EFFET DU GLAUCOME ET DES FACTEURS DE RISQUE DE GLAUCOME
SUR L’HEMODYNAMIQUE CHOROIDIENNE

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La Faculté de médecine, sur le préavis de Monsieur Constantin J. POURNARAS, professeur associé au Département des Neurosciences Cliniques et Dermatologie, autorise l'impression de la présente thèse, sans prétendre par là émettre d'opinion sur les propositions qui y sont énoncées.

Genève, le 26 avril 2007

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Jean-Louis Carpentier
Doyen

N.B. - La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives à la présentation des thèses de doctorat à l'Université de Genève".
Dans la présente étude, nous avons évalué quantitativement l’hémodynamique de la circulation choroïdienne subfovéolaire chez des patients atteints de glaucome à angle ouvert et des patients présentant une hypertension oculaire. Nous avons étudié l'effet des facteurs de risque du glaucome sur la circulation choroïdienne subfovéale en vue de déterminer le rôle de cette circulation dans la pathogénie de cette maladie. De plus, nous avons établi les relations entre les paramètres hémodynamiques et un nombre de paramètres physiologiques tels que l'âge, la pression intraoculaire et la pression de perfusion oculaire.

Les résultats de cette étude indiquent clairement que des altérations de l'hémodynamique choroïdienne subfovéale sont présentes chez les patients atteints de glaucome et d'hypertension oculaire. Ils permettent également de conclure que la circulation choroïdienne est déjà altérée chez les patients présentant des facteurs de risque de glaucome tels que le diabète, l'hypertension systémique et la myopie.
The work on this thesis has been an inspiring, often exciting, sometimes challenging, but always interesting experience. It has been made possible by many other people, who have supported me.

First of all, I would like to thank cardinaly and to express deepest sense of gratitude to Prof. Dr. Mohammed Emarah, Professor Emeritus of Ophthalmology, Faculty of Medicine, Mansoura University, for suggesting this work, his valuable and fruitful guidance, continuous encouragement and keen supervision. Without his help, this work would not be possible.

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Waleed Ali Abu Samra
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Résumé</td>
<td>i</td>
</tr>
<tr>
<td>Introduction <em>(en français)</em></td>
<td>1</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>4</td>
</tr>
<tr>
<td>2. Aim of the work</td>
<td>7</td>
</tr>
<tr>
<td>3. Review of literature</td>
<td>8</td>
</tr>
<tr>
<td>3.1. Definition of POAG</td>
<td>8</td>
</tr>
<tr>
<td>3.2. Prevalence of Glaucoma Worldwide</td>
<td>8</td>
</tr>
<tr>
<td>3.3. Pathophysiology</td>
<td>9</td>
</tr>
<tr>
<td>3.3.1. IOP elevation</td>
<td>9</td>
</tr>
<tr>
<td>3.3.2. Progressive optic nerve cupping and atrophy</td>
<td>10</td>
</tr>
<tr>
<td>3.4. Glaucoma Risk Factors</td>
<td>12</td>
</tr>
<tr>
<td>3.4.1. Intraocular pressure (IOP)</td>
<td>13</td>
</tr>
<tr>
<td>3.4.2. Age</td>
<td>14</td>
</tr>
<tr>
<td>3.4.3. Myopia</td>
<td>15</td>
</tr>
<tr>
<td>3.4.4. Diabetes</td>
<td>16</td>
</tr>
<tr>
<td>3.4.5. Systemic blood pressure</td>
<td>17</td>
</tr>
<tr>
<td>3.4.6. The appearance of the optic disc</td>
<td>18</td>
</tr>
<tr>
<td>3.5. Choroidal hemodynamics</td>
<td>19</td>
</tr>
<tr>
<td>3.5.1. General Vasculature of the orbit and choroid</td>
<td>19</td>
</tr>
<tr>
<td>3.5.2. Regulation of choroidal blood flow</td>
<td>21</td>
</tr>
<tr>
<td>3.5.3. Choroidal blood flow in glaucoma</td>
<td>24</td>
</tr>
<tr>
<td>3.6. Laser Doppler Flowmetry (LDF)</td>
<td>25</td>
</tr>
<tr>
<td>3.6.1. History</td>
<td>25</td>
</tr>
<tr>
<td>3.6.2. Optical Doppler effect</td>
<td>25</td>
</tr>
<tr>
<td>3.6.3. Blood flow parameters of choroidal LDF</td>
<td>27</td>
</tr>
<tr>
<td>3.6.4 Application of LDF on subfoveal region</td>
<td>28</td>
</tr>
<tr>
<td>4. Subjects and methods</td>
<td>29</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>4.1. Subjects inclusion criteria</td>
<td>29</td>
</tr>
<tr>
<td>4.2. Subjects exclusion criteria</td>
<td>32</td>
</tr>
<tr>
<td>4.3. Baseline Examination</td>
<td>33</td>
</tr>
<tr>
<td>4.4. Laser Doppler Flowmetry (LDF)</td>
<td>35</td>
</tr>
<tr>
<td>4.4.1. Procedure of LDF measurements of the subfovea</td>
<td>35</td>
</tr>
<tr>
<td>4.4.2. Typical LDF recordings of the subfoveal region</td>
<td>38</td>
</tr>
<tr>
<td>4.5. Statistical Analysis</td>
<td>39</td>
</tr>
<tr>
<td>5. Results</td>
<td>40</td>
</tr>
<tr>
<td>5.1. Demographic data of the studied subjects</td>
<td>40</td>
</tr>
<tr>
<td>5.2. Baseline LDF data of the all studied groups</td>
<td>41</td>
</tr>
<tr>
<td>5.3. Correlations between each of the LDF parameters and clinical variables of the subjects</td>
<td>44</td>
</tr>
<tr>
<td>5.4. Analysis of LDF data of POAG and OHT groups</td>
<td>46</td>
</tr>
<tr>
<td>5.5. Analysis of LDF data of diabetic patients</td>
<td>47</td>
</tr>
<tr>
<td>5.6. Analysis of LDF data of hypertensive patients</td>
<td>50</td>
</tr>
<tr>
<td>5.7. Analysis of LDF data of myopic subjects</td>
<td>51</td>
</tr>
<tr>
<td>5.8. Comparison of baseline LDF data of groups with various glaucoma risk factors</td>
<td>52</td>
</tr>
<tr>
<td>6. Discussion</td>
<td>53</td>
</tr>
<tr>
<td>6.1. Correlations between each of LDF parameters and age and PP, respectively in normal population</td>
<td>53</td>
</tr>
<tr>
<td>6.2. LDF data of POAG and OHT groups</td>
<td>54</td>
</tr>
<tr>
<td>6.3. LDF data of diabetic patients</td>
<td>57</td>
</tr>
<tr>
<td>6.4. LDF data of hypertensive patients</td>
<td>59</td>
</tr>
<tr>
<td>6.5. LDF data of myopic subjects</td>
<td>60</td>
</tr>
<tr>
<td>6.6. Comparison of baseline LDF data of groups with various glaucoma risk factors</td>
<td>61</td>
</tr>
<tr>
<td>7. Summary, Conclusions &amp; Recommendations</td>
<td>62</td>
</tr>
<tr>
<td>7.1. Summary</td>
<td>62</td>
</tr>
<tr>
<td>7.2. Conclusions</td>
<td>65</td>
</tr>
<tr>
<td>7.3. Recommendations</td>
<td>67</td>
</tr>
<tr>
<td>8. References</td>
<td>68</td>
</tr>
</tbody>
</table>
Le glaucome, une des causes principales de la cécité dans le monde, est caractérisé par la perte progressive de fibres nerveuses combinée à une excavation de la tête du nerf optique dont les conséquences sont une perte plus ou moins grave du champ visuel (Tielsh, 1991). Bien que la description clinique du glaucome soit bien établie, le mécanisme causal exact n'est toujours pas établi. En plus de l’augmentation de la pression intraoculaire (PIO), qui est un facteur de risque établi, beaucoup d'autres facteurs de risque ont été décrits, tels que l’âge et les antécédents familiaux. Il est de plus en plus évident que d'autres facteurs déterminent le déclenchement, la sévérité, le cours, et les conséquences de la maladie. En particulier, comment expliquer les altérations progressives en dépit d'une PIO normale? Pour répondre à cette question, il est nécessaire de considérer d'autres facteurs de risque liés à la neuropathie du nerf optique dans le glaucome, en particulier l'insuffisance vasculaire (Gasser, 1998).

Il est connu de nos jours qu’un certain nombre de patients glaucomateux sont aussi atteints de maladies vasculaires oculaires ou systémiques (Emre et al., 2004). Par conséquent, il est important de déterminer si ces maladies affectent l'hémodynamique oculaire dans les yeux glaucomateux. Dans ce but nous avons analysé des groupes de sujets présentant des facteurs de risque présents dans un nombre important de patients glaucomateux, tels que l'hypertension systémique, le diabète et la myopie. Les mesures hémodynamiques sur ces sujets non glaucomateux ont été comparés à celles obtenues dans un groupe de patients atteints de glaucome ayant les mêmes facteurs de risque. Ceci nous a permis d'évaluer l'effet du glaucome sur l'hémodynamique
Introduction

oculaire chez les patients présentant diverses pathologies considérées comme facteurs de risque du glaucome.

Le diabète, l'hypertension systémique et la myopie ont été sélectionnés pour les raisons suivantes :
- Ces pathologies sont souvent associées au glaucome.
- leur rôle dans les altérations ou la progression du glaucome est controversé.
- le traitement du diabète et de l'hypertension systémique peut affecter la progression du glaucome.

Un grand nombre d'études cliniques ont examiné la circulation rétrobulbaire chez les patients glaucomateux (Akarsu et Bilgili, 2004 ; Bout et al., 1997 ; Cheng et al., 2001 ; Galassi et al., 1992 ; Klemm et Zeitz, 2006 ; Nicolela et al., 1996a), ainsi que celle de la tête de nerf optique et de la région péripapillary (Chung et al., 1999 ; Grunwald et al., 1999 ; Hafez et al., 2003 ; Hamard et al., 1994 ; Michelson et al., 1996 ; Piltz-Seymour, 1999 ; Piltz-seymour et al., 2001 ; Riva et al., 2004). En revanche, très peu d'études ont été consacrées à l'hémodynamique choroïdienne chez ces patients (Emre et al., 2004 ; Grunwald et al., 1998b). En particulier le manque de données sur l'hémodynamique dans les vaisseaux de la choroïde subfovéale, le système vasculaire qui nourrit la région la plus importante de la rétine, à savoir la fovea, représente une lacune importante dans notre connaissance de la pathogénie du glaucome. Pour remédier à cette lacune, nous avons entrepris une étude dont le but fût de déterminer le débit sanguin choroïdien subfovéolaire.

La mesure du débit choroïdien chez l’homme exige une technique non invasive qui soit aussi sensible, précise et reproductible pour pouvoir
détecter les changements pathologiques encore à un stade précoce de la maladie (Petrig et Riva, 1999).

Parmi les diverses techniques appropriées à l’étude de l’hémodynamique choroïdienne, la fluxmétrie laser Doppler (LDF) satisfait au mieux ces conditions idéales. Les mesures obtenues par LDF fournissent des données quantitatives sur le flux sanguin dans les choriocapillaires (Riva et al., 1994). De plus la réponse temporelle de la LDF permet de démontrer des changements de flux pendant le cycle cardiaque. Un avantage de cette technique est qu’elle n’exige pas la dilatation de la pupille. (Riva, 2001).

