

Anterior-chamber hypoxia and iris vasculopathy in pseudoexfoliation syndrome*

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Abstract. Iris vasculopathy is a well-recognized clinical feature in pseudoexfoliation syndrome (PES). In the present study we examined the morphology of the iris vasculature in PES using electron microscopy and we tested whether these iris vascular changes were correlated with an impaired oxygen supply to the anterior chamber. In the affected vessels we found a gradual degeneration of vascular cells, progressing from adventitial to endothelial cells, associated with the production of excess extracellular material, including pseudoexfoliative fibers. Oxygen partial pressure (pO_2) was measured in the anterior chamber during cataract surgery using a polarographic oxygen electrode in eyes with and without PES. The pO_2 value measured in the anterior chamber of 10 eyes without PES was 45 ± 11 mmHg (mean \pm SD) in the chamber angle, 33 ± 12 mmHg in front of the pupillary margin, and 13 ± 8 mmHg in the center of the pupil. This spatial distribution of pO_2 indicates that aqueous humor oxygenation occurs along the anterior iris surface. The mean pO_2 values obtained in 8 patients with PES were 19 ± 6 mmHg in the chamber angle, 16 ± 4 mmHg in front of the pupillary margin, and 8 ± 3 mmHg in the center of the pupil. We conclude that anterior-chamber hypoxia due to iris vasculopathy may represent a complication of PES that could play a role in the pathogenesis of PES-associated alterations in the anterior segment of the eye.

Key words: Pseudoexfoliation syndrome – Electron microscopy – Oxygen – Hypoxia – Iris vasculopathy

Zusammenfassung. Veränderungen der Irisgefäße gehören zum klinischen Bild des Pseudoexfoliationssyndroms (PES). In der vorliegenden Arbeit haben wir die Morphologie des Irisgefäßsystems bei PES mit Hilfe der Elektronenmikroskopie analysiert und untersucht, ob diese Gefäßveränderungen mit Veränderungen der Sauerstoff-

versorgung der Vorderkammer einhergehen. Die morphologischen Untersuchungen ergaben eine von der Adventitia zu den Endothelzellen fortschreitende zelluläre Degeneration. Diese war assoziiert mit einer übermäßigen Produktion von extrazellulärem Material, insbesondere Pseudoexfoliationsfibrillen. Der Sauerstoffpartialdruck (pO_2) in der Vorderkammer von Augen mit und ohne PES wurde im Rahmen von Kataraktoperationen mit Hilfe von polarographischen Elektroden gemessen. Der pO_2 in 10 Augen ohne PES betrug 45 ± 11 mm Hg (Mittelwerte \pm SD) im Kammerwinkel, 33 ± 12 mm Hg vor dem Pupillarsaum und 13 ± 8 mm Hg vor der Pupillenmitte. Diese räumliche Verteilung des pO_2 im Kammerwasser kann durch eine Sauerstoffsättigung des Kammerwassers an der Irisvorderfläche erklärt werden. Die Mittelwerte des pO_2 bei 8 Patienten mit PES betragen 19 ± 6 mm Hg im Kammerwinkel, 16 ± 4 mm Hg vor dem Pupillarsaum und 8 ± 3 mm Hg vor der Pupillenmitte. Wir folgern, daß eine Hypoxie in der Vorderkammer aufgrund einer Irisvasculopathie eine Komplikation dieser Erkrankung darstellt, die eine Rolle in der Pathogenese der Veränderungen des vorderen Augenabschnittes bei PES spielen könnte.

Schlüsselwörter: Pseudoexfoliationssyndrom (PES) – Elektronenmikroskopie – Sauerstoff – Hypoxie – Irisvasculopathie

Introduction

Pseudoexfoliation syndrome (PES) is a common disorder of unknown etiology affecting elderly patients. Its most prominent clinical feature is the deposition of abnormal pseudoexfoliative (PE) material on the anterior lens surface and on the pupillary margin of the iris. The distribution of PE material has been studied extensively and comprises not only the known intraocular sites [16] but also various extraocular tissues throughout the body, suggesting that PES is a systemic disorder [24, 32].

