study what might be the influences of tonometric compensation in a sample of glaucomatous patients with ascertained perimetric deficits of slight or medium levels.

Material and Methods
By means of analysis of the perimetric records of the Eye Clinic of the University of Turin, 160 patients were chosen who had had a sufficient number of perimetric examinations over a period of at least 5 years. Of those, at least 90 had been regularly followed up at the glaucoma outpatient department in the time with more than two annual checks. Each patient was considered with regard to: mean tonometric value over the analysis period, the maximum IOP found in that period and the type of therapy used. Perimetric damage progression was evaluated on two criteria: one eminently clinical, the other statistical. Considered progressive were the visual fields where, in at least four points, there was a sensitivity reduction greater than the fifth percentile in two or more examinations after the first.

Data analysis
We evaluated the difference of the pressor mean between the patients who had had visual field progression and those who had remained stable by Student’s t-test for unpaired samples with confidence level 95%.

To determine whether the percentage of patients tonometrically compensated was significantly different in the ‘progressive’ group to those who had kept stable, we also used the Mann–Whitney non-parametric test for analysis. For this, we used two criteria of tonometric compensation: IOP < 18 mmHg (G) and IOP < 16 mmHg (G).

Results
No statistically significant differences were found between the mean pressure in the progressive visual field group and the stable visual field group. On the other hand, the percentage of patients in tonometric compensation was significantly higher in the stable visual field group, especially if compensation is taken to mean an IOP less than 16 mmHg.

Conclusions and Discussion
Previous authors have shown that there is no significant difference between the IOP values in patients with progressive visual field and stable visual field patients. Our results agree with this observation. At least in our sample, however, we think that this method of data analysis may be amiss. In fact, few anomalous cases in the two groups can cause a dispersion of the values such that no significant difference can be revealed. Indeed, the percentage of patients in tonometric compensation was significantly higher in the group in which there was no visual field progression. That difference is significant mainly if tonometric compensation is interpreted strictly.

That observation would seem to confirm that IOP increase is the prime mover of the functional damage in the glaucomatous patient. Obviously, this does not exclude the possibility of other variables contributing to glaucomatous damage evolution. It is, moreover, important to stress that the situation of a hypertensive patient in which no perimetric damage is found even for several years after IOP alterations have been noted is different to that of a patient with ascertained glaucomatous perimetric damage. It would have been interesting in that respect to have analysed separately the progression of the damage in patients that presented a medium or high grade of perimetric defect. Unfortunately, such data analysis would have meant, even for the patient selection criteria for this study, an
extremely reduced sample and that would invalidate every statistic analysis. We consider it important, however, that such a study should be carried out and we presume that, in that case, the necessity of a strict tonometric compensation might be still more evident.

References

Visual field testing in patients with ocular hypertension and localized RNFL defects
L. Rossetti, S. Miglior, N. Incarnato, P. Fogangnolo, N. Orzalesi
Bicocca University, Milan

Purpose
To evaluate blue-on-yellow (B-Y) perimetry and frequency doubling technology (FDT) in detecting the presence of retinal nerve fibre layer (RNFL) defects in patients with ocular hypertension (OHT).

Methods
Twenty-five patients with OHT, normal standard full threshold 30’ perimetry (Humphrey 30-II) and focal wedge-shaped RNFL defects, were evaluated with scanning laser ophthalmoscopy (SLO, Rodenstock), underwent three series of examinations both with B-Y perimetry (full threshold 30-II) and FDT (full threshold N-30). The tests were repeated in order to avoid significant learning effect and their sequence was randomized. The field tests were considered normal on the basis of the visual field indices (MD and CPSD) and the glaucoma hemifield test (GHT). A probability of 5% or less was considered abnormal. The presence of RNFL defects was based on the agreement of at least 3 well-trained observers.

Results
FDT was found abnormal in 19/25 patients (76%), while B-Y perimetry was abnormal in only 5/25 (20%). This difference was statistically significant (P = 0.03). All the cases with B-Y field abnormalities were also abnormal when tested with FDT. There were 6/25 patients (24%) with RNFL defects that were found normal with all field testing.

Conclusions
FDT seemed to be more sensitive in detecting the presence of focal RNFL defects as compared with B-Y perimetry. About a quarter of the patients with OHT and focal RNFL defects were found perfectly normal at all field examinations.

Pattern electroretinogram losses underlying perimetric losses in early glaucoma
L. Scullica, B. Falsini, T. Salgarello, A. Colotto, M. G. Scullica
Institute of Ophthalmology, The Sacred Heart Catholic University, Rome

Introduction
In recent years, since ERG and PERG patterns have come into clinical practice as sensitive indices of ganglion cell dysfunction (Fiorentini et al. 1981), various studies have evaluated the quantitative correlation between the PERG measurements and the perimetric thresholds in the glaucomatous pathology. Early studies, which reported a total absence of correlation (Van den Berg et al. 1986), have not found confirmation in subsequent studies using more sensitive techniques for PERG recording. Recent studies report a significant correlation between the PERG amplitude and the mean perimetric defect in dB (mean deviation, MD).

It must be pointed out, however, that in the studies reporting an association between the two measurements, the correlation coefficient is never greater than 0.5 (see, for example, Korth et al. 1989; Falsini et al. 1991), which would indicate that the single PERG variations in patients with glaucoma or with suspect glaucoma account for no more than 25% of the variance of the corresponding perimetric losses. In this present study, this aspect of the correlation has been analyzed in greater detail in a group of patients with ocular hypertension (OHT) or early open-angle glaucoma (EOAG).

Methods
The study includes 54 patients (30 males, 24 females, mean age 52 years, range 42–64 years) with a diagnosis of OHT (27) or
EOAG (27). The OHT patients presented an intraocular pressure (IOP) \(> 21 \text{mmHg} \) on two or more separate occasions, with no clinically evident optic disk alterations (Salgarello et al. 1999) and perimetric alterations. The EOAG patients presented an IOP \(> 21 \text{mmHg} \) on two or more separate occasions, with typical glaucomatous alterations of the optic disk (Salgarello et al. 1999) and significant, reproducible perimetric defects in the Humphrey 30–2 test, with an MD \(> 8\text{dB} \). None of the patients was in therapy at the time of the examination, all of them being evaluated on diagnosis. Age and sex distribution did not differ significantly between groups. A control group of 25 normal subjects of comparable age with the patients supplied the normative PERG values.

The PERG was recorded by a method described in the literature (Salgarello et al. 1999), with the use of a sinusoidal grid with spatial frequency 1.7c/degree, moderate contrast (56%) and temporal frequency modulation 7.5 Hz. The responses were subjected to Fourier analysis in order to isolate the second harmonic component whose peak–peak amplitude was measured.

The results were analysed statistically by linear regression, including only the right eye data of each patient. The PERG amplitude values recorded in the normal subjects were used to establish the mean and the lower limits of confidence at 95% of the measurement under examination.

Results

Figures were generated that exhibited the correlational study results. The perimetric MD was expressed in dB for each patient against the logarithm of the corresponding PERG amplitude. The experimental points represented the entire group of patients, without distinguishing between OHT and EOAG. It could be seen that, despite a highly significant correlation, the correlation coefficient was only 0.54, which is not very much higher than that found in the literature. The same graph showed the limits of normality (95% confidence) of the MD and the PERG amplitude (horizontal and vertical lines, respectively). It could also be seen that there is a substantial number of patients whose PERGs are significantly altered while the perimeters are normal. The opposite situation, normal PERG/altred perimetric value, was on the whole found less in the graphs. These results indicate that the relatively low correlation coefficient may be explained by the fact that the PERG alterations are often not accompanied by perimetric losses of a comparable amount. This aspect was examined in greater detail, where the perimetric losses of each patient were considered as a function of percentage losses (therefore on a linear scale) with respect to the mean normal value of the PERG amplitude, the OHT and the EOAG patients being evaluated separately. Given the change of scale on the x-axis, the straight line obtained described a curvilinear relationship. From this the deduction was that most of the patients with significant PERG loss and normal visual field are, as was to be expected, patients with OHT. It also appears clear from the prediction of the regression curve that, to obtain a minimally significant perimetric loss (2 dB), there must be already a PERG amplitude loss of the order of 60%.

Discussion

These data supply evidence that the retinal functional deficits in glaucoma begin before any perimetric defect develops, and that the relationship between these deficits and the perimetric deficit is better described by a logarithmic rather than a linear function. The correlations between PERG perimeter put in evidence in this study agree with the histological studies conducted both on man and on monkey with the aim of evaluating the relationship existing between ganglionic cell loss and the amount of corresponding perimetric defect (Quigley et al. 1989; Harwerth et al. 1999). Furthermore, the results of this present study suggest that the PERG alterations in EOAG do not reflect only a neuronal loss, but may be the combined expression of the cellular dysfunction before the loss and the loss itself. It may be presumed that the complex cortical neuronal circuitry may be able to compensate, at least in part, the dysfunctions or neuronal losses that are demonstrated in the peripheral stations of the visual pathway, and therefore explain the results observed.

In conclusion, the analysis of the PERG and perimetric loss correlations in EOAG indicates that the conventional automatic perimetry is not a faithful indicator of the early deficits in the internal retina associated with ocular hypertension, and that the PERG is a test suitable to precociously put in evidence functional damage in glaucoma. The present results also confirm earlier experimental evidence and support the clinical conviction that a substantial damage of the retinal ganglionic cells takes place before visual field defects appear. Therefore, therapeutic action aimed at ocular pressure reduction and at obtaining a neuroprotective effect on the ganglionic cells should have an optimal efficacy in the very early stages of the disease.

References


Effects of acute topical administration of clonidine 0.125%, apraclonidine 1.0% and brimonidine 0.2% on visual field parameters and ocular perfusion pressure in patients with primary open-angle glaucoma

A. Sebastiani1, F. Parmeggiani1, C. Costagliola1, M. Ciancuglini2, E. D’Oronzo2, L. Mastropasqua2

1Department of Ophthalmology, University of Ferrara, Ferrara
2Department of Ophthalmology, G. D’Annunzio University of Chieti, Chieti, Italy

Introduction

Brimonidine is a less lipophilic analogue of clonidine (Chien et al. 1990) and, like apraclonidine (Robin 1988), provides clinically significant reduction in intraocular pressure (IOP) (Shin et al. 1999). Preclinical studies on brimonidine have documented that it is a potent α-2 adrenoceptor agonist, 1000-fold more selective for the α-2 vs α-1 adrenoceptor. Brimonidine α-2 selectivity is 7- to 12-fold greater than clonidine and 23–32-fold greater than apraclonidine (Burke & Schwartz 1996). The aim of our study was to determine the effects of clonidine 0.125%, apraclonidine 1.0% and brimonidine 0.2% on visual field parameters and ocular perfusion pressure in patients affected by primary open-angle glaucoma (POAG).

Patients and Methods

A randomized, double-masked clinical trial was carried out. Thirty-two POAG subjects (15 men, 17 women, mean age 65.25 ± 5.69 years; range 55–76 years) were enrolled. Informed consent to participate in this clinical trial was given by each patient. Visual field (30–2 full threshold program) was measured by the Humphrey field analyser. The best corrected visual acuity was 20/25 or better, with a range of ametropia between −3 and +2 spheric diopters and ±2 cylinder diopters, with a pupil diameter of at least 3 mm (Johnson 1996).

A baseline determination of brachial artery systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), bilateral IOP and visual field was performed in each subject. The patients were separated randomly into 4 study groups of 8 POAG subjects (16 eyes) to receive in both eyes either clonidine 0.125% (group A), or apraclonidine 1.0% (group B), or brimonidine 0.2% (group C), or placebo (group D) 2 h before the repetition of the clinical evaluations previously described (Table 1). All tests were performed, between 7:30 a.m. and 10:30 a.m., in two separate sessions, 48 h apart.

The comparisons between the baseline and α-agonist-induced values were made for the following parameters of each patient or each eye: mean blood pressure [MBP = DBP + 1/3(SBP – DBP)], HR, IOP, ocular perfusion pressure [PP = 2/3(MBP – IOP)] (Mastropasqua et al. 1998a); moreover, a comparison among the visual field indices [mean defect (MD), pattern standard deviation (PSD), short-term fluctuation (SF) and corrected pattern standard deviation (CPSD)] before and after the treatments was performed. A non-parametric test for paired data was used to compare MBP, HR, IOP, PP and visual field parameters at baseline and 2 h after α-agonist acute

Table 1.

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>clonidine 0.125% patients</td>
<td>apraclonidine 1.0% patients</td>
<td>brimonidine 0.2% patients</td>
<td>placebo patients</td>
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<td>(3 men, 5 women; mean age 66.12 ± 6.99 years; range 55–76 years)</td>
<td>(5 men, 3 women; mean age 64.37 ± 6.11 years; range 56–76 years)</td>
<td>(2 men, 6 women; mean age 64.87 ± 5.48 years; range 59–73 years)</td>
<td>(5 men, 3 women; mean age 65.62 ± 4.98 years; range 57–71 years)</td>
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<td>Average</td>
<td>SD</td>
<td>P</td>
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<td>1.51</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPSD pre</td>
<td>2.3</td>
<td>1.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CPSD post</td>
<td>2.92</td>
<td>1.21</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SD, standard deviation; MBP, mean blood pressure (mmHg); HR, heart rate (during a minute); IOP, intraocular pressure (mmHg); PP, ocular perfusion pressure (mmHg); MD, mean defect (dB); PSD, pattern standard deviation (dB); SF, short-term fluctuation (dB); CPSD, corrected pattern standard deviation (dB). Non-parametric test for paired data was employed for statistical evaluation. A P-value <0.05 was considered.
administration. A probability of $P < 0.05$ was considered statistically significant.

**Results**

The topical administration of $\alpha$-agonist compounds significantly reduced IOP in all groups ($P < 0.01$). At the IOP lowering effects, topical clonidine administration also exhibited a marked reduction in MBP ($P < 0.01$) which, in turn, further affected the PP ($P < 0.001$). Consequently, most visual field parameters (MD, SF and CPSD) were modified negatively by the treatment (Table 1). On the contrary, acute application of apraclonidine not resulted in significant PP modification, whereas brimonidine eye-drop induced a slight positive tendency between the statistical comparison of PP values ($P = 0.16$). Moreover, while apraclonidine eye-drops caused a significant worsening in MD ($P < 0.05$), SF ($P < 0.05$) and CPSD ($P < 0.01$), the acute brimonidine instillation did not induce any significant modification of the visual field indices (Table 1). Lastly, no significant variation in the ocular and systemic parameters was observed after placebo administration (Table 1). Neither placebo nor $\alpha$-agonists topical administration induced any HR significant variation.

**Discussion**

Ocular blood flow, including the haemodynamic condition of the optic nerve head, depends on the relationship between IOP, PP, vascular resistance and the presence or absence of blood flow autoregulation. The comparison between baseline and drug-induced values of PP and visual field parameters, represents an indirect evaluation of the retinal microvascular blood flow modification after administration of different $\alpha$-agonist antiglaucomatous eyedrops.

Our findings demonstrate that the acute administration of clonidine, apraclonidine and brimonidine produces a significant IOP reduction in POAG patients treated chronically with other antiglaucomatous eyedrops. Moreover, our data show a worsening of PP and visual field parameters after acute administration of clonidine, which is related to both central and peripheral actions of this less selective $\alpha$-agonist compound (Kriegstein et al. 1978; Yuksel et al. 1992). Also the apraclonidine instillation induces a visual field deterioration, despite the IOP lowering effect and the consequent PP increase, indicating a possible $\alpha$-mediated vasoconstriction of the posterior pole microvasculature (Mastropasqua et al. 1998a). The comparative evaluation of MBP and HR data confirms the results of previous studies (Jampel et al. 1988; Mastropasqua et al. 1998a), demonstrating the absence of significant cardiovascular changes after topical administration of apraclonidine, yet systemic blood pressure cannot always be considered a true reflection of blood pressure in the intracocular vessels (Hayreh 1989). On the other hand, bromonidine application does not result in any significant visual field parameters worsening, as already demonstrated, employing the blue-yellow perimetry (Mastropasqua et al. 1998b). Moreover, the significant IOP reduction secondary to bromonidine instillation was not associated with MBP modifications, contrary to that occurring with the application of clonidine and apraclonidine. The moderate PP increase observed after bromonidine administration ($P = 0.16$) emphasizes the critical role of its peculiar $\alpha-2$ selectivity when bromonidine effects are compared to those of the other $\alpha$-adrenoreceptor agonists. Although bromonidine is a relatively selective $\alpha-2$ agonist, our results suggest that its acute administration do not critically affect the blood flow or the vasomotor activity at the level of the posterior pole.

The knowledge of the systemic and ocular effects secondary to the administration of $\alpha$-agonist eyedrops is crucial as POAG-treated patients undoubtedly have drug-induced alteration of their basal adrenergic tone. Thus, clonidine or apraclonidine prescription should be avoided as so not to cause further blood perfusion reduction or a critical vasoconstriction at the level of ocular posterior segment, whereas bromonidine selectivity circumvented such side-effects.

**References**


Ibopamine test and frequency doubling perimetry in early glaucoma diagnosis

M. Virno, F. D. E. Gregorio, S. Saccucci, M. J. Angelini, M. Palmieri
Institute of Ophthalmology, ‘La Sapienza’ University, Rome

Aims of the study
The aims of the study were to evaluate the usefulness of frequency doubling perimetry (FDT) and the ibopamine test in the early diagnosis of open-angle glaucoma.

Material and Methods
Twenty-four eyes of 24 patients (mean age 53 years, SD 11.5, M/F = 14/10) with initial signs of glaucomatous optic disease and 16 eyes of healthy volunteers (mean age 54.2 years, SD 13.6, M/F = 8/8) were chosen. An ibopamine provocation test and a full-threshold C-30 program FDT perimetric examination were carried out. Calculations were made of the FDT perimetric examination sensitivity and specificity and of the combined FDT and ibopamine test. Data analysis variables were the mean deviation (MD), the number of altered points and the pressure increase after the ibopamine test.

Results
The MD index sensitivity and specificity were 46% and 81%, respectively, for values < -1 dB. The number of altered points parameter sensitivity and specificity were 54% and 94%, respectively, with cut-off point least two altered points in the visual field. If the MD index and IOP variation after ibopamine (> 3 mmHg) are taken together as the diagnostic criterion, the sensitivity and specificity are considerably increased to 92% and 100%, respectively.

Conclusions
FDT perimetry points up early functional alterations in eyes with initial glaucomatous neuroptiopathy, but the sensitivity of the examination is rather low. The ibopamine test is known to be a test for the early alterations of the outflow pathways that can contribute to the onset or evolution of glaucomatous damage. The associated test use of ibopamine and FDT perimetry provides an optimal diagnostic accuracy and good sensitivity and specificity values.