Les objectifs de ce travail ont été: a) l’étude du débit choroïdien chez les patients atteints de glaucome (glaucome à pression élevée et à pression normale ou avec hypertension oculaire); b) l’évaluation des effets du diabète, de l'hypertension systémique et de la myopie, tous considérés comme facteurs de risque de glaucome, sur ce débit ; c) l’établissement de corrélations entre les paramètres hémodynamiques obtenus de la circulation choroïdienne subfovéale et données cliniques (âge, PIO et pression de perfusion) obtenues d’un groupe de sujets normaux et d’un groupe de patients atteints de glaucome.
1. INTRODUCTION

Glaucoma, one of the leading causes of blindness in the world, is characterized by the presence of chronic optic neuropathy combined with characteristic morphological changes at the optic nerve head and corresponding visual field defects (European Glaucoma Society, 2003). Although the clinical picture of glaucoma is well described, the exact causative mechanism has not yet been elucidated. In addition to increased intraocular pressure (IOP) which is an established risk factor, many other risk factors have been described, such as age, race and family history. Increasing evidence suggests that further factors determine onset, severity, course, and outcome of the disease. In particular, how can one explain progressive glaucomatous optic damage despite a low IOP? To answer this question, one must consider other risk factors associated with glaucomatous optic neuropathy including vascular insufficiency, the so-called ‘vascular risk factors’ (Gasser, 1998).

It is well know nowadays that many glaucoma patients have some kind of ocular or systemic vascular diseases (Emre et al., 2004). From this point of view, it would be interesting to know how these diseases affect the ocular hemodynamics in glaucomatous eyes. Therefore we decided to analyze groups of populations who have not glaucoma, but who have risk factors found in many glaucoma patients, such as systemic hypertension, diabetes mellitus and myopia. These subjects were compared to a group of glaucoma patients having the same risk factors. This allowed us to evaluate the effect of these risk factors on the ocular hemodynamics of the normal population and glaucoma patients.

A large number of clinical studies have been performed to clarify the changes in retrobulbar circulation of glaucomatous patients (Akarsu and Bilgili, 2004; Butt et al., 1997; Cheng et al., 2001; Galassi et al.,
1992; Klemm and Zeitz, 2006; Nicolela et al., 1996a). Also the effect of
glaucoma on the of optic nerve head and peripapillary blood flow has
been investigated by many authors (Chung et al., 1999; Grunwald et al.,
1999; Hafez et al., 2003; Hamard et al., 1994; Michelson et al., 1996;
Piltz-Seymour, 1999; Piltz-seymour et al., 2001; Riva et al., 2004). In
contrast, we found very few studies on subfoveal choroidal blood flow in
glaucomatous patients (Emre et al., 2004; Grunwald et al., 1998b). The
lack of data on the hemodynamic in the subfoveal circulation, the system
that nourishes the most important region of the retina, namely the fovea
provided the rationale for our study. Whether glaucoma or its risk factors
affect the blood flow of the foveal region is an important question from a
research and clinical standpoint.

Assessment of choroidal blood flow has been difficult
eperimentally and clinically. Investigation of the choroidal
hemodynamics in humans requires non-invasive measurement of
choroidal blood flow. Ideally, the measurement technique should be
sensitive enough for pathological changes to be detected as early as
possible. Furthermore, it should be accurate and reproducible and should
have a response time short enough to follow physiological fluctuations in
this blood flow (Petrig and Riva, 1999).

Among the various techniques which have been applied in humans
to investigate choroidal hemodynamics, laser Doppler flowmetry (LDF)
is the closest to fulfill the ideal requirements. It is a powerful technique to
investigate noninvasively changes in blood flow in various ocular tissues
including the subfoveal choroid. The obtained measurements of choroidal
LDF correspond primarily to the determination of choriocapillaris flow
(Riva et al., 1994). This is in contrast to pulsatile ocular blood flow
(POBF) measurements that represent only the overall pulsatile intraocular
blood flow (Silver et al., 1989). The high sensitivity and temporal response of the technique allow demonstrating changes in flux during the cardiac cycle and in response to changes in various physiological parameters such as perfusion pressure, breathing conditions and neuronal activity. Furthermore, the near-infrared laser diodes enable measurements through undilated pupils (Riva, 2001).
2. AIM OF THE WORK

The aims of the work are a) to investigate the choroidal hemodynamic changes in patients with glaucoma (high and normal tension glaucoma) or ocular hypertension; b) to assess the effects of diabetes, systemic hypertension and myopia, all considered as glaucoma risk factors, on choroidal hemodynamics; c) to establish correlations between hemodynamic parameters obtained from the subfoveal choroidal circulation and the clinical findings obtained from the normal population and glaucoma patients, such as age, intraocular pressure and perfusion pressure.
3. REVIEW OF LITERATURE

3.1. Definition

Primary open-angle glaucoma (POAG) is a disorder that demonstrates typical structural changes in the optic disc along with visual field defects related to an abnormal elevation of intraocular pressure (IOP) and no obvious causative ocular or systemic conditions. Normal-tension glaucoma (NTG) is a type of glaucoma that shares clinical features and mechanisms with POAG, except for the abnormal elevation of IOP (Kiriyama et al., 2003).

3.2. Prevalence of Glaucoma Worldwide

It has been estimated that at the start of year 2010, there will be 60.5 million people with open angle glaucoma (OAG) and angle closure glaucoma (ACG) increasing to 79.6 million by 2020. Bilateral blindness will be present in 4.5 million people with OAG in 2010, rising to 5.9 million people in 2020, making glaucoma the second leading cause of blindness worldwide (Quigley and Broman, 2006). It has been demonstrated that glaucoma is one of the most frequent diagnosis associated with visual disability in the elderly population living in an urban area of Geneva region, Switzerland (Donati and Christiaen, 2006).
3.3 Pathophysiology

The exact cause of GON is not known. A detailed discussion of POAG must address two fundamental issues: (1) the mechanism(s) of IOP elevation, and (2) the mechanism(s) of progressive optic nerve cupping and atrophy.

3.3.1. IOP elevation

It is generally accepted that the increased IOP seen in most cases of POAG is caused by a decreased facility of aqueous humor outflow. Although there have been a few reports of patients with hyper-secretion of aqueous humor (Becker et al., 1956), this condition is exceedingly rare and therefore will not be further discussed.

Many investigators have studied the actual site of outflow resistance. The most accepted hypothesis is that the trabecular meshwork or the endothelium of Schlemm's canal is the site of the increased resistance to outflow in POAG. Several theories have been proposed to explain this phenomenon. They are summarized as follows (Stamper et al., 1999):

1) An obstruction of the trabecular meshwork by foreign material.
2) A loss of trabecular endothelial cells.
3) A reduction in pore density and size in the inner wall endothelium of Schlemm's canal.
4) A loss of giant vacuoles in the inner wall endothelium of Schlemm's canal.
5) A loss of normal phagocytic activity.
6) Disturbance of neurological feedback mechanisms.
Various investigators have linked the increased resistance to outflow with altered corticosteroid metabolism (Armaly, 1963), dysfunctional adrenergic control (Becker and Shin, 1976), abnormal immunologic processes (Shin et al., 1977) and oxidative damage (Coupland et al., 1993).

3.3.2. Progressive optic nerve cupping and atrophy

Intense research is currently underway regarding the pathogenetic concept of glaucoma, and today's understanding will be complemented or even supplemented by new aspects in a few years. In glaucoma, glial cells and ganglion cells destruction occurs primarily via a process called apoptosis "programmed cell death”, and a major tissue remodeling causing, among other effects, the visible optic head excavation, but the exact mechanism is largely unknown. IOP is involved in many ways in this process. When the IOP is extremely high, the papilla becomes mechanically damaged and the axo-plasmic flow is blocked. However, it has been supposed that the increased IOP as well as decreased blood pressure can lead to reduced perfusion, and this occurs especially in the presence of vascular dysregulation (Flammer, 2006a) (Fig. 1).

Reducing the perfusion below certain limits leads to a shortage of oxygen with disturbance in oxidative metabolism in the cytochromes of the optic nerve (Novack et al., 1990). However, reduced perfusion is rarely so pronounced that it leads to cell death. One hypothesis has postulated that the relative oxygen shortage rather causes secondary damage during the period when there is a renewed increase in the oxygen concentration because free oxygen radicals are produced in this phase leading to reperfusion injury (Flammer, 2006a) (Fig. 2).
Glutamate concentration can reach toxic levels because oxygen free radicals prevent the astrocytes from absorbing glutamate. This increased glutamate concentration can thus contribute to ganglion cell death. A contemporary hypothesis of possible pathogenic mechanisms that underlie GON include excitotoxic damage of peroxynitrite produced in the axons as a result of oxidative stress and reperfusion injury together with activation of the glial cells by ischemic or mechanical stress (Flammer, 2006a).

![Fig. 1. Concept of pathogenesis. Both increased IOP as well as decreased blood pressure can lead to glaucomatous damage, especially when accompanied by vascular dysregulation (reprinted from Flammer, 2002, with permission from the publisher).](image1)

![Fig. 2. The simultaneous oxidative stress brought about by reperfusion and activation of astrocytes leads to the damaging peroxinitrate (reprinted from Flammer, 2006a, with permission from the publisher).](image2)
3.4. **Glaucoma risk factors**

Risk factors are inherited or inborn characteristics, environmental exposures, or aspects of personal behavior that affect the probability of individuals to develop the disease (*Wilson and Martone, 1996*).

Many risk factors may play an important role and, in certain cases, even a predominant role in the pathogenesis of POAG. The quality of available data regarding potential risk factors for the glaucoma varies among many studies.

Hereby, we have attempted to present the risk factors in a graded format based on the strength of the supporting evidence (Table 1).

<table>
<thead>
<tr>
<th>Strong supporting evidence</th>
<th>Fair supporting evidence</th>
<th>Weak supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular Pressure</td>
<td>Myopia</td>
<td>Steroids</td>
</tr>
<tr>
<td>Age</td>
<td>Diabetes Mellitus</td>
<td>Gender</td>
</tr>
<tr>
<td>Family History of Glaucoma</td>
<td>Circulatory problems (e.g. blood pressure)</td>
<td>Trauma</td>
</tr>
<tr>
<td>Race</td>
<td>Hypothyroidism</td>
<td>Smoking and Alcohol</td>
</tr>
<tr>
<td>Central corneal thickness</td>
<td>Optic disc appearance</td>
<td>Socioeconomic factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood disorders</td>
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</table>

In this review, we will only discuss some of the most important risk factors of glaucoma.
3.4.1. Intraocular pressure (IOP):

Elevated IOP is probably the most significant ocular risk factor for developing GON (Armaly, 1969). Although no conclusive evidence supports this direct correlation, the existing evidence suggests to reveal a strong causal effect of IOP in glaucomatous damage (Krakau, 1981).

A number of reports demonstrated that the prevalence of GON rises as IOP increases (Mason et al., 1989) (Fig. 3 a). The incidence of GON increases from approximately 3% in patients with an IOP between 21 and 25 mmHg, to more than 50% in patients whose IOP is higher than 35 mmHg. The incidence of POAG is also five times greater in patients with an IOP higher than 21 mmHg than in those with IOP lower than 21 mmHg (Armaly et al., 1980; Crichton et al., 1989). Moreover, the causal role for IOP in glaucomatous damage was supported experimentally by induction of high IOP in animals, which results in typical glaucomatous optic nerve cupping (Quigley and Addicks, 1980).

