ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB

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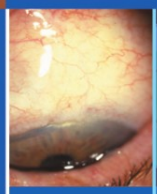

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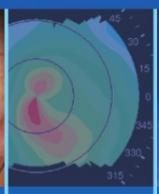

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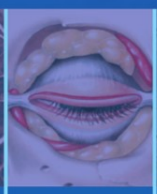

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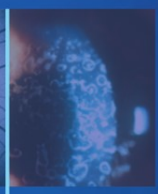

Cornea and External Eye Disease

Glaucoma

Edited by

F. GREHN

R. STAMPER

Springer

Essentials in Ophthalmology

Glaucoma

F. Grehn R. Stamper
Editors

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G. K. Krieglstein R. N. Weinreb
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Cornea and External Eye Disease

Editors Franz Grehn
Robert Stamper

Glaucoma

With 68 Figures, Mostly in Colour
and 18 Tables

Springer

Series Editors

Günter K. Krieglstein, MD
Professor and Chairman
Department of Ophthalmology
University of Cologne
Kerpener Straße 62
50924 Cologne
Germany

Robert N. Weinreb, MD
Professor and Director
Hamilton Glaucoma Center
Department of Ophthalmology - 0946
University of California at San Diego
9500 Gilman Drive
La Jolla, CA 92093-0946
USA

Volume Editors

Franz Grehn, MD
Professor and Chairman
Department of Ophthalmology
University of Wuerzburg
Josef-Schneider-Straße 11
97080 Wuerzburg
Germany

Robert Stamper, MD
Director of Glaucoma Service
Department of Ophthalmology
USCF
10 Kirkham Street, Rm K301
San Francisco, CA 94143
USA

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Desk Editor: Martina Himberger, Heidelberg, Germany
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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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Contributors

Michael Bach, Prof. Dr.
Universitäts-Augenklinik Freiburg
Killianstraße 5
79106 Freiburg
Germany

Andreas G. Böhm, Priv.-Doz. Dr.
Augenklinik der Technischen Universität
Fetscherstraße 74
01307 Dresden
Germany

Paul Foster, MD
Institute of Ophthalmology
Bath Street
London EC1 V 9EL
UK

Jeffrey Freedman, MD, PhD
Department of Ophthalmology
SUNY Downstate Medical Center
450 Clarkson Avenue,
Brooklyn NY 11203
USA

B'Ann True Gabelt, Associate Scientist
Department of Ophthalmology
and Visual Sciences
University of Wisconsin
600 Highland Avenue
Madison, WI 53792-3284
USA

Franz Grehn, Prof. Dr. Dr. h.c.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Rainer Guthoff, Dr.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Murray A. Johnstone, MD
Swedish Medical Center
Department of Ophthalmology
1221 Madison #1124
Seattle, WA 98104
USA

Hartmut E. Kanngiesser, Dr.
Manager R&D
SMT Swiss Mictrotechnology AG
Allmendstrasse 11
2562 Port
Switzerland

Paul Kaufman, MD, PhD
Professor and Chairman
Department of Ophthalmology
University of Wisconsin
600 Highland Avenue
Madison, WI 53792-3284
USA

Thomas Klink, Dr.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Christoph Kniestedt, Dr.
Kantonsspital Winterthur
Augenklinik
Brauerstrasse 15,
8401 Winterthur
Switzerland

Markus Kohlhaas, Prof. Dr.
St. Johannes-Hospital
Johannesstraße 9–17
44137 Dortmund
Germany

Steven Mansberger, MD
Devers Eye Institute
1040 NW 22nd Avenue #200
Portland, OR 97210
USA

Thomas Meigen, Priv.-Doz. Dr.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Emily L. Patterson, MD
Devers Eye Institute
1040 NW 22nd Avenue #200
Portland, OR 97210
USA

Lutz E. Pillunat, Prof. Dr.
Augenklinik der Technischen Universität
Fetscherstraße 74
01307 Dresden
Germany

Günther Schlunck, Dr.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Evelin Schneider, Dr.
Universitäts-Augenklinik Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany

Gail F. Schwartz, MD
Glaucoma Consultants
6565 N. Charles Street, Suite 302
Baltimore, MD 21204
USA

Harri Sintonen, PhD
Department of Public Health
University of Helsinki and FinOHTA
P.O. Box 41
00014 University of Helsinki
Finland

Eberhard Spörl, Dr.
Augenklinik der Technischen Universität
Fetscherstraße 74
01307 Dresden
Germany

Robert Stamper, MD
Professor and Chairman
Department of Ophthalmology
UCSF
10 Kirkham Street, Rm K301
San Francisco, CA 94143
USA

Ravi Thomas, MD
Professor and Chairman
LV Prasad Eye Institute
Banjara Hills
Hyderabad
Andhra Pradesh
India

Anja Tuulonen, MD
Department of Ophthalmology
P.O. Box 5000
University of Oulu
FIN-90014 Oulu
Finland

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.

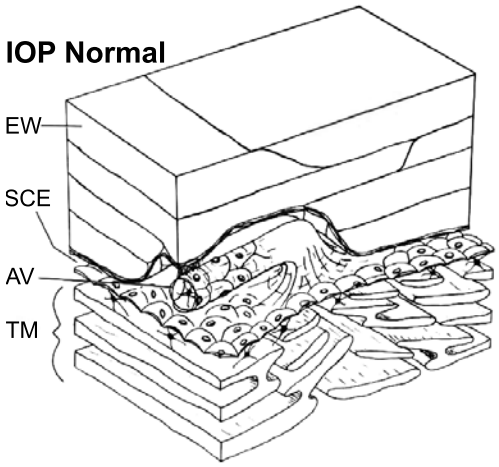
In this model, the pump controls flow and pressure; the problem of glaucoma is explained by a failure of pump function. Pump failure results from abnormally diminished trabecular tissue movement (Fig. 1.4C). Reduced trabecular tissue movement in turn results from two related abnormalities. The first 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-