The influence of photorefractive keratectomy on frequency doubling perimetry patterns

M. Vetrugno, N. Cardascia, G. M. Quaranta, C. Sborgia
Eye Clinic, Department of Ophthalmology-Otolaryngology, University of Bari

Introduction
Frequency doubling perimetry (FDP) has been developed recently to detect early functional alterations in patients progressing towards glaucoma (Maddess & Henry 1992; Quaranta et al. 2000; Choplin & Lundy 2001).
It is based on the retinal perception of a rapid contrast reversal in which the light bars become dark and vice versa. This phenomenon is known as frequency-doubling illusory when the stimulus has a low spatial frequency (<1 cycle/degree) and a high temporal frequency (>15Hz) (Johnson & Samuels 1997). This perimetry provides evidence of M-cell function at eccentricities up to 30°. Impaired critical flicker frequency may be due to an abnormality in M-cell and fibres, but requires transparency of the dioptric means.
Eyes which have undergone photorefractive keratectomy (PRK) have shown reduction of contrast sensitivity (CS) for variable periods of time. This CS, measured by various subjective and objective methods, was related to the amount of myopia and, consequently, to the depth of corneal ablation (Seiler et al. 1992; Vetrugno et al. 2000). The aim of this study was to evaluate the FDP patterns in eyes which had undergone PRK and did not show any change towards glaucoma.

Material and Methods
In January and February 2000, 32 consecutive patients required excimer laser surgery for myopia at the eye clinic of the University of Bari and were considered eligible for this prospective study after written informed consent was obtained. Pre-operative assessment consisted of a complete ophthalmic examination, including gonioscopy and static automated perimetry in order to exclude glaucoma. Exclusion criteria were: history of ocular disease, previous refractive treatment, contact lens worn in the previous 2 months, diabetes, lupus or other collagen disorders, wound healing disorders (e.g. keloids) and myopia above -7D. Twenty patients met all the preoperative criteria and were enrolled in our study. All the surgical procedures were performed by the same surgeon (MV), using Laserscan 2000 (LaserSight, Orlando, FL, USA).

All the data were recorded on the control eyes. Post-operative exclusion criteria were: haze above grade 2 (three patients) and steroid-induced ocular hypertension (one patient).

We used the frequency doubling perimetry (FDP) device (Welch Allyn, Zeiss Humphrey, San Leandro, CA, USA), threshold c-30 program (17 test areas in 20° field and 2 in lateral 30°). As baseline for our study, we took only the second preoperative FDP performed by the patient, the first one being considered as part of the learning curve for this diagnostic tool.

Results with more than 30% of false positive, false negative or fixation loss were excluded. MD and MSD parameters were analysed at baseline (15 days before surgery) and at week 2, month 3 and month 6 time-points.

All the data were recorded on a spreadsheet and analysed using GraphPad InStat.
Results
The 16 patients had a mean age of 32.63 ± 4.79 years. In the treated group, mean spherical equivalent (SE) was −5.03 ± 2.07 dioptres and the mean ablation depth was 56.17 ± 23.67 μm. The control group was made up of the fellow eyes with mean SE of −4.95 ± 1.97 dioptres. No differences were found in SE between the groups (p = 0.96). MD and MSD did not show any statistical difference between the groups at each timepoint. Longitudinally, MD and MSD did not vary during the follow-up in any of the eyes (MD: PRK P = 0.41, control P = 0.99; MSD: PRK P = 0.26, control P = 0.99). MD was influenced by ablation depth only during the first 2 weeks postsurgery (baseline r = 0.70, P = 0.25; 2 weeks r = 0.80, P = 0.002; 3 months r = 0.52, P = 0.061; 6 months r = 0.49, P = 0.055). MSD was not affected by ablation depth at any point (baseline r = −0.05, P = 0.86; 2 weeks r = −0.35, P = 0.18; 3 months r = −0.54, p = 0.065; 6 months r = −0.49, P = 0.052).

Discussion
Since previous studies established a relationship between ablation depth and changes in either contrast sensitivity or retinal fibre layer readings (Vetrugno et al. 2000) this study’s aim was to evaluate whether corneal depth changes may affect FDP postoperative measurements.

According to our longitudinal analysis, PRK does not affect FDP measurements. A significant correlation between ablation depth and FDP patterns was established only during the first two weeks after PRK.

Stromal ablation depth affects corneal transparency. Moreover, centripetal migration of keratocytes from peripheral ablated area could be involved in PRK-induced transparency loss. These findings might indicate a direct relationship between stromal wound healing after PRK and contrast sensitivity examination. Even though stromal reaction is completed in 2–6 months, our data demonstrate that it might influence FDP only in the first 2 weeks after laser surgery. Finally, patients who underwent PRK may be screened with FDP and accurate and reproducible results obtained that are useful in detecting glaucoma and in monitoring its progression.

References

Introductory remarks to the Round Table
B. Boles Carennini
University of Turin

Glaucoma is a disease characterized by loss of retinal ganglion cells and their axons. This damage is irreversible, so the best way of dealing with glaucoma is early diagnosis for an immediate and appropriate treatment. Since Helmutz introduced the augenspigel, which Anagnostakis modified and called the ophthalmoscope (1851), and since Graefe described the optic nerve damage in glaucoma (1855), the appearance of the optic nerve head (ONH) has been used to assess the presence and the progression of the disease.

However, the interpretation of the ONH is subjective and there is wide variation between observers and even between examinations by the same observer in the evaluation of optic disc characteristics. Attempts at the production of objective tools devised to enable an early and sure diagnosis of the disease, and to point out its possible progression, although started at least half a century ago, have shown the greatest advantages only in the last 20 years. One of the oldest and simplest technologies is the stereoscopic ONH photography, extremely useful, permitting an objective permanent recording of the ONH aspect and giving the possibility to observe changes with time. Unfortunately, even experts of value are not able to agree from the photographs on discriminating between normal and glaucomatous disc. Also, the ONH analysers proposed before the development of the confocal scanning laser ophthalmoscope (SLO) did not pass the sieve of time for their variability, lack of resolution and high cost. The SLO giving and analysing a sequential series of coronal sections deeper and deeper through the ONH provides a bulk of information regarding the structure of the optic nerve head in a reliable and comfortable way, since only one spot on the retina is illuminated at any given time. The SLO may today be considered as the gold standard for the examination of the optic disc.

The acquisition about 30 years ago, that a decreased thickness of the retinal nerve fibres (RNF) may be observed as an earliest sign of glaucoma, certainly before the abnormalities of the optic disc and/or the visual field, pushed the investigators to find technologies sophisticated enough to measure this significant sign. This, also, since the clinical direct observation of NFL with the slit lamp or with the ophthalmoscope and/or by photography are methods both subjective and difficult to evaluate and quantify.

To perform objective and quantitative NFL measurements, there are today two different techniques: polarimetry and optical coherence tomography (OCT). The first is
based on the projection into the eye of a polarized light and the measuring of the change in the rotation of this light on its exit from the eye. OCT, as we all know, uses an interferometer with low coherence light to produce a bidimensional cross-sectional retinal image permitting a quantitative measurement of NFL thickness.

Thanks to these two technologies, it is possible to have objective and quantitative information very important for an earlier diagnosis of glaucoma and the changing of the glaucomatous picture with time.

OCT in glaucoma

R. G. Carassa

Department of Ophthalmology and Vision Sciences, S. Raffaele Hospital, Milan

In the last 10 years, thanks to rapid electronic technological development, there has been intense research in systems and methods for quantifying retinal and optic disc morphological modifications caused by glaucomatous disease. In particular, we have helped to develop instruments aimed at optic disc analysis, which can quantify excavation amount and depth and the thickness of the neuroretinal margin, as well as systems to furnish us with data about the peripapillary ganglional fibre layer thickness. These latter have proved especially useful in the study of glaucoma. It has, in fact, been shown that in 60% of eyes affected by glaucomatous periglaucoma there was already evidence of an alteration in the nerve fibre layer thickness. These latter have proved especially useful in the study of glaucoma. It has, in fact, been shown that in 60% of eyes affected by glaucomatous periglaucoma there was already evidence of an alteration in the nerve fibre layer thickness. These latter have proved especially useful in the study of glaucoma.

A new system of non-invasive diagnostic imaging providing images of ocular structure sections. It was put forward in 1991 by Huang and coworkers (Huang et al. 1991) and developed for clinical use by Schuman & Piliafito, who used it for retinal and macular pathology diagnostics as well as for retinal nerve fibre layer quantification in glaucoma (Schuman et al. 1995). Its high resolution power makes it a particularly suitable system for thickness measurements.

OCT is a system comparable with B-scan echography with the difference that uses luminous energy instead of sound energy. The light is projected onto the fundus of the eye and, with low coherence interferometry, the delay times of the reflected rays from the different retinal layers are measured. This process requires the analysis of two light beams, one for the measurement and the other as reference. The main light beam, produced by a superluminescent diode, is divided into two secondary beams by the semitransparent mirror of the Michelson interferometer.

The measurement beam, directed inside the eye, is reflected by all the interfaces separating structures of different optical behaviour and therefore with different refraction indices: vitreous-neuroretina, sensory retina-pigmented epithelium, and so on. The instrument measures the interference that takes place between these multiple reflections and that reflection generated by the second beam produced by the reference arm, whose length is varied during the measurement. The signal so obtained is made up of a time sequence of impulses corresponding to the space sequence of the various structures met by the beam inside the eye with information as to reflectance and absorbance.

By combining this depth measurement with a lateral scan, bidimensional maps are obtained corresponding to the plane sections of the eye. These maps are shown with false colours in order to differentiate tissues with different optic properties: those with high reflectivity are in white or red and those with low reflectivity in blue or black. It must be emphasized that OCT provides information about the optic properties of the tissue and not its morphological characteristics. The system has a very high axial resolution of only 10 μ which allows a perfect differentiation of the retinal components in particular, so far as our argument is concerned, both of the optic disk and its various parameters and above all of the nerve fibre layer without the necessity of arbitrarily fixing a reference plane.

By means of a linear scan, the instrument can reproduce a section image of the optic disk region, thus allowing quantification of cupping depth and wall slope. A new analysis software with a series of radial linear scans also makes it possible to reconstruct a map of the optic disk by quantifying the area of the disk and the excavation, the neuroretinal margin area and the C/D relationships both for the disk as a whole and for the various sectors.

The system’s intrinsic characteristics, however, make it particularly suited to quantifying the peripapillary retinal nerve fibre layer thickness. For this analysis the system has a program to measure the height of the layer along a peripapillary circular zone of 3.4 mm diameter centred on the optic disk. Each scan consists of 100 A-scan measurements (one every 3.6 degrees). The fibre layer is differentiated from its surrounding structures by an algorithm for margin recognition, and the thickness is calculated by counting the pixels between the anterior and posterior margins. The program provides the measurements for the superior, inferior, nasal and temporal quadrants and for the disk divided in 12 sectors. The new software of the system also allows the thickness curve to be superposed within the interval of normality for a simpler evaluation of the results. In this way, it is easier to identify and quantify any thinning of the peripapillary retinal fibre layer and evaluate any modifications with time.

The data supplied by the system are highly reproducible and in excellent correspondence with the perimetric functional data (Schuman et al. 1996; Blumenenthal et al. 2000).

In a recent study (Pakter et al. 2000), Schuman and coworkers evaluated retinal nerve fibre layer thickness by OCT in 1483 eyes: 386 were normal, 455 suspect glaucoma (with ocular tension between 24 and 30 mmHg, normal perimetry and papillary alterations), 399 were affected by initial glaucoma and 243 by advanced glaucoma. The results first put in evidence in normal subjects an inverse correlation between fibre thickness and age with a reduction of 0.35 ± 0.05 μm/year. There were therefore thickness differences among the various groups, with higher values in the normal subjects (119.3 ± 1.0 μm) with respect to those with suspect glaucoma (110.9 ± 1.3 μm), initial glaucoma (97.6 ± 1.3 μm) or advanced glaucoma (64.2 ± 2.0 μm). In general the...
The macular thickness and volume in glaucoma: an analysis in normal and glaucomatous eyes using OCT

A. Giovannini, G. Amato, C. Mariotti
Institute of Ophthalmology, University of Ancona, Italy

Summary

Purpose: To evaluate macular volume in normal and glaucomatous eyes using Optical Coherence Tomography (OCT).

Methods: Fifty eyes of 30 patients (age: 49–68); 20 eyes normal, 15 eyes with early glaucoma and 15 eyes with advanced glaucoma have been studied with the commercially available OCT unit (OCT 2000) (Humphrey Zeiss, Dublin, CA, USA). All eyes were examined at a scan length of 3.44 mm vertically across the fovea. OCT macular retinal thickness maps were used to calculate macular volume.

Results: We observed significant differences between groups. Normals $(7.35 \pm 0.455 \text{ mm}^3)$ and early glaucoma $(7.09 \pm 0.475 \text{ mm}^3)$, each had significantly greater volume than subjects with advanced glaucoma $(6.678 \pm 0.455 \text{ mm}^3)$.

Conclusions: Volumetric analysis of macular thickness with OCT tomograms may be a useful method of documenting and monitoring patients with early glaucoma and advanced glaucoma. In our analysis, and according to the observations of other authors, OCT macular volumes correlates significantly with glaucoma status.

Introduction

Optical coherence tomography (OCT) is a noninvasive, noncontact, trans-papillary imaging technology that can image retinal structures in vivo with a resolution superior to other in vivo imaging techniques such as scanning laser ophthalmoscopy, B-mode ultrasound and ultrasound biomicroscopy (Huang et al. 1991; Hee et al. 1995; Puliafito et al. 1996). This technique provides cross-sectional and tomographic images of the posterior segment of the eye produced using optical backscattering of light in a fashion analogous to B-scan ultrasonography. Operation of OCT is analogous to ultrasound, but OCT utilizes reflections of infrared light waves from different structures in the eye rather than acoustic waves. OCT is based on the principle of low-coherence interferometry, which measures the time of flight delay of light reflected from different structures of the eye. The probe beam is directed into the eye, and reflections from tissue interfaces provides information about the distances and thickness of the ocular structures. The longitudinal resolution (experimentally measured as 14 μ in air and 10 μ at the retina) of OCT is based on the coherence length of the source light. Two dimensional B-mode images are created by performing serial longitudinal scans in transverse direction, and each tomogram is composed of a sequence of 100 A-scans, acquired in 1 s. The final image
of optical reflectivity is displayed in false colors. Although the main applications of OCT are represented by retinal diseases, and alterations of the vitreo-retinal interfaces, many reports have been published on glaucoma applications.

OCT has been previously demonstrated to detect changes in tissue thickness with micrometer-scale sensitivity (Izatt et al. 1994). The RNFL is highly backscattering and therefore is contrasted from the intermediate retinal layers because the nerve axons are oriented perpendicularly to the OCT probe beam. With a prototype instrument, OCT data were collected and reported to correlate with the topography of humans retinas (Hee et al. 1995). OCT has also demonstrated to be able in detecting and well evaluating the induced RNFL changes in monkey (Toth et al. 1997). Many Authors have reported on OCT reproducibility, and have demonstrated Standard Deviations (SD) of RNFL and retinal thickness measurements of approximately 10–20µ (10–20%) in normal and in glaucomatous eyes (Schuman et al. 1995; Schuman et al. 1996; Bausman et al. 1998; Bowd et al. 2000). OCT measurements of nerve fiber layer thickness correlates with functional status of the optic nerve, as measured by visual field examination (Schuman et al. 1995), and it appears promising as a tool for early diagnosis of glaucoma (the soon incoming OCT3 instrument, with a resolution of 8 µ, will guarantee better information).

Many retinal diseases induce a change in retinal thickness that can be monitored by OCT. Based on the rationale that alterations in thickness reflect a change in retinal volume, the estimation of the macular volume may be useful for the follow-up of most retinal diseases (Puliafito 2000). The possibility to calculate the macular volume based on thickness and in an uncomplicated way may have clinical utility. The purpose of our study is to evaluate macular volume in normal and glaucomatous eyes using OCT, and to assess the correlation of macular volume with the glaucoma status (Schuman et al. 2001).

OCT images were obtained with a commercial version OCT scanner (OCT 2000 version). A cross sectional image was displayed in a false-colour scale, which indicated the different reflectivity of the retinal layers. A computer algorithm was used to profile the inner and the outer retinal boundaries, and the retinal thickness was computed automatically from these boundaries by assuming a constant refractive index.

The macular map consists of six radial scans intersecting at the fovea, with a scanning diameter of 6 mm, and on each scan the thickness has been measured at 100 points: the software analyses 600 total thickness measurements in order to obtain the macular volume.

The volumetric study is based on the rationale that 600 thickness measurements represented as average thickness in nine regions, and the weighted average thickness

Fig. 1. Macular volume of a normal eye: 7.5 mm³.

Fig. 2. Macular volume of a glaucomatous eye: 5.97 mm³.
of the nine regions multiplied by the scanning area provide volume estimate (the weighted average thickness \( (T_r)^2 \times \text{volume} \))^\(^{111}\).

### Methods

50 eyes of 30 patients (age: 49–68); 20 eyes normal, 15 eyes with early glaucoma and 15 eyes with advanced glaucoma have been studied with the commercially available OCT unit (OCT 2000) (Humphrey Zeiss, Dublin, CA, USA). All eyes were examined at a scan length of 3.44 mm vertically across the fovea. OCT macular retinal thickness maps were used to calculate macular volume.

### Results

We observed significant differences between groups. Normals (7.35 ± 0.455 mm\(^3\)) and early glaucoma (7.09 ± 0.475 mm\(^3\)), each had significantly greater volume than subjects with advanced glaucoma (6.678 ± 0.455 mm\(^3\)) (Fig. 2).

### Conclusions

Volumetric analysis of macular thickness with OCT tomograms may be a useful method of documenting and monitoring patients with early glaucoma and advanced glaucoma. In our analysis, and according to the observations of J. Schuman\(^{111}\), OCT macular volumes correlates significantly with glaucoma status.

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### GDx in glaucoma

**S. Miglior**

Bicocca University of Milan

**Summary**

The purpose of this paper is to review the clinical applications of GDx in the diagnosis and follow-up of glaucoma. The limits and potential of GDx technology are discussed.

**Introduction**

The GDx is a scanning laser polarimetry for measuring the change in polarization (retardation) of the light reflected from the fundus of the eye after crossing the RNFL, which is characterized by the physical property of double refraction. As such a retardation is correlated strongly with RNFL thickness, an accurate measurement of this retinal layer can be had (Weinreb et al. 1990).

The GDx uses a red laser light (780 nm) and performs 20 scans of the region of interest at different depths on a 15° × 15° view angle. It then builds a 2D image where each pixel has its specific measurement of retardation. Its measurements are independent of a reference plane and take into account the size of the eyeball.

