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The resistance of the trabecular meshwork to aqueous humor outflow

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Abstract. A theoretical model is presented that is able to explain for the first time the pressure drop across the trabecular meshwork. The ramified flow paths in the subendothelial region of the trabecular meshwork can be interpretated as a filter bed. Data from transmission electron microscope (TEM) photographs are the starting point of the theoretical consideration. Taking shrinkage of the sections into account, the pressure gradient across the subendothelial region amounts to 0.05 mm Hg. As these canaliculi are coated by a film of glycosaminoglycans (GAGs), the pressure drop is presumably a function of the film thickness. Only film thicknesses of 0.35 μm lead to pressure gradients in the experimentally verified magnitude. As the whole filter bed probably does not contribute to the filtration but only about 10%, the pressure drop specified is reached when the GAG coating is 0.25 μm. As these values seem to be fairly realistic, it can be concluded that the subendothelial region of the juxtacanalicular meshwork (about 2 μm thickness) can be regarded as the "*locus generis*" of aqueous humor outflow resistance.

Introduction

To produce intraocular pressure in a stationary equilibrium of formation and drainage of aqueous humor, there must be flow resistance in the outlet. It is well known that most of this resistance to aqueous humor outflow originates in the outer part of the trabecular meshwork or in the wall of Schlemm's canal (Grant 1958). Increase of this resistance usually leads to increased ocular pressure. In order to understand the pathomechanism of glaucoma and find the "*locus generis*" of outflow resistance many investigation groups have compared morphological data with hydrodynamic models.

The first of these models was introduced by McEwen (1958), who used numerous cylindrical tubes as exit channels and Hagen-Poiseuille's law to calculate the number of these tubes (with fixed diameters) necessary to produce a pressure drop of 5 mm Hg across the "pore tissue." Bill and Svedbergh (1972) presented a refined model, which took into account new electron microscopical data (invaginations of the endothelium of Schlemm's canal with pores). They showed that less than 10% of the total trabecular resistance resided in the inner wall endothelium of Schlemm's canal. Another study (Moseley et al. 1983) raised this contribution to 18%.

Recently, Kamm et al. (1983) adopted a new approach. Similar to our model (Seiler and Wollensak 1982), they assumed a statistically ramified flow path. The important parameter in this model is the porosity factor, measured by transmission electron microscope (TEM) photographs. The calculated pressure decrease across the juxtacanalicular meshwork (10 μm from Schlemm's canal) is at least 10 times too small. In conclusion, then, it has only been proved that the endothelium of Schlemm's canal and its invagination with pores cannot produce the pressure drop of about 5 mm Hg, and that is necessary to explain this phenomenon.

In the present paper, a model of a statistically formed juxtacanalicular region is presented and compared to data acquired by quantitative electron microscopy, as surveyed and evaluated by Lütjen-Drecoll (1973).

Materials and methods

Following the methods of Lütjen-Drecoll, we shall split the juxtacanalicular meshwork (thickness 7.5 μm) into two morphologically distinguishable regions (Fig. 1): a *subendothelial region* (1.5–2.5 μm thick) in which optically empty spaces are in immediate contact with the inner wall of endothelium and the neighboring *cribriform region* (about 6 μm thick).

The electron micrographs of sagittal sections of the trabecular meshwork of 15 eyes of primates have been evaluated by Lütjen-Drecoll (1973), and she found the following data:

Area of empty spaces in the subendothelial region 14.68 μm^2

Area of empty spaces in the cribriform region 80.9 μm^2

The section length was 75 μm so that the empty spaces were 9.8% and 18.0%, respectively, of the whole area. This amount is usually called porosity factor ε $\left(\text{here } \varepsilon = \frac{80.9}{6 \times 75}\right)$.

