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# Exfoliation glaucoma: Studies on intraocular pressure, optic nerve head morphometry, and ocular blood flow

**by**

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Academic Dissertation

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*To my parents*

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# ABBREVIATIONS

| | |
|---|---|
| ALT | Argon laser trabeculoplasty |
| BP | Blood pressure |
| ExOHT | Exfoliation syndrome with ocular hypertension |
| ExG | Exfoliation glaucoma |
| ExS | Exfoliation syndrome |
| HUEH | Helsinki University Eye Hospital |
| HRT | Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Heidelberg, Germany) |
| HRF | Heidelberg Retina Flowmeter (Heidelberg Engineering GmbH) |
| IOP | Intraocular pressure |
| LV | Loss variance |
| MD | Mean defect |
| MS | Mean sensitivity |
| NTG | Normal tension glaucoma |
| OAG | Open-angle glaucoma |
| OHT | Ocular hypertension |
| ONH | Optic nerve head |
| PRC | Partial regression coefficient |
| POAG | Primary open-angle glaucoma |
| r | Pearson correlation or Spearman's rank correlation coefficient |
| ROC | Receiver operating characteristic analysis |
| RNFL | Retinal nerve fibre layer |
| SLDF | Scanning laser Doppler flowmetry |
| SLO | Scanning laser ophthalmoscopy |
| TIA | Transient ischaemic attack |
| VF | Visual field |

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications which are referred to in the text by their Roman numerals.

I Harju M. Intraocular pressure and progression of glaucoma in exfoliative eyes with ocular hypertension or glaucoma. Acta Ophthalmol Scand 2000; 78: 699-702.

II Raitta C, Tomita G, Vesti E, Harju M & Nakao H. Optic disc topography before and after trabeculectomy for advanced glaucoma. Ophthalmic Surg Lasers 1996; 27: 349-354.

III Harju M & Vesti E. Scanning laser ophthalmoscopy of the optic nerve head in exfoliation glaucoma and ocular hypertension with exfoliation syndrome. Br J Ophthalmol 2001; 85: 297-303.

IV Harju M & Vesti E. Blood flow of the optic nerve head and peripapillary retina in exfoliation syndrome with unilateral glaucoma or ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2000, accepted for publication

V Vesti E, Harju M, Puska P & Immonen I. Blue-field entoptic simulation in exfoliation syndrome and in exfoliation glaucoma. Ann Ophthalmol 2000, accepted for publication

# 1. ABSTRACT

The present investigation on a hospital basis was begun to study the effect of IOP reduction on the risk for progression and factors affecting target pressure (I). Risk factors for progression of glaucoma were studied on 139 eyes of 139 patients with exfoliation syndrome (ExS) and ocular hypertension (ExOHT) or glaucoma (ExG). After a mean (±SD) follow-up time of 5.2 ± 3.6 years (range 1.0-19.8 years), progression was detected in 63 eyes (45.3%), with 76 eyes (54.7%) showing no progression. In order to control the length of follow-up and the different number of available intraocular pressure (IOP) readings between two follow-up visits, a weighted mean IOP was calculated to describe the IOP level between two successive visits. Multivariate survival analysis detected increased age (relative risk 1.042; P-value 0.043), increased mean weighted IOP (1.076; <0.001), and increased stage of glaucoma (1.436; <0.001) as risk factors for progression. History of trabeculectomy was associated with decreased relative risk for progression (0.360; 0.002), even though adjusted for mean weighted IOP in the multivariate analysis. Lower target pressures for older patients and patients with advanced glaucoma is thus supported.

The reversibility of ONH topography in ExG was studied (II, III) as well as the use of scanning laser ophthalmoscopy (SLO) to detect progressive changes in the ONH (III). SLO with the Heidelberg Retina Tomograph (HRT, Heidelberg Engineering GmbH, Heidelberg, Germany) allows objective measurement of the optic nerve head (ONH) topography. This method provides the examiner with a number of parameters describing the amount of nerve fibres in the ONH. These parameters were tested in 80 patients with ExS and glaucoma (69 eyes) or ocular hypertension (11 eyes). Most HRT parameters were associated with the disc area; the larger the disc, the more likely were these parameters to show values in the direction of ‘more glaucomatous’. When the effect of disc area was taken into account, all HRT parameters showed a statistically significant association with the amount of visual field (VF) damage. This result supports the importance of adjusting for disc area when HRT values are compared between different groups of patients.

The most advantageous application of SLO would be its use in follow-up of patients to aid in detecting change or progression in ONH topography. In a prospective follow-up of 56 patients, change in VF index mean defect (MD) was shown to be associated with

subsequent change in one of the HRT parameters, the cup shape measure. This suggest that cup shape measure may be a sensitive indicator for progression.

The reversal of ONH topography was studied in two sets of patients. HRT imaging was performed before and after intervention in 10 eyes of 9 patients who underwent trabeculectomy, and in 80 eyes (see above) treated with topical medication (13 eyes), argon laser trabeculoplasty (42 eyes), or trabeculectomy (25 eyes). Decrease in IOP was associated with reversal changes in most HRT parameters. Reversal changes could still be detected one year after trabeculectomy, provided that the post-operative IOP was kept low enough. It remains to be shown whether reversal of the ONH topography is related to slower rate of progression of glaucoma, as has been suggested.

The concept of a vascular component in pathogenesis of ExG was evaluated by measurements of ocular blood flow in eyes with ExOHT, ExG and ExS (IV, V). Ocular blood flow was measured with two non-invasive techniques. Scanning laser Doppler flowmetry (the Heidelberg Retina Flowmeter, HRF, Heidelberg Engineering GmbH) was used to study ONH and peripapillary retinal blood flow in 50 patients with unilateral ExOHT or ExG, and blue-field entoptoscopy to study macular capillary circulation in 10 patients with unilateral ExG and 11 patients with unilateral ExS. In the ONH, flow in the rim area of the glaucomatous eyes was higher than in fellow eyes ($P = 0.001$), while the difference in the lamina was of borderline significance ($P = 0.065$). However, results indicated that more advanced glaucomatous damage, indicated by greater MD or smaller rim volume, is associated with reduced flow both in the laminar area and in the rim area. Also, treatment with topical timolol seemed to be associated with reduced flow in the lamina and rim area. In the macula, leucocyte velocity (±SD) was significantly lower in glaucomatous eyes ($0.70 \pm 0.25$ mm/s) than in non-glaucomatous fellow eyes ($0.89 \pm 0.34$ mm/s) ($P = 0.02$). In the glaucomatous eyes, correlation of borderline significance was detected between leucocyte velocity and MD ($r = -0.58$, $P = 0.08$), and between leucocyte velocity and loss variance (-0.62, 0.06). The results indicate that alterations in ocular blood flow occur in ExG.

# 2. INTRODUCTION

Glaucoma is defined as a chronic progressive optic neuropathy independent of intraocular pressure (IOP) level and without connection to any neurologic or other systemic disease. Optic neuropathy is the common denominator in all types of glaucoma in which a characteristic acquired loss of optic nerve fibres leads to loss of sight and ultimately blindness. The current concept of glaucoma seems to be that there is a subgroup of patients with glaucoma in which the disease is mainly dependent on IOP, and another subgroup in which it is not (Schulzer et al. 1990). Exfoliation glaucoma (ExG) is considered a high-pressure type of secondary glaucoma, in which high IOP leads to poor outcome if not reduced. Therapy aims at lowering IOP to a level at which no further progression occurs (= target pressure). In glaucoma, no other means or indicator exists than detection of progression to determine whether IOP has been sufficiently reduced. Reversal of optic disc cupping after reduction of IOP has been suggested to be such an indicator (Katz et al. 1989, Tsai et al. 1991). In a recent series including eyes with ExG, the postoperative IOP level after trabeculectomy was not associated with rate of visual field (VF) progression (Popovic & Sjöstrand 1999), which suggests an influence on progression by factors other than IOP. Many investigations have put forward evidence of vascular pathogenesis in ExG (Vannas 1969, Laatikainen 1971, Raitta & Vannas 1971, Vannas 1972, Pohjanpelto 1985, Sonnsjö et al. 1988, Jonas et al. 1990, Cursiefen et al. 1997).

The clinical examination of the optic nerve head (ONH) includes a subjective component, and detection of progressive ONH damage can be difficult. The importance of detecting progression from the ONH is emphasized in early glaucoma, during which no VF defects are yet detectable (Funk et al. 1988). Objective methods for ONH measurements have been introduced to aid evaluation of ONH, but their clinical use in detecting progression is still under investigation.

The present investigation on a hospital basis was begun to study the effect of IOP reduction on risk for progression and factors affecting target pressure (I). The reversibility of ONH topography in ExG was studied (II, III) as well as the use of scanning laser ophthalmoscopy (SLO) to detect progressive changes in the ONH (III). The concept of a vascular component in pathogenesis of ExG was evaluated by measurements of ocular blood flow in eyes with ExG and exfoliation syndrome (ExS) (IV, V).

# 3. REVIEW OF THE LITERATURE

## 3.1 THEORIES OF GLAUCOMA

It seems that different mechanisms of damage occur in glaucoma. Schulzer et al. (1990) identified two subgroups of glaucoma patients: one group in which the degree of VF damage was correlated with IOP level, and one group in which it was not. In glaucoma, ganglion-cell death can be mediated via apoptosis (Quigley et al. 1995). Mechanisms of and stimuli leading to ganglion-cell death have recently been reviewed by Nickells (1996). Stimuli that may lead to apoptotic cell death include neurotrophin deprivation and glutamate toxicity (Nickells 1996). Neurotrophin withdrawal can be caused by blockage of retrograde axonal transport during periods of increased IOP or by defective neurotrophin transport by energy depletion due to ischaemia. Glutamate toxicity is believed to be caused by ischaemia of the optic nerve and retinal ganglion-cells (Nickells 1996).

### 3.1.1 The mechanical theory

According to the mechanical theory of glaucoma, the main cause of glaucomatous ONH damage is elevated IOP or increased susceptibility to IOP. Evidence exist that IOP contributes to the pathogenesis of glaucoma. Elevated IOP and glaucomatous damage are closely related (Armaly 1969, Armaly et al. 1980, Davanger et al. 1991b, Sommer et al. 1991b, Leske et al. 1995, Mitchell et al. 1996a), and glaucomatous damage can be experimentally induced by increasing IOP (Quigley & Addicks 1980).

ExG is traditionally considered a secondary high-pressure glaucoma. The exact mechanism of elevated IOP in ExS and ExG is controversial (Hansen & Sellevold 1970, Aasved 1971, Layden & Shaffer 1974, Klemetti 1988, Puska & Raitta 1992, Gharagozloo et al. 1992), but one widely accepted point of view is that the outflow capacity of aqueous humour is reduced by mechanical obstruction of outflow by deposits of exfoliation material and pigment in the trabecular meshwork (Madden & Crowley 1982, Wishart et al. 1985, Rouhiainen & Teräsvirta 1991, Puska 1995, Schlötzer-Schrehardt & Naumann 1995, Gottanka et al. 1997), by dysfunction of the trabecular cells, and by disorganization of juxtacanalicular tissue and Schlemm's canal (Schlötzer-Schrehardt & Naumann 1995).

Studies on aqueous humour dynamics have revealed higher resistance to outflow in eyes with ExS than in their unaffected fellow eyes or control eyes (Pohjanpelto 1973, Layden & Shaffer 1974, Johnson & Brubaker 1982, Gharagozloo et al. 1992). The exfoliation material may be of both trabecular and exotrabecular origin (transported by the aqueous humour to the trabecular area) (Ringvold & Vegge 1971, Morrison & Green 1988, Schlötzer-Schrehardt & Naumann 1995, Gottanka et al. 1997), whereas pigment deposits are probably liberated from the iris epithelium by mechanical scraping of the pupillary border against the irregular lens surface (Krause et al. 1973, Layden & Shaffer 1974). Exfoliation syndrome has also been associated with breakdown of the blood-aqueous barrier in the iris and ciliary body and subsquent leakage of proteins into the aqueous humour (Vannas 1972, Küchle et al. 1995, Küchle et al. 1996, Vesaluoma et al. 1998), which may further increase outflow resistance.

A widely accepted view is that, in glaucoma, the site of initial damage to the ganglion-cell axons is at the level of the lamina cribrosa (Gaasterland et al. 1978, Quigley et al. 1981). The lamina cribrosa consists of approximately 10 lamellar sheets of connective tissue which have pores that form channels for the ganglion-cell axons to pass through the sclera (Quigley & Addicks 1981, Radius & Gonzales 1981). Increase in IOP may cause backward bowing of the lamina cribrosa (Levy et al. 1981, Levy & Crapps 1984) with sliding of the connective tissue layers in relation to each other, which leads to narrowing of laminar pores (Quigley et al. 1981). This causes impingement of nerve fibres that run through the pores, impeding orthograde and retrograde axoplasmatic transport in the neurons (Minckler et al. 1977, Gaasterland et al. 1978, Quigley & Addicks 1980) and leading subsequently to their death. The pores at the superior and inferior poles of the lamina cribrosa are larger and the lamellar sheets thinner than in the medial and lateral poles, offering less structural support to the nerve fibres (Radius & Gonzales 1981, Quigley & Addicks 1981). The nerve fibres that run through the pores at the superior and inferior poles may therefore be more susceptible to mechanical damage (Quigley & Addicks 1980). These nerve fibres supply the arcuate Bjerrum areas of the VF (Minckler 1980) which are known to be the preferential site of VF damage in glaucoma. In studies on a biomechanical model of the ONH, Bellezza et al. (2000) concluded that IOP-related stress within the load-bearing connective tissues of the ONH is substantial even at low levels of IOP, and furthermore, they found that peripapillary scleral stress was consistently highest near the superior and inferior poles of the scleral canal.

However, it has been argued that the exfoliative process may be a risk factor for ONH damage itself, independent of a raised IOP level. Davanger et al. (1991a) reported a higher probability of glaucomatous damage at a certain IOP level in exfoliative eyes than in non-

exfoliative eyes, indicating increased vulnerability to increased IOP in exfoliative eyes. Similarly, according to Ekström (1993), the presence of ExS increased the standardised relative risk for glaucoma in eyes with ocular hypertension (OHT). In histological studies, more severe elastosis of the lamina cribrosa has been found in ExG than in primary open-angle glaucoma (POAG), and this has been suggested to be a contributing factor for increased susceptibility to glaucomatous damage in eyes with ExG (Netland et al. 1995, Pena et al. 1998).

Not all exfoliative eyes develop glaucoma (Hansen & Sellevold 1969, Henry et al. 1987, Klemetti 1988). Henry et al. (1987) retrospectively followed non-glaucomatous eyes with ExS (469 eyes of 347 patients). They reported the cumulative probability (±SD) of 5.3 ± 0.1% for elevated IOP (above 21 mmHg) at 5 years, and 15.4 ± 1.9% at 10 years. In her study on 206 eyes with ExS, Klemetti (1988) reported that 71 eyes (34.5%) developed OHT (IOP above 21 mmHg) or ExG during the 1 to 23 years of follow-up time. Why most exfoliative eyes remain non-glaucomatous remains unknown. In their recent review, Vesti & Kivelä (2000) postulated that one reason could be degeneration of the ciliary epithelium in exfoliation syndrome and subsequent impaired aqueous secretion. Ultrastructural changes in the ciliary epithelium in eyes with ExG (Lütjen-Drecoll et al. 1988) may indicate malfunction of or damage to the ciliary epithelium. Johnson & Brubaker (1982) reported a lower rate of aqueous humour flow in the anterior chamber in exfoliative eyes than in non-exfoliative fellow eyes. However, in another fluorophotometric study, no difference was found in aqueous humour flow rate between ExS and unaffected fellow eyes or control eyes (Gharagozloo et al. 1992).

### 3.1.2 The vascular theory

Blood flow in a tissue is determined by perfusion pressure, i.e., arterial pressure minus venous pressure, and resistance to flow between arteries and veins. Like other parts of the central nervous system, the optic nerve and ONH exhibit autoregulation of blood flow (Pillunat et al. 1997, Riva et al. 1997, Movaffaghy et al. 1998, Orgül et al. 1999). By autoregulation, the resistance to flow is changed to keep blood flow constant despite changes in the perfusion pressure, for example in cases of change in arterial pressure or when venous pressure is altered by change in IOP. Ischaemia due to increased IOP may result if autoregulation is impaired, for example because of innate deficiency or vasospasm. There is evidence that in glaucoma autoregulation may be impaired (Grunwald et al. 1984, Pillunat et al. 1985, Robert et al. 1989, Graham et al. 1995, Tielsch et al. 1995, Graham & Drance 1999, Ghergel et al. 2000).

The role of systemic blood pressure is somewhat contradictive, as both hypertension (Leighton & Phillips 1972, Wilson et al. 1987, Rouhiainen & Teräsvirta 1990b, Dielemans et al. 1995) and hypotension (Richler et al. 1982, Peräsalo et al. 1992, Kaiser et al. 1993, Graham et al. 1995, Graham & Drance 1999) have been shown to be associated with open-angle glaucoma (OAG). In the Baltimore Eye Study (Tielsch et al. 1995), a trend toward a protective effect was found for systemic hypertension in patients younger than 60 years of age and an increased risk in patients older than 70. This was hypothesised to be caused by increased blood flow early in the course of arterial hypertension (i.e., in younger patients), but in more advanced disease (i.e., in older patients) the cause could have been reduced blood flow due to damage to small vessels and increased resistance to flow. This could explain the increased risk for POAG in the older patients with systemic hypertension (Tielsch et al. 1995).

Ischaemia due to occlusion of small capillaries may also result from platelet or clotting abnormalities. In the series by Schulzer et al. (1990), it was reported that in the presence of clotting abnormalities, there were no relationship between the severity of glaucomatous damage and IOP. Drance (1972) has reported disturbances in the coagulation-fibrinolytic system in 61% of the glaucoma patients with IOP less than 22 mmHg, and O'Brien et al. (1997) found elevated levels of prothrombin 1 + 2 fragments and D-dimer in untreated POAG compared to normal tension glaucoma (NTG) and controls. This suggests that some of the untreated POAG patients are in a hypercoagulable state which may contribute not only to the pathogenesis of glaucoma, but also to the increased prevalence of venous thrombosis in the glaucoma population (David et al. 1988, Mitchell et al. 1996b). ExS also has been reported to be a risk factor for retinal vein thrombosis (Cursiefen et al. 1997), and an association between vein occlusions and ExG has been suspected (Pohjanpelto 1985).

Disc haemorrhages have been shown to precede glaucomatous VF defects (Airaksinen et al. 1981, Krakau 1983, Sonnsjö et al. 1988, Diehl et al. 1990, Bengtsson 1990) and to be associated with progression of glaucomatous nerve fibre loss (Diehl et al. 1990, Ekström 1993, Siegner & Netland 1996). Disc haemorrhage seems to be as frequent in ExG as in other types of glaucoma (Sonnsjö et al. 1988, Jonas et al. 1990). The aetiology of disc haemorrhages is unknown. An ischaemic mechanism (Begg et al. 1971) as well as mechanical trauma at the level of the lamina cribrosa (Quigley et al. 1981) have been suggested. Sonnsjö & Krakau (1993) prospectively followed patients with glaucoma, disc haemorrhages, or venous occlusion. During follow-up, patients with glaucoma developed venous occlusions and disc haemorrhages, patients with venous occlusions developed glaucoma and disc haemorrhages, and so on. They argued that disc haemorrhage, and venous occlusion are two manifestations of the same disease appearing in different size

vessels and that the increase in IOP could be a late consequence of a vascular insult, i.e., thromboses of small venous capillaries in the retina and ONH leading to increased intravenous pressure and subsequent increase in IOP.