Lowering the IOP is important in decreasing the rate of progression of visual field loss (Mao et al., 1991) and regression of optic nerve and visual field damage may occur after substantial IOP lowering (Sogano et al., 1993; Wilson and Martone, 1996). However, belief in the importance of IOP as a causative factor for POAG is not without contention. Some eyes with elevated IOP have no glaucomatous damage while others with normal or even low IOP have definite glaucomatous damage. It is important to remember that there is no cut-off point to delineate "elevated" from "normal" IOP. The lack of a one to one relationship between IOP of 21 mmHg or higher and GON, and the occurrence of damage despite IOP below 21 mmHg suggest that other factors also contribute to the pathogenesis of glaucoma (Krakau, 1981). Therefore,
what is considered "safe" or "normal" level of IOP differs from one patient to another, depending on the vulnerability of the optic nerve and the presence of other risk factors (Dignam and Stutman, 2001).

3.4.2. Age:

Age has been identified as one of the major risk factors of glaucoma (Fig. 3 b). It was reported that persons older than 60 years have a risk of developing POAG and visual field defects over a 13-year period seven times greater than persons below 40 years (Armaly et al., 1980).

The exact nature of age-related changes that contribute to the development of POAG is not known. The higher IOP noted in older age groups is not likely to be the sole explanation because it does not increase with age among the Japanese population, although POAG does (Leibowitz et al., 1980). Older people have higher incidence of pseudoexfoliation, in addition to a higher incidence of vascular accidents, which could explain the increased prevalence of POAG with age (Chihara et al., 1997).

![Fig. 3. a) The higher the IOP, the more frequently glaucomatous damage level. b) The prevalence of glaucomatous damage increase with the age. (reprinted from Flammer, 2006b, with permission from the publisher).](image)
3.4.3. Myopia:

The magnitude of the association between myopia and glaucoma differs considerably between studies. Some show a significant association between high myopia and prevalent field loss (Mitchell et al., 1999; Wilson et al., 1987). Defective connective tissue elements in the optic nerve, lamina cribrosa, and scleral shell may result in a shared pathogenetic pathway (Chihara et al., 1997). On the other hand, a protective effect of myopia for further progression of field damage was noted (Phelps, 1982). However, a great potential for such data may be influenced by selection bias, since individuals with refractive errors are more likely to seek eye care and to be diagnosed early as having glaucoma (Quigley et al., 1994).

Peripheral iris concavity in myopic eyes facilitates irido-zonular contact, thereby increasing pigment liberation and the incidence of pigmentary dispersion syndrome and pigmentary glaucoma in such eyes (Scheie and Cameron, 1981). Impaired retrobulbar (Galassi et al., 1998) retinal (Shimada et al., 2004) and choroidal (Karczewicz and Modrzejewska, 2004) circulations have been demonstrated in glaucomatous eyes associated with high myopia. These abnormalities of the ocular circulation might be interpreted as a vascular risk factor for the pathogenesis of the GON.

Recent studies suggest that the myopic eye has an increased sensitivity to IOP. This means that someone near-sighted is more likely to experience optic nerve damage than an emmetropic individual with the same IOP (Mayama et al., 2002).
3.4.4. **Diabetes Mellitus (DM):**

Whether a positive association between DM and glaucoma exists is still debatable. Although a number of studies has failed to confirm an association between diabetes and glaucoma (*Armaly et al., 1980; Ellis et al., 2000; Jonas and Grundler, 1998; Tielsch et al., 1995a*), reports from several investigators support such an association. The Beaver Dam Eye Study found glaucoma to be more prevalent among persons with older-onset diabetes than in those without diabetes (4.2% versus 2%) (*Klein et al., 1994*). Similarly diabetic patients are at significantly increased risk of developing POAG (*Bonovas et al., 2004*). Of those persons with glaucoma, 13% had diabetes compared with 6.9% without glaucoma (*Wilson and Martone, 1996*). These authors hypothesized that small-vessel disease or systemic blood abnormalities can result in compromised vascular perfusion to the optic nerve, which increases the risk of GON.

It should be noted that persons with diabetes are more likely to be referred for or to seek an eye examination because of the risk of diabetic retinopathy. This might result in a clinical bias towards the detection of glaucoma among persons with diabetes in the general clinic population (*Dignam and Stutman, 2001*).

A recent study assumed that DM is a protective against glaucomatous damage (*Gordon et al., 2002*). However, The authors explained this contradicting results by none confirming the diagnosis of DM in the participants neither by blood tests nor the used medication, moreover patients with diabetic retinopathy were excluded from the study which may explain the paradoxical relationship between the DM and POAG demonstrated in this study.
3.4.5. **Systemic blood pressure:**

Reports on the association between systemic hypertension (SHT) and POAG suggest that this association is more complex than previously assumed. Whereas some authors found no positive association between SHT and POAG (Jonas and Grundler, 1998), others did (Tielsch et al., 1995b; Wilson et al., 1987). Moreover, SHT seems to decrease the relative risk of POAG during 4 years of follow up (Leske et al., 2002). These findings are consistent with the hypothesis that SHT has a protective effect on early POAG development since it maintains an adequate perfusion pressure in the optic nerve (Grunwald et al., 1999). Some authors have considered SHT a weak risk factor for POAG, if it is risk factor at all. The possible role of atherosclerotic and ischemic vascular diseases, alone or in conjunction with SHT, is even less clear (Wilson and Martone, 1996).

Low systemic blood pressure combined with high intraocular pressure was a stronger risk factor for glaucoma than was systemic hypertension per se. Antihypertensive treatment could induce hypotensive episodes, especially at night (Graham et al., 1995).

Marked circadian fluctuation of the mean ocular perfusion pressure associated with nocturnal reduction in blood pressure beyond the physiological limit (20 ± 6 mmHg) (Choi et al., 2006) represents an additional risk for GON, particularly in normal-tension glaucoma (Fig. 4) (Graham et al., 1995; Kaiser and Flammer, 1991).
3.4.6. The appearance of the optic disc:

The greater the tissue damage at the optic nerve head, the more likely a future progression of nerve fiber loss; but whether this is a genuine risk factor is still being debated. Theoretically, it seems possible that an already damaged disc could be more susceptible to increased IOP. Also if the patient has suffered from previous disc damage, chances are high for a further deterioration if the causes have not been eliminated (Flammer, 2006b).

The relation of hemorrhages, at or near the optic disc, to GON is debatable. Some authors assume that the appearance of these hemorrhages points almost with certainty to a progression of existing damage (Siegner and Netland, 1996). In contrast, several authors have found no correlation between disc hemorrhage and disc changes or glaucomatous disk progression (Heijl, 1986; Tuulonen et al., 1987).

The size of an optic disc does not seem to be a risk factor. A given IOP will cause the same degree of damage, regardless of whether the optic disc is large or small (Flammer, 2006b).
3.5. **Choroidal hemodynamics**

3.5.1. **General vasculature of the orbit and choroid** (Fig. 5)

*(most of this part has been quoted from the paper by Cioffi and Buskirk, 1995, with the permission from the publisher)*

The orbital contents receive their vascular supply from several arteries, including the ophthalmic artery, the meningolacrimal artery (a branch from the middle meningeal artery) and palpebral arteries which branch from the facial artery.

The vascular supply to the intraorbital optic nerve, retina, and choroid arises predominantly from the ophthalmic arterial circulation via the posterior ciliary arteries, the central retinal artery, and the pial vascular network along the optic nerve. The ocular branches of the ophthalmic artery are the central retinal artery and one to five posterior ciliary arterial trunks. These trunks branch into the main posterior ciliary arteries. Most individuals have two to three posterior ciliary trunks which supply the medial and lateral posterior ciliary arteries. Each main posterior ciliary artery further divides into several short posterior ciliary arteries, just before or after entering the sclera.

The short posterior ciliary arteries course anteriorly, and pierce the sclera immediately adjacent to the optic nerve, predominantly in the nasal and temporal region. They supply the posterior choroid, as well as the majority of the anterior optic nerve. Often the medial and lateral short posterior ciliary arteries anastomose and form an elliptical circle around the optic nerve, the arterial circle of Zinn and Haller. Branches derived from the circle of Zinn and Haller include recurrent pial branches, choroidal branches, and the branches penetrating the optic nerve.
The venous drainage of the orbit generally does not follow the arterial supply. The venous drainage of the retina and the anterior optic nerve is almost exclusively via the central retinal vein and its tributaries, which subsequently empty into the superior ophthalmic vein (the largest of the orbital veins). The choroid is drained through the vortex venous system, which empties into the superior and inferior ophthalmic veins. Both vessels drain into the cavernous sinus. However, the inferior ophthalmic vein occasionally drains into the pterygoid plexus through the inferior orbital tissue.

Fig. 5. Ocular vascular supply (reprinted from Harris et al., 2003b, with permission from the publisher).
3.5.2. Regulation of choroidal blood flow (ChBF)

Regulation of the blood in the choroidal vascular bed is achieved mainly through a mechanism involving either the autonomic nervous system \( (\text{Alm, 1977; Alm and Bill, 1973}) \) or the release of vascular endothelium related mediators \( (\text{Haefliger et al., 1994a; Pournaras, 1996}) \). The former affects the contraction of the smooth muscle of choroidal arterioles, and the latter affects either the smooth muscle of the arterioles or the contractile state of pericytes surrounding the capillaries \( (\text{Haefliger et al., 1994b}) \).

However, this regulatory mechanism can be disturbed in different pathological conditions such as diabetic retinopathy due to failure of the autonomic nervous system \( (\text{Movaffaghya et al., 2002}) \), and neovascular age related macular degeneration (ARMD) due to inability of the new vessels to increase their flow resistance during acute moderate elevation of blood pressure \( (\text{Pournaras et al., 2006}) \). Herby, we can summarize the determinants of the choroidal circulation in the following manner:

a. Autonomic nervous system

Despite the fact that electrical stimulations of sympathetic and parasympathetic nerves have an influence on choroidal perfusion, the potential role of this phenomenon remains uncertain. It has been suggested that the extensive sympathetic innervation might protect the eye against overperfusion, during increased perfusion pressure, by constriction of the choroidal blood vessels \( (\text{Bill and Sperber, 1990}) \). The dense vasodilative innervation of the choroid, on the other hand, might be important to increase ChBF under certain conditions, such as high light intensity \( (\text{Parver et al., 1982}) \). Although the presence of an active process of ChBF regulation in response to light exposure in humans has not been
confirmed, a reversible decrease in ChBF was demonstrated after a transition from room light to darkness, which could involve a neural mechanism (Longo et al., 2000).

b. Vascular endothelium related mediators

Vascular endothelial cells produce different vasodilating and vasoconstricting mediators such as, nitric oxide (NO), prostaglandins and endothelin-1, both under basal conditions and in response to many chemical and mechanical stimuli.

NO is one of the most important endothelial relaxing factors. Many authors suggest that NO has a role in maintaining basal blood flow to choroid (Deussen et al., 1993; Luksch et al., 2003; Mann et al., 1995). In addition, NO is also released in response to an increase in shear stress. Shear stress is proportional to the viscosity and the flow of blood and inversely proportional to the radius of a blood vessel. Therefore changes in one of these parameters will have an influence on NO release and thus on the degree of relaxation of retinal vascular smooth muscle cells (Delaey and Van De Voorde, 2000).