As a theoretical model, we found flow through a porous medium most appropriate (filter bed, Fig. 2) because the flow paths in the juxtacanalicular meshwork are irregular and seem to be an omnidirectional network rather than directed tubuli. Erikson and Svedbergh (1980) have demonstrated that the inertial effects of the flow in the meshwork

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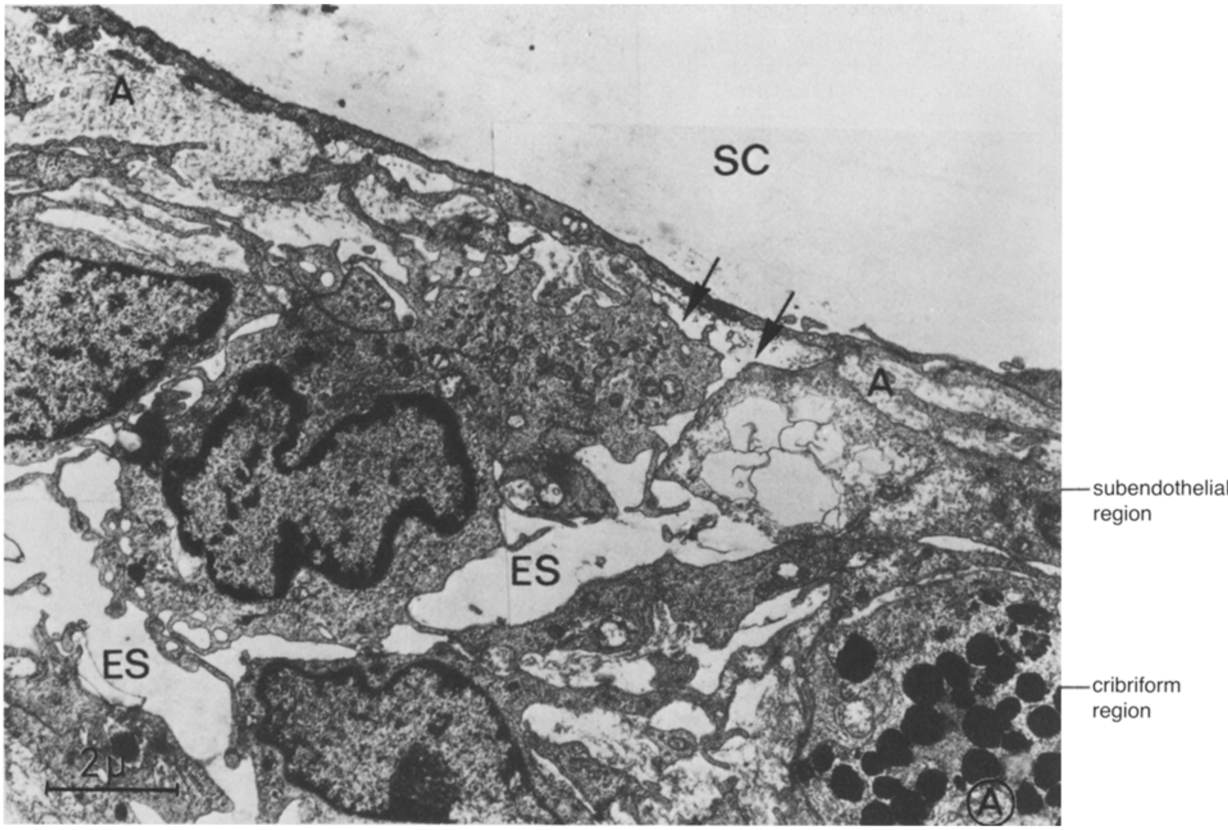

Fig. 1. Electron micrographs of sagittal section of the inner wall of Schlemm's canal and the adjacent areas of the trabecular meshwork (Lütjen-Drecoll 1973). There are three regions: endothelium, subendothelial region and cribriform region of juxtacanalicular meshwork. (Reprinted by permission of C.V. Mosby Co.)

can be disregarded. Hence the well-known Kozeny-Carman equation holds. Expressed in a somewhat more convenient form, the pressure drop across such a filter bed is (Bohl 1980)

$$\Delta p = \frac{1}{\varepsilon^3} \cdot \gamma \cdot L \cdot S_0 \cdot \frac{\varrho}{8} \cdot v_0^2 \qquad (1)$$

where $\Delta p =$ pressure drop across the bed, $\varepsilon =$ porosity factor, $\gamma =$ friction number, $L =$ bed depth, $S_0 =$ surface area of flow path per unit volume, $\varrho =$ specific density of the fluid, and $v_0 =$ superficial fluid velocity.

