Schlemm’s Canal Becomes Smaller After Successful Filtration Surgery

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Objective: To determine whether filtration surgery causes secondary changes in the trabecular meshwork and Schlemm’s canal. Successful filtration surgery allows most aqueous outflow to enter the filtration bleb, bypassing the meshwork and canal, and may result in underperfusion of these structures.

Methods: Eyes with primary open-angle glaucoma (POAG) that had undergone filtration surgery were studied and compared with eyes with POAG that had not undergone surgery. In addition, normal eyes and eyes with pseudoexfoliative glaucoma were studied for comparison. The trabecular meshwork and Schlemm’s canal were examined by light and electron microscopy.

Results: Schlemm’s canal was significantly smaller in eyes with POAG after filtration surgery than in normal eyes (canal width, 178±71 µm vs 276±52 µm; P<.001) or in eyes with medically treated POAG of similar clinical severity (261±60 µm, P=.03). The decrease in canal size seemed to be related to the success of the filtration procedure, since eyes with blebs and low pressures had the smallest canals. Eyes with medically treated POAG at earlier clinical stages of glaucoma did not have a significant decrease in canal size when compared with normal eyes. Eyes with advanced pseudoexfoliative glaucoma had canal widths 20% smaller than those in normal eyes (P=.08).

Conclusions: Filtration surgery was associated with a decrease in the size of Schlemm’s canal, most likely due to underperfusion of the meshwork. A significant decrease in canal size is otherwise not a finding in POAG. In contrast, the canal tended to become smaller in advanced cases of pseudoexfoliative glaucoma.

Clinical Relevance: The decrease in size of Schlemm’s canal after successful filtration surgery could make glaucoma more difficult to control if the filter ultimately fails.


Filtration surgery is a common therapy for the treatment of glaucoma, and may be performed on 28% of patients with glaucoma in the United States. In Great Britain, filtration surgery may be used on the majority of patients with glaucoma, and is often performed early in the course of the disease. An ongoing collaborative trial in the United States is investigating whether immediate filtration surgery is more successful than initial treatment with medication for primary open-angle glaucoma (POAG). In successful filtration surgery, aqueous outflow moves into the filtration bleb and bypasses the trabecular meshwork and Schlemm’s canal. The bypassing of the normal outflow structures can result in underperfusion of these drainage pathways, which has been shown to cause a “silting in” or accumulation of extracellular material in monkey eyes. A similar phenomenon is thought to exist in humans, in which there is a dramatic elevation of intraocular pressure after closure of a cyclodialysis cleft. Underperfusion of the meshwork and canal presumably causes accumulation of extracellular material and increased outflow resistance. What happens in the human eye after filtration surgery: do the meshwork and canal also undergo a silting in with extracellular material?

In addition to the effect of the accumulation of material within the meshwork, a change in the size of Schlemm’s canal may also affect outflow resistance. One study found a 36% decrease in canal width in 3 donors with POAG, which was determined to cause at least a 41% worsening of outflow resistance. (Note that the width of the canal appears as the anterior to posterior “length” of the canal when
MATERIALS AND METHODS

STUDY SAMPLE

Three groups of eyes were studied: 28 eyes with POAG, 53 normal eyes, and 23 eyes with PEX syndrome or PEX glaucoma (Table). Eyes were obtained at autopsy through the Glaucoma Research Foundation, San Francisco, Calif, and the Mayo Clinic eye bank, Rochester, Minn. Records were obtained from the donors’ ophthalmologists in all cases of glaucoma. Because glaucomatous eyes were obtained from a variety of sources around the country, each donor had a different ophthalmologist, and the clinical records varied in completeness. The clinical assessment of cupping in this collection of records ranged from brief descriptions to detailed drawings or photographs; similarly, visual field examinations were assessed with a variety of techniques. The protocol was approved by the Mayo Clinic Institutional Review Board. Permission to study the eyes was obtained from the next of kin.

Information from clinical records was used to assess the stages of clinical severity of glaucomatous damage, and eyes were grouped according to these stages. Stage 0 eyes had POAG but no elevation of intraocular pressure; stage 1 eyes had mild disease, with a history of elevated intraocular pressure and either the use of 1 medication for treatment or no treatment; stage 2 eyes had a history of treatment with at least 2 medications, but did not have obvious disc damage or visual field loss; stage 3 eyes had mild to moderate visual field loss, confined to either the upper or lower hemifields; and stage 4 eyes had advanced field loss in both the upper and lower hemifields. Eyes that had undergone filtration surgery were grouped separately, but assessed by the stages of severity.