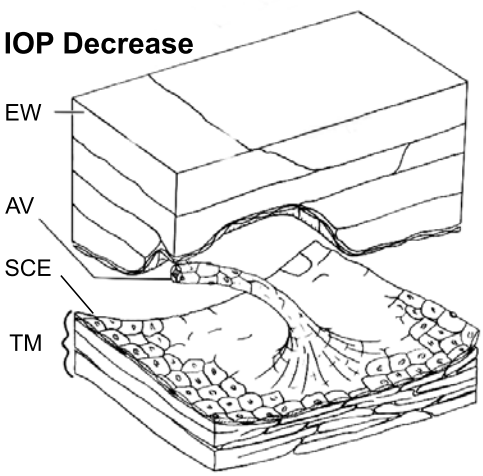


Fig. 1.1 Aqueous outflow anatomy when IOP is normal or decreased. *TM* trabecular meshwork, *SCE* Schlemm's canal endothelium, *EW* Schlemm's canal external wall, *AV* aqueous valve. (From [30])

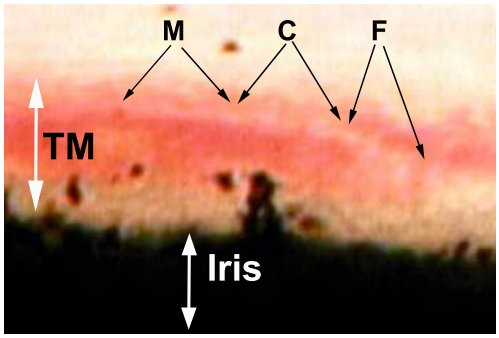


Fig. 1.2 Aqueous valve discharging aqueous into Schlemm's canal. Blood, intentionally refluxed into SC, is visible through the trabecular meshwork tissue (*TM*). Pulsatile movement of clear aqueous is visible in the funnel (*F*) and cylindrical (*C*) portion of the valve. Aqueous ejection to SC is apparent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

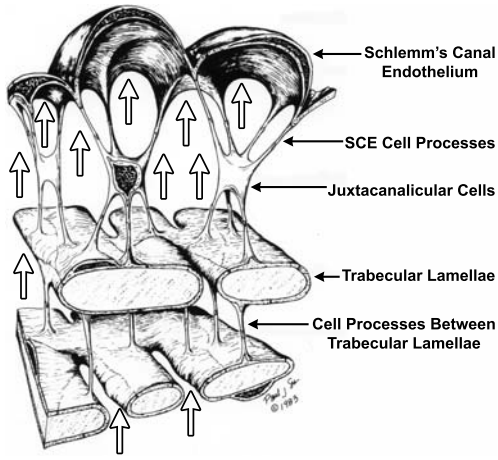


Fig. 1.3 Appearance of aqueous outflow system at physiologic IOP. *Arrows* depict deforming forces of pressure that act on Schlemm's canal endothelium. The IOP forces transmit through cellular processes to the trabecular lamellae. (From [32])

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

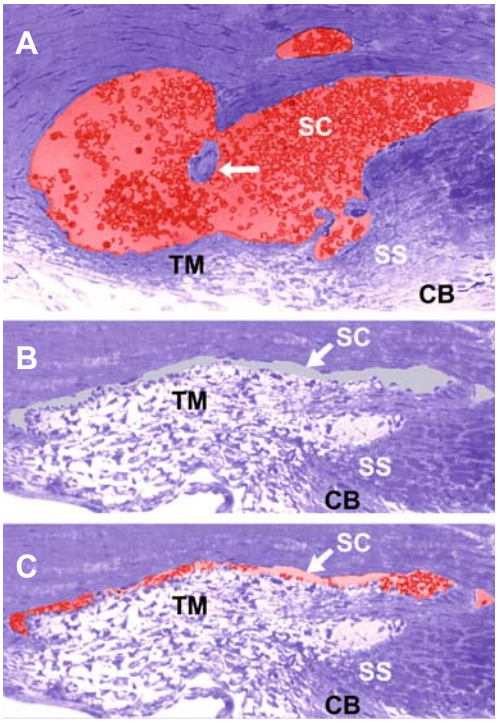


Fig. 1.4 Trabecular meshwork (*TM*) movement following IOP reduction allows TM collapse, Schlemm's canal (*SC*) expansion, and blood reflux. **A** Intraocular pressure zero, episcleral venous pressure (EVP) ~8 mm Hg. The higher pressure in SC causes the highly flexible trabecular TM to collapse. The 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.

1.2.2.3 IOP Increases Stretch the Entire Trabecular Meshwork

An increase in IOP places all trabecular tissues under tension and stretches them (Figs. 1.3, 1.4) [31, 33–35]. Stretching results from the IOP-induced forces placed on SC endothelium. The forces transmit to the restraining juxtacanalicular cells and trabecular lamellae via the connecting cell processes. The tethering mechanism creates a continuous dynamic tension between SC endothelium and the trabecular lamellae through the cell process tethering mechanism.

1.2.2.4 IOP-Induced Trabecular Stretching Narrows the Lumen of SC

Progressive distention of the trabecular tissues into SC causes a progressive reduction in the size of SC lumen eventually reducing much of the canal to a potential space. All tissue-loading studies that examine the issue find such progressive distention with SC narrowing and eventual occlusion as IOP increases.

1.2.3 IOP Decreases Cause Trabecular Tissue Recoil

Trabecular tissues recoil in response to reductions in IOP. At physiologic pressure, all pressure-loading studies demonstrate distention of SC endothelium. Following systematic tissue loading by IOP, a reduction in IOP results in reversal of the tissue deformation caused by the tissue loading [31, 33–35]. Reduction of IOP results in structural reorganization of all the trabecular tissues. This recoil response occurs at both the tissue and cellular level. Schlemm's canal endothelial distension decreases resulting in the cells undergoing a change from a plate-like to a round configuration with development of deep nuclear notches and folds. Juxtacanalicular cell nuclei and cytoplasmic elements change from a stellate to a round configuration. The juxtacanalicular space and intertrabecular spaces decrease. Cell processes in the spaces become thicker and less elongated.

