ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB
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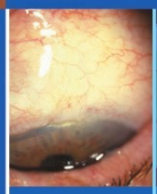
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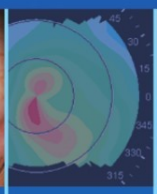
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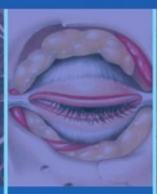
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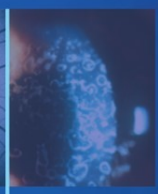
Cornea and External Eye Disease

Glaucoma

Edited by
F. GREHN
R. STAMPER


Springer

Essentials in Ophthalmology

Glaucoma

F. Grehn R. Stamper
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Editors Franz Grehn
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Glaucoma

With 68 Figures, Mostly in Colour
and 18 Tables

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Foreword

The series *Essentials in Ophthalmology* was initiated two years ago to expedite the timely transfer of new information in vision science and evidence-based medicine into clinical practice. We thought that this prospicient idea would be moved and guided by a resolute commitment to excellence. It is reasonable to now update our readers with what has been achieved.

The immediate goal was to transfer information through a high quality quarterly publication in which ophthalmology would be represented by eight subspecialties. In this regard, each issue has had a subspecialty theme and has been overseen by two internationally recognized volume editors, who in turn have invited a bevy of experts to discuss clinically relevant and appropriate topics. Summaries of clinically relevant information have been provided throughout each chapter.

Each subspecialty area now has been covered once, and the response to the first eight volumes in the series has been enthusiastically positive. With the start of the second cycle of subspecialty coverage, the dissemination of practical information will be continued as we learn more about the emerging advances in various ophthalmic subspecialties that can be applied to obtain the best possible care of our patients. Moreover, we will continue to highlight clinically relevant information and maintain our commitment to excellence.

G. K. Krieglstein
R. N. Weinreb
Series Editors

Preface

This second volume in the series *Essentials of Ophthalmology*, as in the first, seeks to bring the ophthalmic practitioner up to date on the important new advances or changes in glaucoma diagnosis and management that has occurred in the last 10 years. The last decade has seen significant changes in our understanding of the pathophysiology of some glaucomas, both in our diagnostic approaches and in our management. Toward the goal of providing the most up-to-date information in a readable fashion, we have asked some of the world's experts to discuss areas to which they have contributed in a way that will be useful for the practicing doctor.

For example, Dr. Johnstone, one pioneer in the study of trabecular meshwork, explains his new theories of how aqueous gets through the meshwork and Schlemm's canal. He proposes that the trabecular drainage system is not just a passive screen as has been conceived for the past century but a much more dynamic system than has been heretofore acknowledged.

Electrophysiology has improved both our understanding of the processes of glaucoma damage but has also provided new diagnostic tools. Thanks to the completion of several randomized controlled trials, we are now able to actually calculate the risk of developing glaucoma in a patient who is a glaucoma suspect. Dr. Mansberger explains this new development.

Our understanding of the complicated issue of what factors drive our patients to follow our prescriptions or not has been given a boost by several studies in recent years. Dr. Schwartz describes some of the advances in our understanding of patient adherence and persistence.

Health economics, rarely discussed before in this kind of ophthalmic venue, has become more important as healthcare groups, health insurers and governments grapple with the problems of providing ophthalmic care with resources that are stressed by ever-increasing demands and options. This issue is addressed by Dr. Tuulonen, as is the problem of glaucoma in the developing world which, as difficult as it may be with first-rate resources, becomes even more daunting when the resources are severely limited.

Drs. Kaufman and Gabelt give us a look at the future of medical treatment. The use of new imaging techniques has given us new insights into the pathophysiology of filtering blebs.

Dr. Freedman updates our concepts of tube-shunt procedures and offers some practical advice on how to improve results. Many of the mechanisms discussed and illustrated in this volume have not appeared in textbook format before. We hope that all the topics and authors we have selected are helpful in improving the understanding of the many faces of glaucoma and will ultimately contribute to reduced visual loss and better care for our patients.