Mathematical analysis

To evaluate the pressure drop across the subendothelial region, all the parameters of Eq. (1) have to be determined.

The superficial velocity can be obtained by

$$v_0 = \frac{\text{volumetric flow rate}}{\text{cross sectional area}} = \frac{2.5\ \mu\text{l/min}}{10\ \text{mm}^2}$$

$$= 4.2 \cdot 10^{-6}\ \frac{\text{m}}{\text{s}}.$$

The specific density ϱ of the aqueous equals

$$1 \cdot 10^3 \frac{\text{kg}}{\text{m}^3}$$

and the filter bed depth L

$$2 \cdot 10^{-6}\ \text{m}.$$

To calculate the surface area, S_0, per unit volume we assume that the 4.6 empty spaces per section can be approximated by flat ellipses with a numerical excentricity of 0.94 and a mean area of 3.19 μm² (Lütjen-Drecoll 1973). For the circumference one then finds 7.8 μm and with a roughness factor of 1.2 for S_0

$$S_0 = 0.287 \cdot 10^6\ \text{m}^{-1}$$

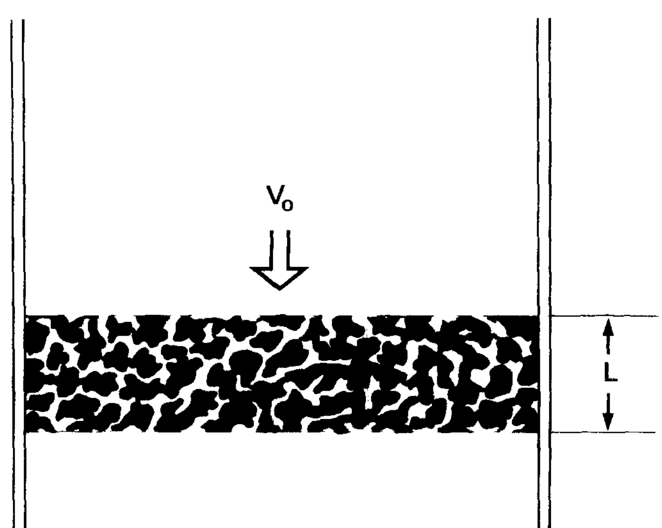

Fig. 2. Schematic diagram of a technical filter bed with the superficial velocity of flow designated V_0 and thickness L

Table 1. Evaluation factors of pressure gradient as a function of lumen narrowing

Narrowing (μm)	Porosity ε	Surface area S_0 (μm^{-1})	Friction γ
0	0.098	0.288	$2.26 \cdot 10^6$
0.1	0.072	0.251	$2.0 \cdot 10^6$
0.2	0.049	0.218	$1.71 \cdot 10^6$
0.3	0.031	0.181	$1.47 \cdot 10^6$
0.4	0.017	0.147	$1.25 \cdot 10^6$
0.45	0.0107	0.131	$1.08 \cdot 10^6$

Table 2. Pressure drops (in mm Hg) for various degrees of partial obstruction of the filter bed

Narrowing of free diameter	Pressure drops (in mm Hg) for effective filter area of		
	100%	50%	10%
0.1 μm	0.045	0.09	0.43
0.2 μm	0.11	0.21	1.01
0.3 μm	0.3	0.59	2.81
0.4 μm	1.24	2.41	11.9
0.45 μm	3.83	7.7	36.8

For the friction factor, γ, we find for low Reynolds' numbers (Bohl 1980):

$$\log \gamma = -1.017 \cdot \log Re + 2.134$$

With $Re = \frac{d \cdot v_0}{\varepsilon \cdot \nu}$, ν = kinematic viscosity $= 0.7 \cdot 10^{-6} \frac{m^2}{s}$ and $d = 2 \times$ small semiaxis, one can find $Re = 7.1 \cdot 10^{-5}$ and therefore $\gamma = 2.26 \cdot 10^6$

Returning to Eq. (1), calculation of the pressure drop yields

$$\Delta p = 2{,}86 \frac{N}{m^2} \approx 0.02 \text{ mm Hg}$$

This value for the subendothelial region is too small by at least a factor of 100.