1.2.4 Trabecular Tissues Respond to IOP Transients

Continually oscillating IOP transients transfer forces directly to SC endothelium. Such transients must be transmitted because tissue-loading studies [31, 33–35] demonstrate no significant resistance elements between the AC and SC endothelium. Clinically visible pulsatile central retinal veins [42] therefore provide a guide to trabecular tissue responses to IOP transients. The central retinal veins experience the same IOP transients as the trabecular tissues. The vein walls have a compliant structure allowing distention and recoil. An endothelium also lines the central retinal vein lumen. The lumen of both the central retinal veins and the lumen of SC in hypotonous eyes are each about 40 μm in diameter [26]. The central retinal vein wall is approximately 2 μm thick. In contrast, SC endothelium is about 0.2 μm thick [26]. Central retinal veins continuously change shape in synchrony with the ocular pulse. The central retinal vein lumen not only narrows but also often collapses during systole but then recoils to its full diameter again during diastole. A pulsatile wave of blood discharges from the vein lumen during each cardiac cycle.

1.2.5 Trabecular Tissues Move with the Ocular Pulse

Pulse-driven trabecular movement is a necessary response of the tissue-loading effects of the ocular pulse. The size of SC lumen is similar to the CRV lumen, while SCE wall thickness is only about one-tenth that of the CRV wall. Trabecular tissues experience the same pulse-driven pressure transients as the central retinal vein. If central retinal veins continuously undergo cyclic deformation in response to the ocular pulse, then trabecular tissues and SC lumen must undergo comparable deformation. Since direct clinical observation tells us that the central retinal vein undergoes continuous cyclic deformation in response to the ocular pulse, we may reasonably conclude that the trabecular tissue and SC lumen undergo comparable cyclic or oscillatory movement.

Summary for the Clinician

- Schlemm's canal endothelium attaches to the trabecular lamellae by cellular processes.
- The force of pressure from the anterior chamber acts directly on SC endothelium.
- SC endothelium distributes pressure to the entire trabecular meshwork by means of the cell processes.
- The progressively distending SC endothelium pulls the entire trabecular meshwork into SC. Because of its attachment to the trabecular meshwork, the scleral spur also moves toward the external wall of SC. The distending TM and associated scleral spur movement cause a narrowing of SC lumen.

1.3 The Aqueous Valves

1.3.1 Appearance and Relationships

Schlemm's canal valves act as collecting vessels that arise from SC inner wall endothelium and attach to SC external wall [30, 34]. When IOP increases, SC inner wall moves outward toward the external wall, thus narrowing SC lumen. As a result, the valves attached between the walls of the canal typically turn to course circumferentially in SC at physiologic IOP (Fig. 1.1). Table 1.1 describes evidence supporting the presence of the aqueous valves.

When IOP is low, blood refluxes into SC and dilates the canal, thus stretching the aqueous valves directly between the canal walls. Table 1.2 describes the dimensions of the aqueous valves in rhesus macaque monkey and human eyes. Schlemm's canal dilation before fixation stretches the aqueous valves directly across SC, thus allowing examination of the aqueous valve dimensions in single radial epon-embedded histologic sections. In the living monkey eye (macacca mulatta), pressure lowing causes blood to reflux into SC, thus dilating the canal before fixation. Enucleated human eyes had SC dilated by tension on scleral spur of radial segments before fixation.

1.3.2 Valves in SC Carry Aqueous

1.3.2.1 Laboratory Evidence

Light, transmission, and scanning electron microscopy [30, 34] document that the lumen of the aqueous valves is continuous with the juxtacanalicular space. At physiologic pressures, the aqueous valve walls expand allowing enlargement of their lumen. Increases in pressure and expansion of the lumen of the aqueous valves in SC provide a means of enlarging the distal opening in response to cyclic pressure transients. Tracer studies [34] demonstrate that when avian red blood cells are infused into the anterior chamber, they enter the aqueous valves and pass to the distal end, providing evidence that aqueous may also easily pass to the distal end by the same mechanism. Avian red cells are 3 μm in diameter and rigid. Avian red cells and other materials > 2 μm in diameter are unable to enter SC. The organizational arrangement at the distal end of the valves similarly limits passage of these large rigid avian red cells into SC; however, tracer studies [34] using flexible non-nucleated 2-μm-thick primate red blood cells do reflux into the distal end of the aqueous valves, at times passing as far as the juxtacanalicular space. We may assume that drainage of aqueous will follow the same antegrade path that exists for the retrograde entry of blood. There is no reason to assume that what applies for passage of blood should not apply for direct flow of aqueous. Episcleral venous blood enters SC when IOP in living primates falls below episcleral venous pressure. The pressure gradient reversal causes some primate red cells to pass through the valves as far as the juxtacanalicular space. The ability of flexible 2-μm-thick primate red cells to pass into the valves from their distal end provides additional evidence of the communication between SC lumen and the lumen of SC valves.

Table 1.1 Evidence of aqueous valves in Schlemm's canal (*SC*). *TM* trabecular meshwork, *RBC* red blood cell

Reference	Year	Observation method	Technique of SC wall separation	Findings
[47]	2002	Dissecting microscope	Viscoelastic dilation of SC	Diaphanous cylindrical structures span between TM and SC external wall ~2/mm around SC circumference
[47]	2002	Operating microscope	SC unroofing	Diaphanous cylindrical structures span between TM and SC external wall, frequently, especially in young "not collagen, these are highly elastic little tubules with a lumen"
[47]	2002	Operating microscope	SC unroofing	Diaphanous cylindrical structures span between TM and SC external wall, frequently present, "provide method of identifying SC entry"
[34]	2004	Gonioscopy	Episcleral venous pressure increase	Pulsatile aqueous flow into SC through cylindrical structures
[30]	1974	Light microscopy	Pressure gradient reversal – living eyes	Cylindrical structures span between TM and SC external wall; arise from SC inner wall endothelium; contain a lumen with material like that in juxtacanalicular space
[47]	2002	Scanning electron microscopy	Viscoelastic dilation of SC	Cylindrical structures span between TM and SC external wall
[34]	2004	Scanning electron microscopy	Tension on scleral spur to dilate SC	Cylindrical structures span between TM and SC external wall
[34]	2004	Transmission electron microscopy	Pressure gradient reversal – living eyes	As in light microscopy. collagenous attachments at distal end with endothelial lined passage to SC
[34]	2004	Light and transmission electron microscopy	Tracer studies, avian RBC introduction into AC, pressure gradient reversal	Avian RBCs pass to distal end of lumen of the cylindrical structures