Some valuable technical characteristics are: the examination is made without pupil dilation, the short time required for image acquisition (0.7 s), and the built-in image quality assessment. A GDx examination may be performed on patients wearing contact lenses (Bhandari et al. 1999), on patients with silicon oil in the vitreous (Hollo et al. 1999) and on patients with intraocular lenses (Collur et al. 2000). On the other hand, it cannot be performed or gives rise to artefacts in patients with corneal diseases, corneal grafts, advanced cataracts, peripapillary and retinal atrophy, myopic conus (or in high myopia) (Hoh et al. 1998) and clinically relevant vitreous floaters (Pons et al. 2001).

GDx measurements are highly reproducible. Based on the several reproducibility studies, the mean standard deviation of repeated analysis is between 4 and 9 μm (Junghardt et al. 1996; Tjon-Fo-Sang et al. 1997; Zangwill et al. 1997; Hoh et al. 1998; Waldo et al. 1998; Colen et al. 2000; Kook et al. 2001).

A large normative database collected in several centres in the United States, Europe and Asia is adopted by the GDx in order to provide a statistically valuable analysis of any new patient. This database is adjusted by gender, age (18–80 year) and ancestry. A series of parameters has been developed to improve the diagnostic capability of GDx. In particular the ‘number’, which is the result of a neural network analysis, seems to reach a good diagnostic capacity.

A technical limitation of GDx is the impossibility of compensating for the corneal-induced polarization in all of the patients. In fact, the built-in compensator allows the corneal polarization to be eliminated in not more than 60–70% of patients (Greenfield et al. 2000). This means that the normative database adopted by the system may be inaccurate for clinical
evaluation of cross-sectional data (i.e. for diagnosis).

Image Page
The image page of GDx includes two large images, the left being a reflective image and the second a colour-coded image, where the brighter the colours the thicker the RNFL. Two small rectangular images adjacent to the reflective image are the vertical and the horizontal cross-section images, whereas the small image on top of the right one is the polar cross-section image where the profile of the RNFL thickness under the ellipse is displayed. A green ellipse concentric to the optic disc contour at a distance of 1.75 disc diameters from the disc contour represents the line under which the RNFL thickness is measured. It is also the inner border of the quadrants where the 1500 pixels with the highest thickness (superior and inferior) or median thickness (nasal and temporal) are identified for further analysis. A single image is not characterized by a standard deviation (SD), whereas a mean image (of at least three repeated images) is characterized by the mean SD, the mean thickness and the variance of the mean thickness. The SD is relevant for follow-up image comparisons.

GDx and RNFL
Anatomy
A high correlation has been found between retardation and RNFL thickness (1). The polar cross-sectional image of normal eyes gives raise to the typical double-hump profile of RNFL thickness, which has been described by histology and by other imaging techniques (Fig. 1). A very high correlation between right and left eyes exists (Essock et al. 1999), and RNFL thickness decreases with age in normal eyes (Poinoosawmy et al. 1997; Toprak & Yilmaz 2000). RNFL is thinner in Afro-Americans than in Caucasians (Poinoosawmy et al. 1997; Tjon-Fo-Sang & Lemij 1998) and in high myopia (Ozdek et al. 2000). Almost 10% of normal subjects may have split superior and inferior bundles (Colen & Lemij 2001) and, interestingly, there is no correlation between corneal and RNFL thickness (Iester & Mermoud 2001).

Correlations between
GDx and Visual Field
Examination
A good correlation has been found between GDx and mean Humphrey perimeter deviation (Weinreb et al. 1995; Marraffa et al. 1997; Chen et al. 1998; Hoh et al. 2000; Kwon et al. 2000), as well as with short wavelength perimetry (Mok & Lee 2000). In patients with primary open-angle glaucoma (POAG), a good correlation has been found between GDx and the ‘neural capacity’ of high pass resolution perimetry (Shirakashi et al. 1997).

GDx and Glaucoma
A statistically significant difference between normal and glaucomatous eyes, as well as between eyes with elevated IOP and glaucomatous eyes, has been reported by several studies (Weinreb et al. 1995; Choplin et al. 1998; Waldock et al. 1998; Xu et al. 1998; Lee and Mok 1999; Kamal et al. 2000). Conflicting results have been reported concerning differences between normal and ocular hypertensive eyes (Xu et al. 1998; Tjon-Fo-Sang et al. 1996; Anton et al. 1997; Choplin et al. 1998; Kamal et al. 2000). Small differences between POAG and normal tension glaucoma and no difference with pseudoxfoliatio glaucoma have been reported (Kubota et al. 1999; Hollo et al. 1997).

Diagnostic Capacity of GDx
The diagnostic capacity (i.e. the sensitivity and specificity) in discriminating between normal and glaucomatous eyes has been reported as very high (above 90%) or quite low (below 70%) (Tjon-Fo-Sang & Lemij 1997; Weinreb et al. 1998; Trible et al. 1999; Essock et al. 2000; Sinai et al. 2000; Vitale et al. 2000; Yamada et al. 2000; Bowd et al. 2001; Choplin & Lundy 2001; Lauande-Pimentel et al. 2001; Paczka et al. 2001; Poinoosawmy et al. 2001; Sanchez-Galeana et al. 2001; Zangwill et al. 2001). Several factors may have influenced these various results. However, the major factor is probably the inaccurate compensation of corneal polarization in a substantial number of eyes. As the normative database does not take into account this factor (as stated above) the accuracy of GDx measurements is often low. As a correct discrimination may often be hampered (and, unfortunately, unpredictable), the number of both false positives and negatives may be relatively high.

GDx and Follow-up of Glaucoma
Monitoring glaucoma or OHT patients by means of GDx seems highly feasible. Although few longitudinal studies have been reported so far (Poinoosawmy et al. 2000; Yamada et al. 2000; Hollo et al. 2001), there are some relevant factors which should be taken into account. First, GDx provides a highly reproducible measurement of RNFL thickness. As stated previously, the mean SD is consistently below 10 μm, thus indicating that GDx measurement is probably one of the imaging techniques with the lowest variability. Secondly, the limitation induced by the incomplete corneal compensation...
does not hold for longitudinal examinations and comparisons. A perfect stability of corneal polarization through time (at least 1 year) has been demonstrated clearly (Figs. 2 and 3) (Greenfield & Knighton 2001).

GDX and Corneal Refractive Surgery
Does corneal refractive surgery affect RNFL thickness measurement by GDX? Or, can corneal refractive surgery induce a change in corneal polarization, possibly affecting longitudinal RNFL measurements? So far, a series of clinical studies have reported no change in PRK for myopia lower than 6 diopters (Ozdek et al. 1998; Choplin & Schallhorn 1999; Vetrugno et al. 2000) as well as statistical changes after PRK and LASIK for myopia higher than 6 diopters (Vetrugno et al. 2000; Gurses-Ozden et al. 2000; Tsai & Lin 2000). Corneal haze after PRK has been reported not to affect GDX measurements. However, this study was performed in the low range of myopic eyes. It is possible that the higher the depth of stromal ablation the higher the possibility of corneal changes (including axis of polarization) which may affect longitudinal RNFL measurements by means of GDX (Hollo et al. 1997).

Conclusions
GDX is a useful imaging technique as it allows RNFL thickness to be measured (at least indirectly). A relevant weakness in compensating for corneal polarization in a substantial number of patients limits the validity of cross-sectional (diagnostic) analysis. A simple way to overcome this problem is to acquire an image of the macular region in order to identify the axis and the quantity of corneal polarization (in those cases where the built-in compensator is not correctly aligned). In this way, it is possible to perform a more precise qualitative (subjective) evaluation of the modular parameters, or at least not to accept an incorrect ‘diagnosis’ of the device. The GDX will soon be complemented with new software which will provide an algorithm to overcome this limitation.

GDX should be used for monitoring purposes given the high reproducibility of the measurement and the stability of corneal polarization which allow accurate comparisons to be performed.

References
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CT and a echography of optic nerve in glaucoma

B. Boles Carenini, E. Tettoni1, B. Brogliatti

Eye Department, University of Turin
1Radiology Department, Eye Hospital, Turin

Introduction

Various authors have reported in the literature on optic nerve thickness measurements made by A-scan echography in normal and glaucomatous eyes (Dichtl & Jonas 1996; Beatty et al. 1998). Other authors have studied the course, morphology and diameter of the optic nerve in the retrobulbar tract by tomography (Carella & Rossi 1992; Tittarelli et al. 1994).

In this study, we have used both methods (standardized A-scan echography and computed axial tomography (CAT)) to measure the diameter of the optic nerve in its first retrobulbar tract with a view to comparing the two methods and checking the correlation, if any, between the optic nerve thickness and the syage of glaucomatous damage. The study was made up of 4 parts, as follows.

1. Part 1: to establish possible correlation between the two methods, we measured the optic nerve diameter in its anterior third retrobulbar tract by echography and CAT in a group of eyes not affected by glaucoma (or by any other eye pathology) and in a matched group of eyes affected by POAG:

2. Part 2: to compare the data of the healthy eyes with data obtained in a group (matched for age and sex) of subjects affected by established glaucoma, to see whether or not there was a difference between healthy and glaucomatous optic nerve diameters.

3. Part 3: to compare both methods in a group of patients affected by asymmetric POAG to test if there might be a nerve thickness difference between the better eye and the worse eye.

4. Part 4: to compare the echographic data of patients affected by bilateral symmetric chronic simple glaucoma (POAG) stages I and II (according to Hodapp et al. 1993 and Sponsel et al. 1995) with those of patients affected by bilateral symmetric POAG stages III and IV, in order to verify possible optic nerve diameter variations related to the stage of the glaucomatous damage.

All the patients examined were under observation at the glaucoma centre of the eye department of the University of Turin.

Methods

We used the classic echographic method described by Ossoining et al. (1981) with standardized A-scan (Ophthoscan S) set to tissue sensitivity. The patient fixes a light spot (in primary position) and the probe is placed temporarily on the eyeball near the equator (at 9 o’clock for the right eye and at 3 o’clock for the left eye). When the ultrasound beam is directed posteriorly, the optic nerve image appears with medium-to-low reflectivity, while its sheaths appear with high reflectivity. Five measurements were made of each optic nerve on its anterior thirds, all by the same operator.

With regard to the tomographic method, we used a Philips Tomoscan LX with parameters: 125 mA, 120 kV, scan time 3.8 s, FOV 250, matrix 512. The examinations were conducted with the patients lying down and the scansions were made on the axial plane with the orbito-mental plane orthogonal to the floor. The patients were asked to fix on a light spot (primary position). When the optic nerve had been identified, scanions of 1 mm were made in order to obtain symmetric images. Measurements were made by computer of the transverse diameter in the anterior third of the nerve, immediately below the sclera, with the calipers.
Refractive error

Tomographic values:

compared the two methods in 30 eyes (15 Student

values 2.41 mm mean ( being 2.28 mm mean ( echographical values in glaucomatous eyes

matous eyes against that in healthy eyes:

stages I–II and that in patients affected by bilateral symmetric POAG stages III–IV using only echography.

Thirty eyes (15 patients) affected by bilateral symmetric POAG (stages I–II) and 30 eyes (15 patients) affected by bilateral symmetric POAG (stages III–IV) with included with the criteria that:

perimetric defects were ≤6 dB (mean defect) in the I–II stages (Hodapp 1933; Sponsel 1995),

perimetric defects were ≥7 dB (mean defect) in the III–IV stages,

IOP was ≥24 mmHg without therapy and ≤20 mmHg with therapy in both eyes,

Refractive error was <±5 D (spherical equivalent).

No patient examined had had para surgical or surgical therapy.

Echographic values:

2.40 mm mean (±0.40, SD 0.14 mm) in the patients with stages I–II bilateral symmetric POAG.

mm mean (±0.30, SD 0.20 mm) in the patients with stages III–IV bilateral symmetric POAG.

The data were analysed statistically by Student's t-test with the result that they showed a significant diminution in optic nerve thickness worse in the eyes with the more advanced POAG (P = 0.0006).

Discussion and Conclusions

The foregoing analyses exhibit an ample correlation existing between the standardized A-scan echography and computed axial tomography in both healthy subjects and POAG patients.

The study also demonstrated a statistically significant diminution in the anterior third optic nerve diameter in:

eyes with established POAG against healthy eyes (and in this we agree with the data to be found in the literature, Dichtl & Jonas 1996; Beatty et al. 1998) reporting a statistically significant diminution in the optic nerve diameter in glaucomatous eyes against healthy eyes;

patients affected by asymmetrical POAG, in the worse eye against the better eye;

patients with bilateral symmetric stages III–IV POAG with respect to those with stages I–II.

Therefore, the evidence is that there is an important and direct relation between optic nerve diameter reduction and the glaucomatous damage stage.

Both methods are reliable. The echographic A-scan running costs are relatively low and the A-scan can be repeated at short time intervals since it is noninvasive. It must, however, be performed by expert personnel for a correct reading of the one-dimensional image and interpretation of the data. The CAT necessitated costly equipment and exposes the patient to noxious radiation, but it has the advantage of visualizing the optic nerve course.

By virtue of the lower costs and, especially, its noninvasiveness, one echographic measurement can be a valid help in monitoring the stadiation of the glaucomatous disease, especially in those cases where the more sophisticated methods (CVF, HRT, SLO) cannot be used.

References


Relationship between retinal nerve fibre layer measurements obtained with scanning laser polarimetry and visual function in normal, ocular hypertensive and glaucomatous eyes

P. Montanari, N. Baccelli, C. Coerezza, M. Mosca, L. Buffagni, R. Ratiglia

‘Maggiore’ Hospital IRCCS, Eye Clinic of the University, Milan

Introduction
The fundamental anatomo-pathological change in glaucoma is the loss of retinal ganglioncell and their axons. With recent developments in ocular imaging techniques based on the optical properties of the retinal nerve fibre layer, it is now possible to obtain a quantitative measure of the layer’s thickness. One of these methods is scanning laser polarimetry which provides objective and reproducible measurements of the retinal nerve fibre layer thickness (Hee et al. 1995; Weinreb et al. 1995; Tjion-Fo-Sang & Lemij 1997; Hoh et al. 1998). Use is made of the birefringence (double refraction) properties possessed by the retinal nerve fibre layer, which changes the polarization of a laser beam near the infrared (780 nm), defined as optical path difference. This optical path difference involves the thickness of the retinal nerve fibre layer in its value (thickness times index of refraction). This work aims to evaluate the relationship that exists between the retinal nerve fibre layer thickness as measured with the scanning laser polarimeter and the visual function assessed by visual field examination in normal subjects, ocular hypertensive patients and glaucomatous patients.

Material and Methods
We examined 45 eyes of 45 Caucasians (21 male and 24 female) of whom: 15 (33.3%) were healthy with mean age 57.7 ± 8.2 years, 14 (31.1%) had ocular hypertension with mean age 58.2 ± 7.1 years and 16 (35.6%) had primary open angle glaucoma with mean age 60.2 ± 3.9 years.

Exclusion criteria included:
- visual acuity > 8/10;
- IOP > 30 mmHg;
- refractive error ≥ 6D spherical and/or 2D cylindrical;
- previous surgery on the eyeball;
- coexistent ocular pathologies.

All the subjects were given a complete oculistic examination: biomicroscopy, gonioscopy, Goldmann applanation tonometry, stereophotography of the optic nerve head, white light computed perimetry with Humphrey perimeter (program 30-2 full threshold), scanning laser polarimetry with GDx instrument (Laser Diagnostic Technologies Inc., San Diego, CA).

In the visual field examination, the idices MD and CPSD were taken into consideration and the patients with MD ≥ 18 dB were excluded. The visual fields were considered reliable if fixation loss ≤ 20%, false positives and false negatives < 25%. The scanning laser polarimetry was always carried out by one or other of two expert doctors using the standard method.

Evaluation of the retinal nerve fibre layer thickness was made using the parameters: the number (N), maximum modulation (MM), ellipse modulation (EM) and ellipse average (EA). If both eyes of a subject satisfied the inclusion criteria, one eye only chosen at random was considered.

In the statistical analysis of the data, the association between the visual field parameters and the GDx parameters was evaluated with Pearson’s correlation coefficient (r). Student’s t-test was used to evaluate the significance of possible differences in the measurements between the different groups and a value of P ≤ 0.02 was considered statistically significant in accordance with the Bonferroni method.

Results
The visual fields of all the healthy subjects and the ocular hypertensive patients were normal, with no significant differences between the two groups either for MD or for CPSD. In the glaucomatous patients, on the other hand, the values of both these parameters showed a significant difference from those of the healthy subjects and the hypertensive patients.

In so far as the parameters evaluated by GDx, a significant difference (P = 0.0128) was found between the number of the healthy subjects (14.27 ± 4.2) and that of the hypertensive patients (24.21 ± 13.81). In the glaucomatous eyes, the index ‘number’ was greater than for the healthy subjects (P < 0.0001) and for the hypertensive patients (P < 0.0001).

The MM in the glaucomatous patients was lower than that in the healthy subjects (P = 0.0001) but not than that of the hypertensive subjects (P = 0.0924). No difference was found between the healthy subjects and the hypertensive patients. Similarly, the EM in the glaucomatous was lower than in the healthy subjects (P = 0.0002), but not than in the hypertensive patients (P = 0.0308). No difference was found between healthy subjects and hypertensive patients. Finally, the EA showed no significant differences between the glaucomatous, the hypertensives and the healthy subjects.

Correlation between the GDx parameters and those of the visual field over the entire cohort of patients was linear as regards all the polarimeter parameters and the MD.

Between N and MD, the correlation index was the highest (r = 0.647, P < 0.001) while between MM, EM, EA and MD the correlation was lower but always statistically significant (MM: r = 0.442, P < 0.01; EM: r = 0.475, P < 0.01; EA: r = 0.381, P < 0.02). Among all the parameters evaluated with GDx and CPSD there was found a lower correlation but, again, here the highest point was between N and CPSD (r = 0.459, P < 0.01). Between MM, EM, EA and CPSD, the correlation index was not statistically significant (MM: r = 0.236; EM: r = 0.315; EA: r = 0.178).

In the analyses for the subgroups (normals, hypertensives and glaucomatous), the wide variability of the data within each group was such that the GDx parameters showed no correlation with either MD or CPSD.

Discussion
For a new technology to be clinically relevant, it must furnish data that correlate well with clinically established investigational parameters such as, for example, the glaucomatous perimetric indices. The GDx parameters we have considered have shown from good (number) to fair (max modulation, ellipse modulation and ellipse average) correlation with the perimeter MD index. One parameter has also shown a good correlation with CPSD, while the correlation shown by the other three parameters was scanty and not significant. Only the number, on the
other hand, unlike that found by other authors (Hoh et al. 1998). As with other studies (Hoh et al. 1998), the GDx evaluated parameters have, in our study, too, a stronger correlation with the perimetric indices (MD) that imply a diffuse damage with respect to those (CPSD) that indicate a focal damage. In interpreting the data one must, however, remember that correlation does not mean causal relationship; linear correlation in fact indicates that two parameters tend to be associated, but many other variables may also have more or less influence. Our study suggests that, by using the parameter number, it would be possible to distinguish healthy subjects from hypertensive patients, a finding with which other authors disagree (Tjion-Fo-Sang et al. 1996; Zangwill et al. 1996; Hoh et al. 2000). In conclusion it can be stated that, notwithstanding a certain overlapping of the data obtained in the three groups, a significant correlation has been found between the GDx parameters and the visual function investigated by perimetry.