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The pathophysiology of PES is of more than academic interest because this syndrome is associated with serious complications such as spontaneous lens dislocation or subluxation due to increased zonular fragility, poor pupillary dilation, and blood-aqueous barrier failure. PES-associated glaucoma represents a distinct subgroup of the glaucomas that is difficult to treat medically and often requires surgery. Moreover, PES is a risk factor for zonular dialysis and vitreous loss in cataract surgery [17, 18].

Iris vasculopathy is a well-recognized clinical feature in PES and may be relevant to the pathogenesis of this disorder. Iris atrophy was recognized as early as in 1917 by Lindberg [13] in his first description of this condition. Fluorescein angiography of the anterior segment of PES patients has revealed iris vessel dropout associated with new vessel formation and fluorescein leakage [1, 2, 33]. Electron microscopy has revealed abnormal accumulation of PE material in the walls of the stromal blood vessels [20, 21, 27], which ultimately leads to vascular disorganization and endothelial degeneration [5, 28, 29].

It has recently been shown that the oxygen saturation of the aqueous humor in the anterior chamber of the human eye occurs at the anterior iris surface [6]. The lens, the posterior cornea, and the chamber angle structures, which lack their own blood vessels, depend on the oxygen and nutrient supply by the aqueous humor. Thus, the iris vasculature not only supplies for the metabolic demands of the iris itself but also delivers oxygen to the nonvascularized tissues lining the anterior chamber.

In the present study we tested whether the clinically observed changes in the iris of PES patients might have a functional correlate and might be associated with impaired oxygenation of the aqueous humor in PES. To answer this question, anterior-chamber oxygen tension was measured in eyes with and without PES during cataract surgery. In addition, a detailed ultrastructural investigation of the iris vasculature in PES was performed using electron microscopy so as to reexamine the nature of the iris vasculopathy in PES.

Materials and methods

Electron microscopy

For electron microscopy, iris tissue was obtained from 2 eyes with PES (both 85-year-old patients) that had been enucleated because of painful absolute glaucoma, 10 autopsy eyes (77 ± 6 years) with macroscopic evidence of PES but no history of glaucoma, and 3 specimens of sector iridectomies from 3 patients with PES (74 ± 3 years) and secondary open-angle glaucoma in 2 cases. Control iris tissue was obtained from 3 age-matched autopsy eyes with no evidence of PES in either eye.

Eyes were fixed either immediately after enucleation or at 4–12 h after death in 1% glutaraldehyde and 4% paraformaldehyde in 0.15 M phosphate buffer. The iridectomy specimens were fixed in 2.5% glutaraldehyde in phosphate buffer. All iris specimens were further processed by postfixation in 2% osmium tetroxide in phosphate buffer and embedded in epoxy resin (Epon) according to the standard technique. Semithin sections were stained with toluidine blue; ultrathin sections were stained with uranyl acetate and lead citrate and examined with a Zeiss EM 9A electron microscope (Oberkochen, Germany).

Measurement of oxygen

Oxygen partial pressure (pO_2) was measured using a polarographic electrode of 320- μ m diameter and 3.5-cm length and a pO_2 -Histogram (Eppendorf, Hamburg, Germany) as described previously [6]. Calibration was performed in sterile saline equilibrated with nitrogen and room air. Oxygen measurements in the anterior chamber were performed during cataract surgery in patients with and without PES. Patients with serious general disease or other eye pathology were excluded. All patients had normal intraocular pressure (≤ 21 mm Hg) and were not on local medication other than artificial tears or "anticalaract" eye drops. Patients receiving antiglaucoma drugs were excluded. Patients were informed about the nature of the surgery and the pO_2 measurements. Written and oral consent was obtained.