Peripapillary atrophy has been extensively studied in glaucoma. Histologically, it represents misalignment of the edges of the neural retina, retinal pigment epithelium, and the choroid (Fantes & Anderson 1989). Peripapillary atrophy has been proposed as a sign of impaired choroidal perfusion (Raitta & Sarmela 1970, Primrose 1971, Laatikainen 1971, Stewart et al. 1995, Jonas & Hayreh 1999). Although the vasculatures of the peripapillary choroid and anterior optic nerve are highly separated, they share a common arterial supply at the level of the short posterior ciliary arteries, and the peripapillary choroid may also give off small branches into the prelaminar and laminar regions of the ONH (Cioffi & Van Buskirk 1996). Several studies have shown peripapillary atrophy, specifically the zone beta atrophy, to be associated with degree of glaucomatous ONH and VF damage (Raitta & Sarmela 1970, Wilensky & Kolker 1976, Hayakawa et al. 1998) as well as with progression of glaucoma (Araie et al. 1994, Stewart et al. 1995, Park et al. 1996, Uchida et al. 1998, Daugeliene et al. 1999, Jonas & Hayreh 1999). Hayakawa et al. (1998) also found an association with frequency of disc haemorrhages. No difference in the size of the peripapillary atrophy between ExG and POAG seems to exist (Jonas et al. 1990, Tezel & Tezel 1993, Jonas & Papastathopoulos 1997). Puska & Raitta (1993) studied patients with unilateral ExG. Although the areas of the peripapillary atrophy did not differ between glaucomatous and their non-glaucomatous fellow eyes, a correlation between area of peripapillary atrophy and extent of ONH damage appeared among glaucomatous eyes.

ExS seems to widely affect the ocular vasculature. Fluorescein angiographic studies of the limbus (Laatikainen 1971, Raitta & Vannas 1971) and iris (Vannas 1969, Vannas 1972, Parodi et al. 2000) have shown that ExS is associated with marked vascular changes. Histological studies of the iris vessels in eyes with ExS have shown abnormal accumulation of exfoliation material in the adventitia, degeneration of the cells of the vessel wall (smooth muscle cells, pericytes, and endothelial cells), changes to the endothelial basement membrane, and complete destruction or obliteration of the lumen (Ringvold 1970, Ringvold & Davanger 1981, Konstas et al. 1993b, Asano et al. 1995, Kivelä et al. 1997). The iris vasculopathy has been associated with anterior segment ischaemia (Vannas 1969, Vannas 1972, Helbig et al. 1994). Local hypoxia may contribute to degenerative tissue changes (Asano et al. 1995) and neovascularisation (Ringvold & Davanger 1981) of the iris. Exfoliation material has also been found electron microscopically in the posterior ciliary arteries (Schlötzer-Schrehardt et al. 1991) (a finding not, however, confirmed histochemically), which are the main supply to the ONH (Cioffi & Van Buskirk 1996).

Vasculopathy of these vessels may result in vascular insufficiency of the ONH blood supply. In a prospective follow-up study on normotensive eyes with ExS (Puska et al. 1999), vascular change due to the exfoliative process was proposed as an explanation for optic disc changes that developed during follow-up.

The presence of exfoliation material in visceral organs in patients with ocular ExS (Streeten et al. 1992, Schlötzer-Schrehardt et al. 1992) may raise a question whether these systemic effects associate ExS with systemic diseases, especially with systemic vascular disorders. In a population-based screening study in Norway (Ringvold et al. 1991), the prevalence of ExG increased with age, but declined in patients aged 80 years or older. This was considered to be a sign of increased mortality associated with ExG. However, a later study found no association between ExS and mortality rate (Ringvold et al. 1997). In a population-based study in Australia (Mitchell et al. 1997), ExS was statistically significantly associated with history of coronary disease or hypertension or a combined history of coronary disease, acute myocardial infarction, or stroke. Repo et al. (1993) found twice the prevalence of ExS among patients with transient ischaemic attack (TIA) as for the general population of Finland; they concluded, however, that this finding supported hypoperfusion as a contributory factor in the development of ExS. Shrum et al. (2000) found no association between ExS and cardiovascular or cerebrovascular mortality. Nor has any increased prevalence of ExS been found among patients operated on for abdominal aortic aneurysm compared to that for the general population (Hietanen et al. 2000). As a sign of altered cutaneous microcirculation, patients with ExG have been shown to have lower cutaneous capillary flow than healthy volunteers or patients with POAG (Holló et al. 1998).

## 3.2 EXFOLIATION GLAUCOMA

### 3.2.1 Prevalence of ExS and ExG

ExG is defined as an open-angle glaucoma in eyes with ExS. A recent paper reviews the prevalence of ExS in the world (Ringvold 1999). The prevalence of ExS seems to be especially high in Finland and in Scandinavian countries (Forsius 1988). In population-based studies in Finland, the following prevalences have been reported: 8.4% in patients > 60 years old (Tampere) (Aine 1988), 8.5% in patients 65 years of age (Kuopio) (Rouhiainen & Teräsvirta 1992), 21% in patients ≥ 65 (Kuusamo) (Krause et al. 1988),

13.2% in patients 75 (Kuopio) (Rouhiainen & Teräsvirta 1992), and 22.1% in patients ≥ 70 (Oulu) (Hirvelä et al. 1995). The prevalence of ExS seems clearly to increase with age (Tarkkanen 1962).

Unilateral and bilateral ExS may represent different stages of the disease. Clinically unilateral cases of ExS have been reported to convert into the bilateral form in 7 to 41% of cases within 5 years (Hansen & Sellevold 1969, Henry et al. 1987, Klemetti 1988), and the proportion of bilateral cases has been reported to increase with age (Tarkkanen 1962, Rouhiainen & Teräsvirta 1992). Furthermore, in cases with unilateral ExS, exfoliation material has been identified electron microscopically and immunohistochemically in the clinically uninvolved eyes (Speakman & Ghosh 1976, Prince et al. 1987, Schlötzer-Schrehardt et al. 1991, Kivelä et al. 1997).

In a population-based study in Finland (Oulu) among inhabitants ≥ 70 years old (Hirvelä et al. 1994), the prevalence of ExG was 5.0% (25/500) and that for POAG was 5.4%. In a study based on hospital records (Kotka) (Valle 1988), the prevalence of ExG was 0.26% among all ophthalmological patients aged 55 to 64 years, 1.39% among patients aged 65 to 74 years, and 2.41% in patients aged 75 to 84 years. The corresponding prevalences for POAG were 0.50%, 1.52%, and 2.06%, respectively. In Finland, the high prevalence of ExG (and high proportion of ExG of all OAG) is probably associated with the high prevalence of ExS (Ringvold 1999).

### 3.2.2 Clinical findings in the anterior chamber

The most typical sign of ExS is deposition of grayish-white material on the anterior lens surface. Deposits can also be found on the pupillary border, iris surface, corneal endothelium, lens zonules, and ciliary processess (Tarkkanen 1962, Morrison & Green 1988). Frequent findings are pigment dispersion and transillumination defects of the iris, most prominent at the pupillary margin (Krause et al. 1973, Prince et al. 1987), as well as heavy pigmentation of the anterior chamber angle (Wishart et al. 1985, Rouhiainen & Teräsvirta 1990a, Puska 1995). In addition, high frequency of narrowness of the anterior chamber angle has been reported, with 18% of cases having occludable angles in an English material (Wishart et al. 1985).

### 3.2.3 IOP level

ExS is associated with increased IOP and constitutes a risk factor for glaucoma. The IOP in the exfoliative eyes of unilateral cases has been shown to be higher than in their non-exfoliative fellow eyes (Hansen & Sellevold 1970, Puska & Raitta 1992). Also in ExG, IOP is typically higher than in POAG (Konstas et al. 1997a,b) and also shows greater diurnal variation (Konstas et al. 1997b).

### 3.2.4 ONH morphometry

It has been claimed that the optic disc is smaller in ExG than in POAG and NTG. Jonas & Papastathopoulos (1997) studied optic disc photographs of 99 patients with ExG, 658 patients with POAG, 42 patients with ExS, and 364 healthy controls. The disc area (± SD) was statistically significantly smaller in ExG (2.52 ± 0.49 $mm^2$) than in POAG (2.71 ± 0.63 $mm^2$). Likewise, the disc area in eyes with ExS (2.48 ± 0.52 $mm^2$) was less than in healthy control eyes (2.67 ± 0.67 $mm^2$). In another study, no differences in mean disc area were found between ExG, POAG, and NTG, but small discs were more frequent in ExG and large discs in NTG (Tuulonen & Airaksinen 1992). In a study of patients with unilateral ExS, no difference in optic disc size was found between exfoliative and non-exfoliative fellow eyes (Puska & Raitta 1992).

#### 3.2.4.1 Covariation of ONH parameters with disc size

The ONH rim is formed by ganglion-cell axons as they pass through the scleral canal, with most nerve fibres entering at the superior and inferior poles of the ONH. Therefore, the retinal nerve fibre layer is thickest at the inferior and superior poles and thinner at the nasal and temporal poles (Quigley & Addicks 1982); in the normal ONH, the rim is broadest inferiorly, followed by the superior, nasal, and temporal regions, subsequently (‘the ISN’T rule’) (Jonas et al. 1988b,c). As axons are lost in glaucoma, the amount of neural tissue in the ONH rim decreases. Several parameters have been derived to describe the amount of neural tissue in the ONH including rim area, cup area, cup/disc ratio, cup/disc area ratio, cup volume, rim volume—and with introduction of SLO—also height variation contour, mean and maximum cup depth, cup shape measure, mean retinal nerve fibre layer (RNFL) thickness, and RNFL cross-section area. Numerous studies have shown significant differences between normal and glaucomatous eyes in these ONH parameters (Airaksinen et al. 1985, Caprioli & Miller 1988, Mikelberg et al. 1995, Uchida et al. 1996, Hatch et al. 1997, Bathija et al. 1998). However, there is marked interindividual variation in the ONH size of the healthy population. (Jonas et al. 1988a,b, Jonas & Papastathopoulos 1997).

A larger disc would allow ganglion-cell axons to be spread within a larger area. Therefore, there is also a physiological correlation between ONH area and ONH parameters (Bengtsson 1976, Caprioli & Miller 1987, Britton et al. 1987, Jonas et al. 1988b,c, Garway-Heath et al. 1998, Mardin & Horn 1998, Wollstein et al. 1998). Because of high interindividual normal variation in ONH topography, marked overlap occurs between normal and glaucomatous eyes in the ONH parameters, and no cut-off values have been established for normal ONH parameters. Correction for optic disc size may improve the diagnostic power of the ONH parameters (Jonas et al. 2000).

#### 3.2.4.2 Glaucomatous RNFL damage

The RNFL can be visualised from stereophotographs or from red-free photographs and with biomicroscopy using red-free light and high magnification. Changes in the RNFL have been detected before changes in the ONH (Airaksinen & Alanko 1983) or VF (Sommer et al. 1977, Quigley et al. 1994). However, when the RNFL has been semiquantatively measured, a correlation has been found between RNFL damage and ONH rim area (Airaksinen & Drance 1985).

In the series by Tuulonen & Airaksinen (1991), the initial glaucomatous RNFL damage was reported to be diffuse atrophy in 52% (12/23 eyes), a wedge-shaped local defect in 30% (7/23 eyes), and a combination of these in 17% (4/23 eyes). The proportion of exfoliative eyes was found to be small in the group with localised damage, but this finding did not reach statistical significance. Localised optic disc and RNFL changes were located in the upper and lower temporal regions. No localised changes were found in the nasal or papillomacular regions. A method recently developed uses scanning laser polarimetry for quantitative measurement of the RNFL (Weinreb et al. 1990), and differences in RNFL thickness between glaucomatous and healthy eyes have been detected (Weinreb et al. 1998, Lee & Mok 1999, Sinai et al. 2000).

#### 3.2.4.3 Glaucomatous ONH damage

Glaucomatous damage in the ONH appear before damage in the VF (Jonas & Gründler 1997). Great variability in the appearance of early glaucomatous ONH damage seems to exist. A local rim notch is a classical finding in glaucoma and clinically may be detected more easily than general cup enlargement. However, general enlargement of the cup has been reported as the most common form of initial damage (Pederson & Anderson 1980, Tuulonen & Airaksinen 1991). The latter group followed 61 eyes with OHT (also including exfoliative eyes), of whom 23 developed glaucoma during the study. Corresponding optic

disc changes included diffuse cup enlargement (10 eyes, 43%), local notching (6 eyes, 26%), diffuse cup enlargement with local notching (4 eyes, 17%), and the neuroretinal rim's turning pale with no change in configuration of the cup (3 eyes, 13%). The proportion of exfoliative eyes in the group with localised damage was small, but the finding did not reach statistical signficance. Linnér et al. (1989) studied disc pallor in eyes with OHT and found it to be more pronounced among exfoliative than non-exfoliative eyes.

In a cross-sectional study, Jonas et al. (1993) studied optic disc photographs of 801 glaucomatous and 496 healthy eyes. In all stages of glaucoma, rim loss could be found in all sectors, but with a preferential rim loss in the temporal inferior sector, followed subsequently by the temporal superior, temporal horizontal, nasal inferior, and nasal superior sectors. The results for ExG were not separately reported. Recent work in differentiating between glaucomatous and non-glaucomatous eyes has emphasized rim damage at the disc poles (Gundersen et al. 1996, Iester et al. 1997e, Iester et al. 1998, Gundersen et al. 1999). The studies by Gundersen et al. (1996, 1999) included eyes with ExG, POAG, and NTG; ONH damage was most pronounced at the poles.

The temporal inferior and temporal superior sectors also seem to be the most common sectors in which notching occurs (Jonas et al. 1988c, Tuulonen & Airaksinen 1991). A connection between localised notching and optic disc haemorrhage has been suggested, optic disc haemorrhage has been reported to be more frequent in eyes with localised notching than in eyes with generalised enlargement of the cup (Tuulonen & Airaksinen 1991, Nicolela & Drance 1996). In addition, disc haemorrhage may predict the location of future rim and RNFL damage (Airaksinen et al. 1981, Tuulonen et al. 1987).

It has been proposed that type of cupping is dependent on IOP: local notching may occur at lower IOP levels and diffuse cupping at higher IOP levels (Shiose et al. 1987, Nicolela & Drance 1996, Eid et al. 1997a). Local damage has, however, been found in eyes with elevated IOP, as well (Pederson & Anderson 1980, Tuulonen & Airaksinen 1991, Iester et al. 1998). Some controversy exists on the type of damage that occurs in ExG. Tezel & Tezel (1993) found only diffuse loss of the rim in ExG without the sectoral preference they found in the eyes with POAG. However, Jonas et al. (1990) found no difference between ExG and POAG in the proportions of localised and diffuse defects of the RNFL, nor in the location of the thinnest part of the neuroretinal rim.

#### 3.2.4.4 Reversibility of ONH topography

ONH topography can change in relation to changes in IOP. In experimental studies on enucleated primate and human eyes, Levy et al. (1981) and Levy & Crapps (1984) examined radiographically the position of a platinum wire placed in the lamina cribrosa and demonstrated the retrodisplacement of the lamina cribrosa after increasing IOP. Coleman et al. (1991) demonstrated the retrodisplacement of the ONH surface after experimental increase in IOP. Reversal of the disc cupping or ONH topography refers to a change in the less 'glaucomatous' direction (decrease in cup volume or cup area, increase in rim volume, rim area, or in other parameters describing the amount of neural tissue in the ONH). In experimental and clinical studies with humans and primates, reversal of cupping and ONH topography has been documented in glaucomatous eyes after reduction in IOP by use of stereophotography, computerized image analysis, or SLO (Pederson & Herschler 1982, Katz et al. 1989, Shin et al. 1989, Tsai et al. 1991, Shirakashi et al. 1992, Sogano et al. 1993, Chavis et al. 1994, Irak et al. 1996, Park & Hong 1998, Topouzis et al. 1999, Lesk et al. 1999). The physiological basis for reversal of ONH topography is unknown, but reduced backward bowing of the lamina seems most likely (Pederson & Herschler 1982, Lusky et al. 1993b, Sogano et al. 1993). The amount of reversal has been shown to correlate with degree of IOP reduction (Shin et al. 1989, Sogano et al. 1993, Lesk et al. 1999, Irak et al. 1996).

Reversibility has been claimed to be dependent on degree of glaucomatous damage. In studies on experimental primate glaucoma (Coleman et al. 1991, Shirakashi et al. 1992), degree of reversal of optic disc cupping has been decreased in those eyes with advanced glaucomatous damage. In humans, as well, (Pederson & Herschler 1982, Quigley 1982), reversal of disc cupping has been apparent in eyes with damage at an early stage, but not in eyes with advanced glaucoma. In human eyes post-mortem, less retrodisplacement of the ONH occurs in relation to the surrounding sclera, as the VF worsens (Zeimer & Ogura 1989). Age may also affect reversibility. In adults, reversal in older patients has been reported to be greater than in younger ones (Lesk et al. 1999). However, reversal of cupping is also a frequent finding after successful IOP reduction in childhood glaucoma (Quigley 1982).

### 3.2.5 VF damage

The VF defect in glaucoma can be diffuse and localised (Mikelberg & Drance 1996). Diffuse damage can be seen as isopter contraction in kinetic perimetry or generalised depression of retinal sensitivity in automated static perimetry (Hart & Becker 1982, Cyrlin 1996). Typical focal defects include nasal step, isolated arcuate scotoma separated from the

blind spot, arcuate blind spot enlargement, and paracentral scotoma (Hart & Becker 1982, Cyrlin 1996). In very advanced glaucoma, usually the only remaining areas in the VF are central and temporal islands (Cyrlin 1996). No difference seems to exist in the pattern of VF defects between ExG and POAG (Lewis & Phelps 1984). Lewis & Phelps (1984) studied VF defects in 224 eyes of 148 patients with POAG and 74 eyes of 63 patients with secondary glaucoma (30% had ExG); similar VF defect patterns were noted for POAG and the secondary glaucomas.

A topographical relationship exists between VF and optic disc damage (Weber et al. 1990, Eid et al. 1997b, Yamagishi et al. 1997). In eyes with local ONH damage, localised VF defects can usually be detected (Nicolela & Drance 1996); however, those eyes with localised glaucomatous VF loss may have observable optic disc damage of either local or diffuse nature (Emdadi et al. 1998).

#### 3.2.5.1 Reversal of VF damage

Evidence exist of improvement in glaucomatous VF damage after IOP reduction (Katz et al. 1989, Tsai et al. 1991, Rolando et al. 1993). Some degree of association has also been detected between improvement in VF and reversal of optic disc topography (Katz et al. 1989, Tsai et al. 1991). Tsai et al. (1991) studied 28 eyes of 28 patients in whom had been detected reversal of disc cupping. Improvement in the mean VF global indices occurred in eyes with IOP reduction of more than 40% in contrast to no improvement in eyes with less than 35% IOP reduction.

A learning effect also appears in VF testing; patients inexperienced with perimetry testing may show some improvement between the first few examinations (Heijl & Bengtsson 1996).

## 3.3 PROGRESSION OF ExG

ExG is known to show more aggressive clinical course than POAG (Konstas et al. 1997c, Olivius & Thorburn 1978). According to Thorburn (1988), 2.5% of all the individuals in one defined population developed VF defects due to ExG within their lifetime. If glaucomatous cupping without VF defects was present at diagnosis, 50% developed VF defects within their lifetime, and of those with a moderate VF defect at diagnosis, 59% had,

within their lifetimes, progression into another stage. In other studies, the outcome of ExG and of POAG has been compared; in general, a worse prognosis can be expected in ExG than in POAG (Olivius & Thorburn 1978, Pohjanpelto 1985).

Differing patterns have been reported in progression of glaucomatous ONH and VF defect: a linear pattern with a constant rate of progression, an episodic pattern with bursts of faster progression periods, and a curvlinear pattern with either faster progression early in follow-up and a slower progression rate later, or slower progression early and an increase in progression rate later (Mikelberg et al. 1986, Airaksinen et al. 1992). Airaksinen et al. (1992) studied ONH rim area and found a linear type of progression in approximately half the patients, an episodic in one-fifth, and a curvlinear type in one-third. No differences in patterns of progression occurred between ExG, POAG, and NTG. Mikelberg et al. (1986) studied VFs of patients with chronic OAG and IOP above 21 mmHg. Of the eyes that progressed (34 eyes), 65% showed linear, 26% curvlinear, and 9% episodic progression. The results for ExG were not separately reported.