It is well known that the canaliculi of the trabecular meshwork are coated by a film of glycosaminoglycans (GAGs) with a thickness of 0.1–2 μm (Richardson 1982). Therefore, it is interesting to determine to what degree those films lead to corrections of the upper value. To evaluate S_0 the coating in the direction of the small semiaxis is assumed to be half of the large semiaxis.

Table 1 shows the corrected values for ε, S_0, and γ and the related pressure drops are:

$\Delta p(0.1) = 0.045$ mm Hg

$\Delta p(0.2) = 0.1$ mm Hg

$\Delta p(0.3) = 0.3$ mm Hg

$\Delta p(0.4) = 1.2$ mm Hg

$\Delta p(0.45) = 3.8$ mm Hg

$\Delta p(0.48) = 8.7$ mm Hg

The numbers in parentheses show the minimal film thickness (along the small semiaxis). Thus, by reducing the free diameter of the canaliculi by a factor of about 3, the pressure drop across the subendothelial region equals the experimentally verified value.

Discussion

All previous theoretical considerations of aqueous outflow resistance have started with single, well-defined outlet structures: McEwen (1958) used cylindrical tubuli, Bill and Svedbergh (1972) investigated invaginations with pores, and Moseley (1983) used a venturi tube model. These findings signify that only a minor part of the pressure gradient across the trabecular meshwork is situated in the endothelium of the inner wall of Schlemm's canal. In interpreting these invaginations it is thought that they act as valves, preventing back flow from Schlemm's canal (Bill 1975).

In an earlier model (Seiler and Wollensak 1982), we considered the trabecular meshwork as built of sheets with pores, one sheet after the other. Starting from the uveal meshwork (pore size 50 μm), the pore sizes decreased to 1.5 μm in the cribriform region, and the number of pores decreased in the same way. The pressure drop amounted to about 1 mm Hg. However, this model is extremely coarse and has poor morphological correlation with the biological meshwork.

Starting from electron micrographs, for the subendothelial region we found a ramified network of optically empty spaces. When the drainage theory of filter beds is used, which has been well tested in paper machines, the data presented lead to a pressure drop that is at least 100 times too small. There are several potential explanations for this:

1. The reason for the pressure drop is located in other structures of the trabecular meshwork.
2. The preparation processing of transmission electron micrographs includes systematic errors that prohibit such an interpretation.
3. Only a part of this subendothelial region filters.

Explanation 1

As already stated, several investigation groups have proved that the location of the pressure head is not inside the endothelium of Schlemm's canal. Going towards the anterior chamber, the proportion of tissue not occupied by the trabeculae and extracellular material increases (in the *cribriform region* already 18.0%). That means that there is less resistance to flow. It can thus be assumed that the *locus generis* of resistance must be located as close to the endothelium as possible, that is, in the subendothelial region.

Explanation 2

When transmission electron micrographs are prepared, the specimens usually shrink. Shrinkage of up to 20% has been reported, and with this shrinkage, the natural lumina become greater. No data are available about the shrinkage factor of the micrographs referred to here, but a usual value is 10%. Dehydration of the GAGs may also artificially extend the canalicular lumen. These substances are found in the juxtacanalicular meshwork and their amount shows significant negative correlation with the facility of outflow (Segawa 1975). Such layers on the surfaces facing the aqueous are much thicker (up to 2 μm in the uveal meshwork) than found in other tissues (30 nm in vascular endothelium).