Cataract surgery was performed using local anesthesia with patients breathing room air. A corneoscleral incision was made at the limbus with a 0.45-mm canula and the electrode was inserted into the anterior chamber and moved parallel to the anterior iris surface. The tip of the electrode was positioned in the opposite chamber angle, above the pupillary margin, and in the center of the pupil until a stable recording was obtained in each position.

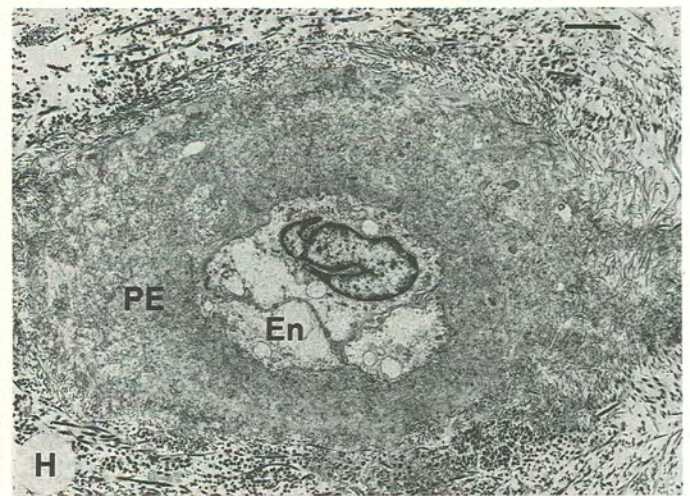
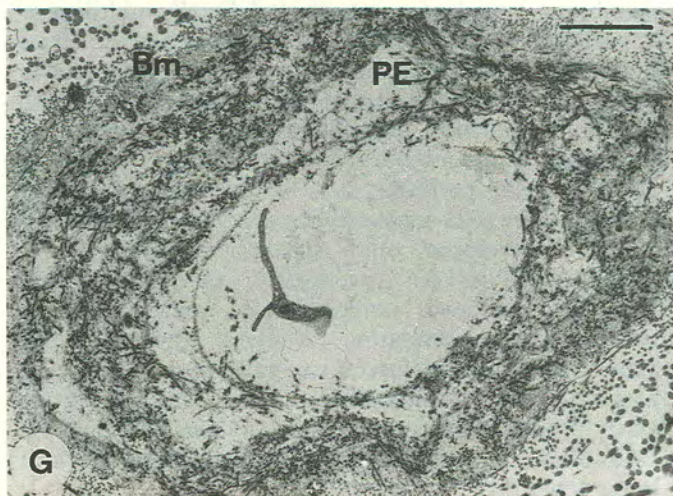
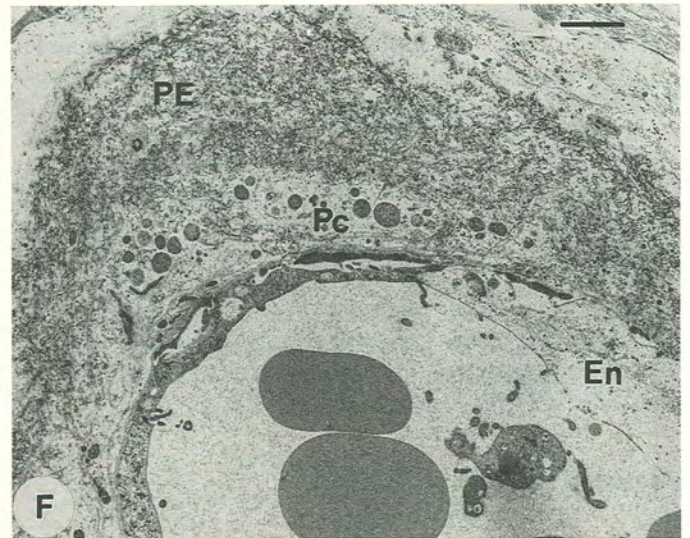
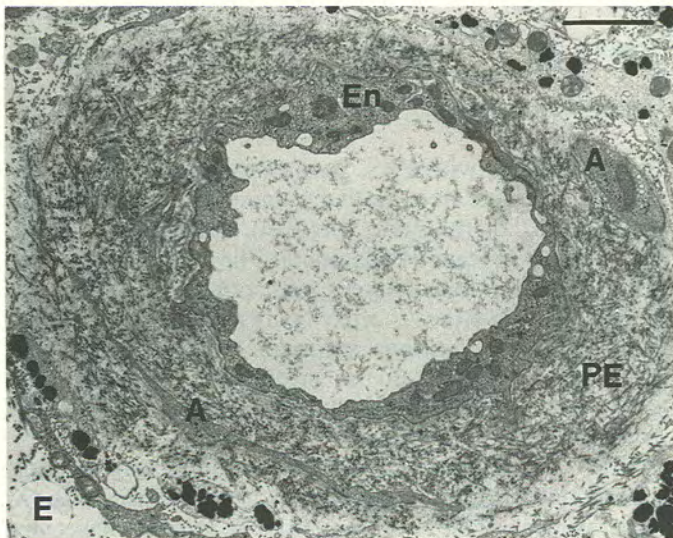