Franz Grehn
Robert L. Stamper

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Basics and Diagnosis

Chapter 1

A New Model Describes an Aqueous Outflow Pump and Explores Causes of Pump Failure in Glaucoma

1

Murray A. Johnstone

Core Messages

- The aqueous outflow system is structurally organized to act as a mechanical pump. The aqueous outflow system is part of a vascular circulatory loop. All other vascular circulatory loops return fluids to the heart by pumping mechanisms.
- The trabecular meshwork actively distends and recoils in response to IOP transients such as the ocular pulse, blinking, and eye movement. Trabecular meshwork flexibility is essential to normal function.
- Aqueous valves transfer aqueous from the anterior chamber to SC. The valves are oriented circumferentially in SC and their normal function requires that trabecular tissues retain their ability to recoil from SC external wall.
- The aqueous pump provides short-term pressure control by varying stroke volume in response to pressure changes.
- The aqueous pump provides long-term pressure control by modulating trabecular meshwork constituents that control stroke volume.
- The aqueous outflow pump fails in glaucoma because of SC wall apposition and trabecular tissue stiffening. The trabecular meshwork (TM) stiffening is progressive and becomes irreversible.
- Clinically visible manifestations of pump failure are lack of pulsatile aqueous discharge into the aqueous veins and gradual failure in the ability to reflux blood into SC.
- Reversal of pump failure requires Schlemm's canal lumen enlargement. Precisely targeted surgical techniques directed at the scleral spur and its ciliary body attachment should reverse the structural abnormality without damaging the pump.

1.1 Introduction

1.1.1 Overview

Primary open-angle glaucoma is an enigma involving abnormal aqueous outflow. Constructing a model that explains normal control of pressure and flow is necessary before the enigma can be resolved. Laboratory studies describe an aqueous outflow system with properties that enable it to act as a pump. A recently proposed model describes such a pump that controls both pressure and flow [34]. This chapter summarizes confirmatory evidence that supports the pump model. It further explores how malfunction of mechanisms central to the model can explain laboratory and clinical abnormalities found in glaucoma. The ability to predict and explain laboratory and

clinical observations provides a means of assessing the model's strength.

The initial reports by both Ascher [2] and Goldmann [16] of the presence of aqueous veins point out that a mechanism is present to transmit the intraocular pulse across the trabecular meshwork to Schlemm's canal (SC) and the aqueous veins. Goldmann, Ascher, and others provide exquisitely detailed descriptions of the effect of the pumping mechanism that moves aqueous from SC into the episcleral veins [4]. It is best to start with a brief overview of the pumping mechanism model. Flexible trabecular tissue movement pumps aqueous from the anterior chamber to SC through a series of valves spanning SC (Figs. 1.1, 1.2). Trabecular tissue movement then pumps aqueous from SC to the aqueous veins. The aqueous outflow pump receives its power from transient IOP increases such as during systole of the cardiac cycle, respiration, blinking, and eye movement. These IOP transients cause deformation of the elastic structural elements of the trabecular tissues (Fig. 1.3). During systole, the pressure increase moves the trabecular tissues outward, toward SC and eventually into it (Fig. 1.4A,B). Outward movement of the Schlemm's canal endothelium (SCE) narrows SC, forcing aqueous from SC into collector channel ostia and then into the aqueous veins. Concurrently, the transient IOP increase forces aqueous from the trabecular meshwork interstices into one-way collector vessels or valves spanning SC. Decay of the pressure spike causes the elastic trabecular elements to respond by recoiling to their diastolic configuration. Trabecular tissue recoil causes a pressure reduction in SC that induces aqueous to flow from the aqueous collector vessels or valves into SC.

Stroke volume is responsible for the amount of aqueous discharged from SC with each IOP transient, thus providing short-term IOP homeostasis. The stroke volume moves up or down an IOP-dependent length–tension curve. Optimization of the stroke volume setpoint is a function of the trabecular tissue properties that determine distention and recoil. Trabecular endothelial cells regulate trabecular tissue properties. Trabecular endothelial cells act as sensors constantly monitoring information related to pressure and flow. Using the information, the endothelial cells employ mechanotransduction mechanisms to optimize their own properties as well as the constituent properties of the formed extracellular elements.