The endothelium also releases prostaglandins. They seem to have a complex vasoregulatory influence on retinal and choroidal blood vessels, depending on their relative vasodilating or vasoconstricting influence (Delaey and Van De Voorde, 2000). They have been suggested to play a potential role during the physiological adaptation of the choroid to the hypercapnia in which a prominent vasodilatation in the choroidal blood vessels with increased ChBF occur (Stiris et al., 1992).

The most potent vasoconstrictor released by endothelial cells is endothelin-1. Administration of endothelin-1 significantly reduces POBF
at concentrations which do not affect systemic hemodynamics (Schmetterer et al., 1997). This indicates that choroidal circulation is particularly sensitive to local endothelin-1 concentration and suggests that endothelin-1 may participate in the regulation of ChBF (Fuchsjager-Mayrl et al., 2003).

c. Autoregulation

Autoregulation can be defined as the ability of a vascular bed to keep blood flow constant despite changes in perfusion pressure (Guyton et al., 1971). Numerous studies have failed to demonstrate autoregulation in the choroidal circulation (Alm and Bill, 1972; Friedman, 1970). More recent studies suggest that the choroid has some capabilities to maintain its blood flow despite changes in perfusion pressure (Lovasik et al., 2003; Riva et al., 1997c). The authors suggested a neural or passive hemodynamical process rather than a myogenic or metabolic compensatory mechanism.

d. Circulating molecules

Some circulating molecules and hormones, such as angiotensin II and the catecholamines, are believed to have an influence on choroidal circulation. Studies of the effect of these molecules on the choroidal circulation, however, have yielded controversial results. Some studies show evidence that angiotensin II contract retinal and choroidal blood vessels (Dollery et al., 1963), while other authors did not observe any effect of angiotensin II on ChBF (Fuchsjager-Mayrl et al., 2003). A similar uncertainty exists in relation to the influence of catecholamines on the ocular circulation (Alm, 1972; Malik et al., 1976).
3.5.3. Choroidal blood flow in glaucoma

Choroidal vascular insufficiency has been implicated as a factor for the pathogenesis of glaucoma. Watershed zones in the choroid have been hypothesized. These zones appear to have a lower vascular supply than other areas of the choroid and are presumably at higher risk for ischemia during elevated IOP (Hayreh and Walker, 1967). Preliminary findings of reduced choroidal filling in glaucoma patients as determined by fluorescein filling times were also reported (Duijm et al., 1997; Jung et al., 1983).

It is widely recognized that POBF and ocular pulse amplitudes are lower in POAG patients than in normal subjects (Agarwal et al., 2003; Fuchsjager-Mayrl et al., 2004; Trew and Smith, 1991). Alterations of posterior ciliary artery circulation in glaucoma patients have been also recorded by many authors using color Doppler technique (Birinci et al., 2002; Nicolela et al., 1996a; Rankin, 1999; Vecsei et al., 1998). However, very few reports have recorded the subfoveal ChBF in glaucoma patients (Emre et al., 2004; Grunwald et al., 1998b).
3.6. Laser Doppler flowmetry (LDF)

3.6.1. History

The first measurements of blood flow velocity in capillary beds and in retinal artery using a laser Doppler technique were published in 1972 (Riva et al., 1972). In a different application, these authors used LDF for measurements of the blood flow in the microcirculation of the optic nerve head (Riva et al., 1989). The widely recognized importance of understanding the pathophysiology of diseases such as diabetic retinopathy, ARMD and others, has recently led to the development of a new technique for the non-invasive measurement of ChBF. The feasibility of near-infrared (811 nm) LDF to quantify the subfoveal ChBF response to physiological stimuli has opened new avenues in the investigation of the physiology of the choroidal circulatory system (Riva et al., 1994).

3.6.2. Optical Doppler effect

LDF is based on the Doppler effect: laser light scattered by moving particle is shifted in frequency by an amount: \( \Delta f = V \left( \cos \alpha_s - \cos \alpha_i \right) \frac{n}{\lambda} \), where \( V \) is the velocity vector of the particle, \( \alpha_i \) and \( \alpha_s \) are the angles of the incident and the scattered light respectively, \( n \) is the index of refraction of the medium containing the particles and \( \lambda \) is the wavelength of the laser light (Fig. 6). When a laser beam illuminates RBCs moving in a net of capillaries with various velocities and directions, the light scattered by the RBCs and reaching the detector consists of a summation of waves with various Doppler shifts (Petrig and Riva, 1999) (Fig. 7).
Fig. 6. Doppler effect of RBC moving at velocity V. Compared to the frequency ($f_i$) of the light incident from the direction $\alpha_i$, the frequency of the light scattered in the direction $\alpha_s$ is shifted by an amount $\Delta f$ (reprinted from Riva, 2001, with permission from the publisher).

Fig. 7. Schematic diagram shows laser light impinging in a tissue and leaving it in the direction of the detector, after having been scattered by static tissue structures (small dots) and RBCs moving in blood vessels (large dots).
3.6.3. Blood flow parameters of subfoveal choroidal LDF

The following flow parameters are obtained from the LDF of the subfoveal region of human ocular fundus:

- **Subfoveal choroidal blood velocity (ChBVel)** = the mean velocity of the RBCs within the volume sampled by the laser light, which is proportional to the mean Doppler frequency shift.

- **Subfoveal choroidal blood volume (ChBVol)** = Number of moving RBCs in the sampling volume.

- **Subfoveal choroidal blood flow (ChBF)** = the flux of RBCs in the volume sampled by the laser. \( \text{ChBF} = \text{Constant} \times \text{ChBVel} \times \text{ChBVol} \).

ChBVel is expressed in Hz, while ChBVol and ChBF are expressed in arbitrary units. This means that LDF does not provide absolute measurements of blood flow. It provides only relative blood flow measurements. The reasons are as follows. Laser radiation upon a tissue undergoes scattering, as well as absorption by the tissue and the RBCs. Both processes influence the penetration pattern of the laser light, which may differ from one region of a tissue to another, depending upon the spatial optical properties of the tissue. Thus, different tissue structures, as well as variations in this structure due to pathologies (for instance macular neo-vascularization) will affect the subfoveal ChBF measurements (Robinson et al., 1986).
3.6.4 Application of LDF on subfoveal region of human ocular fundus

LDF measurement of choroidal blood flow in the foveal region of the human ocular fundus is a recent technology in which non-confocal \cite{riva1994} and confocal \cite{geiser1999} techniques have been used. The high spatial and temporal resolution of the LDF technique, particularly in the continuous mode, makes this technique most suitable for the investigation of the process of regulation of blood flow in response to various physiological stimuli. However, many other applications of choroidal LDF have been performed to study the effects of pathologic processes and various pharmacologic agents on the choroidal circulation.

Many studies have been performed to demonstrate the alterations of the choroidal circulation in response to increases and decreases of perfusion pressure \cite{riva1997a,riva1997b}, valsalva maneuvers \cite{riva1994}, dynamic exercise \cite{lovasik2003}, breathing various gases, such as carbon monoxide \cite{resch2005}. Investigations of various determinants of the ChBF regulation such as NO and endothelin 1 have been conducted using LDF \cite{fuchsjager2003,longo2000,luksch2003}.

Studies of the effect of aging, ARMD and choroidal neovascularization have been reported \cite{grunwald1998a,grunwald1998b,pournaras2006}. Effects of pathological processes such as glaucoma \cite{grunwald1998b}, diabetic retinopathy \cite{nagaoka2004,schocket2004} and SHT \cite{metelitsina2006,niknam2004} have also been demonstrated. Moreover, the pharmacological effects of some drugs, such as oral felodipine on ChBF have been recorded \cite{schocket1999}. 
4. SUBJECTS AND METHODS

The current study was carried out on selected subjects attending the outpatient clinics of Geneva Ophthalmology Center, Geneva University Hospitals, Switzerland, from February 2006 to December 2006.

4.1. Subjects inclusion criteria:

The subjects attending the outpatient clinics were divided into 3 main groups:

**Group I. Subjects with POAG or with OHT:**

This group was further subdivided into 3 subgroups according to the guidelines of the European Glaucoma Society (*European Glaucoma Society, 2003*):

*a) Normal Tension Glaucoma (NTG)*

The diagnosis of NTG is based on the presence of typical glaucomatous optic nerve head changes, visual field defect typical of glaucoma with open anterior chamber angle and IOP < 22 mmHg without treatment (diurnal tension curve).

*b) High Tension Glaucoma (HTG)*

They included patients with POAG exhibiting acquired characteristic glaucomatous optic nerve damage and/or retinal nerve fiber layer changes (localized or diffuse). Visual field defect corresponding to optic nerve damage is usually detected and confirmed in at least two visual field examinations. All patients have open anterior chamber angle and IOP > 21 mmHg without treatment (diurnal tension curve).
Subjects and Methods

c) Ocular Hypertension (OHT)

The diagnosis of the OHT is based on normal optic disc appearance, normal visual field and retinal nerve fiber layer, open anterior chamber angle and an IOP of 22 mmHg or greater without treatment (diurnal tension curve).

NB

1) Central corneal thickness (CCT) measurement was done in certain cases to correct for Goldmann applanation IOP measurement especially when the clinical finding did not match with the IOP level. An approximately 1 mm Hg correction for every 25 micron deviation from a CCT of 550 micron. The correction values were positive as thickness decreased and negative as thickness increased (Kohlhaas et al., 2006).

2) Most of patients with HTG were under glaucoma mediated(s), while most of NTG and OHT patients were investigated before starting their therapy.
Subjects and Methods

Group II. Subjects with glaucomatous risk factors:

This group was further subdivided into 3 subgroups according to the glaucomatous risk factors:

a) Subjects with diabetes mellitus (DM): They included subjects with history of DM or elevated fasting blood glucose ≥ 7.00 mmol/l (140%) (Mitchell and Wang, 1999). Patients with vitreous hemorrhage or advanced retinal problems (such as retinal detachment) were excluded. The severity of diabetic retinopathy was defined according to the modified Airlie House system used in the Early Treatment Diabetic Retinopathy Study (ETDRS, 1991).

These subjects were further subdivided into 2 subgroups:

i) Patients without POAG and with normal IOP (<22 mm Hg).

ii) Patients with POAG.

b) Subjects with systemic hypertension (SHT): SHT was considered as consistently having increased blood pressure with current use of antihypertensive medication or elevated blood pressure (systolic ≥ 160 or diastolic ≥ 95mmHg) (De Lena de Ruotolo et al., 1992). All hypertensive patients included in the current study were under antihypertensive thereby. As in diabetic group, they were subdivided into 2 subgroups (without and with POAG).

c) Subjects with myopia: In the present study, we defined moderate myopia as myopia with spherical equivalent between -3 and -8 diopters, and high myopia as myopia with spherical equivalent greater than -8 diopters (Shimada et al., 2004). Patients with moderate and high myopia were included (Mitchell et al., 1999). To exclude the influence of myopic retinopathy, highly myopic eyes with myopic chorioretinal atrophy were
excluded from the study (Avila et al., 1984). Similarly to subjects with DM, myopic subjects were subdivided into 2 subgroups (without and with POAG).

**Group III. Control subjects:**

They fulfilled the following criteria:

- IOP < 22mm Hg.
- No significant error of refraction (±3 diopters).
- Normal optic disc clinical findings.
- Normal visual field.
- No past history or family history of glaucoma.
- No history of any ocular or systemic disease
- No ocular or systemic medication.
- Neither smokers nor alcoholics.