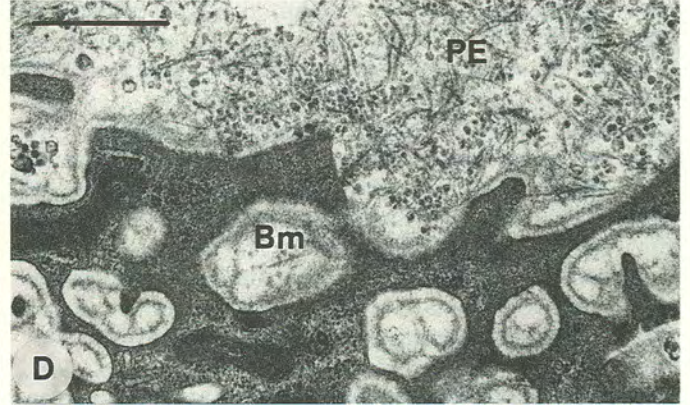
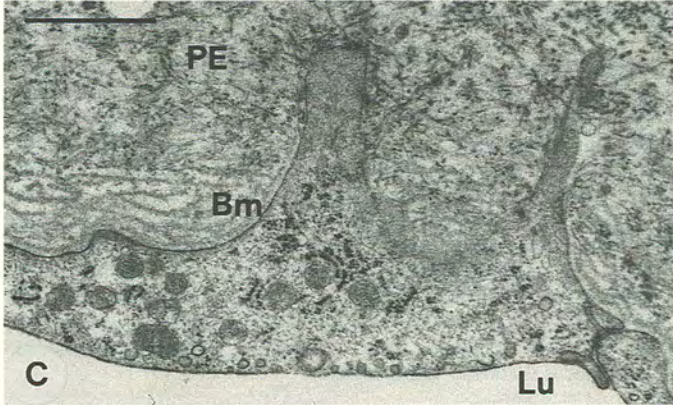
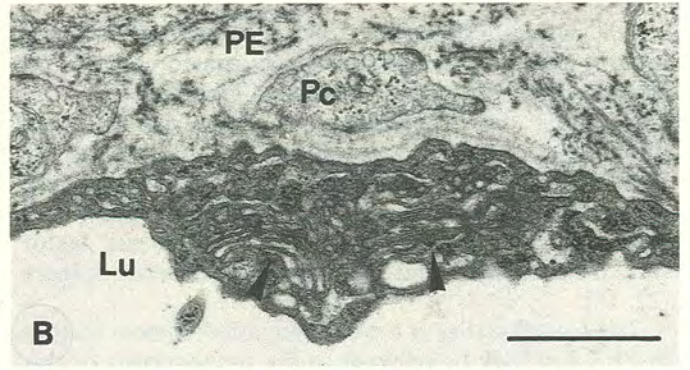
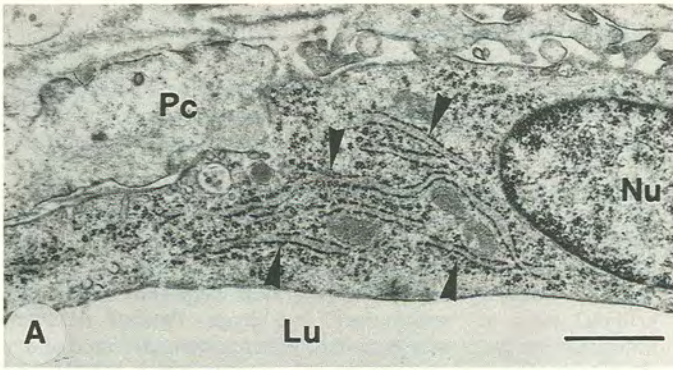
For preoperative mydriasis of the pupil, patients received a drop of 0.5% scopolamine and 0.5% tropicamide in the morning at about 2 h before surgery. At about 60 min and 30 min before surgery, they received another drop of 0.5% tropicamide. Data are presented as mean values \pm SD. Statistical analysis was performed using Student's unpaired *t*-test. *P* values of > 0.05 were considered to be not statistically significant.