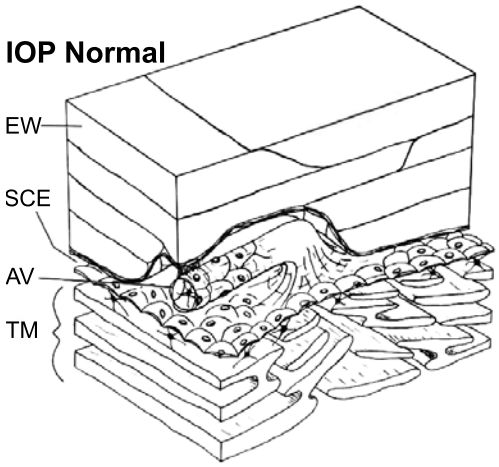
In this model, the pump controls flow and pressure; the problem of glaucoma is explained by a failure of pump function. Pump failure results from abnormally diminished trabecular tissue movement (Fig. 1.4C). Reduced trabecular tissue movement in turn results from two related abnormalities. The first abnormality is intrinsic trabecular tissue stiffening; the second is abnormal persistence of trabecular tissue apposition to SC external wall. Persistent trabecular tissue apposition develops because of both intrinsic excess distention of trabecular tissues and extrinsic factors. Extrinsic factors alter the position of trabecular tissue attachments to the scleral spur, Schwalbe's line, and ciliary body. Alterations in corneoscleral relationships, corneoscleral flexibility, and changes in ciliary body tone are examples of extrinsic factors that move the trabecular insertion within the eye. Laboratory and clinical evidence follows which provides confirmatory evidence to support the model.

1.1.2 The Trabecular Meshwork Is the Wall of a Vessel

Ashton's anatomic studies [5, 6] demonstrate that SC is the wall of a vascular sinus that communicates directly with the venous system; thus, the trabecular side of SC is the highly modified wall of a vessel. When we couple Ashton's observations with those of Ascher [4] and Goldmann [16], it becomes apparent that the aqueous outflow system functions in the broader sense as one of the vascular circulatory loops returning fluids that originated from the blood (blood derived) to the heart.

1.1.3 The Aqueous Outflow System Is Part of a Vascular Circulatory Loop

The cardiac pulse pumps blood to the ciliary processes. Ciliary-process epithelia then convert aqueous constituents of the blood into aque-



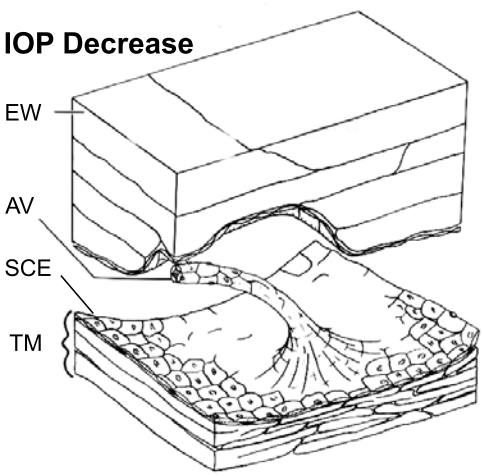


Fig. 1.1 Aqueous outflow anatomy when IOP is normal or decreased. *TM* trabecular meshwork, *SCE* Schlemm's canal endothelium, *EW* Schlemm's canal external wall, *AV* aqueous valve. (From [30])

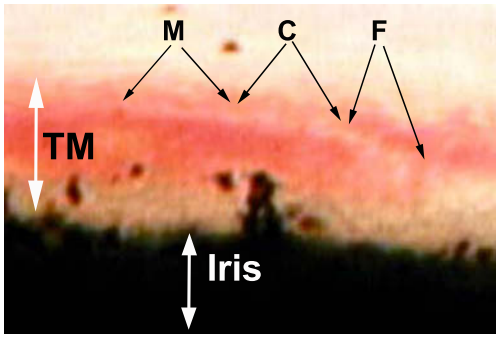


Fig. 1.2 Aqueous valve discharging aqueous into Schlemm's canal. Blood, intentionally refluxed into SC, is visible through the trabecular meshwork tissue (*TM*). Pulsatile movement of clear aqueous is visible in the funnel (*F*) and cylindrical (*C*) portion of the valve. Aqueous ejection to SC is apparent because of the whirling eddies of an aqueous–blood mixture (*M*) that develops with each systole. (Gonioscopic video courtesy of R. Stegmann)