### 3.3.1 Definition and detection

Progression of glaucoma can be defined as an increase either in the glaucomatous ONH damage or in VF defect. Because of overlapping of the receptive fields of the ganglion cells, 20 to 40% of nerve fibres can be lost before defects appear in the VF (Quigley et al. 1989). Thus, progressive RNFL (Airaksinen & Heijl 1983, Sommer et al. 1991a, Tuulonen et al. 1993, Quigley et al. 1994) and ONH damage (Pederson & Anderson 1980, Odberg & Riise 1985, Pohjanpelto 1985, Zeyen & Caprioli 1993, Jonas & Gründler 1997) can usually be detected prior to VF loss. However, new perimetry techniques for assessing early glaucomatous damage, such as blue-on-yellow perimetry and high-pass resolution perimetry, may be superior to conventional perimetry (Martinez et al. 1995, Teesalu et al. 1997, Teesalu et al. 1998, Chauhan et al. 1999). On the other hand, in more advanced glaucoma with definite VF defects, detection of progression is more likely from the VF than from the ONH (Funk et al. 1988); a small further loss in ganglion-cell number affects visual function but is not easily detected in ONH morphology.

Determination of ONH progression is often based on subjective evaluation of the ONH: general enlargement of the cup, enlargement of a notch, or appearance of a new notch. No quantitative cut-off values have been established to tell how much change is indicative of progression. Kamal et al. (2000) compared change over time in parameters of the Heidelberg Retina Tomograph (HRT, Heidelberg Engineering GmbH, Heidelberg, Germany) for healthy eyes and eyes with OHT. A subset of eyes with OHT showed change

in the HRT parameters above the expected level for normal variability in a ‘more glaucomatous’ direction. A forthcoming report on whether these OHT patients will have a higher incidence of glaucoma than those without similar changes in the ONH, is awaited.

The detection of VF progression is a complex problem, and many statistical methods have been developed for this purpose. Because the VFs of healthy individuals and glaucoma patients are subject to both intra-test fluctuation (short-term fluctuation) and inter-test fluctuation (long-term fluctuation) (Heijl et al. 1987), detection of progression requires multiple VF examinations to differentiate between progression and fluctuation (Heijl et al. 1989). The VF defect can progress as an increase in size and depth of a scotoma, as appearance of a new scotoma, or as generalised loss of retinal sensitivity (Mikelberg & Drance 1996). Several definitions of progression have been in use. In some studies using kinetic perimetry, patients have been divided into different stages according to the degree and appearance of ONH and VF damage, and subsequently, progression has been defined as entering another stage (Thorburn 1988, Törnqvist & Drolsum 1991). In automated perimetry, definition of progression can be based on number and depth of adjacent test-points with reduced sensitivity relative to normative data. Several different criteria for progression have been introduced, such as the one in the Glaucoma Laser Trial study (The Glaucoma Laser Trial research group 1991), and the more complex scoring systems used by the Advanced Glaucoma Intervention Study (The Advanced Glaucoma Intervention Study investigators 1994) and the Collaborative Initial Glaucoma Treatment Trial (Musch et al. 1999).

### 3.3.2 Risk factors for progression

#### 3.3.2.1 IOP level

Numerous reports show that a wide consensus exists as to the association of elevated IOP and increased risk for progression of glaucoma. Studies of patients with OHT have shown that the higher the IOP, the higher the incidence of conversion into glaucoma (Kass et al. 1980, Pohjanpelto 1986, Quigley et al. 1994). The rate of progression of glaucoma increases with IOP (Kolker 1977, Shirakashi et al. 1993, Jay & Murdoch 1993, Chihara et al. 1997, Suzuki et al. 1999); moreover, rate of progression decreases in correlation with amount of IOP reduction (Vogel et al. 1990, Migdal et al. 1994).

Studies of exfoliative eyes have shown this to be true also in ExS and ExG. Among exfoliative eyes with OHT, lower IOP has been associated with decreased risk for glaucomatous damage (Pohjanpelto & Palva 1974, Pohjanpelto 1986). In newly diagnosed ExG, a significant relationship has been reported between presenting (untreated) IOP level and VF damage (Teus et al. 1998). However, in a retrospective study by Pohjanpelto (1985), no significant differences existed in the mean IOP of eyes with ExG and stable VFs compared to those with VF progression. It has been claimed that in cases with a similar IOP level, the optic disc in ExG may be more vulnerable to glaucomatous damage than in POAG (Pohjanpelto & Palva 1974, Davanger et al. 1991a, Teus et al. 1998).

Despite intensive treatment and good control of IOP, some eyes with ExG continue to progress. Popovic & Sjöstrand (1999) studied the outcome of high-resolution perimetry in eyes with ExG and POAG after trabeculectomy. They reported similar mean IOP (about 16 mmHg) both in eyes with progressive and non-progressive VFs, and an IOP level unrelated to rate of VF progression. This may support the theory that other factors than IOP are involved in the pathogenesis of both POAG and ExG.

#### 3.3.2.2 IOP variation

Not only mean IOP level, but also variation in IOP should be considered in glaucoma. IOP shows diurnal variation both in healthy and glaucomatous eyes (Drance 1960, de Venecia & Davis 2000), but the variation in glaucomatous eyes has been shown to be greater than in healthy eyes (Drance 1960, David et al. 1992). When different types of glaucoma are compared, the diurnal variation in eyes with ExG has been reported to be greater than in POAG (Jonas & Papastathopoulos 1997, Konstas et al. 1997b). Variation in diurnal IOP has been identified as a risk factor for progression. Diurnal IOP variation has been reported to be greater in eyes with OHT that later developed glaucoma than in those that remained OHT (Odberg & Riise 1987). Among patients with ExG (Bergeå et al. 1999) and POAG (Stewart et al. 1993, Bergeå et al. 1999, Asrani et al. 2000), smaller IOP variation has been associated with better VF prognosis. In a prospective study on eyes with POAG, peak IOP but not mean IOP differentiated between those who had progressive VF defects in high resolution perimetry and those who remained stable (Martínez-Belló et al. 2000).

#### 3.3.2.3 Age

All large population-based cross-sectional surveys report an increasing prevalence of OAG (POAG, NTG and ExG) with increasing age (Hollows & Graham 1966, Leibowitz et al. 1980, Bengtsson 1981, Mason et al. 1989, Ringvold et al. 1991, Klein et al. 1992, Coffey et

al. 1993, Leske et al. 1994, Dielemans et al. 1994, Mitchell et al. 1996a, Kozobolis et al. 2000). Age has also been a risk factor for conversion of OHT to POAG (Quigley et al. 1994, Georgopoulos et al. 1997, Martínez-Belló et al. 2000). In a large 13-year prospective follow-up study of 5000 subjects by Armaly et al. (1980), age was one of the risk factors for glaucomatous VF defect. On the other hand, other follow-up studies have found no effect of age (Wilson et al. 1982, Chihara et al. 1997). In his recent review of the role of age and cardiovascular disease in glaucoma, Hayreh (1999) concludes that the influence of age may be an indirect one, representing the higher prevalence and duration of cardiovascular disease in the elderly population, rather than age, per se. In healthy eyes, the nerve-fibre count of the optic nerve is known to decrease with age (Balazsi et al. 1984, Jonas et al. 1992), which may make the nerve susceptible to any damage caused by glaucoma.

#### 3.3.2.4 Previous damage

In clinical practice it is generally agreed that eyes with far-advanced glaucoma, being more susceptible to further VF damage than are eyes with early damage, require lower IOPs in order to remain non-progressive (Olivius & Thorburn 1978, Wilson et al. 1982, Anderson 1989, Shirakashi et al. 1993, Stewart et al. 1993, Martínez-Belló et al. 2000). This finding may be connected with disruption of the structure of the lamina cribrosa and a decrease in collagen density, resulting in less structural support (Quigley et al. 1991).

#### 3.3.2.5 Disc area

It has been hypothesised that large discs have the biomechanical disadvantage of offering less structural support at the level of the lamina cribrosa than do small discs (Chi et al. 1989), and thus eyes with larger discs may be more vulnerable to IOP (Tuulonen & Airaksinen 1992, Burk et al. 1992, Tomita et al. 1994).

Heijl & Mölder (1993) showed that disc area affects the probability of detecting glaucoma. Larger discs were more likely to be classified as glaucomatous (whether glaucomatous or not), and smaller discs were more likely to be classified as normal. Consequently, patients with larger discs are more likely to attract clinical attention. Thus, any clinic-based study offers the danger of selection bias, and any effect of disc area on risk for glaucoma or its progression may easily be overestimated. Quigley et al. (1999) reported on data from the population-based Baltimore Eye Survey. After adjustment for age, race, and gender in a regression model, eyes with OAG tended to have slightly larger discs than the controls, but only at borderline statistical significance ($P = 0.06$). Data from the population-based Blue

Mountains Eye Study (Healey & Mitchell 1999) showed statistically significantly greater optic disc diameters in glaucomatous eyes (1.556 mm) than in non-glaucomatous eyes (1.506 mm), eyes with OHT (1.494 mm), or eyes with ExS (1.501 mm).

## 3.4 TREATMENT OF ExG

### 3.4.1 To influence IOP

Irrespective of the pathogenesis of glaucoma, IOP remains the only risk factor to be affected. Despite extensive studies on glaucoma, no safe IOP level has been identified for any type of glaucoma (Jampel 1997). More likely, the target pressures have to be set individually and in relation to IOP as well as to other risk factors. It has been hypothesised that the effect of IOP reduction may be mediated through reduction in backward bowing of the lamina and reduced mechanical stress to the ganglion-cell axons, which may improve axoplasmic flow and reduce possible hypoxia (Shin et al. 1989). IOP reduction also increases ocular perfusion pressure (Hayreh 1994), a reduction which may improve ocular blood flow in cases of impaired autoregulation of blood flow, as has been suggested to occur in glaucoma (Pillunat et al. 1985, Robert et al. 1989, Tielsch et al. 1995).

Some differences in success rates for various treatment modalities seem to exist between ExG and POAG. Medical treatment fails more often in ExG than in POAG (Olivius & Thorburn 1978, Blika & Saunte 1982, Pohjanpelto 1985), and more often a combination of drugs is required (Airaksinen 1979, Konstas et al. 1998). As hypothesised by Konstas & Diafas (1999), miotics may play a special role in the treatment of ExG, reducing mechanical scraping of the iris against the lens surface, which results in less deliberation of pigment and exfoliation material.

Argon laser trabeculoplasty (ALT) (Wise & Witter 1979) seems to result in a better initial response in ExG than in POAG (Pohjanpelto 1983, Bergeå 1986, Bergeå & Svedbergh 1992, Threlkeld et al. 1996). Late response results are somewhat more controversial. Bergeå (1986) reported a higher proportion of eyes with ExG than with POAG which showed successful ALT after 2 years, and greater mean IOP reduction has been reported in ExG than in POAG 1 to 5 years after ALT (Tuulonen & Airaksinen 1983, Rouhiainen et al. 1995), but the resulting mean IOP level may be similar (Bergeå et al. 1994). Threlkend et al. (1996) reported the long-term IOP-reducing effect of ALT to be similar in ExG and

POAG. A more favourable outcome in terms of ONH and VF progression in ExG than in POAG after primary ALT has been reported (Bergeå et al. 1995a,b).

Trabeculectomy is more effective than ALT or medical treatment for reduction in IOP (Migdal et al. 1987, Migdal et al. 1994) and may also result in less IOP variation (Migdal et al. 1994). ExG responds well to trabeculectomy (Jerndal & Kriisa 1974, Raitta & Vesti 1991), and the response is equal to (Popovic & Sjöstrand 1999) or better than (Törnqvist & Drolsum 1991, Konstas et al. 1993a, Tanihara et al. 1993) in POAG. Popovic & Sjöstrand (1999) prospectively followed eyes with ExG and POAG after trabeculectomy. Medical treatment had to be reinstated at a similar rate in both types of glaucoma; however, the IOP level in eyes without post-operative glaucoma medication was lower in those eyes with ExG. No difference between the groups appeared in the post-operative rate of VF deterioration. On the other hand, Tanihara et al. (1993) reported a better overall success probability (lower post-operative than pre-operative IOP, no VF or disc deterioration, and no need for further IOP-lowering surgery) in eyes with ExG (73.5 ± 6.3%) after 5 years when compared to eyes with POAG (58.0 ± 3.1%). Similarly, Törnqvist & Drolsum (1991) reported that eyes with ExG experienced less progression (optic disc or VF) after trabeculectomy than did eyes with POAG, and Konstas et al. (1993a) reported lower post-operative IOP in eyes with ExG than in eyes with POAG.

It has been suggested that early or even primary trabeculectomy would result in better prognosis than trabeculectomy after a period of unsuccessful medical treatment (Jay & Murray 1988). In that prospective, randomised study on glaucomatous eyes with IOP ≥ 26 mmHg (including eyes with ExG), they compared treatment with primary trabeculectomy to trabeculectomy after unsuccessful medical treatment. Trabeculectomy was equally effective in both groups of patients in respect to IOP reduction, but less progression of VF occurred in the primary trabeculectomy group, a difference they theorised may have been caused by progression in the medically treated group during the period before trabeculectomy.

Trans-scleral cyclodestructive techniques have usually been limited to eyes with refractory glaucoma with unsuccessful filtration surgery or with an estimated poor response to filtration surgery (Wesley & Kielar 1980, Hampton et al. 1990, Vesti et al. 1992, Immonen et al. 1994, Spencer & Vernon 1999). Aqueous drainage implants, such as the Molteno implant, are also available for these patients (Mills et al. 1996, Välimäki et al. 1998).

Trabecular aspiration has been introduced as a new form of treatment in ExG (Jacobi & Krieglstein 1995). Trabecular debris and pigment are cleared from the trabecular meshwork with an aspiration probe. An IOP reduction of approximately 30% has been achieved in

some patients (Jacobi et al. 1998), and a successful IOP reduction 2 years after therapy with combined phacoemulsification and IOL implantation and trabecular aspiration in 64% of the eyes has been reported (Jacobi et al. 1999).

### 3.4.2 Ocular blood flow and neuroprotection

As there seems to be an association between glaucoma and impaired ocular blood flow, the issue of treatment of glaucoma by improvement of ocular blood flow seems logical. Many studies concern the use of various calcium-channel blockers, especially in NTG. Several investigators have reported calcium-channel blockers to be associated with a reduced progression rate of VF in NTG (Kitazawa et al. 1989, Netland et al. 1993, Sawada et al. 1996, Daugeliene et al. 1999) and even with improvement in VF and colour vision after their administration (Piltz et al. 1998). Some controversy, however, exists (Liu et al. 1996). Evidence exists that treatment with oral calcium-channel blockers reduces the vascular resistance of the retrobulbar arteries (Yamamoto et al. 1998). Results have not been consistent (Wilson et al. 1997). Harris et al. (1997) and Cellini et al. (1997) were able to link improved perfusion after oral administration of calcium-channel blockers with improved visual function; improved perfusion in the retrobulbar arteries was associated with improved contrast sensitivity (Harris et al. 1997) and improved VF indices (Cellini et al. 1997). It remains unknown whether any possible effect of calcium-channel blockers on progression is mediated through vasodilation and improved perfusion, or whether they act directly on the calcium metabolism involved in cell death (Osborne et al. 1999).

It has also been suggested that the carbonic anhydrase inhibitor dorzolamide may improve ocular haemodynamics (Martinez et al. 1999). Harris et al. (1999) detected improved contrast sensitivity, reduced IOP, and shortened retinal arteriovenous time after treatment with dorzolamide in patients with NTG. However, there was no correlation on an individual basis between improved contrast sensitivity and reduced IOP or shortened retinal arteriovenous time.

Not without some controversy (Drance 1997), betaxolol has been suggested to have a better effect on halting VF progression than does timolol (Messmer et al. 1991, Kaiser et al. 1992, Flammer et al. 1993, Tasindi & Talu 1997), although timolol reduces IOP more effectively (Kaiser et al. 1992, Flammer et al. 1993). The more favourable outcome with betaxolol may be due to a vasorelaxant (Harris et al. 1995, Hesse 1995) or a neuroprotective (Osborne et al. 1997) effect. Possible neuroprotective strategies in glaucoma have recently been reviewed by Osborne et al. (1999).

# 4. AIMS OF THE STUDY

To evaluate, among referred patients in a hospital setting, the risk factors for conversion of ocular hypertension with exfoliation syndrome to exfoliation glaucoma and progression of exfoliation glaucoma (I)

To create a formula suitable for clinical use to describe IOP level over time (I)

To evaluate, after IOP-lowering therapy, the reversibility of glaucomatous optic nerve head changes by scanning laser ophthalmoscopy (II,III)

To find the most suitable Heidelberg Retina Tomograph parameter to detect progression (III)

To evaluate optic nerve head blood flow and correlate it with degree of glaucomatous optic nerve head and visual field damage (IV)

To test macular and peripapillary retinal circulation in exfoliation syndrome, exfoliation syndrome with ocular hypertension, and exfoliation glaucoma (IV,V)

# 5. PATIENTS AND METHODS

## 5.1 DEFINITIONS

Glaucomatous optic disc damage = General enlargement of the cup/disc ratio and/or a local notching of the rim.

Glaucomatous VF = VF measured with the Octopus perimeter (Interzeag, Schlieren, Switzerland) using program G1 with 1) ≥ 3 adjacent test points of ≥ 5 dB loss, 2) ≥ 2 adjacent points of ≥ 10 dB loss, or 3) difference of ≥ 10 dB across nasal the horizontal meridian at ≥ 2 adjacent points (Caprioli 1991). By Goldmann's kinetic perimetry, arcuate scotomas within 30°, paracentral scotomas, nasal steps, sector-shaped defects in the periphery, and isopter contractions were considered glaucomatous.

## 5.2 STUDY DESIGN

Study I was retrospective, in which data on IOP levels and VFs was collected from patient charts, as well as from a control visit to which the patients were invited (Table 1). Study II was a prospective follow-up study, in which HRT imaging was performed once before and twice after trabeculectomy. In the cross-sectional part of Study III, HRT parameters were compared to VF indices, and in the prospective follow-up part of Study III, ONH topography was studied at 6-month intervals for up to 2 years after treatment with medication, ALT, or trabeculectomy. Studies IV and V were cross-sectional, in which ocular blood flow was studied in patients with unilateral ExG and ExS.

***Table 1.*** *Characteristics of patients and eyes included in the studies*

| **Study** | **I** | **II** | **III** | **IV** | **V** |
|---|---|---|---|---|---|
| Study type | Retrospective follow-up | Prospective follow-up | Cross-sectional and prospective follow-up | Cross-sectional | Cross-sectional |
| Number of eyes/patients | 139 / 139 | 10 / 9 | 80 / 80 | 100 / 50 | 42 / 21 |
| Mean age (±SD) (range) | 69.9 ± 7.7 (50-88) | 65.6 ± 8.1 (55-75) | 68 ± 7 (50-83) | 67.8 ± 7.4 (51-85) | 62.9 ± 7.9 (50-74) |
| Diagnosis | | | | | |
| Study eyes | ExOHT (n = 34)<br>ExG (n = 105) | ExG (n = 6)<br>POAG (n = 3)<br>NTG (n = 1) | ExOHT (n = 11)<br>ExG (n = 69) | ExOHT (n = 10)<br>ExG (n = 40) | ExS (n = 11)<br>ExG (n = 10) |
| Fellow eyes | | | | ExS (n = 36)<br>Non-ExS (n = 14) | Non-ExS (n = 21) |
| Main outcome measures | Mean weighted IOP<br>Progression of glaucoma | Diurnal IOP<br>ONH topography (scanning laser ophthalmoscopy) | Diurnal IOP<br>ONH topography (scanning laser ophthalmoscopy) | ONH and peripapillary blood flow (scanning laser Doppler flowmetry) | Macular capillary circulation (blue-field entoptoscopy) |

ExS = exfoliation syndrome, ExG = exfoliation glaucoma, ExOHT = Exfoliation syndrome with ocular hypertension, IOP = intraocular pressure, N = number of eyes, NTG = normal tension glaucoma, ONH = optic nerve head, POAG = primary open-angle glaucoma

## 5.3 PATIENTS

The study was performed in the Helsinki University Eye Hospital (HUEH). The procedures followed the tenets of the Declaration of Helsinki and were approved by the Department of Ophthalmology's Ethics Committee. Informed consent was obtained from all patients. The study included a total of 249 patients: 235 with ExOHT or ExG, 11 with unilateral ExS, two with POAG, and one with NTG (Table 1). Four of the patients with ExG in Study I also participated in Study II, 36 of the patients in Study III also participated in Study IV. All the 10 patients with ExG in Study V also participated in Study III, and 7 also in Study IV. In Study IV, 50 fellow eyes (36 with and 14 without ExS), and in Study V, 21 fellow eyes (all non-exfoliative) were also studied.