Results

Electron microscopy

In all 15 cases with PES, part of the vessels in the iris stroma revealed an extensive range of structural abnormalities within the same specimen, independent of the presence or absence of glaucoma. The affected vessels in different pathological stages were randomly distributed within the iris stroma, often being close to normal-appearing vessels. Various amounts of typical, electron-dense PE fibers (18–30 nm in diameter, cross-banding periodicity of about 50 nm, fuzzy outline) were observed subendothelially in the vessel walls.

The disorganization of the vascular architecture seemed to progress in a certain sequence of degeneration. Irregularities in the structure of the endothelial basement membrane, revealing an interrupted, focally multilayered appearance, often preceded the occurrence of PE fibers. Early abnormalities further comprised the focal production of excess extracellular material, including basement membrane material, granular material, PE fibers, and their filamentous subunits (8–10 nm in diameter), by endothelial cells, pericytes, and adventitial muscle cells. Some of these cells appeared hyperactivated as indicated by a well-developed, often dilated rough endoplasmic reticulum (Fig. 1A), prominent Golgi complexes (Fig. 1B), numerous polyribosomes, and cytoplasmic vesicles. The accumulating PE fibers, apparently produced within cell-surface invaginations or along cytoplasmic processes, intermingled with the disrupted and newly produced basement membrane material (Fig. 1C, D) and gradually displaced the original basement membrane toward the periphery.



In advanced stages, the PE material progressively occupied the whole adventitia, forming a compact band of randomly arranged PE fibers around the endothelial cells (Fig. 1 E) that frequently were markedly thinned and revealed irregular cytoplasmic processes. Degeneration of adventitial cells and pericytes resulted in additional accumulation of cellular debris and granular bodies in the vessel wall (Fig. 1 F). Finally, in very advanced stages the endothelial cells were also degenerated and even disappeared entirely, leaving a ring of loosely dispersed PE fibers ("ghost vessels") surrounded by circularly arranged collagen bundles and stromal cells (Fig. 1 G).

In some specimens, a small number of vessels showed extremely narrowed or completely obstructed lumina due to a marked swelling and volume increase of the endothelial cells (Fig. 1 H). Only in one case, however, did we observe newly formed vessels with fenestrated endothelia within the iris stroma close to the anterior iris surface. Examination of control tissues failed to reveal any of the vascular changes described above.

Measurement of pO_2

Anterior-chamber pO_2 was measured in 10 patients without PES and 8 patients with PES. The PES group included 7 women and 1 man whose ages ranged from 73 to 89 years (83 ± 5 ; mean \pm SD). Of the patients without PES, 8 were women and 2 were men. The age of the patients without PES ranged from 68 to 88 years (78 ± 6 years). The pupil diameter at the beginning of the surgery was smaller in eyes with PES (5.2 ± 0.4 mm) as compared with eyes that had no PES (6.4 ± 0.8 mm).