**4.2. Subjects exclusion criteria:**

Subjects fulfilling one or more of following criteria were excluded from the study:

- Other types of glaucoma such as: angle closure or secondary glaucoma.
- Concomitant ocular disease such as uveitis or retinal detachment.
- Any ocular disease that can prevent fair visualization of the posterior segment or interfere with accurate applanation tonometry.
- Ocular disease, other than POAG, potentially associated with optic neuropathy, such as anterior ischemic optic neuropathy or congenital optic nerve anomaly.
- Neurological disorders or retinal diseases affecting the visual field.
Subjects and Methods

- History of intra-ocular surgery or ocular injury.
- All systemic diseases except DM or SHT.
- All patients who are smokers and/or alcohol drinkers.
- Mixed criteria (e.g. diabetic patients having either hypertension or high myopia).
- Patients with any ocular medication except anti glaucoma thereby.
- Patients with systemic medication except for SHT or DM.

4.3. Baseline examination:

The clinical characteristics of the subjects included in this study were based upon the data obtained from history taking and ocular examination.

4.3.1. History taking:

- Personal history
- Complaint and present history
- Past history: A careful history for previous ocular diseases rather than POAG, ocular trauma, or treatment (either medical, surgical or LASER treatment).

- General medical history included: a) cardiovascular diseases such as hypertension, hypotension, peripheral vascular diseases, and coronary artery disease, b) endocrinal disorders such as diabetes mellitus and thyroid diseases, c) collagen diseases, d) blood diseases, e) autoimmune diseases, f) systemic medications such as anti hypertensive drugs, hormonal replacement therapies or corticosteroids.

- Family history of glaucoma
4.3.2. Ophthalmological examination:

- **Visual acuity**: Assessment of visual acuity (unaided and aided) was performed using projector chart with decimal notation.

- **Refraction**: Determination of refraction was achieved using Nidek ARK-700A followed by assessment of best corrected visual acuity.

- **Tonometry**: The IOP was measured by Goldmann applanation tonometer mounted on a slit-lamp.

- **Slit-lamp examination**: The anterior segment of the eye was carefully examined to exclude causes of secondary glaucoma.

- **Gonioscopy**: The anterior chamber angle was examined with the aid of a Goldmann three-mirror contact lens and slit-lamp biomicroscopy. The angle was graded at gonioscopy according to Shaffer grading system (Shaffer, 1960). Angle with grade 3 and 4 are considered open.

- **Fundus examination**: The fundus was examined by direct ophthalmoscopy and with Goldman 3- mirror contact lens to assess optic disc changes in glaucoma and to exclude macular lesions, vascular lesions, optic nerve anomalies, and other lesions that may produce visual field defects.

**NB**

We were masked during the investigation of myopic, hypertensive and control groups as most of them were collected from the emergency unit or the general outpatient clinics without knowing their exact diagnosis. On the other hand, to study a significant numbers of diabetic and glaucoma patients, they should be collected from the diabetic and glaucoma outpatient clinics respectively. However, detailed clinical data of the patients (e.g. grade of retinopathy, IOP, visual field) were hidden till achievements of the measurements.
4.4. Laser Doppler Flowmetry (LDF)

4.4.1. Procedure of LDF measurements of the subfoveal choroidal blood flow

All patients participating in the study were given a detailed explanation of the procedures. An appropriate consent form, approved by the institution, was obtained. The study was approved by the Ethical Committee of the Medical Faculty of the University of Geneva and followed the tenets of the Declaration of Helsinki.

Measurements of choroidal hemodynamic were conducted on one randomized chosen eye of each subject using a Topcon based fundus camera Lased Doppler flowmetry system (LDF) (Fig. 8).

A probing laser beam (wavelength = 810 nm, power at the cornea = 60 μW) was directed to the fundus through the illumination pathway of the fundus camera. The optical fiber aperture, used to detect the scattered light, was placed at the center of the illuminated site (nominal diameter 450 μm, imaged to approximately 150 μm at the fundus) (Fig. 9).

Subjects were asked to fixate on the probing laser beam while proper fixation was confirmed by direct visualization of the foveola through the monitor of a television camera sensitive to near infrared light. During all measurements, the Doppler signal was fed into a loudspeaker, allowing the pulsating pitch of the signal to be heard.

The collected laser light was guided on a photodetector, whose output signal was analyzed by a NeXT computer (NeXT Computer, Inc, Redwood City, California) with software (NeXT Software, Inc, Redwood City) specifically developed for the analysis of Doppler signals from ocular tissue to obtain relative measures of ChBVel, ChBVol and ChBF (see definitions in page 27). Measurements obtained in this fashion, from
the centre of the foveola, correspond mainly to blood flow in the choriocapillaries (Riva et al., 1994) (Fig. 10).

The portion of the Doppler shift power spectrum between 32 and 2500 Hz was used for the determination of the flow parameters. The region between 2500 and 5000 Hz served to determine the shot noise level, which was subtracted from the spectrum before calculating the flow parameters. The direct currency (DC) of the Doppler signal, which is proportional to the total amount of light reaching the detector was also recorded and used to monitor the position of the camera and to remove the portions of recordings associated with blinks. Spikes occurring mainly in ChBVol and lasting less than 0.1 sec were attributed to micro-saccadic eye motion and were also removed from the recording.

Five separate (20–30 seconds) measurements of the choroidal circulation were obtained. Only stable portions of the measurements were included. Analyses of the data from the five separate recordings were averaged.

Upon completion of LDF measurements, brachial artery systolic (BPs) and diastolic blood pressure (BPd) were obtained by sphygmomanometer. Mean brachial blood pressure (BPm) was calculated using the following standard formula: \[ BPm = BPd + \frac{1}{3} (BPs-BPd). \] The mean ophthalmic arterial pressure (MOAP) was assumed to be 2/3 of the (BPm). The mean perfusion pressure (PP) was calculated according to the formula: \[ PP = MOAP - IOP. \] The mean vascular resistance (R) was defined as: \[ R = PP/ChBF \] (Riva et al., 1986).
Subjects and Methods

Fig. 9.  

a: The site of applied laser beam of LDF in the foveal region in the fundus. 
b: A photodetector collects scattered light from a 150um circular area of the fundus surrounding the laser spot.

(reprinted from Harris et al., 2003a, with permission from the publisher)
4.4.2. Typical LDF recordings of the subfoveal region of a normal volunteer

Fig. 11. ChBVel, ChBVol and ChBF obtained from the subfoveal region of a normal volunteer. The changes in these hemodynamical parameters during 2 heart cycles are shown at the right. They were derived from a 20 sec recording segment (shaded area) using the pulse pressure wave from the ear to average all data with the same phase of the cardiac cycle and repeating this operation for all phases.
4.5. **Statistical Analysis**

Data were analyzed using SPSS program (Standard version 10, 1999).

- Quantitative data were presented in the form of mean and standard deviation (mean ± SD).

- A one-way analysis of variance (ANOVA) across the different groups was carried out for each set of variables followed where appropriate by a post hoc t test using the Bonferroni correction.

- The chi-square test was used for categorical data.

- Pearson’s correlation was used for the correlations of different parameters that were assumed to have a normal distribution.

- Multiple regression analysis was carried out to examine the relation between the choroidal circulatory parameters as the dependent variables and certain predictor variables in normal or glaucomatous patients such as IOP and PP.

- Scatterplot graphs were performed by Microsoft Excel set for data analysis, showing the linear correlation between two variables.

- Two independent sample test (Mann-Whitney U) was used to compare the circulatory parameters of the two different groups (e.g. types I and II D.M.)

- Statistical significance was set at $p \leq 0.05$. 
5. RESULTS

5.1. Demographic data of the studied subjects

This study included 389 subjects (190 males and 199 females) collected from outpatient clinics of Geneva Ophthalmology Center. They aged from 14 to 90 years. The best corrected visual acuity ranged from 0.1 to 1.00 and refraction ranged from +3 to -13 diopters. They had an IOP from 10 to 28 mmHg. The Demographic data of the investigated subjects are demonstrated in Table 2.

<table>
<thead>
<tr>
<th>Character</th>
<th>POAG</th>
<th>Subjects with glaucomatous risk factors</th>
<th>Control</th>
<th>p Value</th>
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<td></td>
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<td>DM</td>
<td>SHT</td>
<td>Myopia</td>
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<td>±14</td>
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<td>±0.1</td>
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<td>±10</td>
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<td>±7</td>
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<tr>
<td>PP (mmHg)</td>
<td>±7</td>
<td>±6</td>
<td>±6</td>
<td>±5</td>
</tr>
</tbody>
</table>

i = without POAG  ii = with POAG  No. = number  M = Male  F = Female  IOP = Intra ocular pressure  Ref. = Refraction (spherical equivalent)  UCVA = un corrected visual acuity  BCVA = best corrected visual acuity  BPs = Systolic blood pressure  BPD = Diastolic blood pressure  PP = Perfusion pressure  NS = Non significant at level of 0.05  * Chi square test  P : significant at ≤ 0.05 (ANOVA)

a (Significant difference between OHT group and the other groups)

b, c (Significant difference between myopia group and other groups)
5.2. Baseline LDF data of all studied groups

Table 3 summarizes the baseline choroidal LDF data of all studied groups. One way ANOVA test reveals statistically significant difference among the studied groups. ChBVel, ChBVol and ChBF were significantly decreased and the R was increased in all patients groups compared to the age matched control group. Distribution of the ChBF in the different studied groups is illustrated in Fig. 12. It is important to emphasis that the direct currency (DC) of the Doppler signal is not significantly different among the different population indication that the measurements were similarly adjusted in the different studied groups and not affected by other factors e.g. media opacity as in the case of incipient cataract (Fig. 13). Figure 14 demonstrates the distribution of the LDF parameters among the normal population.

<table>
<thead>
<tr>
<th>Character</th>
<th>POAG</th>
<th>Subjects with glaucomatous risk factors</th>
<th>Control</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTG</td>
<td>DM</td>
<td>SHT</td>
<td>Myopia</td>
</tr>
<tr>
<td>No. Patients</td>
<td>34</td>
<td>51</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>ChBVel (kHz)</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.5</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.14 ± 0.1</td>
<td>0.14 ± 0.1</td>
<td>0.12 ± 0.1</td>
<td>0.11 ± 0.1</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>4 ± 1</td>
<td>4 ± 2</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>DC</td>
<td>2.7 ± 0.7</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 0.6</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>16 ± 8</td>
<td>16 ± 7</td>
<td>15 ± 6</td>
<td>23 ± 12</td>
</tr>
</tbody>
</table>

\( i \) = without POAG  \hspace{1cm}  \( ii \) = with POAG  \hspace{1cm}  \( P \) : significant at \( \leq 0.05 \) (ANOVA)

ChBVel = Choroidal blood velocity  \hspace{1cm}  R = Mean vascular resistance  \hspace{1cm}  ChBVol = Choroidal blood volume  \hspace{1cm}  a.u = arbitrary units  \hspace{1cm}  ChBF = Choroidal blood flow  \hspace{1cm}  DC = Direct Currency
**Results**

![Graph showing distribution of ChBF (a.u.)](image1)

**Fig. 12.** Distribution of the ChBF (a.u.) in the different studied groups.

![Graph showing distribution of DC](image2)

**Fig. 13.** Distribution of the DC in the different studied groups.
Fig. 14. Distribution of the LDF parameters among the normal population.

a) ChBVel
b) ChBVol
c) ChBFlow
5.3. Correlations between each of the LDF parameters and clinical variables of the subjects

5.3.1 Correlations between each of the LDF parameters and age, IOP and PP respectively in normal population.

Table 4 reveals significant correlation between the PP and the R. However, no other significant correlations between each of the choroidal LDF parameters and any of the studied variables were demonstrated. Figures 15 and 16 demonstrate scatter plot association between ChBF and the age and PP respectively. No significant association was noted between the studied variables.