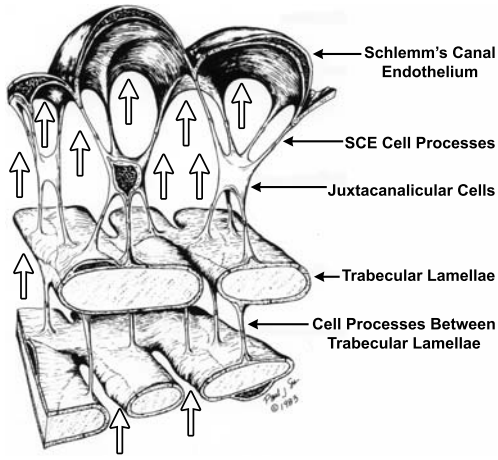


Fig. 1.3 Appearance of aqueous outflow system at physiologic IOP. *Arrows* depict deforming forces of pressure that act on Schlemm's canal endothelium. The IOP forces transmit through cellular processes to the trabecular lamellae. (From [32])

ous humor that flows into the anterior chamber. Aqueous flows from the anterior chamber through the trabecular meshwork into SC. From SC aqueous flows into aqueous veins and episcleral veins completing the closed circulatory loop that returns aqueous to the heart.

1.1.4 Circulatory Loops Return Fluid to the Heart by Pumping Mechanisms

Other circulatory loops, such as the veins and lymphatics, pump fluid back to the heart by

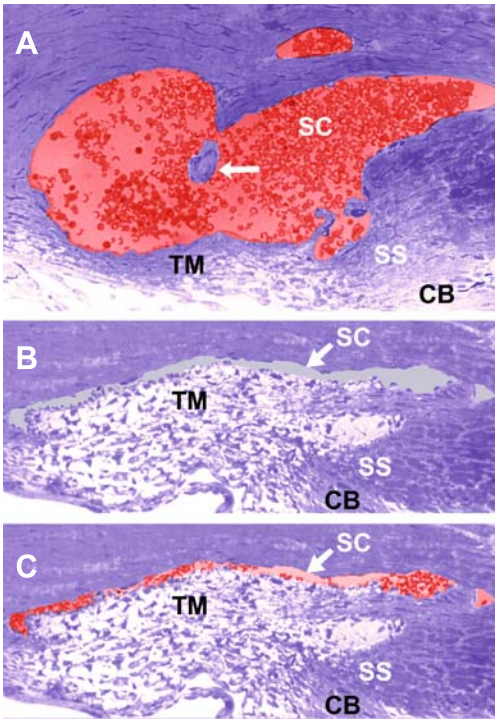


Fig. 1.4 Trabecular meshwork (*TM*) movement following IOP reduction allows TM collapse, Schlemm's canal (*SC*) expansion, and blood reflux. **A** Intraocular pressure zero, episcleral venous pressure (EVP) ~8 mm Hg. The higher pressure in SC causes the highly flexible trabecular TM to collapse. The pressure on the collapsed TM forces it inward and posteriorly carrying the scleral spur (*SS*) and ciliary body (*CB*) attachment with the TM, thus greatly enlarging SC. **B** Intraocular pressure 25 mm Hg, EVP ~8 mm Hg. The IOP causes SC endothelium to distend outward carrying the TM with it. TM movement toward SC also forces the attached SS and CB toward SC causing closure of SC lumen. **C** Tissue fixation in the living eye at 25 mm Hg experimentally stiffens TM tissues. Tissue stiffening then prevents experimentally induced SC blood reflux seen in **A**, and simulates TM sclerosis thought to be the cause of inability to reflux blood into SC in glaucomatous eyes. Rhesus macaque. **A** is the fellow eye of **B** and **C**.

means of pressure transients that drive fluid in one direction through a series of valves. These valves permit pulsatile flow toward the heart in response to transients such as the cardiac pulse, respiration, muscle, and viscera movement. Vascular tissue composition determines the properties that optimize flow and pressure relationships in other vascular circulatory loops [27]. The currently proposed model uses the same physiologic principles to explain mechanisms that optimize pressure and flow relationships in the aqueous circulatory loop.