Table 1.1 *continued*

Reference	Year	Observation method	Technique of SC wall separation	Findings
[34]	2004	Light and transmission electron microscopy	Tracer studies, pressure gradient reversal, primate RBCs enter SC	Primate RBCs reflux from SC into distal end of the lumen of the cylindrical structures; aqueous, therefore capable of same passage

Table 1.2 Aqueous valve dimensions derived from histologic sections. Diameter measurements are from the narrowest location along the valve length. *CI* confidence interval

Species	No. of eyes	No. of segments	No. of valves	Diameter (μm)	95% CI	Length (μm)	95% CI
Monkey	1	7	7	19.2 ± 1.7	15.1, 23.3	101.2 ± 11.5	72.9, 129.4
Human	2	12	14	19.1 ± 0.5	18.1, 20.2	76.3 ± 3.0	69.6, 83.0

1.3.2.2 Clinical Evidence

Stegmann developed an 80-power operating room microscopy video system, and observed circumferential flow of blood in SC when a goniolens flange compressed episcleral vessels, thus causing blood reflux into SC (cited by Johnstone [34]). Johnstone, in reviewing the video provided by Stegmann, observed that a column of clear aqueous was ejected into SC during each cardiac cycle initiating the circumferential flow [34]. Aqueous ejection was made obvious by swirling eddies of aqueous and blood mixing as the column of ejected clear aqueous dissipated (Fig. 1.2)

Blood present in SC outlines the pulse wave of clear fluid originating at the base of the trabecular meshwork. The origin of the pulse wave has a funnel shape with the funnel base just anterior to scleral spur. The aqueous pulse wave proceeds from the funnel into a cylindrical region that expands as the funnel entrance narrows. The pulse wave of aqueous moves distally along the cylindrical region and discharges into SC. At the same time, as the region of the cylinder progressively constricts starting from the region of distal end of the funnel, discharge into the canal from the distal end of the cylindrical region commences.

The burst of aqueous forcefully discharges into SC. The initially clear aqueous develops rapidly swirling eddies of a blood–aqueous mixture providing evidence of aqueous ejection into the canal. As the blood–aqueous eddies move circumferentially in the canal, they gradually dissipate. The length of the aqueous discharge path is similar in length to the path of the clear cylindrical region providing further evidence of forcible ejection.

Summary for the Clinician

- Light, scanning, and transmission electron microscopy document the presence of the aqueous valves. Tracer studies demonstrate that the valves allow aqueous flow.
- Viscoelastic dilation of SC allows easy visualization of SC valves with a dissecting microscope.
- The aqueous valves are clinically visible during surgical unroofing of SC.

1

1.4. Trabecular Tissues and Aqueous Valves Are the Pump

1.4.1 Trabecular Tissues Distend and Recoil with IOP Changes

At physiologic pressures, SC endothelium distends into SC. Attachments to the trabecular lamellae limit the extent of SC endothelial distention. This tensionally integrated relationship distributes the force of IOP throughout the trabecular tissues (Fig. 1.3).

1.4.2 Trabecular Tissue Movement Moves Aqueous

During systole when IOP increases, SC endothelium distends and accordingly causes increased tension throughout the trabecular tissues [31, 33, 34]. Outward movement of trabecular tissues in systole also increases pressure in SC by narrowing it (Fig. 1.4) [31, 33, 34]. As pressure in SC progressively increases, aqueous flows into collector channels and from the collector channels to the aqueous veins. At the same time, during early systole, aqueous enters the funnel as SC inner wall endothelium at the entrance of the funnel distends causing the funnel to enlarge. Since pressure in SC surrounding the valves increases, the pressure in the lumen of the flexible SC valves also increases and aqueous cannot enter them.

During diastole, when IOP decreases, the IOP-induced force distributed from SC endothelium to trabecular lamellae decreases. Recoil of the tendon-like trabecular lamellae during diastole results from elastic energy stored in the trabecular tissues during systole. A form of "diastolic suction" results causing reduction of pressure in SC which causes flow of aqueous from the funnel to the cylindrical section of the valve and then from the valve's distal end into SC. The early phase of the initial pressure increase of the next systole may aid in completing aqueous discharge into the canal.

1.4.3 IOP Transients Provide Energy to Power the Pump

Transients of IOP, as exemplified by the ocular pulse, power the pump. Blinking, eye movements, and respiration provide additional IOP transients to the pump. Clinical studies document pulsatile aqueous flow throughout the aqueous outflow system [34] and support the pump model. Histologic studies demonstrate corresponding trabecular tissue and aqueous valve responses induced by IOP transients [34], further confirming the model.

Summary for the Clinician

- Trabecular tissues are very flexible and experience major excursions in response to clinically visible IOP transients such as the ocular pulse, blinking, and eye movements.
- Similar clinically visible ocular transients cause pulsatile flow in the central retinal vein.
- Trabecular tissues stretch in response to transient IOP increases thus storing energy that is released when IOP decreases.
- Transient IOP increases provide power to the pump.

1.5 Clinical Evidence of a Mechanical Aqueous Outflow Pump

The older literature describes aqueous humor as a stagnant fluid [4]; however, observations of clinician–scientists, such as Ascher [4], Goldmann [16], and others, clearly demonstrate that aqueous discharges from SC into the aqueous veins. Their historic observations establish aqueous humor as a flowing fluid that is part of a continuous circulatory loop. Discovery of an aqueous circulation provides the basis for all current concepts of closed and open angle glaucoma mechanisms; however, the discoveries of these careful clinician scientists are not limited to simple flow of aque-

ous into the venous system. In the same original papers, Goldmann [16] and Ascher [2] also independently discovered an aqueous pumping mechanism that causes pulsatile movement of aqueous from SC into the episcleral veins.