References

Reproducibility of retinal thickness measurements with retinal thickness analyser in healthy and glaucomatous subjects

M. Ciancaglini, A. Sebastiani1, P. Carpineto, C. Costagliola1, M. Ciafrè, F. Parmegiani1, E. Doronzo, L. Mastropasqua
Institute of Ophthalmology and Legal Medicine, University of Chieti
1Department of Medical and Surgical Disciplines, University of Ferrara

Introduction
The retinal thickness analyser (RTA, Talia aatechnologies Ltd. Mevaseret Zion, Israel) is a novel non-invasive instrument developed for multiple optical cross-sectional retinal visualization that provides quantitative measurements of retinal thickness (Zeimer et al. 1996). The RTA operates on the principle of laser biomicroscopy (Zeimer et al. 1989) covering a zone of about 20° × 20° around the fovea. A pilot study demonstrated the ability of RTA to detect localized thinning of the retina in glaucomatous patients (Asrani et al. 1997), indicating a local loss of nerve fibres. In the present study we investigated the reproducibility of retinal thickness measurements in glaucomatous patients and control subjects.

Methods
Twelve patients (6 male and 6 female) affected by bilateral primary open angle glaucoma controlled with hypotensive medication and 10 healthy subjects (6 male and 4 female) were enrolled in this clinical study. Corneal refractive power and refractive error were examined in all subjects and one eye each was randomly selected. Before RTA retinal thickness measurements were made, the pupil was dilated to at least 5 mm diameter. A green helium neon laser was scanned by a slit beam in a 2 × 2 mm area of the posterior pole. Nine areas were scanned, covering the central 20° of the fundus. All the examinations were performed by a trained operator. The images were analysed by an automated software and thickness map and a large number of global indices were calculated: the posterior pole average thickness (PPA), posterior pole pattern deviation (PPPD) and posterior pole corrected pattern deviation (PPCPD) were used in the present study to assess the reproducibility. Two different reproducibilities were assessed: the intravisit reproducibility, evaluating three scans in a single session, and the intervisit reproducibility, evaluating two scans obtained from two different sessions. Reproducibility was calculated using the coefficient of variation (CV) of PPA, PPPD and PPCPD.

Results
No statistically significant difference in mean age between the glaucomatous patients (52.6 ± 6.3 years) and the controls (50.3 ± 5.4) was found. Table 1 shows the values of the posterior pole indices in the normal and the glaucomatous subjects. The intravisit reproducibility was 3.4% for PPA, 5.3% for PPPD and 4.9% for PPCPD in the glaucomatous patients and 3.1%, 4.6% and 4.3%, respectively, in the normal subjects. Table 2 exhibits the intervisit reproducibility of the RTA measurements: the CV of PPA

Table 1. Mean ± SD of posterior pole indices.

<table>
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<tr>
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<th>Glaucoma</th>
<th>Controls</th>
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<tbody>
<tr>
<td>PPA</td>
<td>168.2 ± 14.30</td>
<td>186.1 ± 12.16</td>
</tr>
<tr>
<td>PPPD</td>
<td>17.6 ± 2.96</td>
<td>6.3 ± 1.96</td>
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<tr>
<td>PPCPD</td>
<td>9 ± 6.11</td>
<td>4.7 ± 2.46</td>
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Diagnostic value for glaucoma of a new HRT analysis correcting for disc size

S. Miglior1, M. Guareschi2, S. Zanchi2, M. Casula2, E. Albe2, L. Fontana3, N. Orzalesi2
1Universita’ di Milano ‘Bicocca’, 2Universita’ di Milano, 3Ospedale Maggiore, Bologna, Italy

Purpose
To evaluate a new HRT software by assessing the agreement with the visual field examination in differentiating normal from glaucomatous eyes, and assessing the sensitivity and specificity of optic disc examination in detecting eyes with glaucomatous damage.

Methods
Some 343 patients for a total of 252 eyes underwent imaging of the optic disc by means of HRT (Heidelberg Engineering), performed with a 10° angle view. For study purposes, a mean image of three repeated images was analysed with the version 2.01 software. The eyes included had a disc area between 1.49 and 2.8 mm, according to the software requirements. The original HRT data were analysed by the new software, which consists of a database of normal subjects and takes into account the HRT predefined parameters, i.e. the patient’s age, the optic disc size, and information obtain about the global rim and cup/disc area ratio as well as six sectors (temporal, superior-temporal, inferior-temporal, nasal, inferior-nasal, superior-nasal). Each parameter is defined by the software as being normal or abnormal. Visual field was performed by each patient with the program DS 30 II (Humphrey perimeter). A glaucomatous visual field was defined on the basis of an abnormal glaucoma hemifield test and a statistically significant ‘CPSD > 4.4 dB’. The visual field was normal in 199 cases and met the glaucoma criteria in 53 cases. Agreement between HRT and visual field examinations was calculated by Kappa statistic, and sensitivity and specificity of HRT examination were calculated by means of standard procedures.

Results
The agreement between the ‘visual field’ and HRT definitions of glaucoma were found to be poor, as the Kappa statistic was 0.36 (95%IC: 0.27–0.44). The sensitivity and specificity of the HRT examination were 77% and 69% for the parameter ‘HRT status’. Sensitivity ranged between 22% and 62%, and specificity between 85% and 99% with all the other HRT parameters.

Conclusions
The clinical agreement between HRT examination with new software and visual field examination was poor. The HRT evaluation showed sensitivity and specificity values similar to those found in previous reports, but smaller than those reported by Wollstein et al. in 1998. Although this new analysis represents an improvement of HRT evaluation of the optic disc, as it allows us to take into account the disc size, caution should be taken in the clinical setting when interpreting the HRT results based on such a new software.
Intra- and interobserver reproducibility in the evaluation of the optic disc by HRT

S. Miglior1,2, E. Albe2, M. Guareschi2, L. Rossetti2, N. Orzalesi2
1Università di Milano ‘Bicocca’, 2Università di Milano, Italy

Purpose
To assess intra- and interobserver reproducibility of optic disc evaluation by means of HRT.

Methods
Fifty-five volunteers underwent three sessions of HRT examination of the optic disc performed on three consecutive days. During each session, five single images were randomly acquired by two independent well-trained residents in ophthalmology. One mean topography image (MTI), based on three single images, was then constructed at each session. For the intra-observer, intra-image evaluation, two independent observers traced their own contour line on the MTI of the first session. This procedure was repeated three times. For the intra-observer interimage and interobserver intra/inter-image evaluations, the same two observers traced their own contour line on the MTI of the first session, which was then automatically superimposed on the MTIs of the other two sessions. Reproducibility assessment for the 12 stereometric parameters was then calculated for each observer by means of intraclass correlation coefficient (ICC) and the Altman plots of two randomly chosen tests.

Results
The ICC ranged between 0.60 and 1 for intra-observer intra-image, and between 0.31 and 1 for intra-observer interimage evaluation. The ICC ranged between 0.39 and 1 for interobserver intra-image, and between 0.23 and 0.99 for the interobserver interimage evaluation. Intra- and interobserver reproducibility were substantial to perfect for planimetric measures (0.61 < ICC < 1), almost perfect to perfect for volumetric and cup measures (0.81 < ICC < 1), and fair to almost perfect for RNFL related measures (0.21 < ICC < 0.99). In the case of interobserver reproducibility assessment, the Altman plots of interimage evaluation showed a higher variability than intra-image evaluation (P = 0.012, Wilcoxon test).

Conclusions
Optic disc measurements by HRT are highly reproducible for most of the stereometric parameters. However, the use of RNFL related parameters should be taken cautiously. The image acquisition induced variability seems larger than operator induced variability.

Structural glaucomatous damage vs. visual field defects: longitudinal study in patients with ocular hypertension or early primary open-angle glaucoma

T. Rolle, B. Brogliatti, A. Fea, E. Borasio, A. Fornero, L. Belli, M. Manea
Eye Clinic, University of Turin

Introduction
The diagnosis of primary open-angle glaucoma (POAG) is based on the coexistence of an intraocular pressure (IOP) increase, perimetric alterations and morphological alterations to the optic nerve head and the retinal nerve fibre layer. Studies published in the literature (Sommer 1979; Pederson & Anderson 1980; Caprioli 1989; Taulonen & Airaksinen 1991; Zeyen & Caprioli 1993; Caprioli 1996) have pointed out that the anatomical changes to the optic disk and the retinal nerve fibre layer may precede the perimetric deficits by years. From when the pharmacological treatment of ocular hypertension in its initial stages showed it could slow down or even block the progression of the disease (Mao 1991; Chauhan and Drance 1992; Migdal 1994), it has been imperative to make the diagnosis of glaucoma in its initial phase. To do this, in addition to the perimetric examination, there are now the interesting prospectives of the methods using computed digital analysis of the optic nerve head and the retinal nerve fibre layer, among which the Heidelberg retina tomograph (HRT) is one that furnishes a detailed, reproducible and above all objective evaluation.

Aims
This work was undertaken to evaluate the changes in the morphology of the optic nerve head and retinal fibre layer as well as in the visual field in eyes with ocular hypertension or POAG in its initial phase.

Material and Methods
Our research was conducted on 17 patients (24 eyes) with a mean age of 62.0 ± 10.7 years in our out-patient glaucoma centre at the eye clinic of the University of Turin who were found to have IOP values >22 mmHg. All the patients had a complete ocularic check and morphological examination of the optic disk and the retinal nerve fibre layer by the Heidelberg retina tomograph (HRT software 2.01) with a visual field of 15° × 15°. Three series of images were recorded for each eye. For analysis purposes, a topographic image created by the computer representing the mean of the three images obtained was used and, onto this, an expert examiner drew the contour line of the internal edge of the Elschnig scleral ring. A computed visual field examination by the perimeter OCTOPUS 2000 (program G1,
central 30°, Peritrend analysis) was also made. All the patients had had at least 2 previous examinations with values of RF < 15%.

The inclusion and exclusion criteria for enrolment in the study were as follows.

**Inclusion:**
- IOP values >22 mmHg without therapy;
- visual acuity values ≥8/10;
- transparent dioptric means;
- MD < 6 dB;
- good collaboration at the HRT examination;
- good collaboration at the perimetric examination (RF < 15%).

**Exclusion:**
- congenital malformation of the ocular apparatus;
- opacity of the dioptric means;
- presence of elevated refractive defects (>±3D for myopia and hypermetropia and >±1.5D for astigmatism);
- previous vascular and/or neurological pathologies of the retinal vessels and/or the optic nerve;
- impossibility of lending a suitable collaboration in the perimetric and morphological examinations;
- heavy smoking (>15 cigarettes/day);
- heavy drinking (>60 g/day alcohol).

In 7 (29.16%) of the 24 eyes enrolled, there were no visual field alterations at base time.

Mean IOP base values were 25.15 ± 3.21 mmHg. All the patients were prescribed a local antiglaucoma therapy. After a mean follow-up period of 426.6 ± 161.2 days during which the patients were given routine checks which always showed good tonometric compensation obtained through the local therapy. Further data to confirm or belie these hypotheses may be had by continuing to monitor these patients.

First, we analysed the data overall by Student’s t-test in order to find out if the HRT parameter values were subject to significant modifications between the first and second examinations, independently of the follow-up time between them. Then, for the disk HRT parameters overall, the ANOVA was calculated for corrected repeated measurements for the 2 subgroups of eyes with:
- subgroup 1 – mean follow-up between 161 and 450 days;
- subgroup 2 – mean follow-up between 451 and 755 days.

The statistically significant threshold was fixed at 5% (P < 0.05). Also evaluated was the correlation between the anatomic and the functional data relating to the optic disk totally and to the 4 quadrants by Pearson’s r test.

**Results**

**Visual field**

In all the eyes, an increase of the mean defect over base time was observed (MD from 2.5 ± 1.8 dB to 4.0 ± 1.4 dB; +37.5%) and also of the defect corrected variance (CLV from 2.8 ± 1.7 dB to 4.49 ± 4.49 dB; +37.63%). The data obtained were statistically significant (P < 0.05). In particular, a functional damage (MD > 2 dB) was found in 7 eyes with hypertension. In so far as sector analysis was concerned, the superior temporal proved to have the most functional deficit (MD from 3.1 ± 1.9 dB to 4.3 ± 2.0 dB, +27.90%; P < 0.05).

**HRT parameters**

Base time HRT parameters are exhibited in Table 1. At follow-up end, there was found an increase in the values of the perimetric indices, in particular the MD which was statistically significant. In 7 eyes which had normal visual field at base time there were found glaucoma-type changes. The optic disk and nerve fibre layer morphology had not changed significantly. The evolution of the functional damage might very possibly be a late consequence of the morphological changes already present at base time even in the ocular hypertensive eyes. That no significant changes were found in the HRT parameters might be due to the good tonometric compensation obtained through the local therapy.

**Correlation between anatomical damage and functional damage**

There were good correlations at base time between MD and CA (r: 0.32), C/D ratio (r: 0.31) and CSM (r: 0.53). Data relating to the 4 quadrants showed a good correlation between MD and all the HRT parameters considered in the TS sector. So far as the CLV was concerned, there was a good correlation for all the parameters with the exception of CA and C/D ratio.

**Conclusions**

At follow-up end, there was found an increase in the values of the perimetric indices, in particular the MD which was statistically significant. In 7 eyes which had normal visual field at base time there were found glaucoma-type changes. The optic disk and nerve fibre layer morphology had not changed significantly. The evolution of the functional damage might very possibly be a late consequence of the morphological changes already present at base time even in the ocular hypertensive eyes. That no significant changes were found in the HRT parameters might be due to the good tonometric compensation obtained through the local therapy.
Ganglion cell apoptosis and increased number of NADPH-d-positive neurones in the rodent retina in an experimental model of glaucoma

L. Palanza¹, R. Nuzzi¹, M. Repici², A. Vercelli²

¹Ophthalmologic Clinic, University of Turin
²Department of Anatomy, Pharmacology and Forensic Medicine, University of Turin

Introduction
Increased intraocular pressure in glaucoma causes degeneration of the optic disk and the retinal ganglion cell axons (Garcia-Valenzuela et al. 1995) with the result of a marked decrease in the visual field. Retinal damage may be responsible for neuron loss in the lateral geniculate nucleus as well (Yucel et al. 2000). A concomitant increase in nitric oxide synthase (NOS) activity in retinal cells (especially in amacrine neurones) (Neufeld 1999) and in caspase activity (Lam et al. 1999) have been reported. Both increased NOS activity and caspase activation have been shown to play an important role in the apoptotic mechanism affecting retinal cells in diseases such as glaucoma or ischaemia (Katai & Yoshimura 1999; Lam et al. 1999) and after axotomy (Garcia-Valenzuela et al. 1994; Klocker et al. 1998). Inhibition of caspase activity reduces retinal ganglion cell death (Kermer et al. 1998; Chaudhary et al. 1999). Several other factors are also involved in retinal cell death (see Linden et al. 1999 for a review), such as reactive oxygen species (Kortuem et al. 2000).

In our study, we were interested in the temporal relationship between the increase in NO synthesis and neuronal cell death in the adult mammalian retina in an experimental model of acute glaucoma in the rat, obtained by increasing intraocular pressure for 1 h (Katai & Yoshimura 1999).

NOS activity was detected by means of NADPH-diaphorase (NADPH-d) activity, which colocalizes with NOS (Dawson et al. 1991) and dying neurones were identified by the "terminal transferase method" (Gavrieli et al. 1992).

Material and Methods
All experimental procedures on live animals were performed under the supervision of a licensed veterinarian in accordance with the guidelines for care and use of laboratory animals as published by the Italian Ministry of Health (DDL 116/92). Ten adult Wistar rats were deeply anaesthetized with intraperitoneal injections of ketamine hydrochloride (Inoketam, Virbac, Italy; 100 mg/kg body weight). A cannula was inserted in their left eye, delivering a saline solution at a pressure of 110 mmHg for 1 h. The right eye was sham-operated (a cannula being inserted without delivering saline) and served as control. After surgery, the rats were returned to their cages and allowed to survive different time intervals (1, 2, 4, 7 and 10 days).

The rats were sacrificed with an overdose of anaesthetics and perfused through the left ventricle with saline followed by 4% PAF.

Experimental and control retinas were reacted whole-mount either for NADPH-d histochemistry (Vincent & Kimura 1992) to detect NOS-positive neurones (4 rats), or reacted for TUNEL (Gavrieli et al. 1992) in 10 mm-thick paraffin sections to detect DNA fragmentation in apoptotic neurones (6 rats). In the first case, retinas were reacted for 1 h in a solution of 1 mg/ml NADPH (Sigma) and 0.2 mg/ml nitroblue tetrazolium (Sigma) made up in PB containing 0.5-1% Triton X-100. In the second case, retinal sections were reacted using kit purchased from Roche and following the manufacturer’s instructions.

The distribution of NADPH-d-positive amacrine profiles in the retina was analysed by means of an Eclipse 600 light microscope equipped with a motorized stage interfaced to a personal computer, using program NeuroLucida (Microbrightfield Inc., VT, USA; Glaser & Glaser 1990). Maps of NADPH-d-positive neurones in the retinas were edited, and the nearest-neighbour distance obtained with the program NeuroExplorer. Data were compared with the one-tailed paired t-test.

Results
NADPH-d activity
The expression of NADPH-d activity was increased in the retinas following experimental glaucoma, both as total number and density (nearest-neighbour distance decrease) of positive neuronal profiles (amacrine neurones, Neufeld et al. 2000) and as endothelial labelling in blood vessels. NADPH-d-positive neurones were found in the inner nuclear layer and in the ganglion cell layer, presumably amacrine cells. As glaucomatous retina were more fragile and showed some damage due to histological processing, their areas were usually smaller than those of the controls. Nevertheless, the number of NADPH-d-positive neurones was higher than in the controls at 7 and 10 days after surgery. We therefore decided to use cell density (measured as nearest-neighbour distance) instead of the overall number of neurones as a marker for NADPH-d:positivity in the retinas. In all the animals considered, the nearest-neighbour distance among NADPH-d-positive cell profiles was decreased ($P = 0.04$), with the highest
Difference between glucomatous and sham-operated retinas at 7 days after surgery (74.6 mm vs 100.2 mm) (Figs 1 and 2).

TUNEL labelling

On the control side, there were no TUNEL positive neurones (data not shown); TUNEL positive cell profiles, on the contrary, were markedly increased both in the ganglion cell layer and in the inner nuclear layer during the first 2 days after surgery (Fig.3a), whereas they were rare at 7 days after surgery (Fig.3b).