HISTOLOGIC PROCESSING

Eyes had been fixed by either immersion or perfusion fixation when they were received in our laboratory from different eye banks around the country (Table). For comparison, we also fixed a group of normal eyes by each method. Immersion fixation was performed by bisecting eyes at the equator and then immersing the eyes in a mixture of 4% paraformaldehyde and 2% glutaraldehyde. Perfusion fixation was performed by placing a 27-gauge needle connected to a reservoir of fixative through the cornea, into the anterior chamber, continuing through the pupil, and into the posterior chamber between the iris and lens to prevent deepening of the anterior chamber during the perfusion with fixative. The reservoir was placed above the eye to produce a perfusion pressure of 17 mm Hg. Eyes were then placed in the fixative, and the anterior chamber perfusion with fixative continued overnight. The anterior segments of the fixed eyes were then cut into quadrants, and wedges of limbal tissue were dissected, rinsed in cacodylate buffer, postfixed in 1% osmium tetroxide, dehydrated in a series of ascending alcohols, and embedded in epoxy resin. Sagittally oriented semithin sections (1 μm) from the chamber angle region were cut and stained with toluidine blue. Ultrathin (400 nm) sections of the trabecular meshwork were stained with uranyl acetate and lead citrate.

MORPHOLOGIC ANALYSIS

The trabecular meshwork and Schlemm’s canal were studied with light and transmission electron microscopy. Particular note was made of extracellular material in the meshwork and canal region. Light microscopy was used to measure the width of the canal lumen on sagittal sections (note that this appears as the anterior to posterior “length” of the canal on sagittal sections). In cases where the canal consisted of several channels with intervening solid tissue, the solid tissue was excluded from the measurement (Figure 1). The canal was measured at ×400 magnification, using the Zeiss IBAS 2000 image analysis system (Zeiss Inc, Thornwood, NY). At least 3 quadrants of each canal of glaucomatous eyes were measured because of potential segmental variation around the circumference of each eye. The canals of normal eyes were also measured from 3 quadrants in 17 eyes, and at 1 quadrant in the remaining 36 eyes. Fourteen eyes had undergone laser trabeculoplasty, and care was taken to avoid lasered regions.

STATISTICAL ANALYSIS

Measurements of the canal from multiple quadrants were combined to obtain a mean value per eye. When both eyes from a donor with glaucoma were examined, data were analyzed in 2 ways: (1) combining data from fellow eyes to yield a mean value per donor, and (2) recording the data from each eye separately. This was done to avoid the loss of information that would occur if fellow eyes had different degrees of disease severity. The degree of clinical severity between fellow eyes was similar in 18 of the donors and different in 10 of the donors. Significance testing was performed with unpaired t tests and also with the method of generalized estimating equations. This model allows use of information from both eyes of the same donor and simultaneously takes into account the dependency of both eyes. Reproducibility was determined by reanalysis of at least 1 quadrant from 54 eyes, and gave values within 8%.

viewed with conventional histologic sections in the sagittal plane.) A reversible narrowing or collapse of portions of the canal is thought to be responsible for the relative outflow obstruction that occurs as intraocular pressure increases in both normal and glaucomatous eyes. Descriptive studies of the canal in glaucomatous eyes have found that the canal may decrease in size or even collapse, although these changes may not be found around the entire circumference of the eye. Could a decrease in canal size be an early stage in the pathogenesis of POAG, a late secondary change, or only a variable in-consistent finding? An interesting parallel to this occurs in pseudoexfoliation syndrome (PEX). Eyes with early PEX, manifested by elevated intraocular pressure but minimal nerve damage and field loss, have a normal canal size, while in advanced cases the canal may become smaller or disrupted. This indicates that decrease in canal size is a secondary event in PEX and not an initial cause of elevated intraocular pressure.

The current study was performed to determine whether changes in the trabecular meshwork and Schlemm’s canal occur after filtration surgery from un-
derperfusion of these pathways, as aqueous outflow is diverted into the filtration bleb. In addition, the canals of eyes with POAG were compared with canals of eyes with PEX at early and late phases of disease, to determine whether the sizes of each would differ at different stages of severity of disease.

RESULTS

Because glaucomatous eyes had been fixed by either immersion or perfusion fixation when received from the eye banks, an initial comparison was performed in the normal eyes to determine the effect of fixation on canal size. Normal eyes fixed by perfusion had a canal width about 13% smaller than normal eyes fixed by immersion (P = .03). Because of this difference, the glaucomatous eyes were grouped and analyzed by fixation technique.