Goldmann's original report [16] notes that a mechanism is present to transfer the ocular pulse from the anterior chamber across the trabecular meshwork to SC and the aqueous veins. At the time of their reports, the traditional model of the outflow system posited the trabecular tissues as a fixed syncytium of extracellular matrix material that would not allow transfer of intraocular transients from the anterior chamber to SC. These clinician–scientists were not able to fit their exciting observations into the existing outflow system schema [4]. As a result, their observations of pulsatile aqueous flow languish with no mention in current textbooks. Fortunately, the literature preserves the observations from their seminal studies.

1.5.1 Clinical Evidence of Pulsatile Aqueous Flow

1.5.1.1 Aqueous Flow from the Anterior Chamber into SC Is Pulsatile

Troncoso's studies are the first to report laminar flow of blood and aqueous in SC [4]. Recent observations by Johnstone and Stegmann (cited by Johnstone [34]) using Stegmann's video system demonstrate laminar movement of aqueous into the canal that is pulsatile and synchronous with the ocular pulse (Fig 1.2). When a goniolens compresses the episcleral veins, blood refluxes into SC. Modest pressure in the episcleral region provides enough pressure to allow blood entry to SC but not enough pressure to prevent any aqueous from entering the canal. By achieving this equilibrium, the background of blood permits visualization of clear aqueous entering the canal.

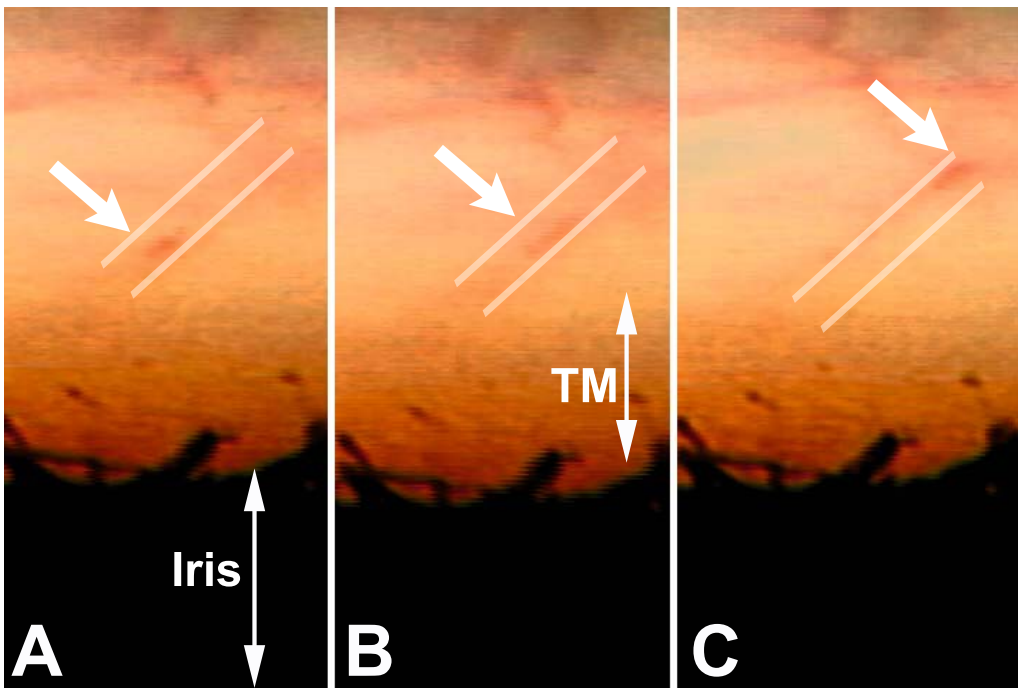


Fig. 1.5 Pulsatile aqueous movement in collector channel. *Parallel white lines* above the area of the trabecular meshwork (*TM*) depict the course of movement of blood-tinged aqueous (*arrows*). **A–C** are sequential video frames encompassing one systolic pulse wave. (Gonioscopic video courtesy of R. Stegmann)

Pulsatile entry of aqueous into SC originates in a funnel-shaped area at the base of the trabecular meshwork. The funnel initially enlarges and then collapses as aqueous flows into a columnar region, followed by discharge into SC. Aqueous entry into SC is apparent, because at the entry site the aqueous is ejected creating swirling eddies as the aqueous mixes with blood.

1.5.1.2 Aqueous Flow in SC and in Collector Channels Is Pulsatile

Stegmann, using his newly developed 80-power microscope, observes pulsatile flow of aqueous from SC into the collector channels that is synchronous with the ocular pulse (cited by Johnstone [34]; Fig. 1.5).

1.5.1.3 Aqueous Flow into Episcleral Veins Is Pulsatile

A number of observations demonstrate origination of pulsatile aqueous flow from SC. Ascher's treatise [4] nicely summarizes the many manifestations of pulsatile aqueous discharge from SC to the episcleral veins.

Summary for the Clinician

- Flow of clear aqueous through the aqueous valves is clinically visible with high-power gonioscopy in young patients following blood reflux into SC to provide a contrasting red background.
- The aqueous valves discharge aqueous into SC in synchrony with the ocular pulse.
- Pulsatile aqueous flow is visible in the collector channel ostia during high-power gonioscopy.
- Many manifestations of pulsatile aqueous flow are visible in the aqueous veins during slit-lamp examination.

1.6 Pump Regulation of Pressure and Flow: Short Term

1.6.1 Length-to-Tension Relationships Govern Stroke Volume

Intraocular pressure changes cause continuously changing tensions in the trabecular tissues. In this model [34], optimized length–tension characteristics in the trabecular tissues govern short-term flow and pressure relationships.