Discussion

We have demonstrated that, in an experimental model of acute glaucoma in rat, the increase in NADPH-d activity and apoptotic cell death peak as shown by TUNEL are not coincident, but high levels of apoptotic cell death occur when NADPH-d activity is only slightly if at all increased. These results suggest that our experimental model of ischaemia-reperfusion in glaucoma causes a significant increase in apoptotic cell death in the early period after surgery, whereas the increase in NADPH-d expression occurs later and is protracted over time. Therefore, NO synthesis increase may not be the only factor responsible for apoptotic cell death in the glucomatous retina.

In fact, other authors have demonstrated that caspase-1 and –3 are up-regulated and TUNEL-positive neurones are frequent 24 h after surgery, and that intravitreal injections of caspase inhibitors decrease the amount of TUNEL-positive neurones (Katai & Yoshimura 1999).

The significant and long-lasting increase in NADPH-d activity in blood vessels and in amacrine neurones could have different outcomes. Blood vessels show an enhanced NADPH-d activity as early as 1 day after surgery, thus creating a vasodilation in the reperfusion phase. The increase in the density of NADPH-d-positive amacrine neurones following BDNF treatment has been described previously (Cellerino et al. 1999). BDNF in transient retinal ischaemia also decreases the number of caspase-2 immunoreactive neurones (Kurokawa et al. 1999). Therefore, several factors are involved in retinal damage following acute glaucoma.

Acknowledgements

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References

Evaluation of central corneal thickness in patients affected by ocular hypertension, primary open-angle glaucoma, normal tension glaucoma

L. Quaranta, S. Battelli, G. Plutino, E. Gandolfo
Eye Clinic Glaucoma Centre, University of Brescia

One of the parameters of great importance in monitoring glaucoma pathology is intraocular pressure (IOP) (Coleman 1999). In the 1950s, when Goldmann proposed and made the application tonometer, that instrument has become the gold standard for IOP measurement (Goldmann & Schmidt 1957).

Applanation tonometry (ATG) according to Goldmann is based on the Imbert–Fick law (Goldmann & Schmidt 1957), which assumes that the corneal surface is perfectly and uniformly elastic and thin, and that therefore the cornea does not exert any additional force against the tonometer’s cone-shaped trunk’s applanation surface over and above the existent pressure inside the eyeball (Whitacre & Stein 1993).

In their original work on applanation tonometry, Goldmann & Schmidt (Coleman 1999) assumed a definite corneal thickness (520 mm) in calibrating the applanation tonometer, although they did point out that changes in corneal thickness could have an influence on IOP measurements. In practice, a corneal thickness greater than the ‘Goldmann standard cornea’ would produce an over-estimate of the IOP, while a corneal lesser thickness would produce an under-estimate of the IOP (Ehlers et al. 1999; Morad et al. 1998; Chatterjee et al. 1999). In addition, recent investigations have shown that normal tension (NT) glaucoma patients have a corneal thickness lesser than the healthy controls and the POAG patients (Whitacre & Stein 1993; Morad et al. 1998; Chatterjee et al. 1999; Copt et al. 1999).

The aims of this study were to evaluate:
- the central corneal thickness (CCT) in NTG, POAG and OH patients;
- possible IOP differences between Goldmann application tonometry (GAT) values and Langham’s pneumotonometry (PT) values.

References
Crossed and uncrossed visual pathways are impaired differently in open angle glaucoma patients

V. Parisi1,2, G. L. Manni1,2, D. Gregori1, D. Olzi1, S. Meconi1, G. Coppola4, M. Scipioni1, M. G. Bucci1,2

1Eye Clinic, ‘Tor Vergata’ University of Rome
2GB Bietti Foundation for Ophthalmology
3AfaR-RCCS, Eye Division, Fatebenefratelli Hospital, Rome
4Il Neurological Clinic, ‘La Sapienza’ University of Rome

Introduction
Recent electrophysiological evaluations, performed by pattern electroretinogram (PERG) and visual evoked potential (VEP) recordings, suggest that patients affected by open angle glaucoma (OAG) present a retinal dysfunction and a delay in neural conduction in the postretinal visual pathways (Parisi 1997). Although an impairment of the innermost retinal layers (ganglion cells and their fibres) is well documented (Quigley et al. 1995), only recently has an impairment of the lateral geniculate nucleus (LGN) been observed in animals in which experimental glaucoma was induced (Weber et al. 2000). Therefore, it is supposed that the abnormal visual cortical responses observed in glaucoma may result from both retinal impairment and the involvement at the LGN level. In our previous study (Parisi 1997), the VEP responses were derived by means of a single electrode placed over both occipital cortices and therefore did not allow a separate evaluation of the neural conduction along the crossed and uncrossed fibre visual pathways. On the basis of recent evidence regarding postretinal involvement in glaucoma, the aim of our work now is to evaluate the neural conduction in crossed and uncrossed visual pathways in OAG patients.

Patients and Methods
Twenty-two OAG patients (mean age 65.6±9.5 years, refractive error between +2 and −2 sph) with mean deviation (MD) between −2 and −27 dB and corrected pattern standard deviation (CPSD) between +2 and +13.5 dB of 24/2 Humphrey computerized static perimetry, and with an IOP<21 mmHg in at least one eye (average of the two highest values of the daily curve in medical treatment with β-blockers only), were enrolled. They were compared to 16 age-matched controls.

In OAP and control subjects, VEP recordings were performed as follows. The subjects under examination were seated in a semidark, soundproof room in front of a display with a uniform field of luminance of 5 cd/m2 surround. Visual stimuli were full field checkerboard patterns (each square subtended an angle of 15’ of visual arc; contrast 80%, mean luminance 110 cd/m2) generated on a TV monitor subtending 18’, and reversed in contrast at the rate of 2 reversals/s. The refection of all subjects was corrected for the viewing and no mydriatic or miotic drugs were used. Cup-shaped Ag/AgCl electrodes were fixed with collodion in positions: active electrode in O1 (left occipital cortex) and O2 (right occipital cortex) Jasper 1958), reference electrode in Fpz, with ground in the left arm. The inter-electrode resistance was kept <3 kΩ. The bioelectric signal was amplified (gain 20000), filtered (bandpass 1–100 Hz) and averaged (200 events free from artifacts were averaged for each trial) by BM 6000. Analysis time was 200 ms. Stimulation was monophasic after occlusion of the other eye and the bioelectric cortical responses were recorded simultaneously in the homolateral visual (HC) cortex and in the contralateral visual cortex (CC), with respect to the stimulated eye. The transient VEP response is characterized by a number of waves with three subsequent peaks of negative, positive, negative polarity: N75, P100, N145.

We accepted VEP signals with signal-to-noise ratio >2. For all VEPs, the implicit time and the peak-to-peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors. The differences between OAG patients and controls were evaluated by ANOVA, and linear regression analyses (Pearson’s test) were used to establish the correlation between perimetric and VEP parameters.

Results
In OAG patients, the VEP P100 implicit times observed in HC and CC were both significantly $(P<0.01)$ delayed compared to those of the controls, and were significantly related $(P<0.01)$ to the MD observed in the nasal and the temporal hemi-fields, respectively (Table 1). We found an asymmetry in the bioelectric responses obtained in HC and CC of all the OAG patients, and the intracortical differences (ID: P100 implicit time in HC–P100 implicit time in CC) converted to absolute values, were significantly higher than those of the controls (4.49±3.72 ms and 1.16±1.04 ms, respectively, $P=0.001$). In 11 (50%) OAG patients, we observed an ID with a negative value (between −1 and −13.6 ms), indicating VEP P100 implicit times longer in CC than in HC, while in 11 (50%) OAG patients, we observed an ID with a positive value (between 1 and 8.8 ms), suggesting VEP

Table 1. Mean values and one (±) standard deviation of VEP P100 implicit time in OAG patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Control (N=16)</th>
<th>OAG (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD (ms)</td>
<td>Mean±SD (ms)</td>
<td></td>
</tr>
<tr>
<td>Homolateral cortex</td>
<td>101.6±2.2</td>
<td>131.9±13.1 $^*$</td>
</tr>
<tr>
<td>Contralateral cortex</td>
<td>102.1±2.6</td>
<td>131.5±12.1 $^*$</td>
</tr>
<tr>
<td>Intracortical difference</td>
<td>1.16±1.04</td>
<td>4.49±3.72 $^*$</td>
</tr>
</tbody>
</table>

| OAG correlation between VEP P100 implicit time and Humphrey 24/2 parameters |
|--------------------------|--------------------------|
| MD | CPSD |
| Homolateral cortex | $r=0.570$, $P<0.01$ | $r=0.170$, $P=0.43$ |
| Contralateral cortex | $r=0.703$, $P<0.01$ | $r=0.570$, $P=0.43$ |
| Intracortical difference | $r=0.185$, $P=0.583$ | $r=0.583$, $P=0.004$ |

$^*$ $P<0.01$, ANOVA vs controls.
P100 implicit times longer in HC than in CC. The ID observed in OAG patients (ranging from −13.6 to 8.8 ms) was correlated significantly with the CPSD (r: 0.58, P = 0.004) (Fig. 1), but not with the MD (r: 0.18, P = 0.409).

Conclusions
The observed asymmetry in visual cortical responses suggests that crossed and uncrossed visual pathways could be impaired differently in OAG patients.

References

Reproducibility of a new technique to analyse retinal blood flow

M. Iester1,2, M. Altier1, P. Vittone2, M. Zingirian1, C. E. Traverso1

1Department of Neurological and Visual Sciences, Ophthalmology B, University of Genoa
2Division of Ophthalmology, G. Gaslini Institute, Genoa

Introduction
Indirect clinical data suggest that vascular factors could be glaucoma risk factors and therefore could be involved in the pathogenesis of the disease (Drance et al. 1988; Morgan & Drance 1975; Flammer 1994; Orgul & Flammer, 1994; Graham et al. 1995; Phelps & Corbett 1985; Hayreh et al. 1994). In this study, we tested the reproducibility of a non-invasive method able to evaluate the topography of perfused capillary vessels of the retina and optic nerve head with simultaneous evaluation of the blood flow variables.

Patients and Methods
Ten subjects were included in the study: 5 were classified as normal and 5 as having glaucoma. The diagnosis of primary angle glaucoma was based on the presence of typical glaucomatous visual field defect and optic disk damage. Normal subjects were recruited from those patients who had one eye with cataract and the other normal.

All the patients had their visual field analysed by Humphrey field analyser, program 30-2, full threshold SITA (Humphrey Inc., Leandro, CA, USA). Blood pressure and heart rate were assessed at the baseline.

Heidelberg retina flowmeter (HRF) combines the principles of a confocal scanning laser and a laser Doppler flowmeter (780 nm; 100 μW). Ater 128 scanings of each point of consideration, the HRF calculates a 2-dimensional map of the laser Doppler shift within a 300 μm slice of tissue, over a rectangular area (2.5 x 10^3) of the posterior pole of the eye. The calculation is done using a fast-Fourier transformation. The laser Doppler shift values recorded at the different locations are displayed on the monitor in a colour code image. For each pixel, a frequency shift is calculated (Michelson & Schaumann 1995; Michelson et al. 1996; Nicolela et al. 1997; Kangemann et al. 1998; Grieser et al. 1999).

The data were read by using a different programme called AFFFPIA (automatic full field perfusion image analyser). The details of this technique are published elsewhere (Michelson et al. 1998). In brief, AFFFPIA calculated the Doppler frequency shift and the haemodynamic factor or flow of each pixel according to the theory of Bonner and Nossal. For a valid estimation of retinal blood flow, some assumptions need to be made: brightness adequate, no artificial movement and Doppler shift below 2000 Hz. In order to meet these requirements, the resulting perfusion image was processed to account for underexposed and overexposed pixels, saccades and the retinal vessel tree. Using AFFFPIA, the operator marked saccades and the location of the rim area. In a second step, the capillaries and large vessels of the retina were identified automatically by a vessel detection algorithm based on the intensity and the perfusion image. Then, underexposed and overexposed pixels and the saccades were automatically excluded. The local dishomogeneities of the perfusion map were softened by a moving average procedure performed with a size of 5 x 5 pixels.

Based on this analysis, the blood flow was automatically analysed in the temporal, nasal and rim area. The heart beat-associated pulsation of capillary blood flow was evaluated by plotting the mean capillary flow of each horizontal line against time.

For each patient, three images were taken and analysed. When the intraimage-reproducibility was studied, the same observer (MI) analysed the flow maps 5 times and the COV was calculated. When the interimage–intra-observer reproducibility was studied, the same observer (MI) analysed three different flow maps of the same patient once and the COV was calculated. All the images included either the superior ONH pole or the inferior ONH pole. When the images were analysed, temporal and nasal peripapillary retina and the optic rim area flow were calculated.

Results
The mean age was 68 ± 5.2 years (mean ± standard deviation) and the mean refractive error was −0.9 ± 1.9 dioptres. The visual field mean deviation was −3.1 ± 2.7 and corrected pattern standard deviation was −3.3 ± 1.6. Mean blood pressure and mean heart rate were 146.5/80 (systolic and diastolic blood pressure) and 80.7, respectively. When the intraimage–intra-observer reproducibility was studied the COV was 4.7%, ranging from 0.5% to 5% for the temporal area, 20.3% ranging from 0.5% to 28% for the rim area and 3.8% ranging from 0.1% to 5.3% for the nasal area. The analysed area...
Influence of pregnancy on ocular blood flow

M. Centofanti1,2, G. L. Manni1,2, R. Migliardi1, D. Zarfatí3, D. Lorenzano1, M. Scipioni1, A. Harris, M. G. Bucci1
1Eye Clinic, University of Rome ‘Tor Vergata’
2GB Bietti Foundation for Ophthalmology, AfaR-RCCS, Oculistic Division, Fatebenefratelli Hospital, Rome, Italy
3Indiana University School of Medicine, Indianapolis, IN, USA

Introduction
Oestrogens’ protection activity in vascular pathologies is already well-known. How this protection operates, however, is still not completely clear, but it seems to be linked to the oestrogens’ vasodilative activity. Oestrogens influence the production and/or the effects of endothelial-derived substances such as NO, ET1 and eicosanoids (White et al. 1995), introducing a final effect of vasodilation and resistance reduction. Oestradiol in particular seems to increase NO and prostacycline activity, both with vasodilative action, and it also appears to reduce the response capacity of the unstriated musculature to ET1.

Recently, we observed that ocular circulation is influenced by the hormonal status; we found that premenopausal women had a significantly higher rate of blood flow than age-matched males and postmenopausal women (Centofanti et al. 2000). As, during pregnancy, a physiological and progressive increase of oestrogen secretion takes place (Wilson et al. 1998), we used this condition as a natural model of increased oestrogen secretion. The aim of our study is to evaluate the pulsatile ocular blood flow (POBF) course during the different phases of pregnancy.

Patients and Methods
In our study, we enrolled 27 healthy pregnant women with no intercurrent disease and 14 non-pregnant healthy women matched for age. In every pregnant woman, at the 10th week of gestation (first quarter of pregnancy), we measured the POBF by a pneumotonometer (OBF Ltd, UK), the IOP by a pneumotonometer, mean blood pressure (MBP) and heart rate (HR). The same examinations were also carried out at the 20th week of gestation in 10 women (second quarter of pregnancy) who came to the second control. The same parameters were measured in the healthy women taken as a control on the first day of menstruation so as to obtain a homogeneous hormonal status in every control. Student’s t-test was used to compare the POBF in both the 27 pregnant women and the 14 control women. As we were comparing the same women, a two-tailed paired t-test was used to examine POBF variations in the two different moments of gestation.

Results
In the first quarter of pregnancy, the mean age was 31.7 ± 5.9 (range 18–41) years, POBF 1516 ± 382 ml/min, IOP 13.2 ± 3.3 mmHg, MBP 92 ± 6.2 mmHg, HR 85.9 ± 14.4 beats/min, in the second quarter, the mean age was 32 ± 3.4 (range 21–38) years, POBF 1629 ± 352.4 ml/min, IOP 12.4 ± 2.8 mmHg, MBP 96 ± 2.8 mmHg, HR 92.8 ± 10.2 beats/min and in the control group, the mean age was 26.7 ± 9.4 (range 25–34) years, POBF 972 ± 329.3 ml/min, MBP 88 ± 4.3 mmHg, HR 79.9 ± 14 beats/min. The results show that the POBF increases significantly during the first quarter of pregnancy (P = 0.00008) when compared to the matched non-pregnant women. Furthermore, in the women in the second quarter of pregnancy, the POBF increases significantly when compared to the first quarter (P = 0.0008). No statistical differences were observed for the other values measured.

Conclusions
In this study, we observed a significant POBF increase in pregnant women in comparison with the non-pregnant controls. We also noticed a further POBF increase in the second quarter of gestation over the first. During an uncomplicated human pregnancy there is an increase of oestrogen secretion which accompanies gestational age (White et al. 1995). Therefore, we suppose that POBF increase during pregnancy may be correlated with the oestrogen secretion. This may depend on the vasodilative effects determined by these hormones acting on the ocular district. Female hormones exert a protective effect on coronary heart disease and oestrogen replacement therapy is effective in the reduction of the vasomotor symptoms of menopause and the prevention of cardiovascular disease (Belchetz 1994). At present, the effect of oestrogen replacement therapy on the ocular blood flow has not been studied, but according to these findings we suggest that these hormones may influence
Nyctohemeral variations of intraocular pressure in three groups of white individuals: healthy young, healthy ageing population and glaucoma patients

A. Bottoli, L. Rossetti, A. Rabadazzo, E. Fumagalli, E. Orzalesi
University Eye Clinic, San Paolo Hospital, Milan

Purpose
To compare the 24-h pattern of intraocular pressure (IOP) in three groups of white individuals: healthy young, healthy aged subjects and untreated patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

Methods
Twenty young volunteers (aged 23–27 years), 20 older subjects (aged 55–75 years) and 20 untreated patients with diagnosis of POAG or OHT (aged 55–75 years) were hospitalized and their IOPs were measured at 3, 6, 9 a.m. and 12 noon, and at 3, 6, 9 p.m. and 12 midnight with a handheld electronic tonometer with the patient in the supine and sitting positions, and then with a Goldmann tonometer, by two well-trained evaluators. Systemic blood pressure was recorded at the same intervals.

Results
Supine position tonometric readings were higher during the night in the young group (P < 0.04), while this pattern could not be observed in the other two groups. A highly significant (P < 0.001) difference between supine position and Goldmann IOPs was found at all points of the curve, although in the young group, more evident during the night. In the older, healthy group, no significant IOP peak or trough could be observed in supine position or Goldmann readings, which were significantly higher than measurements in the young group. POAG/OHT patients showed significantly higher IOPs (P < 0.001) than the other two groups, and a morning-type pattern was observed with a peak of IOP at 9 a.m.