## 5.4 METHODS FOR EXAMINING THE EYE

### 5.4.1 Clinical examination

Clinical examination included measurement of visual acuity, IOP measurement, biomicroscopic examination, and gonioscopy if not previously performed. For pupillary dilatation, 0.5% tropicamide and 2.5% metaoxedrine were instilled. The optic discs were examined with the Volk 90 D lens and/or evaluated from stereophotographs.

### 5.4.2 IOP

All IOP values were obtained with a Goldmann applanation tonometer. To obtain diurnal IOP curves, IOP was measured at 7.30, 11.30, and 14.30. If the patient was using topical glaucoma medication, the first drop of the day was applied after the IOP measurement at 7.30.

### 5.4.3 Visual field examinations

VFs were taken with the Octopus perimeter program G1, and only fields with less than 25% false-negative and false-positive answers were accepted in the analyses. If the patient was unable to perform reliable automated perimetry, Goldmann kinetic perimetry was performed.

### 5.4.4 Grading of glaucoma

Glaucoma was graded according to a system modified from that used by Thorburn (1988); he included only eyes with IOP exceeding 30 mmHg (with normal VF and without glaucomatous cupping) in Stage 1:

Stage 1: OHT = elevated IOP exceeding 24 mmHg on at least two occasions, or one single measurement of 30 mmHg or more with a normal VF and without glaucomatous cupping of the optic disc.

Stage 2: Glaucomatous disc cupping with normal VF.

Stage 3: Glaucomatous disc cupping and one scotoma within 30°, and/or a nasal step or a sector-shaped defect in the periphery.

Stage 4: As in Stage 3, but with the addition of a new scotoma within 30° in the opposite half of the VF, or the creation of a breakthrough to the periphery.

Stage 5: As in Stage 4, with the addition of a breakthrough to the periphery both upwards and downwards from the paracentral scotoma.

Stage 6: A small remnant of the central VF and a temporal remnant.

Stage 7: A temporal remnant; loss of central VF (visual acuity 0.1 or less)

The grading of all eyes with glaucoma or OHT is shown in Table 2. In Study II, the stage of glaucoma was also graded as moderate (arcuate scotoma) or severe (ring-shaped scotoma or only a temporal field).

### 5.4.5 Measurement of ONH topography

SLO imaging was performed with the HRT. Software version 1.11 was used in Study II and version 2.01 in Studies III and IV. Three topographic images were obtained with the 10° x 10° field and approved by the internal quality program of the software (version 2.01). Keratometry values were used for correction of magnification errors, and measurements were repeated after surgery in all eyes operated upon (II, III). A mean three-dimensional image was created from three single images. Stereophotographs of the ONH were used to

***Table 2.*** *Grading of eyes with glaucoma or ocular hypertension. Fellow eyes of the 50 patients in Study IV and the 10 eyes in Study V were all normotensive and non-glaucomatous. Of patients in Study V, only grading of the glaucomatous eyes is shown.*

| | I | | II | | III | | IV | | V | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Stage** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **1** | 34 | 24 | | | 11 | 14 | 10 | 20 | | |
| **2** | 37 | 27 | | | 23 | 29 | 11 | 22 | 2 | 20 |
| **3** | 37 | 27 | 2 | 20 | 26 | 32 | 14 | 28 | 4 | 40 |
| **4** | 20 | 14 | 5 | 50 | 13 | 16 | 10 | 20 | 4 | 40 |
| **5** | 6 | 4 | | | 4 | 5 | 5 | 10 | | |
| **6** | 5 | 4 | 3 | 30 | 2 | 2 | | | | |
| **7** | | | | | 1 | 1 | | | | |

N = number of eyes

aid in drawing the contour line at the inner border of the scleral ring. The contour line of the baseline image was exported to follow-up images (II, III). Pupils were dilated with tropicamide and phenylephrine eye-drops before SLO imaging. A reference plane parallel to the retinal surface was located 50 µm posteriorly to the mean contour line height in the temporal segment between –10° and –4°.

### 5.4.6 Measurement of ONH and peripapillary retinal blood flow

ONH and peripapillary retinal blood flow was measured with a confocal scanning laser Doppler flowmeter (SLDF); the Heidelberg Retina Flowmeter (HRF, Heidelberg Engineering GmbH). All images were obtained with pupils dilated. Several images focused on the peripapillary nerve fibre layer and centered in the upper, mid, and lower parts of the ONH were obtained from each eye. Images were also obtained centered on the cup and focused on the lamina cribrosa. Blood flow was quantified by placing a square of 10 x 10 pixels on the area of interest. These analyses avoided any visible vessels, horizontal strikes caused by eye movements, or areas of peripapillary atrophy. The flow values were measured at three locations on the neuroretinal rim and at five locations on the peripapillary retina 0.6 to 0.8 mm from the scleral ring. One value was obtained from the bottom of the optic cup.

### 5.4.7 Measurement of macular blood flow

Macular leucocyte velocity and density (number of leucocytes within the field of observation) were subjectively measured by a blue-field simulation technique (BSF-2000, Oculix, Inc., Berwyn, PA, USA) (Riva & Petrig 1980, Sinclair et al. 1989). Both eyes were examined, the left eye first. Subjects were seated in a darkened room in front of a blue-field entoptoscope and a TV monitor. After hearing the technique explained, the subjects were asked to adjust two dials until the velocity and density of the computer-simulated particles displayed on the monitor matched those of their own entoptically observed leucocytes. Three matching trials were performed for each eye, with velocity and density readjusted each time. Average leucocyte velocity and density were calculated. To ensure that subjects were able to pass the test reliably, the study included only those with a coefficient of variation (100 x standard deviation / mean) between three measurements of less than 30% in both eyes.

## 5.5 RISK FACTORS FOR PROGRESSION (I)

### 5.5.1 Patients

Patients selected for the study were all 186 patients with ExOHT or ExG who had been admitted into the glaucoma ward in 1993. The charts of these patients were reviewed. Study entry was determined as the first visit to HUEH when a VF examination was performed (also including visits before 1993). All patients (except those with stage of glaucoma > 6) with at least one previous, at least one year old, VF available were invited to one additional follow-up visit which included a clinical examination (by the author), a diurnal IOP curve, and perimetry. After this, patients were included in the study if inclusion criteria were met: 1) at least two reliable VF examinations taken at the hospital glaucoma laboratory, 2) ≥ 1 year follow-up between two successive VFs, and 3) at the time of the first VF examination, stage of glaucoma ≤ 6. Only one eye of each patient was included. In patients with bilateral ExG or ExOHT, the eye diagnosed first was chosen. If ExG or ExOHT was diagnosed at the same time in both eyes, the right eye was chosen. Of the 139 patients who met the inclusion criteria, 101 were women and 38 men (mean age ± SD of 69.9 ± 7.7 years, range 50-88 years) (Table 1). The grading of the eyes at study entry is shown in Table 2.

Of the 47 patients excluded from the study; 14 had unreliable VFs, 27 had < 1 year follow-up, and 6 had stage of glaucoma > 6 at the time of the first VF examination. Of those 27

with < 1 year follow-up, 7 did not accept the invitation for the additional follow-up, 13 had died, and 7 had no previous VF available.

Patients included in the study were referred to HUEH (at study entry) because of uncontrolled IOP (54 eyes, 39%), suspicion of progression (11 eyes, 8%), evaluation of the glaucoma (32 eyes, 23%), cataract (12 eyes, 9%), a subjective (pain, blurred vision, or other) symptom (9 eyes, 6%), recurrent dacryocystitis (1 eye), and some problem with the fellow eye (15 eyes, 11%). Five patients (4%) were not referred, but study entry coincided with a planned examination. Evaluation of glaucoma included cases for which the referral ophthalmologist had no access to VF.

Follow-up ended 1) when progression was detected, or 2) at the time of the final VF in the HUEH, if progression was not detected. The mean (±SD) follow-up time was 5.2 ± 3.6 years (range 1.0-19.8 years). On average, there were 2.0 ± 1.4 (range 1-7) follow-up visits after the first reliable VF at the HUEH. Of the total of 139 patients, 58 had only one follow-up VF included in the analysis: 34 patients with progression and 24 without progression. Of these 34 with progression, 24 had more follow-up visits than this one, but were not included because progression had already occurred. Of the 24 patients without progression who had only one follow-up visit, the author examined 15. The mean time interval between any two of the follow-up visits was 3.0 ± 2.2 years (range 0.5-14 years).

Progression was detected in 63 eyes (45.3%). This end-point was achieved at the additional follow-up visit in 9 eyes (6%), but in 54 eyes (39%) progression had already been detected already from the patient charts, based on earlier visits. Of these 54 eyes (or patients), 26 (19%) still attended the additional follow-up (although follow-up had already ended because progression had occurred), whereas 27 (19%) did not: 8 patients (6%) did not accept the invitation, 13 (9%) had died, and 1 (1%) could not be reached.

In 76 eyes (54.7%) no progression was detected during follow-up. Of these 76 eyes (or patients), 21 patients (15%) did not appear for the additional control visit: 11 (8%) did not accept the invitation, 7 (5%) had died, and 3 (2%) could not be reached. These eyes showed no progression at the last visit in the HUEH, and it remains unknown whether progression would have been detected in some of these 21 patients if they had attended the additional visit.

### 5.5.2 Methods

At study entry and follow-up ambulatory visits, grading of glaucoma was performed. All IOP values obtained from referral notes and measured at the hospital glaucoma laboratory at any time were recorded. IOPs < 3 months after trabeculectomy or cataract operation, and IOPs < 1 month after ALT or cyclodestruction were excluded. Data on intraocular interventions, ocular diseases, and glaucoma medications were recorded as well as the highest IOP value during the whole follow-up time. Treatments of the eyes before and by the end of the study are shown in Table 3.

***Table 3.*** *Treatment of eyes before and by study-end (I)*

| | **Before entrance** | | **By the study-end** | |
|---|---|---|---|---|
| | **Number of eyes** | **%** | **Number of eyes** | **%** |
| No treatment | 49 | 35.3 | 3 | 2.2 |
| Medical treatment only | 63 | 45.3 | 26 | 18.7 |
| Medical + other* | 22 | 15.8 | 91 | 65.5 |
| Other only* | 5 | 3.6 | 19 | 13.7 |
| | **139** | **100** | **139** | **100** |
| ALT | 23 | 16.5 | 87 | 62.6 |
| Surgical intervention | | | | |
| Trabeculectomy | 3 | 2.2 | 45 | 32.4 |
| Cyclodestruction | 0 | 0 | 25 | 18.0 |
| Laser iridectomy | 0 | 0 | 13 | 9.4 |
| Cataract operation | 4 | 2.9 | 48 | 34.5 |
| None | 114 | 82.0 | 29 | 20.9 |

* = ALT or surgical intervention
ALT = argon laser trabeculoplasty

Progression was defined as entering into a more severe stage including conversion from ExOHT to ExG.

In order to control for the length of follow-up and the different numbers of available IOP readings between two follow-up visits, a weighted mean IOP was calculated to describe the IOP level between two successive visits. For the calculations, the following formula was created:

$$\text{Weighted mean IOP} = \sum_{i=1}^{n} x_i t_i \Big/ \sum_{i=1}^{n} t_i ,$$

in which $x_i$ is the mean IOP during the time period $t_i$. In the formula, the means of all IOPs measured between two successive follow-up visits were multiplied by time in years between these two visits. These calculated values from all intervals were then added together, and the sum was divided by the entire length of the follow-up time. Maximum IOP was defined as the highest IOP recorded before the end of the study. Mean IOP was calculated as the mean of the IOPs between follow-ups. IOP range was defined as the difference between the highest and lowest IOP recorded before the end of the study.

To analyze time-to-event data, survival analysis was performed with the Cox proportional hazards model. Progression was selected as the event or hazard, and the simultaneous effect of the following factors on the hazard of progression were studied: age, gender, weighted mean IOP, maximum IOP, mean IOP, IOP range, stage of glaucoma at the beginning of the study, refraction (the spherical equivalent), glaucoma medication, and type of surgical intervention.

## 5.6 EFFECT OF IOP REDUCTION ON ONH TOPOGRAPHY (II)

### 5.6.1 Patients

Ten eyes of nine consecutive patients scheduled for filtration surgery (trabeculectomy) were enrolled in this study (mean age ± SD of 65.6 ± 8.1 years, range 55-75 years) (Table 1); four of the patients with ExG had also been included in Study I. All eyes underwent trabeculectomies between June and November 1993. The indication for surgery was progression or suspected progression of VF defects or uncontrollable IOP despite maximum tolerable medication. A standard surgical procedure was performed on all eyes (Raitta & Vesti 1991, Vesti 1993). The inclusion criterion was that measurable images with HRT could be obtained. The stage of glaucoma was graded as moderate in two eyes and as severe in eight. Grading of the eyes according to Thorburn's classification (1988) is shown in Table 2.

### 5.6.2 Methods

Diurnal IOP curves and SLO-imaging with the HRT were performed once before and twice after surgery. The first follow-up visit was at 2 to 7 months (mean ± SD, 3.7 ± 1.7 months) after surgery (follow-up A), and the second follow-up visit at 7 to 16 months (12.1 ± 3.2 months) after surgery (follow-up B). Cup volume ($mm^3$) cup/disc area ratio, mean cup depth (mm), and mean height of contour (mm) were obtained from the HRT analysis. The percentage changes in IOP and in HRT parameters between the pre-operative and post-operative situation were calculated: (post-values – pre-values) / pre-values x 100%.

## 5.7 ONH TOPOGRAPHY IN ExOHT AND ExG AND USE OF HRT IN FOLLOW-UP (III)

### 5.7.1 Patients

All consecutive patients referred to HUEH between May 1995 and May 1997 because of ExOHT or uncontrolled ExG were included. Further treatment of each patient was decided by a senior ophthalmologist who examined the patients and chose one of the following interventions: medical treatment (13 eyes), ALT (42 eyes), or trabeculectomy (25 eyes). Patients with previous ALT were accepted into the study only if the senior ophthalmologist chose trabeculectomy as the further treatment. Otherwise, patients who had undergone ALT, trabeculectomy, or cyclodestruction were excluded. Only eyes with refraction errors from -5.0 to +5.0 diopters were accepted. Eyes with a dense cataract making SLO-imaging impossible were excluded.

A total of 80 patients, 31 men and 49 women ($P < 0.05$, Chi-Square test), met the criteria (mean age ± SD of 68.7 ± 7 years, range 50-83 years) (Table 1).

### 5.7.2 Methods

Patients were followed prospectively and examined every 6 months, with analyses made at 6 months and 2 years. Examinations included clinical examination, diurnal measurement of IOP, perimetry, and SLO-imaging of the ONH with the HRT. IOP was also measured immediately after imaging. VFs were measured with the Octopus perimeter program G1. If

the patient was unable to perform reliable automated perimetry, Goldmann kinetic perimetry was performed. The grading of the eyes at study entry is shown in Table 2. The analyses were divided into three parts: 1) Study of the linear associations between HRT parameters and disc area, and between HRT parameters and VF index mean defect (MD), 2) Study of the reversal of ONH topography associated with reduction of IOP from pre-intervention level to the level at 6 months after intervention, and 3) Study of the association between change in MD from 6 months to 2 years with subsequent change in HRT parameters. Changes were calculated as '$value_{t2} - value_{t1}$', where t1 is the earlier time-point and t2 the later time-point.

## 5.8 ONH AND PERIPAPILLARY RETINAL BLOOD FLOW IN UNILATERAL ExG AND ExOHT (IV)

### 5.8.1 Patients

Fifty consecutive patients with uncontrolled unilateral ExG or ExOHT referred to the HUEH between May 1996 and December 1997 were included (mean age ± SD of 67.8 ± 7.4 years, range 51-85 years) (Table 1); 36 of these patients had also participated in Study III. All patients had ExOHT or ExG in only one eye, and these eyes comprised the study group. The control group comprised the fellow eyes, which all had IOP less than 22 mmHg. Of the control eyes, 14 were clinically non-exfoliative and 36 exfoliative. The type of glaucoma medications used were topical ß-blocking agent in 29 eyes (25 with timolol, and 4 with betaxolol), pilocarpine in 17 eyes, dorzolamide in 10 eyes, oral acetazolamide in 4 eyes, and dipivefrine in 1 eye. Twenty-four eyes had more than one type of medication, 9 eyes only one type, and in 17 eyes IOP was controlled without medication (2 eyes because of ALT and 15 eyes because of trabeculectomy). Systemic diseases and medications are specified in Table 4.

### 5.8.2 Methods

Examinations included blood flow measurements of the ONH and peripapillary retina with the HRF, SLO imaging of the ONH with the HRT, perimetry (Octopus perimetry program G1 in 46 patients, Goldmann kinetic perimetry in 4), measurement of IOP, clinical exami-

***Table 4.*** *Systemic diseases and medications of patients in Study IV*

| **Systemic diseases** | **Number of Patients** | **%** |
|---|---|---|
| None | 33 | 66 |
| Systemic disease | 17 | 34 |
| Non-insulin-dependent diabetes mellitus | 2 | 4 |
| Systemic hypertension | 12 | 24 |
| Other cardiovascular disease | 6 | 12 |
| | | |
| **Systemic medications** | | |
| None | 35 | 70 |
| Systemic medication | 15 | 30 |
| β-blocking agents | 8 | 16 |
| Calcium-channel antagonists | 5 | 10 |
| Angiotensin-converting enzyme-blockers | 3 | 6 |
| Diuretics | 4 | 8 |
| Acetylsalicylic acid | 5 | 10 |

nation, and measurement of blood pressure (BP). The perfusion pressure of each eye was calculated by the formula (diastolic BP + 1/3(systolic BP - diastolic BP)) - IOP (Hayreh 1994). Grading of the eyes is shown in Table 2. Mean (± SD) IOP measured immediately after HRF measurements was significantly higher in the study eyes than in the control eyes (19.2 ± 6.8 mmHg vs. 16.7 ± 4.1 mmHg respectively, P = 0.022), with no significant difference detected in perfusion pressure (82.7 ± 13.9 mmHg vs. 84.9 ± 12.2 mmHg, P = 0.085). VF indices and all HRT parameters except maximum cup depth were significantly worse in study eyes than in control eyes (Table 5). The mean (± SD) disc area in study eyes was greater than in control eyes (1.92 ± 0.41 $mm^2$ vs. 1.83 ± 0.37 $mm^2$ respectively, P = 0.030).

Flow values were measured at three locations on the neuroretinal rim and at five locations on the peripapillary retina 0.6 to 0.8 mm from the scleral ring. One value was obtained from the bottom of the optic cup. The flow values were independent of location of measurement in the rim area and in the peripapillary retina (F = 0.02 and P = 0.980 for rim, F = 1.14 and P = 0.340 for peripapillary locations; repeated measures ANOVA). Therefore, the mean of the values in three locations of the rim area and the mean of the values in five locations of the peripapillary area were calculated for use in further analyses.