1.6.1.1 Increased IOP Causes Increased Stretch

Length-to-tension and stretch-to-stress relationships are common to soft tissues, are prevalent throughout the cardiovascular system, and provide a means to optimize pressure-flow relationships in both the cardiovascular and lymphatic systems. In this model at the homeostatic setpoint of pressure, trabecular tissue distention is at the lower end of the length–tension curve and tissue stretching is modest. The trabecular tissues are under minimal tension and undergo minimal excursions in response to a systolic pulse wave. Correspondingly, there is minimal trabecular tissue recoil in diastole. When IOP rises above the homeostatic set point, the trabecular tissues move up the length–tension curve causing increased stretch and increased tension with movement toward SC. Systole results in a further increase in tension followed by a corresponding increase in recoil during diastole.

1.6.1.2 Increased Stretch Causes Increased Stroke Volume

As increasing IOP causes the trabecular tissues to move up the length–tension curve, each cyclic IOP increase associated with systole induces greater tension than previously, thus storing more potential energy. During the next diastole, recoil that is more forceful results from the increased release of stored energy. The scleral coat

acts similarly leading to an increase in ocular pulse amplitude as IOP increases.

Trabecular tissues will experience minimal increase in tension in response to systole when they are initially under limited tension (or prestress), just as an unstretched rubber band develops little tension in response to a force when it is under minimal tension. When the IOP increases causing increased tension or prestress, the tissues store more energy in systole. During diastole, the greater trabecular excursion and more forceful recoil increases the fluid volume entering SC. Because of the greater volume of aqueous in SC, the next systole causes a larger aqueous volume to leave the canal. Cyclic oscillations therefore cause total stroke volume per pulse to increase when the mean IOP increases.

1.6.1.3 Increased Stroke Volume Increases Aqueous Discharge Thus Reducing IOP

When stroke volume increases more aqueous leaves the eye. The excess aqueous volume leaving the eye reduces IOP. When IOP reduces to the homeostatic setpoint, stroke volume decreases to the steady-state level closing the feedback loop. Similarly, when IOP decreases below the homeostatic setpoint stroke volume decreases allowing IOP to increase to the setpoint. Trabecular tissues thus control pressure and flow by changing stroke volume to maintain tension at the homeostatic IOP.

1.6.2 Clinical Evidence of Pump-Dependent Pressure Regulation

1.6.2.1 Clinical Recognition of Aqueous Stroke Volume Increases

Changes in the relative relationships of the blood and aqueous columns in recipient episcleral veins permit assessment of changes in stroke volume. A stroke volume increase is apparent because of the amplitude and velocity increase in the aqueous component of the recipient vessel experiencing laminar flow. The rapidity of the upstroke of the aqueous component also increases followed by a slower decay. As the stroke volume increases, manifestations of the oscillating aqueous–blood interface move distally along the recipient vein. Recipient vessel segments previously experiencing laminar flow of both blood and aqueous fill completely with aqueous. Recruitment of more distal anastomotic episcleral veins results in evidence of oscillatory flow in progressively more distal segments of the episcleral recipient veins. Proximal to the junction of aqueous and recipient veins, small episcleral veins discharge blood into the aqueous vein in an oscillatory fashion providing another marker of pulsatile flow. As stroke volume increases, episcleral veins previously at an equilibrium pressure no longer discharge into the aqueous vein during diastole. Instead, an oscillatory aqueous–blood interface moves outward (toward the heart) in these vessels at each systole.

1.6.2.2 Clinical Evidence of Stroke Volume Increase

Goldmann's observations provide the first demonstration of the relationship between increasing IOP and increasing stroke volume in the aqueous veins. The reports by Goldmann [16, 17], de Vries [10], and Thommasen [50] document more forceful pulsations in the aqueous veins resulting from IOP increase associated with force applied to the side of the eye. When water drinking increases IOP, stroke volume in the aqueous veins also increases markedly from the initial resting state [34]. As IOP gradually returns to normal, stroke volume also gradually decreases until it reaches its initial resting state. Increasing pulsatile flow and enhanced stroke volume precede diurnal reductions in IOP. Corresponding reduction in pulsatile flow and stroke volume also precede diurnal elevations in IOP [4].

Miotics used in glaucoma reduce IOP to a new homeostatic setpoint. An increased aqueous stroke volume accompanies pressure reduction to the new lower pressure [1, 4, 10, 25]. Pilocarpine instillation causes an IOP reduction that is at its maximum at about 2 h. Coincident with

the reduction of pressure over this time interval a pulsating transverse borderline between clear aqueous and blood develops. The pulsating borderline between the aqueous and blood phases moves more distally causing the whole portion of the vessel to fill with aqueous, a finding like that seen in the stroke volume increase seen with water drinking [34].

Cambiaggi [8] describes the increase in stroke volume with pilocarpine: "In a vessel without a baseline discernible direction of the flow, intermittent waves of clear fluid appear at about two hours, and become more frequent until all the red cells disappear." An additional 2 h later, the clear current slows down and blood again enters the vessel from the direction of the episcleral vein moving toward the scleral emissaries of the aqueous vein, a phenomenon like that seen with water drinking. Cambiaggi further observes that widening of the aqueous veins, increased velocity of their current, and clearing of their contents precedes a pilocarpine-induced IOP reduction [8].

Adrenergic agent instillation also causes an IOP reduction to a new homeostatic setpoint [4, 10, 16]. Where only blood or stratified aqueous–blood current had been visible in recipient vessels, a pulsating borderline develops at the same locations in response to adrenergic instillation. Relative depletion of blood, a new appearance of pulsating borderlines between the blood and aqueous phases, and the influx of clear aqueous synchronously with or slightly after the peak of the radial pulse develop.

Summary for the Clinician

- Pump short-term regulation of flow results from increasing stroke volume of aqueous in response to increases in pressure.
- An increasing pressure as occurs from water drinking or pressure on the eye provides a clinically visible increase in stroke volume.
- Pilocarpine reduces IOP by causing a clinically visible temporary increase in stroke volume until IOP reaches the new pilocarpine-induced homeostatic setpoint.

1.7 Pump Regulation of Pressure and Flow: Long Term

The lumen of SC is a vascular lumen; the trabecular meshwork is one wall of that vessel. Both extrinsic and intrinsic mechanisms modulate pressure and flow throughout the vascular system [27]. Neural and humoral mechanisms provide the extrinsic control system. Intrinsic mechanisms optimize vascular wall composition and are by far the most important regulatory mechanisms [27]. Vascular wall composition determines mean lumen size as well as intrinsic distention and recoil responses to mean and cyclic forces.