Conclusions
A nocturnal elevation of IOP was found only in the young group and was observed only in the supine position. Posture seemed to have a limited effect in older people, both healthy and diseased. Goldmann IOPs were higher in older than in young volunteers. A morning peak of IOP was observed in POAG or OHT untreated patients.
Effect of brimonidine on patients undergoing uncontrolled IOP with beta-blockers

L. Taverniti, S. Donati, S. Di Staso¹, L. Arrico, I. Giuffrè¹, S. M. Recupero
Eye Clinic, ‘La Sapienza’ University of Rome,
¹Eye Clinic, University of l’Aquila

Summary
The authors evaluated the effect of the replacement of β-blockers with brimonidine drops in patients taking β-blockers only or with dorzolamide, having IOP > 20 mmHg. The study was divided into two sections: one group treated with brimonidine b.i.d. (23 patients) and the other group treated with brimonidine + dorzolamide b.i.d. (17 patients). The effect of the substitution showed after 90 days of treatment with a reduction of 8.59 ± 1.2 mmHg (P < 0.001) in the first group and 6.1 ± 1.7 mmHg (P < 0.001) in the second group. Three patients in the first group and four patients in the second group presented minor adverse effects which did not justify discontinuation of treatment. Brimonidine was effective treatment as a substitute for β-blockers only when associated with dorzolamide.

Introduction
Beta-blockers locally administered are still the drug treatment most used in glaucoma patients but often, after years of continuous treatment, those patients find a reduction in the ocular hypotensive efficacy of the drug which produces IOP values at levels incompatible with the maintenance of a good optic nerve head trophism. In this prospective study, we have evaluated the replacement of the β-blocker with a new-generation α-agonist drug, brimonidine tartrate 0.2% drops as this, by acting on different ocular receptors to reduce IOP, can bring the ocular tension to safe levels.

Material and Methods
Forty patients aged between 46 and 82 years (mean 59 years), 24 men and 16 women, affected by chronic simple glaucoma with gonioscopically open angle, or by ocular hypertension, in both eyes, were chosen. An open clinical study was made and the patients to be admitted to the study had to present an IOP > 20 mmHg after at least 4 weeks’ treatment with β-blockers administered twice daily, either alone (group 1, 23 patients), or in association with a local carbonic anhydrase inhibitor (group 2, 17 patients). The two groups were homogeneous for sex and age.

In order for the study to be acceptable, all the patients underwent an eye examination, including:
- general and ophthalmological anamnesis;
- measurement of the heart rate and arterial systolic and diastolic pressure;
- objective ocular biomicroscopic examination;
- visual acuity;
- applanation tonometry;
- visual field;
- ophthalmoscopic examination.

Then, brimonidine 0.5% twice daily was given instead of the β-blocker and the IOP, the objectivity and cardiac parameters checked after 15, 30, 60 and 90 days.

Results
Mean IOP at the start of the 23 group 1 patients was 24.09 ± 2.2 mmHg with no statistically significant difference from that of group 2 (23.13 ± 1.8 mmHg). At all checks brimonidine alone, in place of the β-blocker, reduced IOP statistically significantly, the average reduction at 90 days being 8.59 ± 1.2 mmHg (P < 0.001). In the patients who were not well tonometrically controlled by the association of the β-blocker and local carbonic anhydrase inhibitor, treatment with associated brimonidine and carbonic anhydrase inhibitor had a good tonometric control after 90 days with a mean reduction of 6.1 ± 1.7 mmHg (P < 0.001). In group 1, 3 patients (13%) had allergic reactions to the brimonidine: marked conjunctival hyperaemia, a feeling of foreign body in the eye and photophobia, while in group 2, 4 patients (24%) reported the same symptoms which did not, however, prevent the study being finished. There were no statistically significant variations in the cardiological parameters.

Conclusions
In our opinion, patients on local ocular therapy with β-blockers, whether alone or in association with other drugs, can find a reduction of efficacy in time, with IOP increase not necessarily linked to a worsening of the pathology. In these patients, the use of an α-blocking drug is indicated in that different receptors are acted upon and in addition, after a certain lapse of time, the eye will regain the capacity to respond to the β-blockers. Systemic tolerability is excellent, while the problems of local tolerability, in line with what has been reported in the literature, were more in the group treated with brimonidine in association with local carbonic anhydrase inhibitor, probably due to the increased strength the two drugs exert on conjunctival reactivity.

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Comparison of latanoprost, brimonidine and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension

N. Orzalesi, I. Rossetti, A. Bottoli, T. Invernizzi, E. Fumagalli, P. Fogagnolo

University Eye Clinic, San Paolo Hospital, Milan

Purpose
To compare round-the-clock intraocular pressure (IOP) reduction induced by latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide in patients with primary open-angle glaucoma (POAG) and ocular hypertension (OHT).

Methods
In a cross-over trial, 10 patients with POAG and 10 with OHT were treated with latanoprost, brimonidine and a fixed combination of timolol and dorzolamide. Treatment sequence was randomized. All patients underwent 4 round-the-clock tonometric curves at baseline and after 1 month of treatment with each trial drug. IOPs were measured at 3, 6, 9 a.m. and 12 noon, and at 3, 6, 9 p.m. and 12 midnight with a handheld electronic tonometer with the patient in the supine and sitting positions, and then with a Goldmann applanation tonometer by two well-trained evaluators masked to treatment assignment. Sample size was estimated assuming a difference in mean IOP of 2.5 mmHg as clinically relevant, \( a = 0.05 \), \( 1 - \beta = 0.90 \), and a SD = 2 mmHg.

Results
All the drugs significantly reduced IOP against baseline at all times except for brimonidine at midnight, 3 a.m. and 6 a.m. Latanoprost was more effective in lowering IOP than brimonidine at 3 a.m. and 6 a.m. and at 3 p.m., while the combination of timolol and dorzolamide was more effective in lowering IOP than was brimonidine at 3 a.m. and 9 a.m. \( (P < 0.04) \) and at 3 p.m. and 6 p.m. \( (P < 0.05) \) and than latanoprost at 9 a.m. \( (P < 0.05) \).

Conclusions
Latanoprost, and the combination of timolol and dorzolamide seemed to provide quite uniform circadian IOP reduction, whereas brimonidine was less effective in lowering IOP particularly during night-time hours.

The pulsatile ocular blood flow behaviour in open angle glaucoma patients after replacing timolol therapy with timolol and dorzolamide fixed combination: preliminary study


Eye Clinic, University of Rome, Tor Vergata

Background
The role of ocular perfusion in the pathogenesis of primary open angle glaucoma (POAG) is increasingly discussed. At present topical beta-blockers are the most common treatment in glaucoma but almost half the patients on this topical beta-blocker treatment require an adjunct therapy to control the glaucomatous damage progression (Centofanti et al. 1999).

Dorzolamide, a topical CA inhibitor, is one of the drugs most used in addition to beta-blocker therapy. This drug inhibits CA-II isoenzyme, which plays an important role in the aqueous humour production in humans. Topically applied, dorzolamide increases retinal blood flow velocity in normal tension glaucoma patients (Sugrue 2000), enhancing CO₂ concentration in ocular tissues. Scanning laser ophthalmoscopy demonstrated how dorzolamide accelerates blood velocity in the retinal and superficial optic nerve head without an apparent effect upon retrobulbar haemodynamics in healthy eyes (Harris et al. 1996). Moreover, dorzolamide accelerates retinal arteriovenous passage time of the fluorescein dye at constant retinal arterial and venous diameters, but failed to change flow velocities in any retrobulbar vessel in normal tension glaucoma patients (Harris et al. 1999).

Purpose
The aim of this study is to evaluate the pulsatile ocular blood flow (POBF) behaviour after adding topical anhydrase inhibitor dorzolamide in POAG patients in treatment with timolol 0.5% twice daily.

Material and Methods
Measurements of POBF, ocular pulse amplitude (PA) and intraocular pressure (IOP) were obtained by an ocular blood flow tonograph (Ocular Blood Flow System, OBF Laboratories, UK) in 12 POAG patients, 6 males and 6 females, mean age 67 years (aged between 59 and 75 years), with a well-controlled IOP using a timolol 0.5% twice-daily monotherapy.

Heart rate, systolic and diastolic blood pressures were also measured at brachial
artery. The first measurements were performed during the timolol 0.5% therapy before morning drop instillation (timolol trough) and 2h after instillation (timolol peak). The second measurements were made after 2 weeks of timolol–dorzolamide fixed combination therapy and again before and after 2h from the instillation (fixed combination trough and peak). A two-tailed paired Student’s t-test was used to compare the timolol group to the fixed-combination group; P < 0.05 is considered significant.

Results
Data obtained at trough and peak during timolol monotherapy were compared to data, respectively, obtained at trough and peak during fixed combination therapy. We found a statistically significant IOP reduction at timolol peak compared to timolol trough (19.5 ± 3.1–17.9 ± 3.0 mmHg, −8.6%, P < 0.05, Table 1) and a statistically significant POBF increase at fixed combination peak compared to timolol peak (705.3 ± 234–769.0 ± 289 μl/min, + 8.7%, P < 0.05, Table 2). Other variables examined did not show any statistically significant change.

Table 1. IOP.

<table>
<thead>
<tr>
<th></th>
<th>IOP trough</th>
<th>IOP peak</th>
<th>Diff. percentage</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timoptol</td>
<td>19.5</td>
<td>17.9</td>
<td>−8.6%</td>
<td>0.04524</td>
</tr>
<tr>
<td>Timoptol/dorzolamide</td>
<td>17.6</td>
<td>16.6</td>
<td>−5.7%</td>
<td>0.159247392</td>
</tr>
</tbody>
</table>

Conclusions
In this study we found no statistically significant differences in IOP reduction between timolol 0.5% monotherapy and timolol–dorzolamide fixed combination therapy either at trough or at peak. The addition of dorzolamide to timolol monotherapy brought about an increase of POBF values which may be attributed to a direct action of the topical anhydrase inhibitor independently of IOP changes. The increasing of POBF without any statistical significant change of systemic blood pressure and heart rate leads to these variables not being considered as possible factors responsible for ocular perfusion improvement. Studies have shown that timolol–dorzolamide fixed combination efficacy in reducing IOP is completely comparable to the same combination given separately (Sugrue 2000) (not fixed).

The advantage is a reduction in the number of daily instillations (from 4 to 2) associated with improved patient compliance. Therefore our results confirm the valid effect of dorzolamide action on ocular blood flow in POAG patients.

References

Table 2. POBF.

<table>
<thead>
<tr>
<th></th>
<th>POBF trough</th>
<th>POBF peak</th>
<th>Diff. percentage</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timoptol</td>
<td>705.3</td>
<td>758.4</td>
<td>−7.5%</td>
<td>0.223877</td>
</tr>
<tr>
<td>Timoptol/dorzolamide</td>
<td>769</td>
<td>824.9</td>
<td>−7.2%</td>
<td>0.007898</td>
</tr>
</tbody>
</table>

Eyelash hypertrichosis induced by topical latanoprost: 6-month follow-up study

G. Stecchi¹, S. Saccucci², S. Molinari², F. De Gregorio²
¹Eye Clinic, ‘L. Sacco’ Hospital, University of Milan
²Institute of Ophthalmology, ‘La Sapienza’ University, Rome

Aims
To verify and quantify hypertrichosis, if any, of the eyelashes during 6 months of topical treatment with latanoprost.

Methods
Forty-four patients (mean age 69 years, range 33–91, M/F =20/24) affected by POAG or ocular hypertension were enrolled and put into two groups. One group was treated with latanoprost 0.005% daily (n = 26) and a control group (n = 18) with timolol 0.5% b.i.d. Eyelid eyelash lengths were measured with a surgical compass before treatment and after 2, 4 and 6 months during treatment. A variance analysis for repeated measurements was used to evaluate the significance of the results. The sample sizes were enough to establish a significance (α = 0.05) of an eyelash length variation above 1 mm with a power (1 – β) of 80%.

Results
Two patients in the group treated with latanoprost and none in the control group showed an aesthetically apparent growth
patients with open-angle glaucoma are not long-term antihypertensive treatments in 1990). It has also been reported that topical aspect adequately ascertained (Lavin et al. on the success ratio in

B. Boles Carenini, E. Boldrini, B. Brogliatti for long-term glaucoma therapy preparations in special containers

Real advantages of preservative-free preparations in special containers for long-term glaucoma therapy

B. Boles Carenini, E. Boldrini, B. Brogliatti

Long-term use of topical medications for glaucoma therapy is often associated with alterations of corneal and conjunctival epithelium. The origin of the damaging mechanism is not entirely known yet, but particular attention is given to benzalkonium chloride (BAC) that is the most frequently used preservative in ophthalmic preparations and is specially present in timolol-based eye drops.

Ophthalmic preservatives interfere with the growth, metabolism and reproduction of microbial organisms but, on the other hand, they cause similar effects on eukaryotic cells and this justifies their toxicity (Olson & White 1990). Long-term treatments required for patients suffering from glaucoma can deliver to serious damages for the ocular surface whose epithelia have a fundamental role in the formation and stability of the lacrimal layer (Kuppens et al. 1995).

Reactions induced by preservatives on epithelia are both toxic and immunological ones, and this aspect is also described for BAC on the ocular surface. The toxicity is aimed at epithelial apical cells, at goblet cells and also at the lacrimal film, due to the cleansing properties of the preservative altering its stability and yield (Feher et al. 1990; Kuppens et al. 1995). Recent studies showed that BAC produces cellular necrosis at the concentrations usually present in eye drops, while causing apoptosis at lower concentrations (Debbasch et al. 2000, 2001).

The influence of antiglaucoma treatments on the success ratio in filtering surgery is an aspect adequately ascertained (Lavin et al. 1990). It has also been reported that topical long-term antihypertensive treatments in patients with open-angle glaucoma are not

infrequently linked with the development, in the conjunctiva and trabecular tissue, of inflammatory infiltrates predisposing fibrosis and thus determining a certain rate of failures in filtering surgery (Baudouin et al. 1999).

Authors are now asserting the conviction that preservatives can induce a local stimulation of the immunity system, with the development at the conjunctival level of inflammatory infiltrates in the subepithelial stroma. Moreover, there are reports of a remarkable expression by the epithelium of proteins dependent from cytokines, such as HLA-DR and ICAM-1 (De Saint Jean et al. 2000). It is known that the human conjunctiva is commonly colonized by cells belonging to the immune system. T-lymphocytes, macrophages, Langerhans cells and, occasionally, β-lymphocytes have been identified in the epithelium and in the substance typical of conjunctival tissue (Chang et al. 2000).

Experimental studies recently performed in animals confirm that preservatives are for the most part responsible for the tissue iatrogenic alterations described after topical long-term applications of β-blocking drugs (Beccuet et al. 1998; Baudouin et al. 1999).

In all the cases cited here, BAC seems to be able to provoke an increased expression of both inflammatory cells at the conjunctival level and in the trabeculum area, and of apoptotic markers such as Fas and APO 2.7, also in the absence of a noticeable inflammatory reaction (Debbasch et al. 2000).

It is opportune to consider the role that eye drops devoid of preservatives can produce in a long-term therapy. A key step in this direction was obtained with the use of ophthalmic preparations in ‘monodose’ containers, such as in the case of timolol. In the monodose container, the preparation, preservative-free, is always sterile, as there is no possibility at all of any form of pollution, as the use of the dose is immediate and in its entirety. A monodose container is anyhow insufficient to cover a daily treatment and the cost of this type of treatment is rather higher than the one with the conventional formulation.

A valid alternative to monodose containers is represented by the use of reclosable minicontainers useful for a daily therapy (Van Santvliet et al. 1996). These preparations are ophthalmic solutions, preservative-free, usable within 12 h from their first opening.

As far as monodose sterile preparations are concerned, the validity after the first opening proposed by the European Agency for the Evaluation of Medicinal Products (EMEA) must be around 3 h. Such a limit is fixed considering a possible environmental pollution and the resulting development of potential pathogens. In the case of ophthalmic solutions usable during a 12-h period, such a risk can be regarded as higher, considering the possible contact of open containers with the ocular surfaces of patients.

In order to verify all polluting possibilities, an experimental analysis was performed considering the spontaneous contamination of timolol-based solutions packaged in reclosable minicontainers (Table 1).