***Table 5.*** *Mean of VF indices and HRT parameters of study eyes and control eyes (IV)*

| **Parameter** | **Study eyes** Mean ± SD | **Control eyes** Mean ± SD | **P-value** |
|---|---|---|---|
| VF index (n = 46) | | | |
| MS (dB) | 17.4 ± 7.1 | 25.3 ± 2.3 | <0.001* |
| MD (dB) | 9.1 ± 7.2 | 1.3 ± 2.1 | <0.001* |
| LV (dB) | 32.2 ± 31.7 | 6.0 ± 4.7 | <0.001* |
| HRT parameters | | | |
| Disc area ($mm^2$) | 1.92 ± 0.41 | 1.83 ± 0.37 | 0.030* |
| Cup area ($mm^2$) | 0.84 ± 0.52 | 0.51 ± 0.31 | <0.001* |
| Cup/disc area ratio | 0.43 ± 0.21 | 0.27 ± 0.13 | <0.001* |
| Rim area ($mm^2$) | 1.01 ± 0.41 | 1.32 ± 0.29 | <0.001* |
| Height variation contour (mm) | 0.31 ± 0.10 | 0.37 ± 0.09 | 0.001* |
| Cup volume ($mm^3$) | 0.21 ± 0.25 | 0.10 ± 0.09 | 0.001* |
| Rim volume ($mm^3$) | 0.23 ± 0.16 | 0.33 ± 0.12 | <0.001* |
| Mean cup depth (mm) | 0.29 ± 0.13 | 0.20 ± 0.08 | 0.008* |
| Maximum cup depth (mm) | 0.56 ± 0.21 | 0.53 ± 0.16 | 0.151 |
| Cup shape measure | -0.10 ± 0.08 | -0.18 ± 0.12 | <0.001* |
| Mean RNFL thickness (mm) | 0.17 ± 0.07 | 0.22 ± 0.06 | <0.001* |
| RNFL cross-section area ($mm^2$) | 0.84 ± 0.34 | 1.07 ± 0.32 | <0.001* |

* = statistically significant
HRT = Heidelberg retina tomograph, LV = loss variance, MD = mean defect,
MS = mean sensitivity, VF = visual field, RNFL = retinal nerve fibre layer

The analyses were divided into two parts: 1) Study of factors associated with difference in flow between study eyes and control eyes, and 2) Study of what factors associated with the flow in study eyes only. In both situations, analyses were repeated for lamina area, rim area, and peripapillary area separately. Differences were calculated as value of study eye minus value of control eye.

Regarding differences in flow between study eyes and control eyes, associations with the following factors were tested: difference in IOP, difference in VF index MD, differences in the HRT parameters rim volume and RNFL cross-section area, stage of glaucoma in the study eye, and whether the study eye was treated with timolol, betaxolol, pilocarpine and/or dorzolamide, and whether ExS of the fellow eye had been diagnosed.

Regarding the flow in study eyes only, associations with the following factors were tested: IOP, VF index MD, HRT parameters rim volume and RNFL cross-section area, stage of glaucoma, whether the study eye was treated with timolol, betaxolol, pilocarpine and/or dorzolamide, perfusion pressure of the eye, age of patient, whether the patient had systemic hypertension or any cardiovascular disease, and whether the patient had been treated with a systemic ß-blocker.

## 5.9 MACULAR BLOOD FLOW IN UNILATERAL ExG AND ExOHT (V)

### 5.9.1 Patients

The study included 21 patients (mean age ± SD of 62.9 ± 7.9 years, range 50–74 years). Three patients were excluded because of coefficient of variation above 30% of the blood flow measurements. Patients were divided into two groups: one group with unilateral ExG (n = 10, mean age ± SD of 61.1 ± 8.4 years, range 50–74 years) and the other group with unilateral ExS (n = 11, mean age ± SD of 64.5 ± 7.5 years, range 49–74 years) (Table 1). All of the 10 patients with ExG participated in Study III and 7 also in Study IV. In the group with unilateral ExG, all fellow eyes were healthy, clinically non-exfoliative, and normotensive. Of the glaucomatous eyes, two had early glaucoma (with only optic disc changes), one had nasal step in the VF, four had nasal step combined with Bjerrum scotoma, and in three eyes the Bjerrum scotoma extended to the edge of the paracentral 10° field. Grading of the eyes according to Thorburn's classification (1988) is shown in Table 2. All glaucomatous eyes had been receiving topical medication and four subjects received systemic carbonic anhydrase inhibitor, as well. Topical medication included timolol in all 10 eyes, pilocarpine in seven eyes, and dipivefrine in four eyes. One patient with ischaemic heart disease was receiving a systemic calcium-channel blocker. In all glaucomatous eyes, IOP (measured immediately after blue-field simulation) was less than 28 mmHg (mean ± SD, 23.5 ± 3.8 mmHg) and in all non-glaucomatous eyes, IOP was less than 22 mmHg (17.3 ± 2.2 mmHg), which difference was statistically significant (P = 0.01).

The group with unilateral ExS showed no signs of glaucoma in either eye. All patients had ExS in one eye, and the other eye was clinically non-exfoliative. None had ever received IOP-reducing medication. Four patients had systemic hypertension, and one also diabetes mellitus type II. Systemic medication included calcium-channel blockers (1 patient), β-blocking agents

(2 patients), and angiotensin-converting enzyme-blockers (2 patients). The mean (± SD) of the highest IOP of the diurnal IOP curve obtained the same day was 15.7 ± 2.2 mmHg for the exfoliative eyes and 14.7 ± 1.9 mmHg for the non-exfoliative eyes; they did not differ significantly (P = 0.33).

### 5.9.2 Methods

Examinations included clinical examination, measurement of IOP, perimetry (Octopus perimetry program G1), and measurement of macular leucocyte velocity and density with blue-field entoptic simulation.

Macular capillary leucocyte velocities and densities were analyzed for asymmetry within the ExG and ExS groups. Differences were calculated as value of affected eye minus value of clinically non-exfoliative eye, where the affected eye is the one with ExS or ExG. Leucocyte velocity was correlated with MD, loss variance (LV), and IOP.

## 5.10 STATISTICAL METHODS

Statistical analyses were performed with the SPSS software package (version SPSS 8.0 for Windows, SPSS Inc., Chicago, IL, USA) in Studies I, III, and IV, and the SAS software package (SAS Institute Inc., Cary, NC, USA) in Studies II and V.

Variables were tested for normality with the one-sample Kolmogorov-Smirnov test (I-V). For parametric comparisons of the means, the independent samples t-test was used for non-paired comparisons (I) and a paired t-test for pairwise comparisons (III, IV, V). For non-parametric variables, the Mann-Whitney U-test was used for unpaired comparisons (II) and the Wilcoxon signed-rank sum test (II, V) for paired comparisons. Repeated measures ANOVA was used to study whether location of measurement had any effect on flow values (IV).

To test proportions, the Pearson chi-square test (I, III) was used and, if the expected frequency was less than 5, Fisher's exact test (I).

Pearson correlation (II, IV, V) and Spearman's rank correlation (II, V) coefficients were used for correlation analyses. Multiple linear regression analyses were performed with the enter and stepwise procedures to study linear associations between variables in multivariate situations (III, IV). Mallow's $C_p$ with a stepwise procedure was performed to select variables for multiple linear regression analyses (IV); variables in the model with the smallest Mallow's $C_p$ criterion were selected. The residuals were tested and found to be normally distributed, homeoscedastic, and non-biased.

To analyze time-to-event data (I), survival analysis with the Cox proportional hazards model was performed. In the Cox proportional hazards model, a forward stepwise procedure was used. A probability of the score statistic of 0.05 or less was required for entry into the model, and removal was based on a probability greater than 0.10 for the likelihood-ratio statistic.

A P-value $< 0.05$ was considered statistically significant.

# 6 RESULTS

## 6.1 RISK FACTORS FOR PROGRESSION (I)

Progression of glaucoma (entering into a more severe stage) was detected in 63 eyes (45.3%), whereas 76 eyes (54.7%) showed no progression. Factors affecting progression were studied with the Cox proportional hazards method, which resulted in the model shown in Table 6. A significant association with progression was found for age, weighted

***Table 6.*** *Results of Cox proportional hazards model (I). Factors associated with progression of exfoliation glaucoma shown.*

| **Covariate** | **Regression coefficient** | **Relative risk** | **95% Confidence Interval** | **P-value** |
|---|---|---|---|---|
| Age | | | | |
| by 1 year increase | 0.041 | 1.042 | 1.001-1.084 | 0.043* |
| Weighted mean IOP | | | | |
| by 1 mmHg increase | 0.073 | 1.076 | 1.037-1.116 | < 0.001* |
| Stage of glaucoma | | | | |
| by 1 stage increase | 0.362 | 1.436 | 1.173-1.756 | < 0.001* |
| History of | | | | |
| trabeculectomy | -1.022 | 0.360 | 0.187-0.694 | 0.002* |

* = statistically significant
IOP = intraocular pressure

mean IOP, and stage of glaucoma. History of trabeculectomy was related to decreased risk. No significant association with progression was found for gender, maximum IOP, refraction, glaucoma medication, history of ALT, or history of cyclodestruction. A one-year increase in age increased relative risk for progression by 4.2%. Similarly, a one-mmHg increase in weighted mean IOP increased relative risk by 7.6%, and a one-step increase in

staging of glaucoma increased relative risk by 43.6%. If trabeculectomy was not performed, the estimated risk for progression was 2.78 times as great (1 / 0.36 = 2.78). The effect of trabeculectomy on progression is also shown graphically in Figure 1, in which the estimated survival curves for eyes operated on and not operated on are plotted separately. Eyes that had been operated on remained non-progressive longer than those not operated on. The weighted mean IOP did not differ significantly between eyes with and without a history of trabeculectomy (mean ± SD, 19.71 ± 6.3 mmHg and 21.0 ± 5.7 mmHg respectively, P = 0.226).

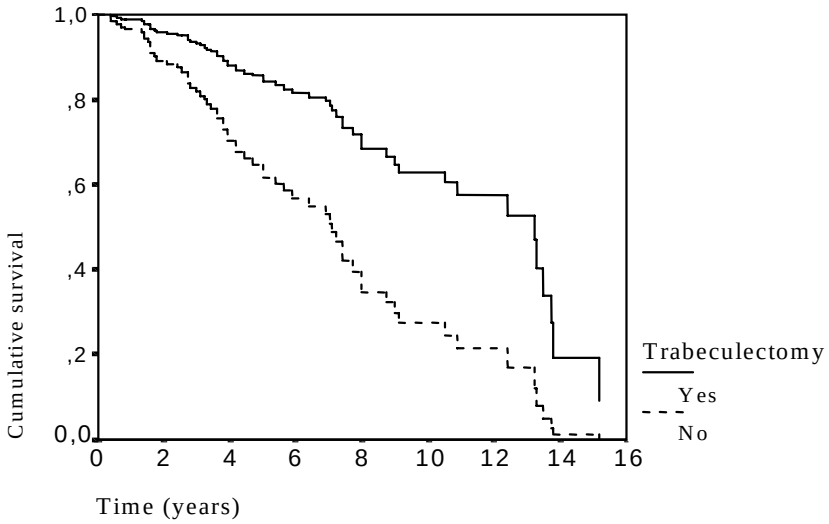


***Figure 1.*** *Cumulative survival for eyes with and without a history of trabeculectomy*

There were 21 eyes without progression that did not attend the additional follow-up visit. Comparison of these patients with the others revealed that these patients were older and more often treated with dipivefrine (Table 7). There were no statistically significant differences in the other covariates that were used in the analyses. The length of follow-up of these 21 patients did not differ significantly from that of all other patients (mean ± SD, 4.4 ± 3.7 and 5.4 ± 4.4 years respectively, P = 0.238), nor from follow-up lenght of the other 55 censored (non-progressing) patients (4.4 ± 3.7 and 5.5 ± 3.1 years, P = 0.151). Analysis with the Cox proportional hazards method was repeated for 118 eyes with these 21 eyes excluded, but the results remained unaffected.

***Table 7.*** *Covariates used in the Cox proportional hazard model compared between 21 eyes without progression that did not attend the additional follow-up and all the other 118 eyes (I)*

| **Covariates** | **N = 118** | **N = 21** | **P** |
|---|---|---|---|
| Age (mean ± SD, years) | 69.1 ± 7.5 | 74.6 ± 7.6 | 0.003* |
| Gender (men/women) | 35 / 83 | 5 / 16 | 0.585 |
| Maximum IOP (mean ± SD, mmHg) | 29.1 ± 11.7 | 27.0 ± 7.6 | 0.429 |
| Mean weighted IOP (mean ± SD, mmHg) | 20.7 ± 6.8 | 19.8 ± 4.1 | 0.511 |
| Stage of glaucoma# | | | |
| 1 | 28 (24%) | 6 (28%) | 0.487 |
| 2 | 31 (26%) | 6 (29%) | |
| 3 | 30 (25%) | 7 (33%) | |
| 4 | 19 (16%) | 1 (5%) | |
| 5 | 5 (4%) | 1 (5%) | |
| 6 | 5 (4%) | 0 | |
| Refraction (D) | -0.27 ± 3.0 | 0.35 ± 1.5 | 0.369 |
| Medication for glaucoma | | | |
| β-blocking agent | 95 (80%) | 15 (71%) | 0.345 |
| Pilocarpine | 79 (67%) | 12 (57%) | 0.383 |
| Oral acetazolamide | 42 (36%) | 3 (14%) | 0.055 |
| Dipivefrine | 16 (14%) | 7 (33%) | 0.049* |
| Dorzolamide† | 8 (7%) | 0 | 0.260 |
| Surgical intervention | | | |
| ALT | 72 (61%) | 15 (71%) | 0.364 |
| Cyclodestruction | 21 (18%) | 4 (19%) | 1.000 |
| Trabeculectomy | 40 (34%) | 5 (24%) | 0.363 |

* = statistically significant
# = Stages 4, 5, and 6 were combined as one group in analysis
† = Fisher's exact test
ALT = argon laser trabeculoplasty, IOP = intraocular pressure, N = number of eyes

For descriptive statistics, a risk score for each of the 139 patients was calculated from the Cox proportional hazards model. The formula for the risk score can be written as follows: Risk score = (0.041) (age) + (0.073) (weighted mean IOP) + (0.362) (stage of glaucoma) + (-1.022) (history of trabeculectomy), i.e., the value of each covariate is multiplied by the regression coefficient (Table 6) of the same covariate. The value for history of

***Table 8.*** *Based on the Cox proportional hazards model, a risk score was calculated for every patient (I). Based on risk score, patients were divided in three groups equal in size, to show characteristics of covariates in the low-, medium-, and high-risk groups.*

| **Covariate** | **Descriptive statistic** | **All eyes Mean (± SD) risk score = 4.976 ± 0.793 N = 139** | **Low risk Risk score < 4.633 N = 46** | **Medium risk Risk score ≥ 4.633 and ≤ 5.315 N = 47** | **High risk Risk score > 5.315 N = 46** |
|---|---|---|---|---|---|
| Age (years) | Mean (±SD) | 69.9 ± 7.7 | 65.1 ± 6.4 | 71.1 ± 7.2 | 73.6 ± 7.1 |
| | Range | 50.8-88.7 | 51.7-81.6 | 50.8-82.5 | 58.3-88.7 |
| Weighted mean IOP | Mean (±SD) | 20.6 ± 5.8 | 18.5 ± 4.0 | 19.7 ± 5.2 | 23.6 ± 6.8 |
| (mmHg) | Range | 8.2-42.0 | 8.2-25.0 | 11.0-42.0 | 14.5-40.8 |
| Stage of glaucoma | Mean (±SD) | 2.6 ± 1.3 | 2.3 ± 1.3 | 2.2 ± 1.1 | 3.2 ± 1.4 |
| | Range | 1-6 | 1-6 | 1-5 | 1-6 |
| History of trabeculectomy | Frequency | 45 eyes | 33 eyes | 8 eyes | 4 eyes |
| | Percent | 32.4% | 71.7% | 17.0% | 8.7% |

IOP = intraocular pressure, N = number of eye

trabeculectomy is 1 if operated on and 0 if not. Based on risk scores, the patients were divided into three groups of equal size: 1) a low-risk group with risk scores less than 4.633, 2) a medium-risk group with scores between or equal to 4.633 and 5.315, and 3) a high-risk group with scores above 5.315 (Table 8). Progression was observed in 14 (30%), 22 (47%), and 27 eyes (59%) in the low-, medium-, and high-risk groups, respectively. Mean age, weighted mean IOP, and stage of glaucoma increased towards the high-risk group. Frequency of trabeculectomy was lowest in the high-risk group: of the 46 eyes classified as low-risk, 33 (71.7%) had undergone trabeculectomy compared to only 8 (17%) and 4 eyes (8.7%) in the medium- and high-risk groups, respectively. In the low-risk group, no eye had a weighted mean IOP above 25 mmHg (range 8.2-25.0 mmHg).

## 6.2 EFFECT OF IOP REDUCTION ON ONH TOPOGRAPHY (II)

At follow-up A (3.7 months after trabeculectomy), the mean (± SD) drop in mean diurnal IOP was 13.4 ± 6.9 mmHg or 52.2 ± 12.5% (Table 9). Mean values for cup volume and mean cup depth were significantly smaller than pre-operative values. The cup/disc area ratio and mean height contour showed no significant changes. At follow-up A, all eyes showed a drop in diurnal IOP of more than 35% (36.4–60.6%). Three eyes showed a decrease in cup volume of less than 10%: one eye with 6% decrease in cup volume had experienced an IOP > 25 mmHg during the first post-operative week, one eye with a 10% decrease had NTG, and one eye with a 46% increase in cup volume had bleb failure and underwent bleb revision 1.5 months after surgery. All other eyes underwent a decrease in cup volume of 24% to 53%.

At follow-up B (12.1 months after trabeculectomy), measurable images of two eyes could not be obtained because of cataract, and these eyes were not included in the analyses of this follow-up. The mean (± SD) drop in IOP when compared to preoperative values was 11.8 ± 8.2 mmHg or 41.4 ± 23.8% (Table 9). A statistically significant decrease was found for cup volume, cup/disc area ratio, and mean height of contour. No significant change was found for mean cup depth. A more than 30% decrease in cup volume (34–57%) was detected for six of eight eyes; all these eyes showed a drop in IOP of more than 30% (33–67%). The other two eyes showed slight increases in cup volume (12% and 5%, respectively) and had the smallest percentage decrease in IOP (14% and 0%) and the smallest IOP reduction (3

***Table 9.*** *Mean IOP, mean HRT parameters, and percent change in parameters from before trabeculectomy (Pre) to the first (Post A) and second (Post B) follow-ups (II)*

| | **Pre** **Mean (± SD)** | **Post A** **Mean (± SD)** | **% Change** **Mean (± SD)** | **P value** |
|---|---|---|---|---|
| IOP (mmHg) | 24.4 ± 6.9 | 11.0 ± 2.8 | -52.8 ±12.5 | < 0.05* |
| Cup volume ($mm^3$) | 0.65 ± 0.44 | 0.50 ± 0.35 | -31.8 ± 16.2 | < 0.05* |
| Cup/disc area ratio | 0.66 ± 0.15 | 0.62 ± 0.19 | -5.9 ± 22.2 | NS |
| Mean cup depth (mm) | 0.48 ± 0.30 | 0.34 ± 0.19 | -13.8 ± 12.1 | < 0.05* |
| Mean height of contour (mm) | 0.14 ± 0.44 | 0.12 ± 0.03 | -11.0 ± 23.7 | NS |

| | **Pre** **Mean (± SD)** | **Post B** **Mean (± SD)** | **% Change** **Mean (± SD)** | **P value** |
|---|---|---|---|---|
| IOP (mmHg) | 25.5 ± 7.3 | 13.8 ± 3.1 | -41.4 ± 23.8 | < 0.05* |
| Cup volume ($mm^3$) | 0.76 ± 0.42 | 0.52 ± 0.38 | -32.0 ± 25.9 | < 0.05* |
| Cup/disc area ratio | 0.71 ± 0.12 | 0.64 ± 0.16 | -12.3 ± 16.7 | < 0.05* |
| Mean cup depth (mm) | 0.55 ± 0.30 | 0.42 ± 0.14 | 15.6 ± 18.6 | NS |
| Mean height of contour (mm) | 0.15 ± 0.04 | 0.09 ± 0.05 | 36.9 ± 28.9 | < 0.05* |

* = statistically significant
IOP = intraocular pressure, NS = not significant

and 0 mmHg); they were one eye with IOP > 25 mmHg during the first post-operative week and one eye with NTG.

## 6.3 ONH TOPOGRAPHY IN ExOHT AND ExG AND USE OF HRT IN FOLLOW-UP (III)

Before intervention, mean (± SD) diurnal IOP was 24.4 ± 6.1 mmHg, mean IOP (± SD) measured after HRT imaging 28.2 ± 9.0 mmHg, and mean (± SD) VF index MD 8.6 ± 6.6 (Table 10). At this baseline examination, the associations between HRT parameters, VF index MD, and disc area were studied.