The trabecular lamellae and SC endothelium are the structural elements driving the pump in this model of aqueous outflow. The trabecular lamellae and SC endothelium must maintain responses of distention and recoil within a narrow range to satisfy the requirements of maintaining the resting IOP within a narrow range [34]. We may ask what mechanisms maintain the intrinsic tissue composition that determines mean lumen size and the boundaries of distention and recoil. What signals and responses allow trabecular tissues to maintain that narrow range of structural shape and composition?

1.7.1 Trabecular Tissue Information Networks

The previously described cellular attachment mechanisms unify the entire trabecular meshwork into a tensionally integrated information-processing network able to optimize its own structure [27–29]. Such a system is able to sense, to respond, and to continuously optimize distention and recoil properties of the constituent tissues. By concurrently optimizing all constituent tissue properties, this beautifully organized system continuously optimizes IOP-determining resistance characteristics.

1.7.2 Trabecular Tissue Tethers and Signaling Mechanisms

Signaling mechanisms continuously optimize collagenous constituents of vessel walls throughout the vascular system to maintain optimized pressure and flow. The signaling mechanisms include stresses of pressure and flow that tug on the integrin-based endothelial cell attachments to basement membranes of vessel walls. Although SC endothelial cells do not have basement membrane of their own, surrogates are the basement membrane of endothelial cells covering trabecular lamellae. Schlemm's canal pressure gradient increases transmit through cellular pathways of the cytoplasmic processes to the cells and basement membranes of the trabecular lamellae. This adaptation allows the trabecular tissues to sense forces of pressure and flow, and to optimize the mix of collagenous tissue constituents.

1.7.3 Endothelial Cells Regulate Trabecular Tissue Composition

As the wall of the vessel, an endothelium lines SC lumen. Special adaptations to reversal of flow gradients dictate that SC endothelium anchors to the underlying vessel wall by a specialized attachment mechanism in place of a basement membrane. The specialized attachment mechanism provides attachment of SC endothelium to trabecular lamellae endothelial cells via juxtacanalicular cells. Trabecular lamellae endothelial cells in turn attach to the basement membrane of the lamellae. The attachment mechanism involves both SC endothelial cells and endothelial cells lining trabecular lamellae. Cells lining the trabecular lamellae experience continuous cellular prestress associated with normal IOP. Furthermore, the same endothelial cells experience continuous cyclic oscillatory stresses associated with changing pressure transients. Stresses perpendicular to cell walls represent wall stresses. Oblique stresses are torsional, and stresses along the plane of a cellular monolayer are tractional. All endothelial cells of the trabecular meshwork experience these stresses.

1.7.3.1 Endothelial Cells Sense Pressure (Wall Stress)

The entire vascular endothelial cell is a sensor. These endothelial cells constantly sense wall stresses by means of flow- and pressure-induced deformation of receptors and the cytoskeleton. Forces generated by IOP act directly on SC inner wall endothelium. The SC endothelial cells in turn transmit the forces to the endothelial cells as well as the basement membranes and integrins of the cells lining the trabecular lamellae. Force-dependent changes in cytoskeletal scaffold geometry and cell-surface receptors then transduce the forces into biochemical responses, the process of mechanotransduction.

1.7.3.2 Endothelial Cells Sense Flow (Shear Stress)

Fluid flowing tangentially along the surface of endothelial cells induces shear stress, a major stress signal regulating vascular endothelial cell function. Numerous shear stress receptors are present on endothelial cell surfaces and these tangential stresses on the cell surface transfer through the cytoskeleton to the basement membrane of vessels, where they are experienced as torsional stresses. As a counterpart, Schlemm's canal endothelium transmits torsional stresses to the basement membranes of the trabecular lamellae via juxtacanalicular cell processes. Clinical observation demonstrates that the velocity of flow in the aqueous valves, in SC, in the collector channels, and in the aqueous veins is very similar to that in the central retinal vein thus providing comparable shear stress stimuli.

1.7.3.3 Endothelial Cells Optimize Their Own Internal Structure

The forces of pressure and flow mediate remarkable adaptive responses in vascular endothelial cells [27–29, 34]. Such adaptive responses are necessary because constantly changing forces cause changing prestress and topography in response to pressure and flow oscillations around a

homeostatic setpoint. Changing stresses and topography in turn alter physical responses of the cells to the changing forces. Equally important, changes in both cellular prestress and topography alter sensory input to the cells.

Cytoskeletal reorganization begins within seconds after shear stress increases, first involving the intermediate filaments, followed by actin filament reorganization within minutes. These profound cytoskeletal rearrangements are concomitant with both reorientation of the entire cell in the direction of flow and with cell stiffening. Cell junctional architecture also adapts concurrently, as does the arrangement of intracellular organelles and the nucleus. Stress changes activate numerous intracellular signaling pathways by sensing shear stress and by modifying the position of both extracellular organelle and intermediate pathways arrayed along the cytoskeleton.

1.7.3.4 Endothelial Cells Optimize Extracellular Matrix Structure

Not only do endothelial cells optimize their own internal structure, they also induce changes in the composition of the extracellular matrix of the contiguous vessel walls. Extracellular matrix composition in turn determines distention and recoil of the vascular wall. In vasculature elsewhere, integrin attachments to basement membranes provide a signaling system. The signaling system directs extracellular matrix elaboration as well as directing growth-factor induction which determines the extracellular matrix composition. In the vasculature, pressure gradients are higher in the lumen than in the extracellular space, providing a mechanism for movement of the signals toward the extracellular elements. Elaborated extracellular materials respond to the signals by organizing into functionally optimized structures.

In the aqueous outflow system, pressure gradients do not favor signaling by SC endothelium as a means of optimizing the extracellular matrix of the trabecular lamellae. Instead, the trabecular tissues through their attachment mechanisms transmit both pressure and flow information to endothelial cells lining the trabecular lamellae throughout the trabecular meshwork. These endothelial cells, attached to a basement membrane overlying the trabecular lamellae, have both the proximity and signal-enabling architecture necessary to utilize universal optimization principles found elsewhere in the vascular system.