<table>
<thead>
<tr>
<th>LDF parameter</th>
<th>AGE (Years)</th>
<th>IOP (mmHg)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
<td>t</td>
</tr>
<tr>
<td>ChBVel (kHz)</td>
<td>0.48</td>
<td>NS</td>
<td>0.26</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.36</td>
<td>NS</td>
<td>0.14</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>0.24</td>
<td>NS</td>
<td>1.00</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>0.33</td>
<td>NS</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Correlation is Significant at \( p \leq 0.05 \)
NS = Non significant

Fig. 15. Linear correlation between the ChBF and the age in the control group. \((r = 0.098, p=0.33)\)

Fig. 16. Linear correlation between the ChBF and the PP in the control group. \((r = 0.049, p=0.63)\)
5.3.2. Correlations between each of the LDF parameters and IOP, PP and C/D respectively in POAG and OHT patients

Multiple regression analysis was used also to examine the relation between each of LDF parameters as the dependent variables and IOP, PP and C/D respectively as predictor variables in patients with POAG or OHT. Table 5 and 6 reveal no significant correlation among the studied variables in either group.

**Table 5.** Multiple regression analysis showing correlations between each of the LDF parameters and IOP, PP and C/D respectively in POAG patients.

<table>
<thead>
<tr>
<th>LDF parameter</th>
<th>IOP (mmHg)</th>
<th>PP (mmHg)</th>
<th>C/D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
<td>t</td>
</tr>
<tr>
<td>ChBVel (kHz)</td>
<td>1.15</td>
<td>NS</td>
<td>1.37</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.24</td>
<td>NS</td>
<td>0.16</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>0.87</td>
<td>NS</td>
<td>0.15</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>0.62</td>
<td>NS</td>
<td>1.25</td>
</tr>
</tbody>
</table>

*Correlation is Significant at *p* ≤ 0.05 NS = Non significant*

**Table 6.** Multiple regression analysis showing correlations between each of the LDF parameters and IOP, PP and C/D respectively in OHT patients.

<table>
<thead>
<tr>
<th>LDF parameter</th>
<th>IOP (mmHg)</th>
<th>PP (mmHg)</th>
<th>C/D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
<td>t</td>
</tr>
<tr>
<td>ChBVel (kHz)</td>
<td>0.11</td>
<td>NS</td>
<td>1.20</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>1.97</td>
<td>NS</td>
<td>1.33</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>1.67</td>
<td>NS</td>
<td>0.94</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>1.76</td>
<td>NS</td>
<td>1.67</td>
</tr>
</tbody>
</table>

*Correlation is Significant at *p* ≤ 0.05 NS = Non significant*


5.4. Analysis of LDF data of POAG and OHT groups

All the measured circulatory parameters (ChBVel, ChBVol, and ChBF) were significantly reduced and the R was increased in the patients with NTG, HTG or OHT, in comparison to age matched controls, while there was no statistically significant difference among the three groups using post hoc Bonferroni test for multiple comparisons (Table 7). Descriptive analysis of the studied groups is demonstrated in box blot graph (Fig. 17).

Table 7. LDF parameters (mean±SD) in control group, NTG, HTG and OHT patients (One way ANOVA analysis)

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (1)(n=100)</th>
<th>NTG (2)(n=34)</th>
<th>HTG (3)(n=51)</th>
<th>OHT (4)(n=25)</th>
<th>ANOVA (P value)</th>
<th>Post hoc test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>&lt; 0.05</td>
<td>1-2,1-3,1-4</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.1</td>
<td>0.14 ± 0.06</td>
<td>0.14 ± 0.1</td>
<td>0.13 ± 0.05</td>
<td>&lt;0.01</td>
<td>1-2,1-3,1-4</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>4 ± 1</td>
<td>4 ± 2</td>
<td>3 ± 1</td>
<td>&lt;0.01</td>
<td>1-2,1-3,1-4</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>7 ± 2</td>
<td>16 ± 8</td>
<td>16 ± 7</td>
<td>15 ± 6</td>
<td>&lt;0.01</td>
<td>1-2,1-3,1-4</td>
</tr>
</tbody>
</table>

a.u= arbitrary units

*Bonferroni test for multiple comparisons (P : significant at ≤ 0.05)

Fig. 17. Box plots show the median, interquartile range, outliers, and extreme cases of ChBF in control, NTG, HTG and OHT groups
5.5. Analysis of LDF data of diabetic patients

The three choroidal circulatory parameters (ChBVel, ChBVol, and ChBF) and the R differed significantly among the three analyzed groups (diabetics without and with POAG and the controls) as revealed by one way ANOVA analysis (Table 8).

Using the Bonferroni test for multiple comparisons, the diabetic patients showed statistically significant reduction of the all circulatory parameters with significant increase in the R in comparison to age matched controls. Meanwhile, there was no significant difference in any parameter between the two subgroups of diabetics (without and with POAG). To clarify the effect of DM as a risk factor in the glaucomatous patients, the analyzed data of the diabetic patients with glaucoma were compared with those of glaucoma without DM. Significant reduction of the ChBF and increased R were noted in the glaucoma group with DM (Table 9).

<table>
<thead>
<tr>
<th>Table 8. LDF parameters (mean±SD) in the control group, diabetic patients without POAG and diabetic patients with POAG (ANOVA test).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDF Parameter</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ChBVel (kHz)</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
</tr>
<tr>
<td>R (a.u)</td>
</tr>
</tbody>
</table>

**Significance**: at the level of \( p \leq 0.05 \)
Table 9. LDF parameters (mean±SD) of the controls, diabetic patients (without and with POAG) and glaucoma patients (Bonferroni test for multiple comparisons).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (n=100)</th>
<th>p</th>
<th>DM (n=68)</th>
<th>p</th>
<th>DM+POAG (n=25)</th>
<th>p</th>
<th>POAG (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>&lt;0.05</td>
<td>1.1 ± 0.5</td>
<td>NS</td>
<td>1.2 ± 0.5</td>
<td>NS</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.1</td>
<td>&lt;0.01</td>
<td>0.12 ± 0.06</td>
<td>NS</td>
<td>0.11 ± 0.07</td>
<td>NS</td>
<td>0.14 ± 0.06</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>&lt;0.01</td>
<td>3 ± 1</td>
<td>NS</td>
<td>3 ± 1</td>
<td>&lt;0.05</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>7 ± 2</td>
<td>&lt;0.01</td>
<td>23 ± 12</td>
<td>NS</td>
<td>22 ± 9</td>
<td>&lt;0.01</td>
<td>16 ± 7</td>
</tr>
</tbody>
</table>

NS = Non Significant at the level of 0.05  
Significance: at the level of $p \leq 0.05$

Table 10 shows the comparison of the LDF parameters among diabetic patients with different grades of retinopathy. There was a tendency of the circulatory parameters to decrease and the R to increase with more advanced diabetic grade. However, one way ANOVA analysis showed no statistically significant difference among the four subgroups

Similarly, we did not find any significant difference in the measured parameters between patients with type I or type II DM (Table 11). Moreover no significant correlation was detected between the duration of diabetes and the ChBF (Fig. 18).

Table 10. Comparison of LDF parameters (mean±SD) among diabetic patients with different grades of retinopathy (ANOVA test).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>G0 (n=22)</th>
<th>G1 (n=17)</th>
<th>G2 (n=14)</th>
<th>G3 (n=15)</th>
<th>ANOVA (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.1 ± 0.8</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.5</td>
<td>1.0 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.12 ± 0.06</td>
<td>0.12 ± 0.06</td>
<td>0.11 ± 0.05</td>
<td>0.09 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>3 ± 1.2</td>
<td>3 ± 1.1</td>
<td>3 ± 1.2</td>
<td>3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>22 ± 10</td>
<td>23 ± 7</td>
<td>23 ± 11</td>
<td>25 ± 12</td>
<td>NS</td>
</tr>
</tbody>
</table>

G0=Non diabetic retinopathy  
G1=Mild/Moderate non proliferative diabetic retinopathy  
G2=Severe non proliferative diabetic retinopathy  
G3=Proliferate diabetic retinopathy  
NS = Non significant
## Results

**Table 11.** Comparison of LDF parameters (mean±SD) between patient with type I and type II DM.

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>TYPE I (n=20)</th>
<th>TYPE II (n=48)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.11 ± 0.03</td>
<td>0.12 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>2.9 ± 0.7</td>
<td>3 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>23 ± 7</td>
<td>22 ± 10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Unpaired t test, significance at p ≤ 0.05  
NS = Non significant.

**Fig. 18.** Linear correlation between the duration of DM and the ChBF in diabetic patients (r = -0.9, p=0.52).
5.6. Analysis of LDF data of hypertensive patients

Our results demonstrated significant differences of the LDF parameters between the hypertensive patients and age matched controls (Table 12). Using Bonferroni test, we noticed that the all measured LDF parameters were significantly reduced and the R was increased in the patients with SHT compared to age matched controls, while there was no statistically significant difference between hypertensive patients without and with POAG except in the R which was significantly increased in hypertensive patients with glaucoma. We also noticed significant reduction in the ChBF and increased R in glaucomatous patients with SHT compared to glaucomatous patients without SHT (Table 13).

### Table 12. LDF parameters (mean±SD) in the control group, SHT patients without POAG and SHT patients with POAG (ANOVA test).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (n=100)</th>
<th>SHT (n=27)</th>
<th>SHT +POAG (n=30)</th>
<th>ANOVA (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.10</td>
<td>0.18 ± 0.34</td>
<td>0.16 ± 0.08</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>7 ± 2</td>
<td>18 ± 7</td>
<td>26 ± 14</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Significance: at the level of \( p \leq 0.05 \)

### Table 13. LDF parameters (mean±SD) of the controls, SHT group (without and with POAG) and POAG group (Bonferroni test for multiple comparisons).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (n=100)</th>
<th>SHT (n=27)</th>
<th>SHT +POAG (n=30)</th>
<th>POAG (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>NS</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.1</td>
<td>0.18 ± 0.3</td>
<td>NS</td>
<td>0.14 ± 0.06</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>3 ± 1</td>
<td>NS</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>R(a.u)</td>
<td>7 ± 2</td>
<td>18 ± 7</td>
<td>&lt; 0.05</td>
<td>16 ± 7</td>
</tr>
</tbody>
</table>

NS = Non Significant. Significance: at the level of \( p \leq 0.05 \)
5.7. Analysis of LDF data of myopic subjects

One way ANOVA test revealed a significant difference in the measured choroidal LDF parameters among the myopic subjects (without and with POAG) and the age matched controls (Table 14).