The pO_2 values measured in the anterior chamber of eyes without PES were 45 ± 11 mm Hg in the chamber angle, 33 ± 12 mm Hg in front of the pupillary margin, and 13 ± 8 mm Hg in the center of the pupil. The respective mean values of the patients with PES were 19 ± 6 mm Hg in the chamber angle, 16 ± 4 mm Hg in front of the pupillary margin, and 8 ± 3 mm Hg in the center of the pupil (Fig. 2). The differences between the groups with and without PES were statistically significant (Student's *t*-test) for the values obtained at the chamber angle ($P < 0.001$) and at the pupillary margin ($P < 0.005$) but were not significant for those obtained at the center of the pupil.

Fig. 1 A–H. Electron micrographs of different iris specimens obtained from patients with PES; bar in A–D = 1 μ m, bar in E–H = 2 μ m. **A** Vascular endothelial cell showing well-developed rough endoplasmic reticulum (arrowheads). *Lu*, Vessel lumen; *Nu*, endothelial cell nucleus; *Pc*, pericyte. **B** Endothelial cell with prominent Golgi complexes (arrowheads). *Lu*, Vessel lumen; *Pc*, pericyte; *PE*, pseudoexfoliative material. **C** Production of multilaminar basement membrane (*Bm*) and pseudoexfoliative material (*PE*) along cytoplasmic processes of an endothelial cell. **D** Production of basement membrane sheets (*Bm*) and pseudoexfoliative material (*PE*) in surface invaginations of an endothelial cell. **E** The vascular endothelium (*En*) is surrounded by a compact ring of pseudoexfoliative material (*PE*). *A*, Adventitial cell. **F** Accumulation of pseudoexfoliative material (*PE*) is followed by degeneration of pericytes (*Pc*) and endothelial cells (*En*). **G** "Ghost vessel" consisting of pseudoexfoliative fibers (*PE*) and basement membrane material (*Bm*). **H** Obstructed vessel lumen with swollen endothelial cells (*En*)

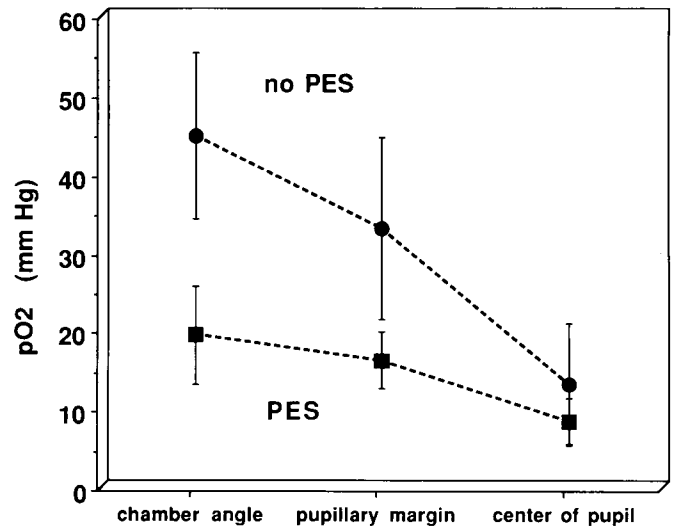


Fig. 2. Mean values \pm SD of pO_2 measured at different locations in the anterior chamber of 8 eyes with PES and 10 eyes without PES

All PES patients had typical circular deposits of PE material on the anterior lens surface. Five of them showed significant atrophy of the iris (pigment and/or stroma) on slit-lamp examination. In three patients, no iris atrophy was visible with the slit lamp. In these three eyes without clinically detectable iris atrophy, the pO_2 values were higher (25 ± 5 mm Hg in the chamber angle, 19 ± 2 mm Hg in front of the pupillary margin, and 11 ± 3 mm Hg in the center of the pupil) than those obtained in the eyes with clinically visible iris atrophy (15 ± 3 mm Hg in the chamber angle, 14 ± 3 mm Hg in front of the pupillary margin, and 6 ± 2 mm Hg in the center of the pupil). These differences were statistically significant ($P < 0.05$ for all three locations).