***Table 10.*** *Mean of IOP and VF indices before intervention and at follow-up visits at 6 months and 2 years*

| | **Pre-intervention Mean (±SD)** | **6 months Mean (±SD)** | **P-value** | **2 years Mean (±SD)** | P-value |
|---|---|---|---|---|---|
| Mean diurnal IOP (mmHg) | 24.4 ± 6.1 | 16.2 ± 3.9 | <0.001* | 17.7 ± 3.2 | <0.001* |
| IOP after HRT (mmHg) | 28.2 ± 9.0 | 17.7 ± 6.1 | <0.001* | 19.2 ± 5.0 | <0.001* |
| MS (dB)# | 17.9 ± 6.5 | 18.6 ± 5.9 | 0.022* | 19.3 ± 5.8 | 0.011* |
| MD (dB)# | 8.6 ± 6.6 | 7.7 ± 5.9 | 0.020* | 7.1 ± 5.8 | 0.003* |
| LV (dB)# | 26.4 ± 24.0 | 29.6 ± 28.4 | 0.750 | 27.2 ± 27.2 | 0.954 |

* = statistically significant
# = tested with Wilcoxon signed-rank sum test, the others with paired t-test
HRT = Heidelberg retina tomograph, IOP = intraocular pressure, LV = loss variance, MD = mean defect, MS = mean sensitivity

### 6.3.1 Correlation of HRT parameters with VF index MD

At the baseline examination, when the effect of disc area was taken into account in the multiple regression analyses, a statistically significant linear association existed between MD and all HRT parameters (Table 11).

### 6.3.2 Covariation of HRT with disc area

At the baseline examination, the optic disc area showed a significant association with cup area, cup/disc area ratio, rim area, cup volume, and mean RNFL thickness; the larger the disc, the more likely that the HRT parameters would show values in the direction of ‘more glaucomatous’ (Table 11). Associations with borderline significance occurred between disc area and height variation contour and cup shape measure. Rim volume, mean cup depth, maximum cup depth, and RNFL cross-section area appeared to be unaffected by area of the ONH.

***Table 11.*** *Results of multiple linear regression analysis showing associations between HRT parameters and MD (dB) and disc area ($mm^2$)*

| Dependent variable | R-square | Explanatory variable | PRC | P-value |
|---|---|---|---|---|
| Cup area ($mm^2$) | 0.65 | MD | 0.030 | < 0.001* |
| | | Disc area | 0.787 | < 0.001* |
| Cup/disc area ratio | 0.32 | MD | 0.013 | < 0.001* |
| | | Disc area | 0.119 | 0.006* |
| Rim area ($mm^2$) | 0.26 | MD | -0.030 | < 0.001* |
| | | Disc area | 0.213 | 0.018* |
| Height variation contour (mm) | 0.24 | MD | -0.006 | 0.001* |
| | | Disc area | -0.041 | 0.065 |
| Cup volume ($mm^3$) | 0.53 | MD | 0.024 | < 0.001* |
| | | Disc area | 0.294 | < 0.001* |
| Rim volume ($mm^3$) | 0.21 | MD | -0.010 | < 0.001* |
| | | Disc area | 0.006 | 0.861 |
| Mean cup depth (mm) | 0.28 | MD | 0.010 | < 0.001* |
| | | Disc area | 0.045 | 0.130 |
| Maximum cup depth (mm) | 0.17 | MD | 0.011 | 0.001* |
| | | Disc area | 0.047 | 0.317 |
| Cup shape measure | 0.26 | MD | 0.006 | < 0.001* |
| | | Disc area | 0.042 | 0.052 |
| Mean RNFL thickness (mm) | 0.26 | MD | -0.004 | < 0.001* |
| | | Disc area | -0.029 | 0.042* |
| RNFL cross section area ($mm^2$) | 0.20 | MD | -0.021 | < 0.001* |
| | | Disc area | 0.040 | 0.561 |

* = statistically significant
HRT = Heidelberg retina tomograph, MD = mean defect, PRC = partial regression coefficient, RNFL = retinal nerve fibre layer

### 6.3.3 Reversal of ONH topography

After intervention, the mean IOP of the diurnal curve and IOP measured after HRT decreased significantly from pre-intervention levels (Table 10). Of the VF indices, MD and MS improved significantly compared to pre-intervention values. The reversal of HRT parameters associated with reduction of IOP from pre-intervention to the level at 6 months after intervention was studied.

Decrease in IOP (measured after HRT) was associated with a significant decrease in cup area, cup/disc area ratio, cup volume, mean cup depth, and maximum cup depth, and a significant increase in rim area and rim volume, when effects of age, stage of glaucoma, and disc area were taken into account (Table 12). No association appeared between change in IOP and height variation contour, cup shape measure, mean RNFL thickness, or RNFL cross-section area. Stage of glaucoma showed a significant association only with changes in cup volume and mean cup depth; these variables decreased more in eyes with advanced glaucoma than in eyes with early glaucoma. Age showed a significant association with changes in cup volume, mean cup depth, and maximum cup depth; in older patients, values for these variables decreased more than in younger patients.

### 6.3.4 Association between change in MD and changes in HRT parameters at sequential examinations

To study whether change in MD was associated with change in HRT parameters, the period from 6 months to 2 years was analyzed. Reliable VFs taken with Octopus G1 both at 6 months and at 2 years were available for only 56 eyes. IOP (±SD), measured after imaging, increased from 16.8 ± 3.8 mmHg at 6 months to 18.0 ± 4.5 mmHg at 2 years (P = 0.052). A total of 31 eyes showed improvement in MD (range 0.10-5.20 dB) and 25 eyes impairment in MD (range 0.1-4.10 dB). The mean change in MD was non-significant (mean ± SD, 6.9 ± 4.9 dB at 6 months, 6.7 ± 5.2 dB at 2 years, P = 0.487).

Possible factors affecting HRT parameters (mean diurnal IOP at 2 years, change in IOP measured after imaging from 6 months to 2 years, age of patient at first visit, and disc area) were put into the multiple linear regression model as a block with the enter procedure. Then a second block which included all HRT parameters (changes from 6 months to 2 years) was added to the model with the stepwise procedure. The only HRT parameter picked up with the stepwise procedure was change in cup shape measure, and it was taken into the model. The analysis with cup shape measure and the other factors (mean IOP, change in IOP, age, and disc area) was performed with the enter procedure, and resulted in a partial regression coefficient (PRC) of 17.21 (P = 0.013) for cup shape measure. After exclusion of three eyes considered outliers, the enter procedure was repeated, the result of which is shown in Table 13. Increase in MD was associated with increase in cup shape measure (PRC = 6.3, P = 0.046). The partial regression plot for change in cup shape measure and change in MD is shown in Figure 2.

***Table 12.*** *Results of multiple linear regression analysis, showing associations between changes in HRT from pre-intervention to 6 months with change in IOP (from pre-intervention to 6 months, mmHg), disc area ($mm^2$), age of patient (year), and stage of glaucoma*

| **Dependent variable (change in)** | **R-square** | **Explanatory variable** | **PRC x $10^{-3}$** | **P-value** |
|---|---|---|---|---|
| Cup area ($mm^2$) | 0.29 | IOP change | 5.25 | < 0.001* |
| | | Disc area | -5.77 | 0.814 |
| | | Age | 2.22 | 0.164 |
| | | Stage of glaucoma | -4.52 | 0.678 |
| Cup/disc area ratio | 0.26 | IOP change | 2.16 | < 0.001* |
| | | Disc area | 1.39 | 0.902 |
| | | Age | 1.06 | 0.150 |
| | | Stage of glaucoma | -2.82 | 0.573 |
| Rim area ($mm^2$) | 0.26 | IOP change | -4.50 | < 0.001* |
| | | Disc area | 2.96 | 0.900 |
| | | Age | -2.54 | 0.098 |
| | | Stage of glaucoma | 1.83 | 0.861 |
| Height variation contour (mm) | 0.22 | IOP change | -1.02 | 0.085 |
| | | Disc area | 29.58 | 0.022* |
| | | Age | -1.54 | 0.063 |
| | | Stage of glaucoma | 7.51 | 0.184 |
| Cup volume ($mm^3$) | 0.39 | IOP change | 3.04 | 0.003* |
| | | Disc area | -42.87 | 0.046* |
| | | Age | 4.39 | 0.002* |
| | | Stage of glaucoma | -22.62 | 0.018* |
| Rim volume ($mm^3$) | 0.16 | IOP change | -1.38 | 0.006* |
| | | Disc area | 11.78 | 0.272 |
| | | Age | -0.42 | 0.547 |
| | | Stage of glaucoma | 3.36 | 0.479 |
| Mean cup depth (mm) | 0.35 | IOP change | 1.24 | 0.007* |
| | | Disc area | 1.30 | 0.893 |
| | | Age | 1.61 | 0.001* |
| | | Stage of glaucoma | -13.94 | 0.002* |
| Maximum cup depth (mm) | 0.24 | IOP change | 2.33 | 0.008* |
| | | Disc area | -9.01 | 0.629 |
| | | Age | 2.44 | 0.045* |
| | | Stage of glaucoma | -15.11 | 0.071 |
| Cup shape measure | 0.06 | IOP change | 0.32 | 0.513 |
| | | Disc area | 10.54 | 0.319 |
| | | Age | 0.25 | 0.713 |
| | | Stage of glaucoma | -7.41 | 0.117 |
| Mean RNFL thickness (mm) | 0.08 | IOP change | -0.51 | 0.154 |
| | | Disc area | 13.31 | 0.084 |
| | | Age | -0.44 | 0.376 |
| | | Stage of glaucoma | -1.42 | 0.675 |
| RNFL cross-section area ($mm^2$) | 0.08 | IOP change | -2.66 | 0.141 |
| | | Disc area | 65.51 | 0.094 |
| | | Age | -2.551 | 0.319 |
| | | Stage of glaucoma | -7.70 | 0.655 |

* = statistically significant

HRT = Heidelberg retina tomograph, IOP = intraocular pressure, PRC = partial regression coefficient, RNFL = retinal nerve fibre layer

***Table 13.*** *Results of multiple linear regression analysis for changes from 6 months to 2 years, with associations between change in MD and explanatory variables*

| Dependent variable | R-square | Explanatory variable | PRC | P-value |
|---|---|---|---|---|
| Change in MD (dB) | 0.25 | Mean IOP at 2 years (mmHg) | $-2.49 \times 10^{-2}$ | 0.581 |
| | | Change in IOP (mmHg) | 0.127 | 0.056 |
| | | Age (year) | $6.69 \times 10^{-2}$ | 0.033* |
| | | Disc area ($mm^2$) | 1.185 | 0.010* |
| | | Change in cup shape measure | 6.305 | 0.046* |

* = statistically significant
MD = mean defect, PRC = partial regression coefficient, IOP = intraocular pressure

The analysis was repeated with the enter procedure by taking each of the HRT parameters separately, each together with all the other variables (mean IOP, change in IOP, age, and disc area) as explanatory variables. MD served as the dependent variable. Still, only cup shape measure reached statistical significance at the 0.05 level.

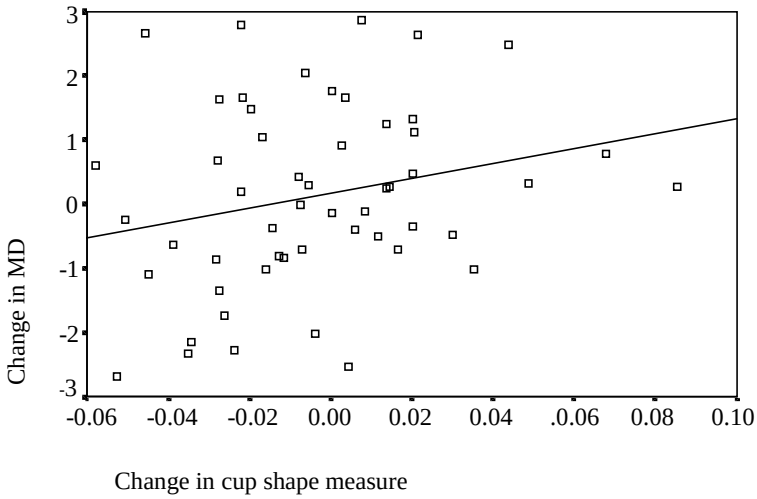


***Figure 2.*** *Partial regression plot of change in cup shape measure and change in MD (dB) (III)*
*MD = mean defect*

## 6.4 ONH AND PERIPAPILLARY RETINAL BLOOD FLOW IN UNILATERAL ExG AND ExOHT (IV)

The results of all analyses of HRF measurements of laminar, rim, and peripapillary retinal blood flow are summarized in Table 14.

### 6.4.1 Blood flow in study eyes versus control eyes

Flow in the rim area of the study eyes was 172.1 arbitrary units higher than in control eyes (P = 0.001). Similarly, flow in the laminar area of the study eyes was 39.5 arbitrary units higher than in control eyes, but was only of borderline significance (P = 0.065). No significant difference existed in peripapillary retinal blood flow (P = 0.531).

### 6.4.2 Blood flow related to degree of glaucomatous damage

More advanced glaucomatous damage was associated with reduced flow both in the laminar area and in the rim area. In the analysis of difference in flow between study eyes and control eyes, reduced rim area flow was associated with greater difference in MD (PRC = -8.8; P = 0.013). In analysis of study eyes only, smaller rim volume was associated with lower flow values in the lamina (PRC = 169.1; P = 0.024) and rim area (PRC = 284.6; P = 0.020).

### 6.4.3 Blood flow in eyes treated with timolol

Treatment with timolol was associated with reduced flow in the lamina and rim area. In the analysis of difference in flow between study eyes and control eyes, treatment with timolol was associated with increased difference in flow in the lamina (PRC = -76.4; P = 0.022) and rim area (PRC = -146.2; P = 0.004). Also in the analysis of study eyes only, treatment with timolol was associated with reduced flow in the lamina (PRC = -63.0; P = 0.001). The association in the rim area (PRC = -63.6) was of borderline significance (P = 0.077).

***Table 14.*** *Results of multiple linear regression analyses for flow in the laminar, rim, and peripapillary area. In analyses of differences between study eyes and control eyes, differences in flows were used as dependent variables. In analyses for flow in study eyes only, flows of the study eyes in corresponding areas were used as dependent variables*

| | **Difference between study eyes and control eyes** | | | | **Study eyes** | | | |
|---|---|---|---|---|---|---|---|---|
| | **R-square** | **Explanatory variable** | **PRC** | **P-value** | **R-square** | **Explanatory variable** | **PRC** | **P-value** |
| **Laminar flow** | 0.14 | Timolol | -76.4 | 0.022* | 0.32 | Rim volume ($mm^3$) | 169.1 | 0.024* |
| | | Pilocarpine | 55.6 | 0.108 | | Timolol | -63.0 | 0.001* |
| | | Intercept | 39.5 | 0.065 | | Age of the subject (year) | 5.1 | 0.002* |
| **Rim area flow** | 0.25 | Difference in MD (dB) | -8.8 | 0.013* | 0.15 | Rim volume ($mm^3$) | 284.6 | 0.020* |
| | | Timolol | -146.2 | 0.004* | | Timolol | -63.6 | 0.077 |
| | | Betaxolol | -197.7 | 0.026* | | | | |
| | | Intercept | 172.1 | 0.001* | | | | |
| **Peripapillary area** | 0.04 | ExS of fellow eye | 30.5 | 0.173 | 0.13 | Perfusion pressure (mmHg) | 1.8 | 0.021* |
| | | Intercept | -38.4 | 0.531 | | | | |

* = statistically significant
MD = mean defect, PRC = partial regression coefficient, ExS = exfoliation syndrome

### 6.4.4 Other findings

Four eyes treated with betaxolol seemed to have reduced flow in the rim area; the difference in rim area flow between study eyes and control eyes increased in these eyes (PRC = -197.7, P = 0.026). In study eyes, higher age was associated with increased flow in the lamina (PRC = 5.1, P = 0.002). Increased perfusion pressure was associated with increased flow only in the peripapillary retina (PRC =1.8, P = 0.021).

## 6.5 MACULAR BLOOD FLOW IN UNILATERAL ExG AND ExOHT (V)

### 6.5.1 Macular blood flow in unilateral ExG

Mean leucocyte velocity as measured with the blue-field simulation technique differed significantly between eyes (P = 0.02). Mean (± SD) leucocyte velocity was 0.70 ± 0.25 mm/s for the glaucomatous eyes and 0.89 ± 0.34 mm/s for their non-glaucomatous fellow eyes (Table 15). Leucocyte velocity was lower in the glaucomatous eye in six patients, equal in two, and higher in the glaucomatous eye in two patients. Leucocyte densities did not differ significantly between eyes (P = 0.89).

Difference between eyes in leucocyte velocity did not correlate significantly with difference in MD (r = -0.25, P = 0.49), with difference in LV (r = -0.33, P = 0.36), or with difference in IOP (r = -0.46, P = 0.18). However, in the glaucomatous eyes, correlation of borderline significance was detected between leucocyte velocity and MD (r = -0.58, P = 0.08; result not presented in V) (Figure 3), and between leucocyte velocity and LV (r = -0.62, P = 0.06) (Figure 4). Leucocyte velocity did not correlate in the glaucomatous eyes with IOP (r = -0.12, P = 0.75).

### 6.5.2 Macular blood flow in unilateral ExS

Neither leucocyte velocity nor leucocyte density differed significantly between eyes (P = 0.69 and P = 0.74, respectively).

***Table 15.*** *Mean leucocyte velocity (mm/s) and density (particles/field) of macular capillaries measured with blue-field entoptic simulation in 10 patients with unilateral exfoliation glaucoma and 11 patients with unilateral exfoliation syndrome.*

| | Glaucomatous eye | | Non-glaucomatous eye | | Difference between eyes | |
|---|---|---|---|---|---|---|
| **Patient** | **Velocity** | **Density** | **Velocity** | **Density** | **IOP** | **Velocity%** |
| 1a | 1.08 | 211 | 1.45 | 182 | 10 | -25.5 |
| 2a | 0.66 | 126 | 1.05 | 167 | 3 | -37.1 |
| 3a | 0.45 | 113 | 0.91 | 103 | 11 | -50.5 |
| 4a | 0.36 | 101 | 0.63 | 162 | 12 | -42.9 |
| 5a | 1.06 | 67 | 1.47 | 83 | 4 | -27.9 |
| 6a | 0.43 | 112 | 0.65 | 77 | 8 | -33.8 |
| 7a | 0.66 | 68 | 0.64 | 100 | 3 | 3.1 |
| 8a | 0.86 | 91 | 0.73 | 78 | 7 | 17.8 |
| 9a | 0.62 | 123 | 0.54 | 111 | 2 | 14.8 |
| 10a | 0.77 | 92 | 0.80 | 56 | 2 | -3.8 |
| **Mean (±SD)** | 0.70 ± 0.25* | 110 ± 41 | 0.89 ± 0.34* | 112 ± 44 | 6.2 ± 3.9 | |

| | Exfoliative eye | | Non-exfoliative eye | | Difference between eyes | |
|---|---|---|---|---|---|---|
| **Patient** | **Velocity** | **Density** | **Velocity** | **Density** | **IOP** | **Velocity%** |
| 1b | 0.62 | 185 | 0.77 | 196 | -1 | -19.5 |
| 2b | 0.65 | # | 0.71 | # | 0 | -8.5 |
| 3b | 0.93 | # | 0.50 | # | 2 | 86.0 |
| 4b | 0.63 | 222 | 0.71 | 146 | -2 | -11.3 |
| 5b | 0.58 | 234 | 0.60 | 251 | 0 | -3.3 |
| 6b | 1.06 | 65 | 1.25 | 53 | 0 | -15.2 |
| 7b | 0.65 | 179 | 0.67 | 191 | 4 | -3.0 |
| 8b | 0.72 | 77 | 0.55 | 88 | 2 | 30.9 |
| 9b | 0.66 | 154 | 0.47 | 170 | 2 | 40.2 |
| 10b | 0.84 | 33 | 0.70 | 93 | -1 | 20.0 |
| 11b | 0.63 | 65 | 0.78 | 63 | 0 | -19.2 |
| **Mean (±SD)** | 0.72 ± 0.15 | 135 ± 76 | 0.70 ± 0.21 | 139 ± 68 | 0.5 ± 1.8 | |

* = Statistically significant, P = 0.02 (paired t-test)

# = Excluded from analysis of leucocyte densities because of coefficient of variation > 30%

IOP = intraocular pressure

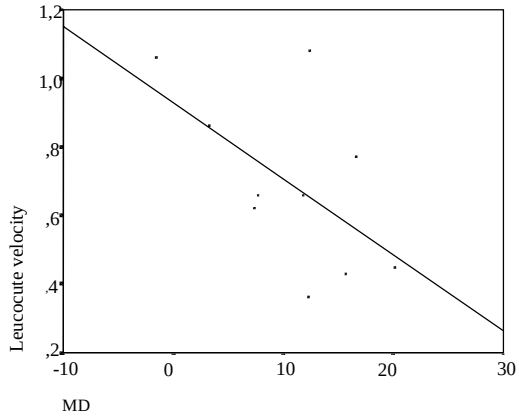


***Figure 3.*** *Scatterplot showing correlation between MD (dB) and leucocyte velocity (mm/s) measured by blue-field entoptoscopy in the macular area of glaucomatous eyes (V)*
*MD = mean defect*

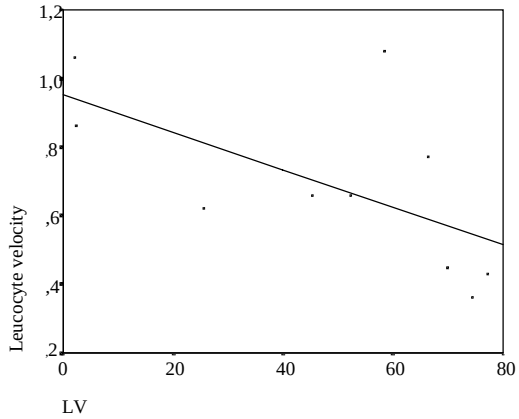


***Figure 4.*** *Scatterplot showing correlation between LV (dB) and leucocyte velocity (mm/s) measured by blue-field entoptoscopy in the macular area of glaucomatous eyes (V)*
*LV = loss variance*

The difference between eyes in leucocyte velocity did not correlate significantly either with difference in MD (r = -0.15, P = 0.66), LV (r = 0.22, P = 0.52), or IOP (r = 0.46, P = 0.15). Similarly, neither in exfoliative eyes nor in non-exfoliative eyes did leucocyte velocity correlate with MD (r = -0.07, P = 0.83 and r = -0.43, P = 0.18), LV (r = -0.27, P = 0.41 and r = -0.31, P = 0.35), or IOP (r = 0.18, P = 0.60 and r = -0.06, P = 0.85).