With Bonferroni test, the myopic eyes revealed significantly reduced LDF parameters and increased R in comparison to age matched controls. These parameters did not differ significantly between myopic subjects without and with POAG. Compared to emmetropic glaucomatous patients, significant reduction of the ChBVol and ChBF and increased R were recorded in glaucomatous myopic patients (Table 15).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (n=100)</th>
<th>Myopia (n=17)</th>
<th>Myopia +POAG (n=12)</th>
<th>ANOVA (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.10</td>
<td>0.11 ± 0.08</td>
<td>0.08 ± 0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>2 ± 1</td>
<td>2 ± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>7 ± 2</td>
<td>24 ± 9</td>
<td>26 ± 9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Significance : at the level of p ≤ 0.05

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>Control (n=100)</th>
<th>Myopia (n=17)</th>
<th>Myopia +POAG (n=12)</th>
<th>POAG (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>NS</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.27 ± 0.1</td>
<td>0.11 ± 0.08</td>
<td>NS</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>8 ± 2</td>
<td>2 ± 1</td>
<td>NS</td>
<td>2 ± 0.7</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>7 ± 2</td>
<td>24 ± 9</td>
<td>NS</td>
<td>26 ± 9</td>
</tr>
</tbody>
</table>

NS = Non Significant. Significance : at the level of p ≤ 0.05
5.8. **Comparison of baseline LDF data of groups with various glaucoma risk factors.**

Comparing the effect of various risk factors (HTG, DM, SHT and myopia) on the choroidal hemodynamics using one way ANOVA analysis revealed significant difference in the ChBF and the R among the four groups (Fig. 19). The reduction in the ChBF and the increased R are most marked in diabetic and myopic patients when compared with the glaucomatous group. On the other hand there was no significant difference among the different groups as regard the ChBVel and ChBVol (Table 16).

### Table 16. Comparison of baseline LDF data (mean±SD) of groups with various glaucoma risk factors (HTG, DM, SHT and myopia).

<table>
<thead>
<tr>
<th>LDF Parameter</th>
<th>HTG (1) (n=51)</th>
<th>DM (2) (n=68)</th>
<th>SHT (3) (n=27)</th>
<th>Myopia (4) (n=17)</th>
<th>ANOVA (P value)</th>
<th>Post hoc Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel (kHz)</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>ChBVol (a.u)</td>
<td>0.14 ± 0.1</td>
<td>0.12 ± 0.1</td>
<td>0.18 ± 0.3</td>
<td>0.11 ± 0.1</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>ChBF (a.u)</td>
<td>3.8 ± 2.4</td>
<td>2.8 ± 1.1</td>
<td>3.3 ± 1</td>
<td>2.3 ± 1</td>
<td>&lt;0.01</td>
<td>1-2,1-4</td>
</tr>
<tr>
<td>R (a.u)</td>
<td>16 ± 7</td>
<td>23 ± 12</td>
<td>18 ± 7</td>
<td>24 ± 9</td>
<td>&lt;0.01</td>
<td>1-2,1-4</td>
</tr>
</tbody>
</table>

*NS = Non Significant at the level of 0.05 *(Bonferroni t test for multiple comparisons)*

**Fig. 19.** ChBF (a.u) in HTG, DM, SHT and myopia groups (data are presented as mean ± SD). There is significant decrease of the ChBF in the diabetic and myopic groups in comparison with the HTG group (p<0.01).
6. DISCUSSION

The role of vascular factors in the pathogenesis of glaucoma continues to be an active area of research. The identification of circulatory disorders, vascular risk factors and compromised blood flow in glaucoma patients firmly link impaired ocular perfusion to glaucomatous damage. The development of new techniques such as LDF to evaluate the ocular circulation has greatly improved our ability to obtain high quality measurements of ocular blood flow.

In this clinical study, different groups of glaucoma patients were investigated by LDF to measure the choroidal circulation and to correlate the obtained parameters with a number of glaucoma predictor variables such as IOP and PP. Moreover, this study assessed the angiopathic effect of glaucoma risk factors (DM, SHT and myopia) on choroidal circulation and subsequently their role in GON.

6.1. Correlations between each of LDF parameters and age and PP, respectively, in the normal population

6.1.1. Age

Our data revealed that there is no significant correlation between ChBF and the age (Fig. 15, page 44). These results are in agreement of other studies demonstrating that the age has no effect on ChBF (Pournaras et al., 2006; Riva et al., 1994; Schocket et al., 2004). However, the results of the current study do not agree with many authors revealing a negative correlation between the age and ChBF using different techniques such as POBF measurement (Dallinger et al., 1998; Lam et al., 2003; Ravalico et al., 1996) and LDF (Grunwald et al., 1998a; Niknam et al., 2004; Straubhaar et al., 2000).
6.1.2. PP

With regard to the PP, our findings demonstrated that there is no significant correlation between the PP and ChBF in normal population (Fig. 16, page 44). These findings support that the choroidal circulation has a regulatory capacity that maintain constant ChBF in spite of some changes in the PP. This maintenance may be achieved through an increase in choroidal vascular resistance (Riva et al., 1997b).

Investigations in rabbits, in which systemic blood pressure had been manipulated, demonstrated a nonlinear relationship between ChBF and PP suggesting that the choroid may well have some capability to autoregulate in this animal (Kiel and van Heuven, 1995). Not only rabbits exhibit some autoregulation in the choroid but also humans can do. Many investigators have suggested that the relationship between choroidal circulatory parameters and PP is not linear across the whole range of PP in normals due to some autoregulatory potency of the choroidal circulation (Hasler et al., 2002; Niknam et al., 2004; Riva et al., 1994; Riva et al., 1997c; Schocket et al., 2004).

6.2. LDF data of POAG and OHT groups

6.2.1. LDF data of POAG compared to controls

To our knowledge, only few studies have been conducted to detect the subfoveal ChBF in glaucomatous patients using LDF technique. Our data demonstrated that all LDF parameters are significantly lower with increased R in the glaucomatous patients compared with the control subjects. Reduced blood flow to the posterior pole of the glaucomatous eye has been reported by many authors using other different techniques for the assessment of ChBF (Agarwal et al., 2003; Duijm et al., 1997;
Discussion

Fuchsjager-Mayrl et al., 2004; Kerr et al., 1998; Nicolela et al., 1996b). On the other hand, it was revealed that the ChBF measurements obtained in the foveola of glaucomatous eyes were no significantly different from those of normals (Grunwald et al., 1998b). However, the authors mentioned that the small sample size (19 patients) in this study might be too small to demonstrate significance.

The possible hemodynamic effect of the antiglaucoma medication on choroidal circulation should be considered in HTG patients. However, most of NTG patients were not yet under medications. In spite of this fact, the two subgroups (HTG and NTG) showed a similar reduction of the LDF parameters, suggesting that the choroidal circulatory alterations are not related to the drug effects. This suggestion is supported by other studies demonstrating no significant difference in ChBF between treated and untreated glaucoma subjects (Fuchsjager-Mayrl et al., 2004; Zeitz et al., 2004), which assumed that the vascular changes in glaucoma are more likely a result of the glaucomatous process rather than of its treatment. However, the possible vascular effect of the anti glaucoma drugs on the ChBF is still a matter of debate and needs to be further clarified.

6.2.2. LDF data of OHT compared to the controls and POAG patients

The studies of ocular hemodynamic in OHT patients show conflicting results. Some studies agree with our results, demonstrating a significant reduction of ChBF in OHT patients compared to normal subjects with no significant difference in measurements between OHT and POAG patients (Fuchsjager-Mayrl et al., 2004; Kerr et al., 2003). Other studies found POBF (Kerr et al., 1998; Trew and Smith, 1991) and posterior ciliary artery (PCA) circulation (Akarsu and Bilgili, 2004) did
not differ significantly between normotensive and ocular hypertensive groups. These studies revealed a significant difference in the choroidal circulatory parameters between OHT and glaucoma groups.

In summary, the findings of our study support the assumption that choroidal vascular abnormalities are an early event in the process of glaucoma and hence, the importance of monitoring closely the OHT patients whose IOP over 25 mmHg as they may get benefit from the prophylactic treatment of lowering the IOP (Fuchsjager-Mayrl et al., 2004).

### 6.2.4. Correlations between each of LDF parameters and IOP, PP, respectively, in POAG and OHT patients

The data of the study showed no significant correlation between each of the subfoveal LDF parameters and any of the independent variables (IOP and PP) neither in the glaucoma group nor in the OHT one (see table 5 and 6, page 45). Therefore, factors other than IOP elevation or PP reduction must be involved in the initiation and progression of the vascular dysregulation in glaucoma, especially if we know that the ischemic damage of the neurons in the CNS is histopathologically similar to changes seen in glaucoma. Further, glaucoma patients with normal IOP show clear evidence for cerebral and ocular ischemia (Harris et al., 2001). The results of the present study also support the hypothesis that assumes some autoregulation in patients with POAG during a moderate increase in IOP (Weigert et al., 2005).
6.3. **LDF data of diabetic patients**

6.3.1. **LDF data of diabetic patients without POAG**

Our findings are in agreement with other studies demonstrating significant reduction of choroidal LDF parameters in patients with non diabetic retinopathy (NDR), non proliferative diabetic retinopathy (NPDR) (*Nagaoka et al.*, 2004) and proliferative diabetic retinopathy (PDR) (*Schocket et al.*, 2004). As the measurements obtained by LDF correspond primarily to determination of choriocapillary flow, our findings of decreased ChBF values obtained in the NDR group suggest that the circulatory changes in the choriocapillaris may occur before the clinical manifestations of DR. Previous histopathological studies demonstrated the dropout of the choriocapillaris in diabetic eyes which could increase vascular resistance resulting in decreased blood flow in the choriocapillaris (*McLeod and Lutty*, 1994).

The results of studies concerning the effect of severity of DM on the choroidal hemodynamics are conflicting. POBF was reported to decrease (*Langham et al.*, 1991) or increase significantly with the severity of retinopathy (*Findl et al.*, 2000). A recent study demonstrated no significant changes in PCA circulation measured by CDI with the progression of DR (*Dimitrova et al.*, 2003). Although there was tendency of the LDF parameters to decrease and R to increase with progression of diabetes, no significant difference was demonstrated in the LDF parameters among diabetic patients with different grades of retinopathy (see table 10, page 48). Also we did not find a significant correlation between subfoveal ChBF and the duration of DM (see figure 18, page 49).
6.3.2. LDF data of diabetic patients with POAG

Compared to non diabetic glaucomatous patients, the diabetic patients with POAG show statistically significant reduction of the ChBF and increased R (see table 9, page 48). To our knowledge, no studies have been conducted to assess the subfoveal choroidal circulation in diabetic patients with glaucoma. However, the speed of blood perfusion and the pulsation curve in ciliary arteries were measured using Doppler ultrasonography in patients treated for glaucoma and diabetes. It was assumed that the increase of the IOP reveals a larger and earlier impairment of the regulating mechanism of the ciliary microcirculation in diabetic patients with glaucoma in comparison with the group of glaucomatous patients without diabetes (Augustyniak and Swietliczko, 1991).

The biological mechanism by which DM can affect the glaucomatous process is still unclear. The effect of diabetes on small blood vessel disease or systemic blood abnormalities can result in compromised vascular perfusion to the optic nerve, which increases the risk of GON (Wilson and Martone, 1996). Although epidemiological studies have not reached firm conclusions, recent basic studies strongly indicate that diabetes could be a risk factor of GON by compromising the glial and neuronal activities of the retina (Nakamura et al., 2005).
6.4. **LDF data of hypertensive patients**

6.4.1. **LDF data of hypertensive patients without POAG**

In the current study, we demonstrated that LDF parameters are significantly decreased and R is increased in hypertensive patients, under antihypertensive therapy, when compared with age matched controls (see table 13, page 50). These findings do not agree with the results of a recent study measuring the choroidal LDF parameters in hypertensive patients controlled by antihypertensive therapy. The authors assumed that SHT does not seem to have a significant effect on the choroidal circulation in those patients. They mentioned that the small sample size (15 patients) might not be able to give a strong conclusion (Niknam et al., 2004). However, further studies are needed to examine whether SHT or its treatment have an effect on the ChBF of hypertensive patients.