Summary for the Clinician

- Since the trabecular meshwork is the wall of a vessel, we can expect it to have anatomic features and physiologic behavior analogous to vessels elsewhere.
- Examination of vascular system behavior points to pumping mechanisms as a means of returning fluids to the heart.

1.2 Laboratory Evidence of a Mechanical Aqueous Outflow Pump

1.2.1 Anatomic Relationships That Permit Pulsatile Flow

1.2.1.1 SC Pressure Gradients Are in the "Wrong Direction" Requiring Adaptations

Although Schlemm's canal is the modified wall of a vessel, in other vessels pressure levels are higher in the vessel lumen than in the tissues around them. By contrast, pressure is higher in the tissue outside SC lumen than it is on the inside. Fluid also moves into rather than out of SC lumen. Pressure gradient and flow reversals require a unique series of adaptations of the trabecular wall of SC. The adaptations provide a means of resisting the pressure gradients that would otherwise force SC endothelium away from the trabecular lamellae and toward Schlemm's canal.

1.2.1.2 Trabecular Tissue Attachment Mechanisms Provide a "Right Direction"

At the heart of the current model is a system of cellular attachments that integrate the trabecular tissues into a functional unit (Fig. 1.3) [31]. Pressure does not force SC endothelium against a basement membrane to provide intimate contact as in other vessels. The SC inner wall endothelium has only a sparse – and in some areas an absent – basement membrane; instead, in place of a basement membrane, numerous cytoplasmic processes of Schlemm's canal endothelial cells project into the juxtacanalicular space. Cytoplasmic processes of SC endothelium attach to processes projecting from juxtacanalicular cells. Juxtacanalicular cells also have processes projecting toward the trabecular lamellae. Endothelial cells covering the trabecular lamellae in turn have processes projecting toward and attaching to the juxtacanalicular cells' cytoplasmic processes. The result is that cellular processes of SC endothelium attach to cellular processes of endothelial cells covering trabecular lamellae.

Trabecular lamellae also attach to one another by cytoplasmic processes rather than by intertrabecular collagen beams that are infrequent and difficult to find microscopically. Endothelial cells covering the trabecular lamellae are the origin of the cytoplasmic processes. The cellular processes throughout the trabecular meshwork meet in the intertrabecular space with a complex zone of apposition involving robust desmosomes and gap junctions [23, 24].

1.2.2 IOP Transients Move Trabecular Tissues to Power the Pump

1.2.2.1 IOP Increases Cause Trabecular Tissue Distention

As pressure increases, the entire tissue monolayer of SC endothelium moves outward into SC (Fig. 1.4) [31, 34, 35]. At the same time individual endothelial cells throughout the monolayer change shape from a round appearance to an elongated plate-like shape. Individual cells tether to underlying processes and in the areas between tethering processes balloon outward to create the appearance of a series of undulating spherical structures along the monolayer when seen from SC lumen. The ballooning appearance of the distending endothelial cells is associated with the misnomer of "giant vacuoles."

Only tissues resisting a force undergo force-induced deformation [27]. All studies examining IOP-induced tissue changes observe that SC endothelium is the principal tissue undergoing force-induced deformation (See [34] for complete reference list). All these studies thus point to the Schlemm's canal endothelial monolayer as the site of resistance to aqueous flow within the trabecular meshwork.

1.2.2.2 SC Endothelium Tethering to Trabecular Lamellae Limits Movement

The following observations demonstrate that the trabecular lamellae limit SC endothelium outward movement by means of restraining tension exerted through cell processes (Fig. 1.3) [31, 35]. At cell process origins of SC endothelium, the cytoplasm and nucleus of the cells reorganize from a flat to an elongated cone-shaped configuration. Juxtacanalicular cell cytoplasmic process origins also change from a round- to a cone-shaped appearance. Cytoplasmic processes throughout the meshwork undergo progressive changes from an orientation parallel to trabecular beams to a perpendicular orientation. At the same time, the cytoplasmic processes change from a short, stubby appearance to an elongated and thin configuration. As SC endothelium stretches and moves outward into SC, the juxtacanalicular space enlarges. As IOP increases further, the trabecular lamellae stretch progressively outward toward SC lumen increasing the space between adjacent lamellae.