# 7. DISCUSSION

## 7.1 PATIENTS AND METHODS

The study included a total of 249 patients, 238 of whom had glaucoma or OHT in at least one eye. Most patients referred to the HUEH for consultation represent more complicated cases than do the glaucoma cases in the total population, on average. This is a handicap in this and all clinic-based studies, because results may not be generalisable to the whole population. In Study I, of all 139 eyes, 65 (47%) were referred because of uncontrolled IOP level or suspicion of glaucoma; however, some were also referred because of cataract, problems with the contralateral eye, or symptoms not necessarily associated with glaucoma. In the studies on ocular blood flow (IV, V), patients had unilateral ExG, unilateral ExOHT, or unilateral ExS. The fellow eyes were used as controls to minimise the effect of systemic diseases and medications, because these were expected to have similar effects on both eyes. The population of Study IV can be criticised to be non-homogenous, because study eyes had ExOHT (10 eyes) or ExG (40 eyes), and fellow eyes had ExS (36) or non-ExS (14 eyes). However, it is known that eyes with ExS in combination with high IOP (ExOHT) are at increased risk for developing glaucoma (Pohjanpelto 1986). Further, eyes with OHT and clinically non-glaucomatous ONHs have been shown, when examined with scanning laser tomography, to have ONH changes that distinguish them from healthy eyes (Hatch et al. 1997). They may therefore represent an early stage of glaucoma—one not yet clinically detectable. Similarly, the non-exfoliative fellow eye of an exfoliative eye may also be exfoliative, but at too early a stage to be detected clinically (Schlötzer-Schrehardt et al. 1991, Kivelä et al. 1997).

Glaucoma was graded in 7 stages according to a system which is a slight modification from that of Thorburn (1988). He admits that the system is rough and the steps between stages are unequal. Early stages may require more damage to the nerve fibres than do advanced stages before progression to another stage is evident. Study I covered risk factors for

progression of ExG; progression was defined as entering another stage. Since grading of glaucoma was rough, a change from one stage to another would indicate real progression and not fluctuation. On the other hand, some damage to nerve fibres may have occurred without the VF's advancing to another stage. However, the rough staging system was advantageous also because of the retrospective nature of the study, in which standardisation of the VF examination was impossible. In the other studies, the grading system was used merely to describe current glaucoma status.

Study I had 21 patients without progression that did not attend the additional follow-up. Comparison of these 21 patients with all the others showed that these patients were older (Table 7). Thus, their inclusion have diminished the effect of age on the progression, but age was still a significant risk factor in the survival analysis. When analysis was performed with only 118 eyes, these 21 eyes excluded, the result of the Cox regression model remained the same.

Ocular blood flow was examined with SLDF and blue-field entoptoscopy. SLDF offers a method for non-invasively measuring actual blood flow, instead of blood flow-related parameters such as velocity (Pillunat 1999). However, the HRF may have some restrictions because of variability of measurements. Reliability coefficients for repeated volume, flow, and velocity measurements have been reported to be between 0.81 and 0.85 (Michelson & Schmauss 1995, Michelson et al. 1996b). However, others have questioned the reproducibility and variability of this method (Kagemann et al. 1998, Jonescu-Cuypers et al. 1999). One problem also in this study is that small movements of the measurement square may lead to considerable variation in flow values. Recently, a new method has been developed for calculation of blood flow which includes all pixels of the perfusion image, and this has improved the coefficient of reliability (Michelson et al. 1998b). Such software, however, was unavailable for this study. The rather small R-squares in the multiple regression analyses in this study may be explained by high variation in blood flow measurements, or by the fact that other factors not examined in the present study also may affect ocular blood flow.

It is not known exactly from what layers HRF measures blood flow. Blood flow to the most superficial nerve fibre layer on the rim is mainly supplied by recurrent retinal arterioles branching from the retinal arteries (Cioffi & Van Buskirk 1996). It is possible therefore that values obtained in this study from the rim area may be affected not only by flow from the short posterior ciliary arteries, but also by flow from the recurrent retinal arterioles. Blood flow to the prelaminar and laminar regions of the ONH is supplied mainly by the short posterior ciliary arteries (Cioffi & Van Buskirk 1996). Flow in the laminar area was

measured while focusing on the lamina, and the square used for measurement was placed in the middle of the excavation. It can therefore be argued that the flow values obtained in the laminar area should mainly reflect the flow supplied by the short posterior ciliary arteries. It is, however, unknown whether the penetration depth of the HRF is appropriate for study of the flow of these arteries. Petrig et al. (1999) studied ONH blood flow with a laser Doppler flowmetry technique based on principles similar to HRF, but which penetrates to a depth of 1000 µm (Koelle et al. 1993) instead of 300 µm in HRF (Michelson et al. 1996). When they occluded experimentally the central retinal artery or posterior ciliary arteries or both and then measured ONH blood flow, they concluded that this technique was most sensitive for blood flow measurements of the superficial layer of the ONH, but less sensitive for blood flow in the deeper ONH layers; the latter they considered the area of interest in glaucoma. Thus it may be questionable whether HRF with even less penetration depth is actually affected by flow from the short posterior ciliary arteries. In the peripapillary retina, the HRF measurements may reflect not only the retinal capillary bed, but also more deeper layers, i.e., the choriocapillaris (Holló et al. 1997a).

The HRF measurements are affected by the image brightness, so that a brighter image or image area results in lower flow values (Tsang et al. 1999, Kagemann et al. 2001). This is probably due to the HRF noise-correction algorithm, which automatically corrects (i.e., reduces) the flow values more in bright images or areas (Tsang et al. 1999). Another problem is that the acquisition of an HRF image takes two seconds, thus containing flow values during one or two heartbeats. The difference between systolic and diastolic flow measured with HRF may be up to 50% (Michelson et al. 1998b). Differences in image brightness, and the pulsatility of flow may both cause bias. In the present study, however, there should be no systematic error; the images acquired from glaucomatous eyes would tend to be systematically darker or brighter than the images from fellow eyes, or the images would be measured during a particular pulse phase. The peripapillary retinal and rim flow was measured from the same images focused at the peripapillary retina. This causes the rim to appear darker, because it is positioned posterior to the focal plane, and subsequently leads to excessively high flow-values for the rim. To some extent, this effect was reduced by excluding the nasal retina from the image, which seems to result in more accurate brightness and flow values for the rim, even though the image is focused upon the peripapillary retina (Jonescu-Cuypers et al. 2001).

Blue-field entoptoscopy measures leucocyte velocity in the macular vasculature (Riva & Petrig 1980, Sinclair et al. 1989). The patient adjusts two dials until the velocity and density of computer-simulated particles displayed on a monitor matches those of her own entoptically observed leucocytes. This system requires good cooperation from the patient

and is prone to a subjective component. Therefore, only those examinations with coefficients of variation less than 30% were accepted for analysis. Because poor visual acuity may also affect results, asymmetry in visual acuity was limited to two Snellen lines, and no eyes had scotomas within the central 10 degrees.

## 7.2 RISK FACTORS FOR PROGRESSION (I)

Irrespective of the pathogenesis of glaucoma, the main risk factor to be treated is IOP. Elevated IOP is the most important risk factor for glaucoma, and relative risk for POAG has been shown to be increased even at an IOP level of 16 mmHg (Sommer et al. 1991b). In ExG and POAG, Popovic & Sjöstrand (1999) reported a mean IOP of 16 mmHg after trabeculectomy in eyes with both progressive and non-progressive VFs, and reported that IOP level was unrelated to rate of VF progression. This was considered an indicator that factors other than IOP affected progression. In the present study, survival analysis with the multivariate Cox proportional hazards model was performed to study factors affecting progression and it showed that the older the patient, the higher the IOP; and the more advanced the glaucomatous damage, the more probable was the progression of glaucoma to another stage. A history of trabeculectomy was associated with decreased relative risk for progression.

The effect of IOP on progression was clear. Four different variables reflected IOP level: weighted mean IOP, maximum IOP, mean IOP, and IOP range. In clinical studies, a mean IOP is often calculated to describe IOP levels during the time of follow-up. Especially in retrospective follow-up studies, it can be difficult to standardise the length of follow-up visits and differing numbers of available IOP readings between these visits. Therefore, the weighted mean IOP was calculated to emphasize IOP levels that had been measured during longer periods of time, with less weight for IOP levels during shorter periods. This process was considered to better describe IOP level than a mere calculation of the mean of all IOP values. According to survival analysis, a one-mmHg increase in weighted mean IOP increased relative risk for progression by 7.6%. Maximum IOP, mean IOP, and IOP range did not reach statistical significance in the analysis.

ExG responds well to trabeculectomy (Jerndal & Kriisa 1974, Raitta & Vesti 1991), and trabeculectomy was found in this study to be associated with decreased risk for progression. Based on the Cox proportional hazards model, estimated survival curves were

calculated and plotted (Figure 1). Eyes that had been operated on survived progression longer than those not operated on. At about 13 years there occurred a drop in both survival curves, and the difference between groups seemed to diminish; only a few patients, however, had this long a follow-up, and so the estimation may be biased.

Undoubtedly, any beneficial effect of trabeculectomy on glaucoma is mediated through a reduced IOP. However, because history of trabeculectomy reached statistical significance in multivariate analysis even though adjusted for mean weighted IOP, some effect from trabeculectomy must exist separate from weighted mean IOP. One explanation is that after trabeculectomy, fluctuation in IOP is smaller than in eyes not operated on (Migdal & Hitchings 1986, Bergeå et al. 1999). A (weighted) mean IOP would remain basically unaffected in an eye with both high and low IOPs at various times. Thus, a positive effect of trabeculectomy other than on the weighted mean IOP may be mediated through decreased variation in IOP compared to that in eyes not surgically treated. It has been reported that smaller IOP variation is associated with better VF prognosis among patients with ExG (Bergeå et al. 1999) and POAG (Stewart et al. 1993, Bergeå et al. 1999, Asrani et al. 2000). Another explanation for the beneficial effect of trabeculectomy may be an effect mediated through patient compliance. After a successful operation, no glaucoma medication is needed. In patients using topical medication, IOP level is affected by patient compliance.

Stage of glaucoma and age of patient were also associated with progression. In clinical practice it is generally agreed that eyes with far advanced glaucoma are more susceptible to further VF damage than eyes with early glaucoma (Wilson et al. 1982, Anderson 1989, Shirakashi et al. 1993, Stewart et al. 1993). This belief is supported by the present findings, since eyes with advanced VF defects were associated with increased risk for progression. However, this result may have been biased by the glaucoma grading system used, if the steps between stages are considered ‘shorter’ in the more advanced stages. The risk for progression increased also with increasing age, which has also been shown previously (Kass et al. 1980, Armaly et al. 1980, Quigley et al. 1994, Georgopoulos et al. 1997). No conclusions as to the mechanism by which stage of glaucoma or patient age affect the progression can be drawn, but since IOP is the only treatable risk factor, this study supports lower target pressures in advanced glaucoma and in older patients.

As shown here, total risk for progression is a combination of several risk factors. In clinical practice, it can be difficult to estimate the risk for progression of individual patients and to estimate target pressure. In this study, a risk score was calculated based on the four covariates that reached statistical significance in the Cox proportional hazards model, and

patients were divided into groups with low, medium, and high risk for progression. A risk score for any patient could be calculated with the same formula in order to determine risk group. This may prove to be a useful tool for a clinician deciding on whether IOP needs to be further reduced and whether or not to perform trabeculectomy. That this study was performed on a selected sample limits the use of the regression coefficients. A similar formula from a larger and different set of patients should be obtained in a future study. Moreover, risk factors other than those included in this study may be included.

## 7.3 ONH MORPHOMETRY (II, III, IV)

Evaluation of the ONH is an essential part of glaucoma diagnosis and follow-up of the disease. SLO imaging with the HRT allows acquisition of reproducible and reliable images of the ONH (Mikelberg et al. 1993, Lusky et al. 1993a, Rohrschneider et al. 1994) and in the present study offered a means for objective and quantitative evaluation of the ONH topography. The parameters calculated by the software have been shown to be correlated with VF indices in glaucoma patients (Brigatti & Caprioli 1995, Iester et al. 1997b,e, Eid et al. 1997b, Tole et al. 1998). There has thus been great interest in studying the capability of the HRT to differentiate between healthy eyes and eyes with OHT and glaucoma (Mikelberg et al. 1995, Uchida et al. 1996, Zangwill et al. 1996, Iester et al. 1997a,c,d, Hatch et al. 1997, Wollstein et al. 1998, Bathija et al. 1998, Mardin et al. 1999). Iester et al. (1997d) performed receiver operating characteristic (ROC) analysis of the HRT parameters of 97 glaucoma patients with VF defects and 129 healthy, non-glaucomatous patients. At best, a sensitivity of 73% and specificity of 73% to differentiate the groups was found for cup shape measure, and at worst, a sensitivity of 53% and specificity of 60% for height variation contour. With similar statistics, Uchida et al. (1996) reported their highest sensitivity and specificity values as being for cup shape measure (83% and 86%, respectively), to differentiate between glaucoma (with VF damage) and controls. Somewhat higher sensitivity and specificity have been achieved with combinations of several parameters (Iester et al. 1997c, Mardin et al. 1999).

In the present study (III), disc area showed an association with most of the HRT parameters. Interestingly, rim volume, mean cup depth, maximum cup depth, and RNFL cross-section area appeared to be unaffected by disc area (III), a fact supported by the findings of others concerning HRT in healthy eyes (Mardin & Horn 1998, Wollstein et al.

1998). The results of the present study support the importance of adjusting for disc area when comparing HRT values between differing groups of patients. This is also shown by Wollstein et al. (1998), studying by linear regression analysis the relationship between disc area and HRT parameters in healthy eyes. They used the 99% prediction interval of the linear regression to define the normal range of HRT parameters and used it to differentiate between groups with glaucoma (early VF defect) and normals; when controlling for disc area, a sensitivity of 84% and specificity of 96% were found for the parameter rim area.

In the present study (IV) with 50 patients with unilateral ExOHT or ExG, all HRT parameters except maximum cup depth differed significantly between eyes (Table 5). Furthermore, mean optic disc area was greater in eyes with ExOHT or ExG than in the fellow eyes. The reason for this is unknown. Mardin & Horn (1998) and Wollstein et al. (1998), in their studies with HRT, reported no statistically significant differences in disc area between glaucomatous eyes and healthy eyes, but comparisons were not made between eyes of the same patient, as was done in this study. Some evidence exists that glaucomatous eyes have larger optic discs than non-glaucomatous eyes (Healey & Mitchell 1999), and that eyes with larger discs may be more vulnerable to IOP (Tuulonen & Airaksinen 1992, Burk et al. 1992, Tomita et al. 1994). However, the discs of both the present study and fellow eyes (mean ± SD, 1.92 ± 0.41 $mm^2$ and 1.83 ± 0.37 $mm^2$ respectively) seemed to be small or medium sized rather than large, when compared to the discs measured with HRT in glaucomatous and healthy eyes by Mardin & Horn (1998) (2.6 ± 0.7 $mm^2$ and 2.6 ± 0.87 $mm^2$ respectively) and Wollstein et al. (1998) (1.89 ± 0.34 $mm^2$ and 1.98 ± 0.35 $mm^2$). This is in accord with the findings of Jonas & Papastathopoulos (1997), who reported smaller discs in eyes with ExG than in eyes with POAG, and discs smaller in eyes with ExS than in healthy control eyes. A study of patients with unilateral ExS (Puska & Raitta 1992) found no difference in disc area between eyes. However, their result may not be comparable to the result of the present study, because eyes corresponding to the study eyes of this study were excluded from their study. Bias is possible due to the higher probability that a large disc will be classified as glaucoma (Heijl & Mölder 1993).

Because of interindividual normal variation in ONH topography and overlap of the HRT parameters between normal and glaucomatous eyes, no cut-off values for normal ONH parameters have been established. The most advantageous application of SLO would be its use in follow-up of patients to aid in detecting change or progression in ONH topography. In the present study (III), change in VF index MD was examined for any subsequent associations with change in HRT parameters. Of all HRT parameters, only change in cup shape measure in a positive direction, indicating ‘more glaucomatous’, was associated with change in MD to higher values, and vice versa. Change in MD may not be the ideal

measure for progression, since MD has been shown to be sensitive to cataract formation (Guthauser & Flammer 1988, Yao & Flammer 1993), to long-term fluctuation (Heijl et al. 1987), and to other physiological factors. No actual cut-off criteria for progression based on a defined change MD was used. Not only was an association between HRT parameters and MD concerning 'progression' studied, but also subsequent 'improvement' in HRT parameters and MD. This may be an advantage when only small overall changes exist in MD, as in the present study. These results suggest that the cup shape measure may be a sensitive indicator for progression. Similarly, cup shape measure has been reported to be one of the best parameters to differentiate among healthy eyes, eyes with OHT, and eyes with glaucoma (Uchida et al. 1996, Hatch et al. 1997, Iester et al. 1997d, Bathija et al. 1998, Vihanninjoki et al. 2000), and to show correlations with early glaucomatous VF loss (Mikelberg et al. 1995).

When HRT is used in sequential measurements to evaluate progression of glaucoma, any effect of change in IOP should be accounted for. Because reduction in IOP can result in reversal of the ONH topographic parameters (II,III), i.e., changes in a 'less glaucomatous' direction, a subsequent rise in IOP may lead to changes in the ONH topography in a 'more glaucomatous' direction without a true loss of nerve fibres. In experimental studies, an IOP increase has been reported to cause backward bowing of the lamina cribrosa (Levy et al. 1981, Levy & Crapps 1984).