FILTERED EYES

In eyes with POAG that had been filtered, the width of the canal lumen was significantly smaller than in age-matched normal eyes by either immersion (immersion fixation; 178±71 µm vs 276±52 µm; P < .001) or perfusion fixation (97±61 µm vs 241±62 µm; P = .001). In 7 of 8 filtered eyes, Schlemm’s canal was small, and the juxtacanalicular tissue was abnormal. Light microscopy revealed the accumulation of amorphous extracellular material in the region of the canal bed and adjacent juxtacanalicular tissue, shortening the ends of the canal and narrowing the lumen. Electron microscopy found this material to consist of an accumulation of fine fibrillar material in the juxtacanalicular region external to the endothelial cells of the canal, filling in the former region of the lumen of the canal. This material often caused the canal to be split into several small channels. Although the endothelial cells of the inner and outer walls were no longer present in regions of the canal without a lumen, the former canal region could be identified by its location and by the surrounding tendon and tendon-sheath material (SD plaques) seen with electron microscopy.

One filtered eye did not have a small canal. Of interest, this eye did not have a filtration bleb on clinical examination, and required timolol maleate postoperatively to control the intraocular pressure. This suggested a relationship between success of filtration surgery and canal size. Correlation with clinical records indicated that eyes with definite filtration blebs, low intraocular pressure, and no ongoing treatment with medications had the smallest canals (2 eyes, canal width 42 µm and 109 µm, respectively). These eyes had canals that were often segmented into 3 or 4 small channels, while the remainder of the canal region was filled with extracellular matrix. Eyes with partially successful surgery had lowered intraocular pressures but required the use of medications. Canals in these eyes were also small compared with normal eyes (5 eyes, 149±50 µm vs 256±60 µm).

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<th>Schlemm's Canal Width*</th>
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<td><strong>Immersion Fixed</strong></td>
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<td>No. of Eyes (No. of Donors)</td>
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<tr>
<td>Normal</td>
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<td>POAG</td>
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<td>Stage 1 + 2</td>
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<td><strong>Perfusion Fixed</strong></td>
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*All data are given as mean ± SD unless otherwise indicated. POAG indicates primary open-angle glaucoma; PEX, pseudoexfoliative glaucoma.
†P = .03 vs normal eyes, immersion vs perfusion.
‡P < .001 vs normal eyes.
§P = .03 vs stage 3 + 4 POAG eyes.
¶P = .001 vs normal eyes.
¶P = .05 vs stage 3 + 4 POAG eyes.
#P = .08 vs normal age-matched eyes.
The appearance of the canals varied among quadrants in these eyes, from small segmented channels surrounded by abnormal extracellular matrix to a normal appearance with a large lumen, although the canal was small in most quadrants. Eyes that received laser trabeculoplasty did not have a smaller canal when compared with normal control eyes (data not shown).

To determine whether the decrease in canal size found in the filtered eyes was due to severity of glaucomatous disease, and not a result of filtration surgery, comparison was made with glaucomatous eyes that had not undergone filtration surgery. Nineteen eyes had a clinical severity of glaucoma similar to that of the filtered eyes (stages 3 and 4, as determined from the clinical records and visual field examinations). The canal was smaller in the filtered eyes than in the nonfiltered eyes (immersion fixation: 178±71 µm vs 232±77 µm; P = .03; perfusion fixation: 97±61 µm vs 226±88 µm; P = .05). Duration of disease in eyes that underwent filtration surgery was longer than in eyes that did not (18±7 years, vs 12±8 years; P = .06). There were 4 donors in which surgery was performed on only 1 of each eye pair. The canals in the operated eyes were smaller than those in the fellow nonoperated eyes, suggesting that the surgery itself, and not duration of disease, accounted for the smaller canal (145±101 µm vs 232±77 µm).

In regions of the trabecular meshwork (not including the juxtacanalicular tissue and canal bed), the trabecular lamellae and trabecular cells appeared similar between filtered and nonfiltered eyes. Marked cell loss was not apparent by subjective examination. Lamellae varied in thickness among eyes, but did not appear consistently thicker in filtered eyes.

**NONFILTERED EYES**

Of interest, the canal width in nonfiltered eyes with severe clinical disease (stage 3 and 4) was not significantly smaller than in eyes with milder disease (stage 1 and 2), indicating that the canal does not become smaller with advancing severity of POAG in nonfiltered eyes (immersion fixation; stages 1 and 2 vs stages 3 and 4, 252±49 µm vs 261±60 µm). These values did not differ significantly from age-matched normal eyes (276±52 µm). In contrast, eyes with PEX glaucoma tended to have a smaller canal with increasing severity of disease, decreasing about 20% when compared with age-matched normal eyes (P = .08) and also when compared with stage 0 PEX eyes. The 3 PEX eyes that had been filtered had small canals, but it is unclear whether this was due to severity of PEX disease or due to the effect of filtration surgery.