Discussion

The results of the present study show a significantly reduced oxygen concentration in the aqueous humor as well as substantial morphological alterations of the iris vasculature in PES. Since oxygen saturation of the aqueous humor occurs at the anterior iris surface [6, 7], we conclude that the iris vasculopathy in PES leads to anterior-chamber hypoxia.

Our ultrastructural observations in 15 iris specimens with PES confirm previous reports describing deposition of PE material in the walls of iris stroma vessels [20, 21, 27], disorganization of normal vessel structure [5, 28, 29], and production of PE material by endothelial and adventitial cells [28]. Whereas previous studies have pointed out the obliteration of vessel lumina by protruding or invading PE masses [28, 29], the present findings indicate that gradual degeneration of vascular cells, culminating in the loss of all cells, represents the main feature of iris vasculopathy. Vessel occlusion was restricted to a small number of vessels in only a few specimens due to a volume increase of endothelial cells, confirming the earlier observations of Ringvold and Davanger [22].

Atrophy of the vascular cells is apparently associated with an accumulation of excess extracellular matrix. At an earlier stage, the hyperactivated cells are stimulated to synthesize increased amounts of extracellular material, predominantly PE fibers, before they lose their ability to maintain a proper extracellular matrix and finally degenerate. Specific matrix alterations in the iris vasculature of PES specimens have been demonstrated by immunohistochemistry [10].

These morphological changes in the iris vasculature led us to investigate whether the oxygen supply to the anterior segment of the eye might be impaired in PES. Indeed, we found a substantially reduced pO_2 in the aqueous humor of eyes with PES. The spatial distribution of pO_2 in the anterior chamber showed a similar pattern in eyes with and those without PES. The highest values were found near the chamber angle and the lowest, in the center of the pupil anterior to the lens. This distribution most likely reflects a diffusion gradient from a high pO_2 near the vascularized iris stroma to the low-oxygen compartment of the lens [6, 7].

The pupillary diameter in our study was smaller in patients with PES as compared with eyes without PES. This finding is in agreement with previous observations of a reduced response to mydriatics in PES [3]. The reason for the reduced dilation of the pupil in PES may be atrophy of the iris dilator muscle, a reduction of cholinergic receptors, or a lack of iris stroma elasticity due to fibrous or infiltrative changes in PES [3]. The pupil size itself is probably not an important factor for anterior-chamber oxygenation. Atropine dilation of the pupil has been shown to have no significant effect on aqueous-humor oxygen tension in experimental animals [19, 30]. In contrast, adrenergic mydriatics do substantially reduce anterior-chamber pO_2 , most likely by contraction of iris vessels [6, 19, 30]. In the present study we therefore used only anticholinergics for preoperative pupil dilation, and adrenergics were avoided.

In many cases, atrophy of the iris stroma as well as iris pigment epithelium is an early event in the development of ocular changes in PES, often being visible before deposition of PE material on the anterior lens occurs. Patients with these atrophic changes in the iris can be considered to be PES suspects. However, there are eyes in which the typical lens deposits are present, although no significant change in the iris can be detected by slit-lamp examination. In eyes with PES and clinically visible iris atrophy we found lower oxygen values in the anterior chamber as compared with those patients without clinically obvious iris atrophy. However, in the latter eyes the pO_2 value was nonetheless lower than that measured in control eyes. Thus, it seems that physiologically relevant changes in the iris vasculature can occur before obvious PES-typical changes in the iris may be detected on slit-lamp examination.

The significant decrease in aqueous humor pO_2 to about one-half of the normal value may possibly affect anterior-segment function. In addition, in eyes with PES there is evidence for a defective blood-aqueous barrier causing alterations in aqueous humor composition [1, 2, 11, 33]. Several abnormalities have been described in PES in the tissues lining the anterior chamber, and it is possi-

ble that a hypoxic aqueous humor with an altered composition may have contributed to these abnormalities.