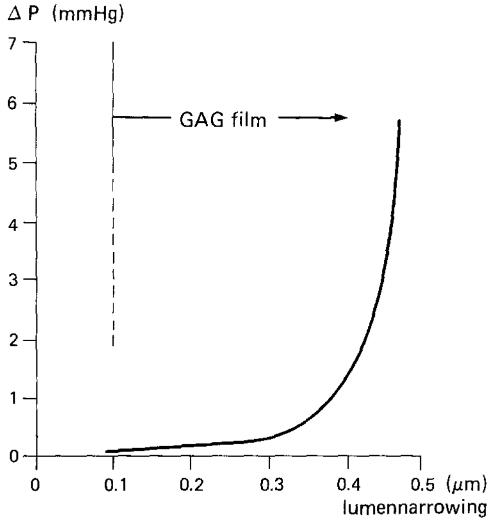

Fig. 3. Influence of lumen narrowing in the subendothelial region on pressure gradient. The first narrowing that occurs (0.1 μm) is presumed to be caused by shrinkage

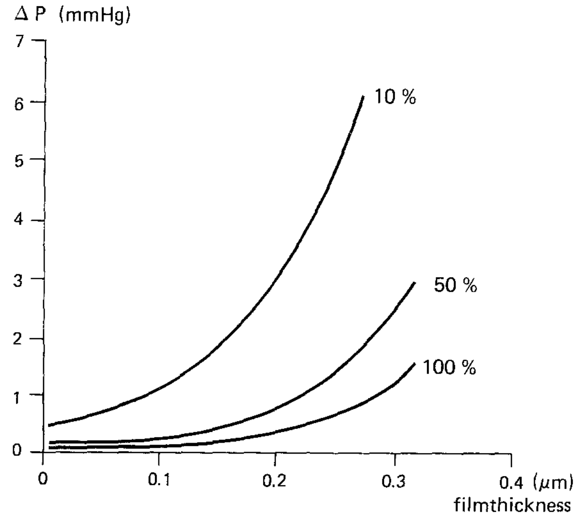

Fig. 4. Pressure gradient as a function of the effective filter area and the GAG film thickness. The *abscissa* values are the same as in Fig. 3 minus the 0.1 μm shrinkage. The 100% curve corresponds to that of Fig. 3

This explanation is in line with the following picture (Fig. 3).

In the natural state (without shrinkage) the pressure gradient across the filter bed in the subendothelial region of the juxtacanalicular region is about 0.05 mm Hg. If these canaliculi are coated by a GAG film of 0.45 μm thickness, which seems to be a little too high, this pressure drop increases to 3–5 mm Hg, which is in the experimentally verified region. Further narrowing of only 0.1 μm, caused either by accumulated amorphous substances (Segawa 1975) or by thickening of the trabeculae, results in a remarkable increase in the pressure drop.

Explanation 3

An alternative way of interpretating the small pressure drop would be to say that only a part of this subendothelial region filters (Bill 1984 pers. comm.). In other words, only a part of the filter bed has connections with Schlemm's canal. Recent experiments with perfusion of the outflow routes with low-viscosity plastic material (A. Bill, personal communication 1984), as well as earlier electron micrographs (Bill and Svedbergh 1972), indicate that there are only a limited number of filter bed contacts with Schlemm's canal. To estimate the influence of such a partial obstruction, the effect on the velocity, v_0, must taken into consideration. If, for example, 50% of the filter bed has contact with Schlemm's canal, the effective cross sectional area is only 50% and therefore twice v_0.

The pressure drop for 50% and 90% restriction (50% and 10% effective filtering, respectively) in combination with narrowing is shown in Table 2 and Fig. 4.

In this filter theory a pressure drop of about 5 mm Hg across the subendothelial region can be calculated with two assumptions: (1) the empty spaces in the trabecular meshwork are narrowed by a GAG film or (2) a part of the meshwork is hydrodynamically ineffective because the filter has no contact with Schlemm's canal. In our opinion, a realistic model can only be established by combining these two assumptions.

From the pore frequency of about 1,000 mm^2 one can assume that the effective cross-sectional area is not more than 10% of the total cross-sectional area. This hypothesis could be verified by further experiments of perfusion with low viscosity plastics.

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