Table 1. Evaluation of spontaneous contamination of preparations after first opening kept at room temperature for 24 h.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Timolol solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>=</td>
</tr>
<tr>
<td>2</td>
<td>=</td>
</tr>
<tr>
<td>4</td>
<td>=</td>
</tr>
<tr>
<td>8</td>
<td>=</td>
</tr>
<tr>
<td>24</td>
<td>=</td>
</tr>
</tbody>
</table>

Note: =, absence of microorganism. Five different samples were used for each preparation.
Table 2. Fate of bacteria in 0.5-mL containers of ophthalmic BAC-free timolol.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Time (h)</th>
<th>Cfu/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Room temp.</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.6 × 10⁴</td>
<td>3.9 × 10⁴</td>
</tr>
<tr>
<td>2</td>
<td>1.6 × 10⁴</td>
<td>1.4 × 10⁴</td>
</tr>
<tr>
<td>4</td>
<td>1.5 × 10⁴</td>
<td>1.2 × 10⁴</td>
</tr>
<tr>
<td>8</td>
<td>9 × 10³</td>
<td>1 × 10⁴</td>
</tr>
<tr>
<td>24</td>
<td>2.6 × 10³</td>
<td>1 × 10³</td>
</tr>
<tr>
<td><strong>Staphylococcus epidermidis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5.8 × 10⁴</td>
<td>5.8 × 10⁴</td>
</tr>
<tr>
<td>2</td>
<td>5.8 × 10⁴</td>
<td>2.1 × 10⁴</td>
</tr>
<tr>
<td>4</td>
<td>2.3 × 10³</td>
<td>1 × 10³</td>
</tr>
<tr>
<td>8</td>
<td>2.2 × 10³</td>
<td>1.5 × 10³</td>
</tr>
<tr>
<td>24</td>
<td>3.9 × 10³</td>
<td>2.1 × 10³</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3.2 × 10⁴</td>
<td>3.2 × 10⁴</td>
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<td>2</td>
<td>3.2 × 10⁴</td>
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<td>4</td>
<td>1 × 10³</td>
<td>5 × 10³</td>
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<tr>
<td>8</td>
<td>1.1 × 10³</td>
<td>6 × 10²</td>
</tr>
<tr>
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<td>9 × 10²</td>
<td>2 × 10³</td>
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<tr>
<td><strong>Streptococcus haemolyticus</strong></td>
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<td></td>
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<tr>
<td>0</td>
<td>3.7 × 10⁴</td>
<td>1.2 × 10⁵</td>
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<td>2.9 × 10³</td>
<td>2 × 10³</td>
</tr>
<tr>
<td>24</td>
<td>&lt;10</td>
<td>10&lt;</td>
</tr>
<tr>
<td><strong>Streptococcus spp.</strong></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>2.5 × 10⁵</td>
<td>3.2 × 10⁵</td>
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<td>2</td>
<td>2.4 × 10⁵</td>
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<td>8</td>
<td>7.2 × 10⁴</td>
<td>1 × 10⁵</td>
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<tr>
<td>24</td>
<td>2.1 × 10⁴</td>
<td>1.7 × 10⁴</td>
</tr>
<tr>
<td><strong>H. influenzae</strong></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>4.2 × 10⁴</td>
<td>2.6 × 10⁵</td>
</tr>
<tr>
<td>2</td>
<td>2 × 10³</td>
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<tr>
<td>24</td>
<td>&lt;10</td>
<td>&lt;10&lt;</td>
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<tr>
<td><strong>Neisseria spp.</strong></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>2.5 × 10⁴</td>
<td>3.4 × 10⁵</td>
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<tr>
<td>2</td>
<td>6.1 × 10³</td>
<td>1 × 10⁵</td>
</tr>
<tr>
<td>4</td>
<td>3.7 × 10³</td>
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<td>8</td>
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<tr>
<td>24</td>
<td>&lt;10</td>
<td>&lt;10&lt;</td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 × 10⁴</td>
<td>2 × 10⁴</td>
</tr>
<tr>
<td>2</td>
<td>7 × 10³</td>
<td>2.5 × 10⁴</td>
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<td>8</td>
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<td>7 × 10³</td>
</tr>
<tr>
<td>24</td>
<td>2.6 × 10⁵</td>
<td>3.1 × 10⁵</td>
</tr>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.5 × 10⁴</td>
<td>3.2 × 10⁵</td>
</tr>
<tr>
<td>2</td>
<td>2.4 × 10⁵</td>
<td>2.7 × 10⁵</td>
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<td>1.1 × 10⁵</td>
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<td>7.2 × 10⁴</td>
<td>1 × 10⁵</td>
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<tr>
<td>24</td>
<td>2.1 × 10⁴</td>
<td>1.7 × 10⁵</td>
</tr>
<tr>
<td><strong>Acinetobacter spp.</strong></td>
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<td>0</td>
<td>4.1 × 10⁴</td>
<td>1 × 10⁸</td>
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<td>8</td>
<td>8 × 10³</td>
<td>6 × 10³</td>
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<tr>
<td>24</td>
<td>4 × 10⁵</td>
<td>2.9 × 10⁶</td>
</tr>
<tr>
<td><strong>C. albicans</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6.3 × 10⁵</td>
<td>1.5 × 10⁷</td>
</tr>
<tr>
<td>2</td>
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<td>6.8 × 10⁷</td>
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<td>6.4 × 10⁷</td>
</tr>
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<td>1.7 × 10⁴</td>
<td>8 × 10⁷</td>
</tr>
<tr>
<td>24</td>
<td>6.4 × 10⁴</td>
<td>4.4 × 10⁷</td>
</tr>
</tbody>
</table>

The study also evaluated the fate of known amounts of different bacterial species added to the ophthalmic preparations aiming at simulating a contact pollution with the infected conjunctiva (Table 2).

These results show that preservative-free eye drops in reclosable minicontainers can be used for a daily therapy without any risk of ocular infection, even beyond 12h after the first opening of the sterile package.

**Conclusions**

It seems clear that preservatives in the eye drops can damage the ocular structures, so probably aggravating the alterations caused by the disease. Published data confirm that long-term use of BAC-free timolol eye drops is a safe way to improve local tolerance and to reduce filtering surgery failure.

In comparison with preservative-free solutions packaged in monodose containers, the most remarkable advantage of 0.5-mL reclosable minicontainers is the possibility of more than one instillation of preservative-free medication during the same day.

**References**


An *in vitro* model for post-trabeculectomy: evaluation of drugs differently controlling cell proliferation

N. Pescosolido¹, G. Scarsella², G. Risuleo³

¹Institute of Ophthalmology
²Department of Cell Biology and Development
³Department of Genetics and Molecular Biology, ‘La Sapienza’ University of Rome

**Aims and Scope**
Experience over many years points to extremely variable therapeutic success in different individual eyes due essentially to the cicatrizing reactions. Several drugs have been evaluated as to the pharmacological modulation of this response. All these compounds have necrotic effects. This *in vitro* study aimed to evaluate various drugs. Three different agents: 5-FU, interferon α2 (IFN) and cyclosporin A (CsA) were assayed as to their ability to interfere with cell proliferation and survival. In addition, apoptosis can be inhibited in these cells by trolox. This is a nontoxic potent antioxidant water-soluble drug analogue to vitamin E. Trolox is known to penetrate biological membranes with ease and behaves as a powerful peroxy radical scavenger. The authors also present here the data obtained with heparin in the same model system. This drug is known also for its antiproliferative activity and therefore it was evaluated as to its ability to induce apoptosis and/or necrosis.

**Methods**
The antifibrotic activity of CsA, IFN, 5-FU and heparin was investigated on 3T6 cells in culture. Cell viability and proliferation was assessed after drug treatment. Molecular analysis of DNA degradation was evaluated by means of radioactive labelling and gel electrophoresis. Treatment with trolox lasted for 24 h with a final concentration of 1 mM.

**Results**
All three drugs (CsA, IFN and FU) were shown to affect cell proliferation and viability in a differential fashion (Fig. 1). However, only cyclosporin A was able to control cell proliferation by inducing apoptosis. This phenomenon was controlled by contemporary supplementation of trolox, a compound known to inhibit programmed cell death. These results strongly suggest that this model system might be useful as a test of pharmacological functionality. Concerning heparin, results reported here give evidence that, at a concentration between 5 mM and 10 mM, the aggregation of cells, possibly due to membrane modification, occurs. In addition, care should be taken since at higher drug concentrations (20 mM) extensive necrosis may occur.

**Conclusion**
A rapid and efficient model system is described for the assessment of cell viability and proliferation after treatment with agents of potential pharmacological use. Cyclosporin A induces a significant apoptosis. This is important for the negative control of fibrotic degeneration in post-trabeculectomy that is required for successful surgery in glaucoma patients. Therefore, cyclosporin A might become a clinically interesting drug for the antifibrotic treatment of post-trabeculectomy. In addition, heparin shows interesting features since it is able to control proliferation via stimulation of necrosis. However, the authors urge an experimentation *in vivo* of the action of this drug, possibly on animal models subjected to trabeculectomy. In particular, the study of the mechanisms triggering cell necrosis with respect to those mediating the cell fusion phenomena observed at low concentration will be of relevance. It can, however, be concluded that the value of these drugs consists in their moderate and controllable effect in the production of necrosis.

**Reference**
Advanced flap trabeculectomy

F. M. Grignolo, R. Gallo, L. Tonini, M. M. Rabbione, A. M. Fea

Eye Clinic, University of Turin

Aims

After Cairns (Cairns et al. 1968) presented trabeculectomy in 1968 as a surgical solution for primary open-angle glaucoma (POAG), numerous variants (Fronimopoulos et al. 1970; Watson 1970; Della Porta et al. 1971) to the original technique have been proposed with the object of obtaining a stable and long-lasting reduction of the intraocular pressure (IOP) avoiding the complications which the earlier techniques could bring. We have tried to potentiate the filtering effect of trabeculectomy, that is the capacity of aqueous humour outflow from the anterior chamber of the eye after the operation, by introducing a modification to the suture of the scleral flap which is advanced by about 2 mm with respect to the limbus and then sutured so that a tunnel is made circumferentially, which improves the filtering effect.

Material and Methods

A retrospective analysis has been carried out on 34 advanced flap trabeculectomy operations performed at the eye clinic of the University of Turin from January 1995 to April 1999 on 19 men (55.88%) and 15 women (44.12%) aged between 17 and 86 years, mean 66 ± 16 years, of whom 16 operations were on the right eye (47.06%) and 18 on the left eye (52.94%). These operations were on the right eye (47.06%) and in 14 years, of whom 16 operations were on the right eye (47.06%) and 18 on the left eye (52.94%). These patients had a trabeculectomy operation according to the protocol:

1. stabilization of the eyeball;
2. conjunctival flap;
3. scleral window;
4. trabeculectomy with an Elliot trepan (a Crozafon–De Laage punch was used on one patient only);
5. basal iridectomy;
6. scleral flap advanced suture;
7. anterior chamber formation;
8. tenon-conjunctival flap suture.

After the operation, the patients were followed-up by a tonometric and a visual acuity examination immediately postoperatively, and at 1 week, 1 month, 3 months, 6 months, 1 year (34 patients, 100%), 18 months (30 patients, 88.24%) and 2 years (24 patients, 70.59%). All the parameters were analysed by a statistical evaluation with the one way ANOVA test for paired measurements and the Bonferroni test.

Results

In these 34 patients, preoperation mean IOP was 27.00 ± 4.48 mmHg and mean visual acuity 6.76 ± 3.34 tenths. In our case file at the last check, in 32 of the 34 patients (94.12%) an IOP normalization with values under 21 mmHg had been obtained. In 5 of the 32 patients (15.62%), the tonometric compensation had been obtained with a monotherapy and in another 6 (18.75%) with a polytherapy. The IOP mean value after 1 year (34 patients, 100%) was 15.71 ± 3.29 mmHg, after 18 months (30 patients, 88.24%) it was 15.17 ± 2.51 mmHg and after 2 years (24 patients, 70.59%) it was 14.92 ± 3.19 mmHg. The IOP improvement was statistically significant (F = 11.53; P < 0.001). So far as the immediate postoperation visual acuity was concerned, there was a reduction (3.51 ± 3.26 tenths) against basal values. That reduction was not statistically significant. At subsequent checks, the visual acuity progressively improved. The improvement was statistically significantly after 18 months (6.04 ± 3.31 tenths) and after 2 years (6.12 ± 3.18 tenths) with respect to that immediately postoperational (F = 3.17; P = 0.002).

Discussion

Subsequent to a simple trabeculectomy, patients have sometimes had complications. Some are experienced precociously, within 1 month of the operation: in 20 cases (58.82%) there was a hypothalamia; in 14 cases (41.18%) there was an ophthalmia; in 12 cases (35.29%) a haemorrhage formed early (after 1 to 4 days after the operation) and disappeared within 1–3 weeks; in 9 cases (26.47%) synechiae formed in patients with ophthalmia, athalamia or hyphaemia; in 3 cases (8.82%) there was a marked hypotone immediately postoperatively, an IOP < 6 mmHg; in 5 cases (14.71%) there was a choroid detachment; in 1 case (2.94%) there was a transient hypertension immediately postoperatively, an IOP > 21 mmHg. Other complications, on the other hand, were found later: in 10 of 30 patients (33.33%) there was a visual acuity reduction of more than 30% at a distance of 18 months after the operation, but not after 1 year in the other 4 patients; in 2 cases (5.88%) a cataract developed and in 2 cases (5.88%) the cataract already there worsened.

Conclusions

The good results obtained are linked, in our opinion, to the fact that advancing the scleral flap permits a better filtration at the sclerostomy and a reduction of scarring phenomena at the filtering bleb. The positioning of the scleral stitches, by forming a sort of protected tunnel from the scleral window, prevents the scleral flap from slipping into its original place and thus reduces the possibility of an occluding scarring process being set up. The advantage of this operation is also linked to the fact that good results are obtained without recourse to the use of antimetabolites (5-fluorouracil and mitomycin C), compounds that are not complication-free. Furthermore, with this type of operation there have been none of those serious complications (keratitis, corneal ulcer, endophthalmitis, uveitis, maculopathy, lasting hypotony) which, according to the literature (Braun 1996; Colignon-Brach 1996), might have their onset particularly at least 1 month after the operation. The absence of such complications has certainly been enhanced by the use of viscoelastic substances at the end of the operation itself, since they avoid an excessive filtration in the immediate postoperative period. In conclusion, we can also affirm the validity of advanced flap trabeculectomy because, in comparison with the literature (Bell et al. 1997; Lanzl et al. 1997; Lerner et al. 1997; Allen et al. 1998; Anand et al. 1998; Beatty et al. 1998; Sidoti et al. 1998; Stone et al. 1998), it emerges that our results are comparable, if not actually better, with those obtained by trabeculectomy operations performed in recent years with or without the use of antimetabolites.

References


Anand N et al. (1998): Modification of trabeculectomy with single-dose intraoperative
Five-year follow-up of LSL trabeculectomies with low dosage mitomycin-C in primary open-angle glaucoma

A. Reibaldi, M. G. Uva
Medico-Surgical Speciality Department, University of Catania, Ophthalmology Section

Introduction
The main aim of every antiglaucomatous operation ought to be the attainment of a postoperative intraocular pressure low enough to guarantee permanent visual field conservation without the necessity for adjunct hypotensive therapy and without complications in the short or long-term. The use of antimetabolites, especially mitomycin C, with a view to increasing the hypotensive efficacy of the filtering operations and their duration has always been a source of conflicting opinions, principally because of the short- and long-term complications described in the literature. Previous prospective studies we have carried out (Reibaldi et al. 1994; Uva et al. 1996a) have put in evidence the validity from the hypotensive efficacy point of view and from that of safety (absence of major complications) the surgical approach to primary open-angle glaucoma (POAG) of a controlled filtration trabeculectomy by laser lysis of the suture plus low dosage (0.2 mg/ml for 2 min) intraoperative application of mitomycin. We present here the long-term follow-up (>5 years) results on the same patients enrolled in the earlier studies.

Material and Methods
From the original cohort of enrolled patients, we have taken into consideration in this study only those who have continued during the last 5 years to undergo the programmed check examinations at the glaucoma centre of our institute. We therefore report the data of 28 eyes of 28 patients (12M, 16F) of mean age 58.2 ± 4.1 years with a range of 49–65 years, who all had a previous diagnosis of uncompensated POAG. These patients account for 93.4% of the original case-file, which was subdivided according to a prospective study plan and randomized into 2 groups: A (MMC) and B (control). The case-file actually considered includes 14 eyes in group A and 14 eyes in group B (2 patients, 1 per group, were lost during the follow-up, respectively, 1 deceased and 1 transferred to another centre). All the patients had a trabeculectomy with similar technique by the same surgeon between June 1994 and June 1995. The surgical technique called for positioning traction suture, preparing the conjunctival flap on a limbar hinge, as far posterior as possible; haemostasis by bipolar diathermy; scleral flap dissection of about 4 x 4 mm on a limbar hinge; positioning on the episclera of the repositioned flap a merocel about 4 x 4 x 2 mm surgical sponge soaked in mitomycin C at a concentration of 0.2 mg/ml and left there for 2 min in the group A (MMC) eyes, and soaked in physiological solution in the group B (control) eyes; lavage with physiological solution; excision of the scleral wedge; basal iridectomy, instillation of atropine 1% eye-drops; serried scleral flap suture with 5 nylon 10/0 stitches, continuous conjunctiva suture in vicryl 8/0; subconjunctival injection of steroids and antibiotics. Postoperatively, where necessary, we laser lysed the suture with the appropriate Hoskins lens (Ocular Instruments, Inc.) according to criteria based on the evaluation of the OP of the conjunctival bleb, the depth of the anterior chamber, in conjunctival Seisdel absence and chorioidal detachment. We always lysed the suture one stitch at a time with an interval of 48 h between one lysing and another and only after re-evaluating the reference parameters. The results, reconsidered in light of the protracted follow-up with respect to the earlier studies, derive from the comparison between the two groups in terms of ocular pressure, the necessity of adjunct hypotonizing therapy or further surgery (originating from the evaluation of the tonometric, perimetric and optic papilla objective data), visual acuity variations and percentage of short and long-term complications. In order to evaluate the differences between the groups, we used a 2 statistical analysis of the results for the category variables with Student’s t-test for continuous variables.

Results
Pre-operational mean IOP of group A (MMC) was 23.9 ± 5.7 mmHg, of group B (control) 24.2 ± 5.9 mmHg, with a nonstatistically significant (P > 0.4) difference between the two groups. The preoperative mean number of hypotensive medications was 2.6 in group A and 2.7 in group B (NS). After a mean follow-up of over 5 years (range 76–65 months), IOP mean value (the mean of the measurements in the last three checks) was 11.6 ± 2.2 mmHg in group A and 16.8 ± 4.8 mmHg in group B (P < 0.01).
Assuming a hypothetical pressure target of 18 mmHg, this was reached in 82.9% of group A cases and 57.1% of group B cases. A pressure target of 15 mmHg was reached in 71.4% of group A cases and 42.9% of group B cases. A pressure target of 12 mmHg was reached in 57.1% of group A cases and 42.9% of group B cases. At the end of follow-up, no group A patient required adjunct hypotensive therapy, while 14.3% of group B patients required monotherapy after evidence of perimetric worsening, with a difference between the groups which was not statistically significant ($P = 0.44$).

Visual acuity was reduced significantly (variation $> 0$ – a 2 lines) because of an asymmetric increase of lens opacity in the fellow eye in 1 case (7.1%) of each group. From the point of view of complications, at the end of follow-up we recorded: 1 case (7.1%) of corneal in group A; 2 cases (14.3%) of transient or partial peripheral detachment of choroid (ophthalmoscopic finding without anterior chamber reduction) in group A, 1 case (7.1%) in group B; 4 cases (28.6%) of bleb encapsulation (resolved after needling) in group A, 3 cases (21.4%) in group B; 1 case (7.1%) of asymmetric cataract evolution in the fellow eye in group A and 1 case in group B.

As surgical or parasurgical procedures postoperatively necessary, we did not find any differences between the groups, except that laser lysis was required more often in group B (64.3% of cases) than in group A (42.9% of cases). Needling was necessary almost to the same extent in both groups (see above).

**Discussion and Conclusions**

The literature carries descriptions of case-files with a high incidence of serious complications related to the use of antimetabolites; for example: athalamia, cataract, choroid detachment, maculopathy from hypotension, late endophthalmitis. Gradually, in the course of these recent years, experience in the use of these substances has been increasing and some causes of the onset of complications have been clarified and the modality of antimetabolite usage has been better defined, with an improvement in the risk–benefit ratio that characterizes them. In our experience of the use of mitomycin C in the treatment of refractory glaucoma at a dosage (0.4 mg/ml for 4 min), higher than that used in the case-file of this present study, complications have been of an acceptable number and seriousness (Uva et al. 1996a). That, we think, is due to the combined action of two factors. A first factor is the use of the technique of trabeculectomy with filtration controlled by laser lysis of the suture, the cd. trabeculectomy LSL which permits aqueous humour filtration regulation in the immediate postoperative period, thus avoiding all the complications bound up with precocious hyperfiltration. The second important factor in avoiding complications, especially in the long term, such as hypotone-induced maculopathy and late endophthalmitis, is the way in which the antimetabolite is used.