6.4.2. **LDF data of hypertensive patients with POAG**

To our knowledge, assessment of choroidal blood flow in glaucoma patients with SHT has not been previously reported. We found that there is no significant difference in the LDF parameters between hypertensive patients (under medical therapy) without and with glaucoma. These finding may assume persistence of some regulatory mechanisms in hypertensive patients in response to glaucoma. Compared with the glaucomatous group, the hypertensive patients with POAG, showed statistically significant reduction in the ChBF and increased R (see table 13, page 54). These results might suggest that SHT or antihypertensive therapy is an important systemic vascular risk factor that can lead to more vascular dysregualtion in glaucomatous eye.
6.5. **LDF data of myopic subjects**

### 6.5.1 LDF data of myopic subjects without POAG

A significant reduction of LDF parameters and increased R were demonstrated in myopic eyes when compared with the age matched controls (see table 15, page 51). ChBF was reported to decrease as the axial length increases using Langham ocular blood flow computerized tonometry (*James et al., 1991*). Another study reported a reduced PCA circulation in highly myopic patients (*Akyol et al., 1996*). The authors assumed that the reduced ChBF may be partly due to increased vascular resistance.

The exact mechanisms underlying the development of myopia and myopic retinopathy are largely unknown. However, the altered ChBF in high myopia could have a role in the retinopathy that occurs in high myopia. Whether the reduced ChBF in high myopia is a result of axial elongation of the eyeball or could possibly be involved in the development of high myopia is not known.

### 6.5.2 LDF data of myopic subjects with POAG

To our knowledge, assessment of subfoveal ChBF in glaucoma patients with myopia has not been demonstrated in previous studies. However, studies of PCA velocities in myopic patients without and with POAG are conflicting. PCA velocities were demonstrated to decrease similarly with no significant difference between both subgroups of myopic eyes (without and with glaucoma) (*Galassi et al., 1998*). On the other hand, PCA velocities were recorded to decrease significantly in myopic eyes with POAG in comparison to myopic eyes without POAG (*Karczewicz and Modrzejewska, 2004*). In the present study, no
significant difference was revealed in the LDF parameters between myopic patients without and with POAG. A significant reduction of the ChBVol and ChBF and increased R were noted in the group of myopia with POAG when compared with glaucomatous emmetropic patients (see table 15, page 51).

One hypothesis suggested that in glaucoma patients, the longer the axial eye length and the thinner the ocular wall the more reduced the retinal and choroidal microcirculation. The reduced microcirculation found in myopic glaucomatous eyes might contribute to the development of glaucomatous damage in these eyes (Nemeth et al., 2001).

### 6.6. Comparison of baseline LDF data of groups with various glaucoma risk factors.

Finally, we compared the effects of the various studied risk factors (HTG, DM, SHT and myopia) on the choroidal hemodynamics.

Diabetic and myopic patients showed the most marked reduction in the LDF parameters and increased R when compared with the glaucomatous group. On the other hand, there was no significant difference in ChBVel or ChBVol among the different groups (see table 16, page 52).

These results indicate that other factors, not necessary related to glaucoma, may influence ocular blood flow findings and therefore altered blood flow parameters may not necessary be associated with glaucomatous damage. As so many glaucoma patients have systemic diseases, care should be taken when relating reduced blood flow parameters to glaucomatous damage (Ferdinand et al., 1999).
7. Summary, Conclusions and Recommendations

7.1. Summary

Glaucomatous optic neuropathy (GON) is characterized by progressive loss of retinal ganglion cells, including their axons, and by tissue remodeling of the optic nerve head. This is followed by visual-field defects. Traditionally, diagnosis and treatment has been directed towards lowering the IOP, which has been considered the most important risk factor. However, not all patients with glaucomatous damage have an elevated IOP, and progression of GON may occur even at IOP in the low teens. These facts challenge the pathophysiological concept of glaucoma based only on IOP. Hence disturbed ocular blood flow has been regarded as a potential risk factor of great interest.

In the present study, we have assessed the choroidal hemodynamic changes in glaucoma patients (high and normal tension glaucoma) and in patients with ocular hypertension. Also we have studied the effect of glaucoma risk factors on subfoveal choroidal circulation to determine its role in the pathogenesis of GON. Among the many risk factors described, DM, systemic hypertension (SHT) and myopia deserved special attention for the following reasons:

- They are often associated with glaucoma.
- Their role in glaucomatous damage or progression of the disease is controversial.
- Control of DM and SHT may influence the progression of the disease.

Furthermore, we studied the relations between the measured subfoveal choroidal hemodynamic parameters and certain clinical findings of glaucoma patients to determine the predictive role of theses
parameters in the diagnosis of glaucoma and assessment of its progression.

The current study was carried out at the Geneva Ophthalmology Clinic, Switzerland. It included 389 patients (190 males and 199 females) whose age ranged from 14 to 90 years and the IOP from 10 to 28 mmHg. All patients were subjected to history taking with special attention to general medical history, full ophthalmological examination, including visual acuity (unaided and aided), refraction, applanation tonometry, anterior segment examination, gonioscopy and fundus examination.

The subjects were classified into three main groups: 1) group of subjects with POAG or OHT, which further subdivided into three subgroups (HTG, NTG and OHT), 2) group of subjects with glaucoma risk factors which subdivided into diabetic, hypertensive and myopic subgroups. Subjects with each risk factor were further subdivided into two subgroups (without and with POAG), 3) group of age matched healthy controls. The subfoveal choroidal LDF parameters (ChBVel, ChBVol, and ChBF) and choroidal vascular resistance (R) were assessed in all subjects (see page 36).

**Summary of the results**

We studied baseline subfoveal choroidal LDF parameters and established correlations between these parameters and R, one side, and a number of characteristics (age, IOP, and PP) in the normal population, POAG and OHT patients on the other side. Apart from the positive correlation between PP and R in the normal population, we found no significant correlation between any of the three patients’ characteristics and either one of the LDF parameters, in any of the studied groups.
Summary and Conclusion

All LDF parameters were significantly reduced and the R was increased in the patients with HTG, NTG or OHT when compared with age matched controls, while there was no statistically significant difference in the LDF parameters among the three groups. Patients with glaucoma risk factors (diabetic, hypertensive, and myopic patients) revealed significant reduction of all measured LDF parameters and increased R when compared with the control group.

Although there was a tendency of the LDF parameters to decrease and the R to increase in the more advanced diabetic stage, the difference did not reach the significant level among various grades of diabetic retinopathy. Similarly there was no significant difference in the choroidal LDF parameters between both types of diabetes. Moreover, no correlation was found between the duration of DM and ChBF.

Analysis of the results of patients with glaucoma risk factors revealed, generally, no statistically significant difference in the LDF parameters between the two subgroup of each risk factor (without and with POAG). However, hypertensive patients with POAG showed significantly increased R in comparison with hypertensive patients without POAG.

The LDF data of glaucomatous patients with risk factors demonstrated significant reductions of ChBF and increase of the R in comparison to glaucomatous patients without risk factors. In addition, significant reduction of the ChBVol was observed in myopic patients with glaucoma.

Lastly, the collected data from patients with different risk factors (HTG, DM, hypertension and myopia) revealed that the reduction in ChBF and the increased R were most marked in diabetic and myopic patients when compared with the glaucomatous group. On the other hand
there was no significant difference in ChBVel and ChBVol among the different groups.

7.2. Conclusions

We may summarize our conclusions in the following points:

1. The results of the current study clearly reveal alterations of the subfoveal choroidal LDF parameters in POAG and OHT patients. These alterations appear to be an early manifestation in glaucomatous patients. They are neither affected by IOP nor by pharmacological intervention, as we noted altered LDF parameters in patients with treated HTG, untreated NTG and OHT.

2. The development of GON seems to be multifactorial. Combined occurrence of two or more risk factors such as slightly increased IOP together with myopia or DM might often lead to damage much more than occurred by marked IOP elevation alone. In the current study, *glaucomatous patients with risk factors* such as DM, SHT, or myopia reveal significant reductions of ChBF and increase of the R in comparison to *glaucomatous patients without risk factors* (see tables 9, 13, and 15, pages 48, 50 and 51). Such data suggest that the impaired choroidal circulation caused by these risk factors might be an important additional risk factor involved in the glaucomatous damaging process.

3. Other factors, not necessarily related to glaucoma may alter the choroidal LDF parameters. In other words, not all the cases of altered ocular blood flow develop GON. Therefore other factors, besides vascular insufficiency, seem to be responsible for the glaucomatous damage.
4. Although our present study cannot comprehensively address the nature of the mechanisms controlling subfoveal choroidal blood flow, it is nonetheless evident from our findings that an increase in the PP is not accompanied by an equivalent increase in ChBF. Also there was no significant difference in most of the LDF parameters between the risky patients without and with glaucoma. These data strongly support the presence of some blood flow autoregulation in the human choroid. Previous studies suggest a neural or passive process rather than a myogenic or metabolic mechanism (Riva et al., 1997c). Also, it is evident that this autoregulatory mechanism is also present in old age subjects, POAG, and OHT patients.

5. Our data support the contention that significant changes in choroidal microcirculation occur during the pathogenesis of diabetic retinopathy, even before the appearance of the signs of retinopathy.

6. Our findings may raise concerns that SHT or antihypertensive drugs may affect the choroidal blood flow leading to compromised ocular perfusion which may be a risk factor for GON.

7. Although LDF does not provide absolute measurements of flow, it is noninvasive method that appears to provide continuous and sensitive measurements of relative choroidal blood flow in the foveal region of the human fundus. Therefore, LDF can be considered to be an attractive non-invasive tool for investigation of the alterations in the choroidal circulation in physiological and many pathological conditions.

8. However, validation and interpretation of the published data are difficult. Also, it remains unclear wither alterations of ChBF just accompany the GON or encroach on axonal survival of the optic nerve. In addition, the influence of additional factors such as sex, plasma levels of endothelin, and systemic blood pressure remains to be clarified.
Nevertheless, there is overwhelming evidence that subfoveal choroidal blood flow in patients with GON is altered. Thus, vascular evaluation seems to be meaningful for glaucoma patients whose disease progresses despite controlled IOP.

7.3. Recommendations

Due to the fact that we are dealing with multifactorial disease, it is more meaningful in the clinical practice to proceed as follows:

- Quantification of glaucomatous damage.
- Analysis of risk factors which might have contributed to such damage.
- Initiation of the treatment according to weighting of associated risk factors.

Much further researches are needed for the following purposes:

- Better understanding of the pathogenic mechanism and how it may be different in various cases. This is needed to predict more successfully an individual’s risk of glaucomatous damage, to make decisions about the aggressiveness of treatment, and one day to direct therapy at the type of vascular abnormality present in addition to or instead of lowering IOP.
- Confirmation of the predictive and prognostic values of reduced choroidal hemodynamic in glaucomatous process.
- Understanding of the physiology of vascular regulatory mechanism in different parts of the eye.
8. REFERENCES


References