Apart from the present study, few reports exist on the use of HRT in follow-up. Rabinowitz et al. (1995) followed 44 glaucomatous eyes with cup/disc ratios of $\geq 0.85$: 12 eyes experienced an increase in IOP and/or clinical progression of VF defects. In these 12, statistically significant changes in cup/disc area ratio, cup area, and rim area were found, despite the fact that biomicroscopical assessment of the ONH was judged to be unchanged. Recently, Kamal et al. (1999) reported on changes in HRT parameters in 13 OHT patients who subsequently developed glaucoma. From the global HRT parameters, they found significant changes in cup area, cup/disc area ratio, and rim area, but not in cup shape measure (nor in cup volume or rim volume). However, they did not evaluate change in IOP during the follow-up period. In another prospective study on eyes with OHT (Kamal et al. 2000), they identified eyes that clinically remained OHT but showed a change in HRT parameters above the level expected for normal variability. It remains to be seen whether these eyes later also convert to glaucoma.

Reversal of optic disc cupping after reduction in IOP has been documented in a number of studies (Quigley 1982, Pederson & Herschler 1982, Shin et al. 1989, Katz et al. 1989, Tsai et al. 1991, Shirakashi et al. 1992, Sogano et al. 1993, Chavis et al. 1994, Irak et al. 1996,

Park & Hong 1998, Topouzis et al. 1999, Lesk et al. 1999). The most likely physiological response seems to be reduced backward bowing of the lamina cribrosa (Lusky et al. 1993b, Sogano et al. 1993, Pederson & Herschler 1982). In the present study, decrease in IOP was associated with reversal changes in cup area (III), cup/disc area ratio (II,III), rim area (III), cup volume (II,III), rim volume (III), mean cup depth (II,III), and maximum cup depth (II,III). HRT parameters such as cup volume and mean and maximum cup depth can easily be considered to be directly related to the backward bowing of the lamina. However, reversal in cup area, cup/disc area ratio, rim area, and rim volume after IOP reduction may indicate that, during periods of elevated IOP, the rim is pulled backward together with the lamina cribrosa.

Interestingly, cup shape measure seemed to be a sensitive indicator for progression, but was insensitive to change in IOP (III). It would be an advantage of the cup shape measure if it proves to be sensitive to progression, i.e., true loss of nerve fibers, but insensitive to change in IOP. Cup shape measure describes the overall shape of the ONH cupping. It represents the skewness of the frequency distribution of cup depth values. In normal eyes with their flat-edged cups and with small depth values most frequent, the frequency distribution is skewed to the left, and cup shape measure gets a negative value. In glaucomatous eyes with their steep cups, and with large depth values most frequent, the frequency distribution is skewed to the right, and cup shape measure gets a positive value. The fact that cup shape measure was not associated with IOP reduction indicates that the skewness of the frequency distribution remained unchanged. However, the kurtosis of the frequency distribution must have changed, because reversal of ONH cupping did occur, as shown by reversal of other HRT parameters. In other words, after IOP reduction, the number of small depth values in relation to high depth values remained unchanged, but the number of intermediate values in relation to small and high values increased.

At least three other studies have recently documented reversal changes shown by the HRT after reduction in IOP (Table 16) (Irak et al. 1996, Topouzis et al. 1999, Lesk et al. 1999). The findings of the present study accord best with those of Lesk et al. (1999) who, when correlating changes in HRT with percentage changes in IOP, found, 6 months after glaucoma surgery, reversible changes in the same parameters that we did. Irak et al. (1996) found that percentage changes in IOP correlated with changes in cup shape measure and RNFL cross-section area, but not with changes in maximum cup depth. No correlation existed between mean change in IOP and cup volume or rim volume. Topouzis et al. (1999) compared HRT parameters before and after trabeculectomy, but were unable to correlate these changes with IOP. Two weeks after treatment they reported reversal changes in some HRT parameters, but after 4 months only in cup shape measure, and at 8

***Table 16.*** *Reversal changes in HRT parameters in this study and three others*

| | **HRT parameter:** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **CA** | **C/D** | **RA** | **HVC** | **CV** | **RV** | **MnCD** | **MxCD** | **CSM** | **RNFL1** | **RNFL2** | **Comments** |
| Lesk et al, 1999 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | No | correlation with percent change in IOP, 6 months |
| Irak et al, 1996 | Yes (Yes) | Yes (Yes) | Yes (Yes) | - - | Yes (No) | Yes (No) | - - | No No | Yes (Yes) | - - | Yes (Yes) | correlation with percent change, and (mean change) in IOP, 4.5 months |
| Topouzis et al, 1999 | No (No) [No] | No (No) [No] | No (No) [No] | Yes (No) [No] | Yes (No) [No] | No (No) [No] | yes (no) [no] | No (No) [No] | Yes (Yes) [No] | no (no) [no] | No (No) [No] | Pairwise comparison before and after surgery at 2weeks, (4 months), and [8 months] |
| Study II | - - | No Yes | - - | - - | Yes Yes | - - | Yes No | - - | - - | - - | - - | Pairwise comparison before and after surgery at 4 months and (1 year) |
| Study III | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | No | Association with change in IOP, 6 months |

Yes = significant correlation, association, or difference found
No = no significant correlation, association, or difference found
- = did not report
CA = cup area, C/D = cup/disc area ratio, RA = rim area, HVC = Height variation contour, CV = Cup volume, RV = Rim volume, MnCD = Mean cup depth,
MxCD = Maximum cup depth, CSM = Cup shape measure, RNFL1 = Mean RNFL thickness, RNFL2 = RNFL cross section area,
HRT = Heidelberg retina tomograph, IOP = intraocular pressure, RNFL = retinal nerve fibre layer

months in no parameters, although mean IOP was still significantly reduced compared to pre-operative readings.

Stage of glaucoma was shown to be associated with reversibility of the ONH. In Study III, stage of glaucoma was included in the analyses and was found to be associated with reversibility of cup volume and mean cup depth; reversal in these parameters was greater the more advanced was the glaucoma. In the study with advanced cases (II), reversal changes could still be detected one year after trabeculectomy, provided that the post-operative IOP was kept low enough. The results of the present study are contradictive to those of other studies, in which it has been claimed that with increasing glaucomatous damage, the reversibility of optic disc cupping decreases (Pederson & Herschler 1982, Coleman et al. 1991, Shirakashi et al. 1992, Topouzis et al. 1999). Differences may be methodological and due to the subjects chosen. Topouzis et al. (1999) suggested in their study that lack of reversal changes in the HRT parameters 8 months after trabeculectomy may have been due to the advanced glaucoma of their patients. Of their 25 patients, 10 had POAG, 8 NTG, but only 3 had ExG. The mean (± SD) pre-operative IOP of their patients was 19.3 ± 6.4 mmHg compared to 28.2 ± 9.0 mmHg in Study III.

The number of patients with cup reversal in the study by Pederson & Herschler (1982) was small. They reviewed sequential photographs of 259 patients (and an unknown number of patients in their clinical practices), and found cup reversal in only six eyes, of whom none were considered as advanced glaucoma. The studies of Coleman et al. (1991) and Shirakashi et al. (1992) were done on a limited number of monkey eyes (seven and five eyes, respectively). Further, Coleman et al. (1991) measured acute changes within 15 minutes after IOP reduction, whereas in the present study, changes were measured 3 months to one year after IOP reduction. Zeimer & Ogura (1989) also studied acute changes but not the reversibility of the ONH topography, rather the acute retrodisplacement of the ONH surface after IOP increase in post-mortem human eyes. In 15 eyes with VF data available, they found that the retrodisplacement decreased as the VF worsened, but at only borderline significance ($P < 0.2$). Results of histological studies have reported in ExG and POAG a marked and widespread elastosis (aberrant proliferation and degeneration of elastic elements) of connective tissue in the lamina cribrosa, and shows that this elastosis is even more pronounced in ExG than in POAG (Netland et al. 1995, Pena et al. 1998). Elastosis would lead to increased stiffness of the lamina cribrosa.

Age was also associated with reversibility of cup volume, mean cup depth, and maximum cup depth. Older patients had greater reversal changes than did younger ones, in accord with the findings of Lesk et al. (1999). However, their findings concerned only a subgroup of patients with IOP reduction of 40% or more.

It can be hypothesised (Shin et al. 1989), that reduced backward bowing of the lamina cribrosa reduces any mechanical stress upon nerve fibres in this region, subsequently improving axoplasmic transport in the neurons. It remains to be shown whether reversal of the ONH topography is related to a slower rate of progression of glaucoma. There exist, however, reports on improved VF indices of eyes in which reversal of disc cupping has occurred after IOP reduction (Katz et al. 1989, Tsai et al. 1991).

## 7.4 OCULAR BLOOD FLOW IN ExG (IV, V)

The role of ocular blood flow abnormalities and other vascular risk factors for glaucoma has attracted increasing interest in the past few years, with recent reviews of ocular blood flow in glaucoma and various techniques to measure it (Flammer & Orgül 1998, Pillunat 1999, Harris et al. 1999, Anderson 1999). In the present study, ocular blood flow was measured with scanning laser Doppler flowmetry (the HRF) (IV) and with blue-field entoptoscopy (V). In ExG, changes in blood flow in the lamina and rim area were found with the HRF (IV) and in the macular flow with blue-field entoptoscopy (V).

Flow in the rim area in glaucomatous eyes was detected to be higher than in the non-glaucomatous fellow eyes (IV). Similarly, flow in the laminar area in glaucomatous eyes was higher than in the fellow eyes, but only at borderline significance (IV). However, the more advanced the glaucomatous damage, the more reduced was flow both in the laminar area and in the rim area. This may seem contradictory, but may be explained by autoregulation of the ONH flow, with upgrading of flow early in the course of glaucoma, and decrease in flow later in the course, because of breakdown of autoregulation (Pillunat et al. 1985, Robert et al. 1989, Tielsch et al. 1995). In this study (IV), a large proportion of the patients had ExOHT (20%) or early glaucoma with glaucomatous ONH changes but a normal VF (22%).

Previous studies with the HRF have concentrated on healthy eyes and eyes with POAG, NTG, and OHT, with no reports on eyes with ExG. In patients with POAG, reduced flow in the laminar (Nicolela et al. 1996b, Kerr et al. 1998, Findl et al. 2000) and rim area (Michelson et al. 1996a, Kerr et al. 1998, Michelson et al. 1998a, Findl et al. 2000) have been reported compared to flow in healthy eyes and in eyes with OHT. On the other hand, some reports have shown no difference in rim area flow between healthy eyes and eyes with POAG and NTG (Nicolela et al. 1996b, Holló et al. 1997b). Michelson et al. (1996a) in comparing healthy eyes and eyes with POAG, found a significant correlation between reduced flow in the rim area and cup/disc ratio; but not, as in the present study, between reduced flow and MD. Findl et al. (2000) found a significant correlation between reduced flow in the lamina and MD and between reduced flow in the rim and MD. Reduced ONH blood flow in POAG has been reported also with types of laser Doppler techniques other than the HRF (Hamard et al. 1994, Grunwald et al. 1999).

In glaucoma, damage to ganglion-cell axons has been found at the level of the lamina cribrosa (Gaasterland et al. 1978, Quigley et al. 1981). Thus, an association between glaucoma and deficiency in blood flow in this area can be expected, but one may question the relevance of measuring retinal, choroidal, or retrobulbar flow. There are, however, several studies in which parameters of blood flow have been detected to be altered in the peripapillary retina (Nicolela et al. 1996b, Michelson et al. 1996a, Michelson et al. 1998a, Chung et al. 1999), macula (Sponsel et al. 1990, Sponsel et al. 1997), choroid (Trew & Smith 1991, Fontana et al. 1998), and retrobulbar arteries (Rojanapongpun et al. 1993, Butt et al. 1995, Kaiser et al. 1997, Butt et al. 1997, Yamazaki & Drance 1997) in patients with POAG and NTG when compared to parameters of healthy eyes and eyes with OHT.

In the present study (IV), no difference in peripapillary retinal flow appeared between eyes with ExG and their non-glaucomatous fellow eyes, nor was there any association between peripapillary flow and amount of glaucomatous VF or ONH damage (IV). Controversially, some studies have reported decreased flow in the peripapillary retina in eyes with POAG, compared to flow in healthy eyes (Nicolela et al. 1996b, Michelson et al. 1996a, Michelson et al. 1998a). However, Kerr et al. (1998) have reported increased minimum velocity in the temporal retina of eyes with POAG compared to velocity in eyes with OHT, and Holló et al. (1997a,b) found ‘high’ flow values to be more frequent in glaucomatous eyes than in healthy ones (Holló et al. 1997a). In the present study, mean macular leucocyte velocity was statistically significantly lower in eyes with ExG than in their non-glaucomatous non-exfoliative fellow eyes (V). In six patients, leucocyte velocity was lower in the glaucomatous eye, and in two patients lower in the fellow eye. However, differences in leucocyte velocity between the eyes were greater when the glaucomatous eye had the lower

flow (26-50%), compared to the two cases in which the leucocyte velocity was lower in the healthy eye (15% and 18%). Further, only glaucomatous eyes showed a negative correlation (with borderline significance) between leucocyte velocity and MD, and between leucocyte velocity and LV (V). When leucocyte velocity in all four groups of eyes is compared, it seems that only the non-glaucomatous eyes in unilateral ExG differed from the others, having higher (mean ± SD, 0.89 ± 0.34 mm/s) leucocyte velocity than the glaucomatous eye (0.70 ± 0.25 mm/s), and higher than the exfoliative and non-exfoliative eyes in unilateral ExS (0.72 ± 0.15 mm/s and 0.70 ± 0.21 mm/s respectively). However, comparison between these separate groups of patients may be inappropriate, because of differences in systemic diseases and medications, and differences in how patients perform the subjective measurement. This was the reason for the choice of patients with unilateral ExG and ExS. The results of the present study are in accord with the results of Sponsel et al. (1990, 1997) who also studied macular circulation with blue-field entoptoscopy, but in patients with POAG. Similarly to the present study with ExG (V), they found a correlation between macular leucocyte velocity and VF indices; reduced leucocyte velocity was associated with increased VF damage.

Overall, in only a few works has ocular blood flow been measured in eyes with ExS or ExG. Sibour et al. (1997) studied choroidal blood flow with a pulsatile ocular blood flow (POBF) system in nine patients with unilateral ExS. Their mean POBF was 14% lower in the exfoliative eyes than in the non-exfoliative fellow eyes. Repo et al. (1995) performed color Doppler ultrasound measurements of the ophthalmic artery in 32 healthy individuals (64 eyes) and in 46 patients (92 eyes) who had suffered TIA. They found a high frequency of ExS among patients who had suffered TIA and had positive iris transilluminance. Those patients also had higher resistivity indices of the ophthalmic arteries than did healthy subjects without iris transilluminance. A vessel diameter can be considered only an indirect measurement of blood flow; however, the diameter of the retinal arterioles at the disk border has been reported to be smaller in POAG and ExG than in normal eyes (Jonas & Papastathopoulos 1997).

It remains to be determined whether in glaucoma reduced ocular blood flow is a cause or a consequence. Another issue in ExG is whether similar pathophysiology is behind the reduced flow, as in other types of OAG, or whether reduced flow is in some way connected with the presence of exfoliation material; in the iris, the vasculopathy associated with ExS (Ringvold 1970, Ringvold & Davanger 1981, Konstas et al. 1993b, Asano et al. 1995, Kivelä et al. 1997) has also been associated with anterior segment ischaemia (Vannas 1969, Helbig et al. 1994). In 11 eyes with unilateral ExS, no difference was found in macular leucocyte velocity between exfoliative eyes and non-exfoliative fellow eyes (V). Of the

fellow eyes in Study IV, 36 were clinically exfoliative and 14 clinically non-exfoliative. The diagnoses of the fellow eyes (exfoliative or non-exfoliative) were included in the multivariate analyses of difference in flow between glaucomatous and non-glaucomatous eyes, but they seemed to have no association with lamina, rim, or peripapillary flow. Therefore, this association between glaucomatous damage and blood flow (IV, V) can be considered to be associated with the glaucomatous defect and not with the presence of ExS. However, this does not exclude the possible effect of ExS per se on ocular blood flow. It is possible that also in the early course of ExS vasculopathy has some effect on ocular blood flow, but later, when the vasculopathy is more severe or has persisted longer, it begins to cause damage to the nerve fibres, damage which can be detected and diagnosed as glaucoma. Further, a difference in flow due to exfoliation material may be difficult to detect in a study comparing exfoliative eyes and non-exfoliative fellow eyes, because the clinically non-exfoliative eyes may also be exfoliative if examined electron microscopically or immunohistochemically (Schlötzer-Schrehardt et al. 1991, Kivelä et al. 1997). Perhaps comparison would be more appropriate between patients with ExS and patients without ExS in either eye.

The effect of topical β-blocking agents on ocular blood flow is an important issue. In Study IV, topical treatment with timolol was associated with reduced blood flow in the lamina and rim area. This was apparent both in analyses of differences in flow between glaucomatous eyes and the non-glaucomatous fellow eyes, and in analyses of glaucomatous eyes only. Between peripapillary flow and treatment with timolol, no association appeared. Macular leucocyte velocity was statistically significantly lower in glaucomatous eyes than in their fellow eyes (V). All 10 glaucomatous eyes were treated with timolol, and therefore any effect of timolol on the results cannot be excluded. However, treatment with timolol does not explain the correlation (though of borderline significance) between leucocyte velocity and VF indices. Thus, treatment with timolol seems to be associated with reduced flow in the ONH, but not in the peripapillary retina or macula. This issue has been studied extensively. Several studies report timolol treatment to be associated with decreased ocular blood flow values (Richard & Weber 1987, Van Buskirk et al. 1990, Langham 1990, Yoshida et al. 1991, Boles Carenini et al. 1994, Nicolela et al. 1996a, Schmetterer et al. 1997), but opposite findings also exist (Jay et al. 1984, Grunwald 1986, Baxter et al. 1992), and reports of no effect at all (Green & Hatchett 1987, Harris et al. 1995, Morsman et al. 1995, Wang et al. 1997, Holló et al. 1997b, Michelson et al. 1998a).

Timolol is a non-specific β-adrenergic blocker with effects both on $\beta_1$ and on $\beta_2$ receptors. In the eye, β-adrenoreceptors of mainly the $\beta_2$-subtype have been demonstrated in the anterior part of the optic nerve and ONH (Dawidek & Robinson 1993), choroid (Grajewski

et al. 1991), retinal blood vessels (Denis et al. 1990), and ciliary body (Wax & Molinoff 1987). No conclusion can be drawn as to whether reduced blood flow in the lamina and rim area is mediated through blockade of the $\beta_2$ receptors in the ONH (Dawidek & Robinson 1993), but this is at least possible. Diffusion of topically applied timolol to the posterior pole of the eye is uncertain, but after topical administration of radio-labeled timolol to rabbit eyes, it has been measured in the choroid, retina, and vitreous (Schmitt et al. 1980). Topically applied timolol has also been shown to cause vasoconstriction of retinal vessels (Martin & Rabineau 1989) and of the arteries that supply the ciliary processes (Van Buskirk et al. 1990). The ocular $\beta_2$ receptors can also be reached through the systemic circulation. Topically applied timolol can be absorbed into the systemic circulation (Schmitt et al. 1980, Vuori et al. 1993, Uusitalo et al. 1999). Drug concentrations of clinical significance in the contralateral eye may be reached after topically applied timolol (Saari et al. 1993), as shown by lowering of IOP also in the contralateral eye (Radius et al. 1978). A crossover effect of timolol on the ocular blood flow may also occur, but this would have diminished the difference in flow that was found between the eyes (IV). In the examination of study eyes only, treatment with a systemic β-blocker may also have confounded the results. Of 50 patients, 8 were receiving a systemic β-blocker for some systemic condition (IV), but no statistically significant effect of this appeared in the multivariate analyses.

In short, exfoliation glaucoma often shows an aggressive clinical course. Good control of intraocular pressure is required, especially in elderly patients and patients with more advanced disease. New imaging methods, such as scanning laser ophthalmoscopy, may offer tools for more sensitive evalution of the optic nerve head and its progression. Even though considered a secondary glaucoma, it seems that exfoliation glaucoma is a matter not only of increased intraocular pressure, but also of altered ocular blood flow.

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