Some authors, including Krieglstein (1995), have theorized a reduced production of aqueous humour through a transcleral cytotoxic effect of the antimetabolite on the ciliary bodies. Application of the drug-soaked sponge of the same size as the window, above the scleral flap, and not below it, in the bed of the window itself, to avoid its contact with the conjunctiva, together with the minimum efficacious dose (in terms of concentration and application duration) plays, in our opinion, an important role in guaranteeing fewer long-term complications, as other authors have hypothesized through clinical and experimental studies (Geijssen 1993; Kitazawa & Yamamoto 1993; Nuysts et al. 1994), to mention but three among others.

In conclusion, convinced of the necessity, in the interests of the patients and the conservation of their visual fields, of obtaining a postoperation pressure as low as possible, beyond ‘philosophical discourses’ of pressure targets cut to measure for each individual glaucomatous patient and which, unfortunately, can be validated only a posteriori, we think the results obtained in the light of over 5 years of follow-up are encouraging.

However, it is necessary to recommend, once again, a meticulous management of the patient both pre- and postoperation with a careful and scrupulous follow-up, especially in the short term.

**References**


Deep sclerectomy in primary open angle glaucoma: comparison among different implants

F. Galassi, A. Sodi, F. Ucci, B. Pieri, G. Renieri
Department of Oto-Neuro-Ophthalmological Sciences, University of Florence

Introduction
Deep sclerectomy is a recent surgical technique which is becoming increasingly common in glaucoma management. This surgery procedure avoids postoperative ocular hypotony with its classic related complications of shallow or flat anterior chamber, choroidal detachment, intraocular inflammation and cataract formation, which frequently occur with trabeculectomy. Deep sclerectomy is a non-penetrating filtering surgery promoting IOP reduction by inducing a filtration through a natural membrane, the trabeculo-Descemet membrane, with no penetration of the anterior chamber. Aqueous humour filters into a decompression sclero-corneal space and then flows into the uveo-scleral pathway, the aqueous veins and through the flap margins. With a view to keeping the intrascleral chamber patent, various kinds of implants have been proposed.

Aims
In this study, we compared the results of deep sclerectomy with various types of implants in patients with primary open angle glaucoma (POAG) after 12 months of follow-up. Three different implants had been used, all containing hyaluronic acid: Healon GV, Healon 5 (Pharmacia-Upjohn, Uppsala, Sweden) and a reticulated hyaluronic acid implant, SkGel (Corneal Laboratories, Paris, France).

Material and Methods
Our case-file consisted of 29 eyes of 26 patients with POAG who had had deep sclerectomy surgery. Two patients were excluded from the study because of severe postoperative complications (one, ocular hypertension with iris prolapse, the other, scleral flap rupture), and their results were not used in the statistical analysis. Conclusive estimates were therefore made on 27 eyes of 24 subjects, separated into three groups according to implant: Healon GV (7 eyes), Healon 5 (9 eyes) and SkGel (11 eyes). The three groups were homogeneous for age, sex, preoperative IOP, preoperative medications and failure an IOP >16 mmHg, were treated by laser goniopuncture. We considered complete success to be an IOP≤16 mmHg without medication, partial success an IOP≤16 mmHg with pharmacological monotherapy, and failure an IOP >16 mmHg with pharmacological therapy.

We used a variety of tests for statistical analysis:
• comparisons among the mean postoperative IOPs of the three groups at each control examination (ANOVA);
• comparison among the number of postoperative medications of the three groups at 12 months of follow-up (ANOVA);
• comparison among each single group of IOPs and postoperative medications (Bonferroni t-test for multiple comparisons);
• comparison among successes (complete or partial) and failures in the three groups (χ² test);
• the trend with time of the results in complete success cases (Kaplan–Meier survival analysis and intercurve analysis by means of the log-rank test).

Results
IOP and number of medications data in the three groups are shown in Table 1. At 12 months’ follow-up, a lower IOP was found in patients receiving SkGel (P < 0.05) than in the HGV group. The overall complete success rate was 77% (HGV 57.1%, H5 66.6%, SkGel 100%) even though the χ² test showed no statistically significant differences among the groups. Kaplan–Meier survival analysis for complete successes showed better results for surgeries with the use of SkGel, even though the curves of the three groups did not differ significantly. The incidence of minor complications (hyphaema, shallow anterior chamber, microperforation) were relatively low and similar in the three groups. The two eyes excluded from the study due to severe complications had received, one Healon 5 and the other SkGel.

Conclusions
Our data show a high success rate with rare severe postoperative complications, confirming the validity of deep sclerectomy as surgical treatment of POAG. In this study we had better results placing SkGel in the scleral decompression space. SkGel is resorbed more slowly than Healon 5 or Healon GV and this would allow a longer and more efficient influence on aqueous humour outflow.

Table 1.

<table>
<thead>
<tr>
<th>No. of eyes</th>
<th>HGV</th>
<th>H5</th>
<th>SkGEL</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>No. preoperative</td>
<td>4.71 ± 1.98</td>
<td>4.11 ± 0.93</td>
<td>4.36 ± 1.12</td>
<td>NS</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. postoperative medications</td>
<td>2</td>
<td>2.67 ± 0.58</td>
<td>0</td>
<td>0.000*</td>
</tr>
<tr>
<td>Preoperative IOP</td>
<td>20.29 ± 2.69</td>
<td>19.33 ± 2.45</td>
<td>20.55 ± 3.91</td>
<td>NS</td>
</tr>
<tr>
<td>1 day</td>
<td>9.14 ± 6.89</td>
<td>9.56 ± 6.31</td>
<td>7 ± 2.45</td>
<td>NS</td>
</tr>
<tr>
<td>1 week</td>
<td>20.13 ± 5.72</td>
<td>14 ± 5.10</td>
<td>11.27 ± 5.93</td>
<td>NS</td>
</tr>
<tr>
<td>1 month</td>
<td>16.43 ± 2.76</td>
<td>14 ± 3.35</td>
<td>12.82 ± 3.12</td>
<td>NS</td>
</tr>
<tr>
<td>6 months</td>
<td>14.14 ± 3.34</td>
<td>12.78 ± 2.91</td>
<td>11 ± 1.41</td>
<td>NS</td>
</tr>
<tr>
<td>12 months</td>
<td>15.29 ± 1.80</td>
<td>13.44 ± 3.47</td>
<td>11.91 ± 1.70</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

ANOVA.
Deep sclerectomy and viscocanalostomy: critical revision of the results obtained during the learning curve

L. Bauchiero, A. Demarie, L. Belli, B. Brogliatti
Eye Clinic, University of Turin

Introduction
In recent years, new trabeculectomy filtering surgical techniques have been proposed for open angle glaucoma treatment with a view to ensuring an effective surgery with lesser complications. In particular, deep sclerectomy is an example of protected filtration like trabeculectomy but differs from it in that it is non-perforating. Similarly, viscocanalostomy differs in that it uses viscoelastics instead of a reticular collagen implant to delay scarring at the sclerectomy site and thus increase the possibility of filtering success. Both can be associated or not with the use of antimetics (5FU) and mitomycin.

On the wave of the results reported in the literature and after training in the oculistics division of Ivrea Hospital, in the early months of 1998 we began to perform our first deep sclerectomies and viscocanalostomies and these soon became the main surgery option proposed to our glaucomatous patients uncompensated by medical therapy, relegating Cairns’ trabeculectomy with its variants to the alternative treatment in cases of unsatisfactory outcome with the others.

Aims
Our aims were the critical reviewing of the personal results obtained in the first series of operations by a refined and promising technique not yet perfectly codified, with the intention of reporting our difficulties, our enthusiasms and our delusions of the so-called ‘learning curve’.

Material and Methods
We made our retrospective study on 50 patients (42 sclerectomies and 8 viscocanalostomies) whose operations were performed between February 1998 and September 2000 by the same surgeon. An adequate preoperation documentation and regular conclusion of postoperative follow-up were available for 37 patients for a total of 41 eyes (37 sclerectomies, 4 viscocanalostomies). In particular, 13 of these were combined glaucoma and cataract operations (11 sclerectomies and 2 viscocanalostomies). Among the exclusion criteria normally considered risk factors for unsuccessful trabeculectomy surgery in similar case files, we considered age not less than 35 years, ALT test within the last 3 months, while it was proposed all the same to melanodermic patients (2 eyes) with previous lack of success in filtering surgery (pseudoaphakic) specifically for the foreseeable lower incidence of complications compared to a lower probability of expected success. Our case-file included 20 women (mean age 65.46 ± 9.1 years) and 17 men (mean age 61.35 ± 9.5 years), of whom 36 were Cauasian and 1 was black. The pathologies were: 34 eyes with open angle glaucoma, 4 eyes with hypertensive uveitis, 2 eyes with neovascular glaucoma and 1 eye with plateau iris. We took into particular consideration the subconjunctival filtering characteristics, hypotone or athalama, the presence of hyphaemia or fibrin in the anterior chamber postoperatively, pupil deformation and iris involvement, the gonioscopic aspect in cases brought to term without complications as well as in cases of intraoperative perforation and also in cases of YAG laser application on the Descemet. We considered the pressure results obtained with regard to the levels of 21 mmHg and 16 mmHg with and without therapy. We are in the process of selecting a control group with similar trabeculectomy characteristics so as to be able to evaluate the incidence of complications and the efficacy on IOP control. All our patients presented elevated IOP notwithstanding maximal medical therapy, perimetric defects, cupped disk and in 47.3% a preceding ALT had been carried out.

Surgical Technique
Deep sclerectomy
We used peribulbar anaesthesia (bupivacaine 0.75%, xylocaine 4%, hyaluroidase 50 μ), conjunctival flap with fornix base, haemostasis if necessary, dissection of scleral window 5 × 6 mm on limbic hinge of about one-third scleral thickness extended into the clear cornea, which is removed together with the roof of Schlemm’s canal which will, however, be removed later if still present, so exposing the deep trabeculate and the Descemet and obtaining percolation of the aqueous humour. In 9 cases, a 3 × 5 mm sodium hyaluronate triangle was implanted, in 8 cases, a reticulate collagen implant was chosen. All the other cases had their coreosclesal spaces filled with high molecular weight viscoelastic substance. Suturing was two nylon 10.0 stitches for the superficial scleral window and two vicryl 10.0 stitches for the conjunctiva. A 5FU subconjunctival application on the superficial scleral window (50 mg/ml) was made for 3 min before deep window dissection (3 cases with sodium hyaluronate, 3 cases with reticulate collagen, 2 with no implant).

Viscocanalostomy
The technique is the same up to the moment when the uncovered Schlemm’s canal is cannulated (cannula specification: 190 μ diameter) and filled with high molecular weight viscoelastic substance (Healon GV or Healon 5), as also is the intrascleral chamber.

In 3 cases there was a macroperforation involving the iris with conversion into classical trabeculectomy and inclusion in the control group. In 5 cases there were microperforations without iris prolapse and no conversion.

Results
The mean follow-up period was 10 months ± 6.1 months (2–24). Mean preoperative

References
IOP was 29.38 ± 8.14 mmHg (range: 22–48 mmHg, in therapy with 2.62 ± 0.77 eyedrops). On the day after the operation, mean IOP was 8.34 ± 3.77 mmHg (range: 4–17 mmHg). A week later, the mean IOP was 10.53 ± 3.65 mmHg (range: 4–17 mmHg). The mean IOP at the last check (mean follow-up: 10 ± 6.1 months) was 15.36 ± 3.66 mmHg (range: 8–21 mmHg) in medical therapy with 0.16 ± 0.21 eyedrops, pre/post IOP reduction = 52.28%. Tonometric value progress against time is shown in Fig. 1.

We compared the tonometric progress of the combined operations (13.54 ± 3.24 mmHg) and not combined (16.54 ± 3.05 mmHg) and the difference is not statistically significant (Student’s t: P = 0.061). We compared also the results in terms of IOP of the operations with implants against those in which viscoelastic substance was used. Again there was no statistically significant difference (Student’s t: P = 0.40). Comparison of the use of 5FU (8 cases, mean IOP 12.33 ± 3.56 mmHg) and non-use (33 cases, mean IOP 15.65 ± 3.62 mmHg) did, however, show a statistically significant difference (Student’s t: P = 0.033). We found IOP values lower than or equal to 21 mmHg in 36 cases (87.8%), 29 (70.73%) without any postoperative medical therapy and 7 (17%) when antiglaucomatous therapy was restarted. In three cases, for tonometric compensation against time is shown in Fig. 1.

Intra-operative Problems
- Bleeding: from our experience, a limited use of cautery is necessary with respect to the deep scleral vessels.
- Problems in dissecting the superficial scleral window: if too thin, it perforates or breaks; if too thick, it makes it difficult if not impossible to prepare the deep one and making it easier to perforate it.
- Problems in dissecting the deep scleral window: if it is not deep enough, it will not include Schlemm’s canal ‘roof’ impeding percolation and requiring subsequent removal by microforceps; if too deep, the ciliary bodies will be exposed posteriorly and Descemet’s membrane will be perforated anteriorly, with eventual iris prolapse and the necessity of converting to trabeculectomy plus iridectomy.

Table 1. Incidence of complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative perforations</td>
<td>8</td>
<td>19.51%</td>
</tr>
<tr>
<td>Hypotone</td>
<td>6</td>
<td>14.63%</td>
</tr>
<tr>
<td>Hypothalamic</td>
<td>1</td>
<td>2.43%</td>
</tr>
<tr>
<td>Hyphaemia</td>
<td>6</td>
<td>14.63%</td>
</tr>
<tr>
<td>Fibrin in anterior chamber</td>
<td>3</td>
<td>7.3%</td>
</tr>
<tr>
<td>Choroidal detachment</td>
<td>1</td>
<td>2.43%</td>
</tr>
<tr>
<td>Iris involvement</td>
<td>3</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

- Chamber collapse: happens through excessive filtration. It can be reconstituted with reverse corneal cut but with increased risk of Descemet’s membrane rupture.
- Difficulty of keeping the implant in place: it can be inserted after suturing the superficial scleral window or sutured to the edges of the two radial cuts.
- Implant rupture.

Early Postoperation Complications
- Hyphaema: we found 6 cases of slight hyphaema. It happens by ex-vacuum mechanism or by intraoperative Descemet microperforation.
- Hypotone: found in 6 eyes, it was resolved without apparent consequences (accompanied in one case by hypothyroidism and hyphaema with evident filtering bleb from the first day and as such could be accounted for by excessive filtering which we attributed to the concomitant use of 5FU.
- Fibrin in the anterior chamber: in 3 cases, of which 2 were converted to trabeculectomy during the operation and were put in the control group. The other was an eye with megalocornea characterized by a particular thin corneoscleral shell.
- Hypertone: in one eye we had a hypertone resistant to gonipuncture and lysis with argon laser of the suture and which, after a week, was converted to trabeculectomy and put into the control group. In 4 eyes a hypertension developed between 1 and 6 months after the operation (late post-operation complications) which the gonioscopic examination showed to be due to a partial iris involvement that in 3 cases resolved without adjunct therapy after gonipuncture, while the fourth is still compensated with monotherapy.

Discussion
The use of 5FU, reserved by us for younger or melanodermic patients, on one hand, brings lower tensile values, at least within the range of our follow-up, but on the other hand exposes the patient to a greater risk of postoperation hypertension (and prolonged recoveries). Our data would not seem to justify the use of implants. The combined operation would not seem to be beset by a greater incidence of complications and would lead to lower tension values (the difference not statistically significant). A microperforation of the deep window does not seem harmful on the tonometric control effects. Iris involvement, even if partial, however, is the most frequent event that...
vitiated the tonometric control obtained in the short and medium terms.

Conclusions
The main enthusiasm is that deriving from the feeling of at last being able to have at disposition an effectively refined technique to which the data we have in our possession attributes an efficacy certainly comparable to the ‘gold standard’ in antiglaucomatous surgery represented by trabeculectomy, and characterized moreover by a compliance incidence quite acceptable with suspension of all therapies in the greater number of cases (from 2.62 ± 0.77 eyedrops to 0.16 ± 0.21).

The main setbacks are those met with by the surgeon in the preparation of the pre Descemetocoeilac window. It is an extremely delicate time which often ‘turns traitor’ at the last passage and develops into a frank perforation just when one is appreciating the aqueous percolation at last obtained in the upper portion of the trabeculo-Descemetocoeilac surface. Also, numerous authors agree on a certainly lower hypotensive efficacy of viscocanalostomy and still under discussion is deep sclerectomy comparison with trabeculectomy. The very progress of our data would seem to indicate a certain tendency to efficacy loss with time. There are still many questions: the effective use of the implant, whether it be sodium hyaluronate or swine collagen, which in our casebook does not show itself significantly advantageous over the viscoelastic substance. The lower incidence and seriousness of complications has, in terms of saving resources, appreciable consequences: a shorter mean recovery time (5 ± 0.4 days) against that of trabeculectomy (8 ± 2.1 days).

References

Short-term results of a miniature draining implant for glaucoma in combined surgery with phacoemulsiﬁcation

1Department of Ophthalmology, University of Parma
2DSNV Ophthalmology Section B, University of Genoa
3Service d’Ophthalmologie, University of Dijon, France
4Optonol, Neve Ilain, Israel
5Goldscleger Eye Institute, Tel Aviv, Israel

Objective
To evaluate the safety and the efficacy of a stainless steel miniature glaucoma device (ExPress™, manufactured by Optonol, Israel) in reducing the intraocular pressure in eyes affected by primary open-angle glaucoma and cataract when implantation was combined with phacoemulsiﬁcation.

Methods
Prospective multicentre study. The protocol was approved by each Institution’s Ethics Committee. Selection criteria were: visually significant cataract with uncontrolled POAG, wide open-angle, Caucasian race. Phacoemulsiﬁcation was performed ﬁrst, with a clear cornea approach. After placement of the IOL in the capsular bag, the implant was introduced through the sclera at the limbus via a small conjunctival opening 10–15 mm posterior to it. Routine FU were scheduled at 1 day, 1 week, 1 month and then every 2 months. All patients were implanted using a stainless steel device with 27G external diameter and a 50µ internal opening.

Results
All the patients included were implanted successfully. At the mean follow-up of 6 months (min. 3; max. 16), the mean IOP was reduced from 24 mmHg (±2) to 15.5 mmHg (±2). Mean IOP reduction was 36% from baseline. The probability of maintaining an IOP of 16 mmHg on no medication at 9 months, estimated with a survival curve, is 67%. Complications encountered included 1 case of conjunctival erosion, 1 case of hyptonky, which was treated with removal of the implant and 2 cases of transient ﬂat anterior chamber with choroidal detachment. One of these 2 cases was a failure and required reoperation for further IOP reduction. Bleb needling for early bleb failure was required in 6 eyes.

Conclusions
The early results obtained with this implant support the continuation of clinical trials to assess its role as a substitute for ﬁltration surgery.