In the corneal endothelium, morphological abnormalities and a reduced number of cells have been repeatedly found in PES by specular microscopy [9, 15]. Electron microscopy has revealed focal production of PE material by degenerating corneal endothelial cells [26]. The corneal endothelium serves as a very active electrolyte pump, dehydrating the cornea [35]. As this pump is dependent on an intact energy metabolism, a reduced oxygen and nutrient supply by the aqueous humor may contribute to these changes in PES.

Lens changes are prominent in PES and cataract is a common feature. The lens is a very low-oxygen compartment [6, 12]. In vitro the lens consumes oxygen [8], but it is not known to which extent oxygen is necessary for the lens to maintain clearness in situ or whether oxygen may even be deleterious for the lens [4]. Thus, the role of anterior-chamber hypoxia for the development of cataract in PES remains unclear.

The trabecular meshwork is the site of regulation of aqueous humor outflow and intraocular pressure. The physiology of outflow regulation remains under discussion, and the causative mechanism for PES-associated glaucoma is not yet clear, although a simple obstruction of the outflow channels by PE material deposits in the juxtacanalicular connective tissue next to Schlemm's canal [14] could account for the increased resistance. It is nevertheless possible that hypoxia in the trabecular meshwork also contributes to dysfunction of endothelial cells and dysregulation of outflow resistance and intraocular pressure in PES.

Neovascularization of the iris in PES is a point of controversy. Most patients with neovascularization of the iris suffer from occlusive vascular disease of the posterior segment of the eye, but pathological processes in the iris itself are rarely the cause of iris neovascularization. The current concepts for development of rubeosis of the iris assume the formation of presumed retina-derived vasoproliferative factor(s) in the retina, triggered by retinal hypoxia, which reach the iris by diffusion [31]. In PES, however, we attribute anterior-segment hypoxia to vascular changes in the iris itself. In only 1 of 15 iris specimens could a minor neovascular reaction be seen in the anterior iris stroma. Clinically evident rubeosis of the iris in PES is present only exceptionally, not as a constant feature. The observed dye leakage in iris angiography in PES in most cases appears to be associated not with newly formed vessels with fenestrated endothelia [22, 34] but rather with a general disturbance of the blood-aqueous barrier function of the existing vasculature [11, 25]. This barrier dysfunction might further increase the deposition of abnormal protein material in the perivascular tissue and subsequently promote vascular degeneration and hypoperfusion.

The morphological and physiological results of the present study suggest an ischemic component in PES in the iris. Two recent papers describe the deposition of PE material in several extraocular visceral organs, suggesting that PES is a systemic disorder, not restricted to the eye [24, 32]. It is not known whether these morphological

changes in PES outside the eye are associated with any extraocular disease. PE material inside and outside the eye has often been found in proximity to blood vessels, and it has been suggested that a blood-derived factor may trigger PE-fiber formation [24, 32]. The extraocular vascular changes in PES described thus far are minor as compared with the iris vascular changes. No association between PES and general vascular or ischemic disease has been described. However, interestingly, one patient with systemic PES died of dissecting aneurysm of the aorta [24]. Thus, it remains unclear why the iris vasculature appears to present a main target in PES.

The demonstrated morphological abnormalities support the concept of PES as a degenerative metabolic disorder involving a disturbed extracellular matrix synthesis throughout the body. The degenerative changes might well explain the focal vessel dropout and hypoperfusion of the iris [1, 2, 33] as well as the significant fall in oxygen tension found in the present study. The vascular changes seem to be a result rather than a cause of the condition, and hypoxia seems to develop subsequently rather than to precede the PE process. The resulting ischemia of the iris tissue might, however, cause atrophic changes in the iris stroma, and the hypoxia of the aqueous humor may contribute to the pathophysiology of PES-associated changes in the tissues lining the anterior chamber.

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