**COMMENT**

Schlemm’s canal becomes smaller after successful filtration surgery. The canal was smallest in eyes with filtration blebs, low intraocular pressure, and no ongoing treatment with medications. We speculate that underperfusion of the remaining meshwork is responsible for the filling in of the canal region with extracellular material, because aqueous outflow is diverted into the fil-
Ultrastructural study revealed this extracellular material to consist of abnormal fine fibrils within the juxtacanalicular region and canal area. Underperfusion of the meshwork has also been found experimentally in monkeys after filtration surgery, with the resulting accumulation of extracellular material. Underperfusion of the meshwork is thought to occur after successful cyclodialysis surgery. The normal appearance and size of the canal in fellow eyes that were not filtered supports the idea that it was the filtration surgery and subsequent underperfusion of the remaining meshwork that caused the decrease in canal size. In support of this, the canal in the eye in which no filtration bleb was evident appeared normal and was of normal size.

An alternate explanation for small canals could be that eyes with abnormally small canals are predisposed to severe glaucoma, and thus require surgery. This is unlikely given the normal canal size in the unoperated fellow eyes of the 4 patients. It is also possible that the canal becomes smaller with prolonged duration of disease. Although the group of eyes undergoing filtration surgery had a longer duration of glaucoma than the group not undergoing surgery, the normal size of the canal in the unoperated fellow eyes again suggests that it was the filtration surgery and subsequent underperfusion of the remaining meshwork itself, and not duration of disease, that caused the canal to become smaller.

In contrast to filtration surgery, Schlemm’s canal is not smaller in eyes with medically treated POAG. Regardless of the severity of the disease or method of fixation, the canal was not significantly smaller when compared with normal control eyes. This suggests that a decrease in canal size is not involved in the patho-

**Figure 5.** Electron micrograph of small canal after filtration surgery, probable true underperfusion. Tendon and sheath material form boundary of original canal bed, and appear as irregular dark structures (arrowheads). Surgery performed 2 years previously was successful in eliminating the need for medications and resulted in an intraocular pressure of 12 mm Hg with excellent filtration bleb. SC indicates Schlemm’s canal. This overview picture shows the canal to be reduced to several small lumens (m denotes a small middle channel of canal), with the remainder of the canal region filled with loose extracellular matrix. Note compaction of meshwork lamellae (asterisk). This eye was unique in having an overgrowth of corneal endothelial cells and formation of Descemet membrane (arrows) along uveal meshwork (70-year-old, clinical stage 4, immersion fixation) (original magnification ×750).

**Figure 6.** Enlargement of middle canal region shown in Figure 5. Small canal lumen (m) is lined with enlarged endothelial cells; other lumens (L) are not lined with endothelial cells. SC indicates Schlemm’s canal. Tendon and sheath material (SD) are denoted by arrowheads (original magnification ×6250).
genesis of POAG. Previous reports found a decrease in canal size of about 36% in eyes with advanced POAG, but the findings were based on smaller numbers of eyes.8,15

Unlike eyes with POAG, eyes with PEX tended to have a smaller canal width with increasing severity of disease. The PEX material appeared to build up along the inner wall of the canal and at the anterior and posterior ends. Electron microscopy revealed that clumps of PEX material caused the endothelial cells of the inner wall to bulge into the canal and touch the outer wall, resulting in the subsequent loss of the endothelial cells and fragmentation of the canal lumen. This has been reported by others who have studied advanced cases of PEX, although it does not appear early in the disease process.16-18 Thus, a decrease in canal size is not the earliest pathologic change in PEX, and it is not responsible for the initial elevation of intraocular pressure. In advanced cases, however, loss of portions of the canal could add to the outflow resistance.

Study of eyes at all stages of severity of glaucomatous disease can be helpful in understanding the pathogenesis of the elevated intraocular pressure in glaucoma. Most studies have been performed on surgical specimens that were removed at the time of trabeculectomy, and are thus limited by the small piece of meshwork and the advanced stage of glaucoma in the eye that had required filtration surgery. A recent study of POAG at various stages of severity found that the accumulation of sheath and tendon SD plaques described in POAG does not occur in the earliest stages of the disease, when the intraocular pressure elevation is first present.21 This indicates that accumulation of SD plaque material accompanies the disease process, but is not the initial pathophysiologic mechanism of the elevated intraocular pressure in POAG. Our study also used eyes at all stages of severity of disease and did not find a change in canal size to be a feature of POAG. A smaller canal was found in eyes with filtration surgery, however, suggesting that changes in the canal region of the meshwork can indeed occur.

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