1.7.4 Regulation of Trabecular Tissue Composition Is Pump Regulation

Modulation of the load-bearing elements of the trabecular meshwork determines both mean lumen size of SC and cyclic IOP-induced distention and recoil. Extracellular structural elements determine wall-stress characteristics. Collagenous constituents of the extracellular matrix of trabecular lamellae provide a mechanism to limit trabecular wall distention, whereas elastic elements provide the ability to recoil following reductions in tension.

Trabecular distention and recoil responses determine pump function; therefore, regulation of trabecular tissue composition regulates pump function [34]. There is an inverse relationship between trabecular tissue distention into SC and SC lumen size. Both the size of SC lumen and the ability to respond to constantly changing IOP transients thus reside in the constituent properties of the trabecular tissues.

Summary for the Clinician

- Vector forces induced by IOP are distributed to endothelial cells throughout the trabecular meshwork.
- Throughout the vascular system, endothelial cells sense pressure and flow allowing these cells to regulate vessel wall composition.
- Regulation of vessel wall composition regulates intrinsic responses of distention and recoil.
- Distention and recoil determine mean lumen size as well as pump characteristics.
- The trabecular tissues thus contain an intrinsic regulatory system to provide long-term control of pressure and flow.

1.8 The Pump Fails to Control Pressure in Glaucoma

In the currently proposed model, the pump controls flow and pressure [34]. Flow and pressure control is abnormal in glaucoma; therefore, in this model the failure in glaucoma is a failure of the pump. Pump failure involves progressive reduction in trabecular tissue movement. Progressive reduction of visible pulsatile flow provides a clinical marker to identify this reduction in normal trabecular tissue movement.

Normal movement is dependent on both the composition and position of the trabecular tissues. Reduced trabecular tissue movement results from two related abnormalities. The first abnormality is intrinsic trabecular tissue stiffening (Fig. 1.4C). Pump function requires precisely controlled properties of distensibility and recoil which are dependent on optimized composition. Such properties define force-dependent tissue movement.

The second abnormality is increased persistence of trabecular tissue apposition to SC external wall which is dependent on both intrinsic and extrinsic factors. Persistent trabecular tissue apposition can develop because of an intrinsic abnormality of trabecular tissue distention and recoil.

Extrinsic factors alter the position of trabecular tissue attachments to the scleral spur, Schwalbe's line, and ciliary body. Such factors include alterations in corneoscleral relationships, corneoscleral flexibility, and changes in ciliary body tone. Increasing trabecular tissue stiffness may cause IOP increases that force SC endothelium against SC external wall.

Reduced motion associated with persistent trabecular tissue apposition to SC external wall may also cause trabecular tissue stiffening. Clinical and laboratory studies point to an interplay between trabecular tissue stiffening and SC wall apposition in glaucoma.

1.8.1 Overview of the Failure Mechanism

Clinical and laboratory studies together provide converging lines of evidence that trabecular tissues stiffen and that SC lumen closes in glaucoma. A confluence of evidence demonstrates that in glaucoma the trabecular tissues lose their ability to move in response to transient IOP oscillations as well as to spontaneous or induced IOP elevations. In advanced glaucoma, the tissues not only lose their ability to move actively, but also stiffen sufficiently that a marked pressure gradient reversal will no longer cause trabecular tissue movement.

Loss of the ability to actively stretch and recoil eliminates the ability of trabecular tissues to respond to transient IOP oscillations thus providing an explanation for early pump failure in glaucoma. The resultant more frequent pressure rises force the trabecular tissues farther into SC causing more persistent canal lumen closure. Persistent SC collapse further limits trabecular tissue movement necessary for normal flow. Aqueous cannot enter the persistently collapsed lumen of SC and aqueous cannot flow circumferentially in SC to enter collector channels. The resulting increased resistance to aqueous flow results in further aqueous retention and increasing IOP.

1.8.2 Laboratory Evidence: Pump Failure Mechanisms in Living Eyes

1.8.2.1 Trabecular Tissues Stretch to First Narrow, Then Close SC Lumen

Tissue-loading studies in living eyes of primates demonstrate that increases in IOP place trabecular tissues under tension and cause them to stretch. Stretching results from the IOP-induced tension on SC endothelium that transmits to the trabecular lamellae through cell processes. All tissue-loading studies examining the issue find such progressive distention. Progressive distention of trabecular tissues into the canal causes them to move outward toward the unyielding external wall of the canal. Progressive increases in IOP thus cause a progressive reduction in SC lumen size eventually reducing the canal lumen to a potential space.

1.8.2.2 At Physiologic Pressures SC Transiently Closes

In the normal living eye, experimental evidence indicates that trabecular tissues stretch far enough to occlude SC at relatively low pressures. In living primates with normal episcleral venous pressure and ciliary body tone, extensive canal wall apposition is present at pressures between 20 and 25 mm Hg. Normal ocular transients, such as blinking and eye movements, cause a 10-mm-Hg pressure increase, and eyelid squeezing causes pressure of over 50 mm Hg.

Figure 1.6 illustrates compression of an aqueous valve between SC walls. Histologic sections are from a rhesus macaque eye fixed in vivo at 25 mm Hg. The entire length of an aqueous valve was studied as it coursed circumferentially in SC. Some areas contained an open lumen (Fig. 1.6A), whereas in other areas, compression was sufficient to collapse the valve and close the lumen (Fig. 1.6B). Similar but more extensive compression of an aqueous valve was present in a second monkey eye fixed at 35 mm Hg.

We may thus conclude from available evidence that normal physiologic pressure transients routinely cause intermittent SC closure in normal eyes. In other vascular tissues, such as the venous system and lymphatics, intermittent lumen closure in response to changing pressure gradients is a normal mechanism that causes fluid movement through the circulation. In fact, ophthalmologists observe such behavior routinely in the central retinal veins. That intermittent closure of SC lumen is a normal phenomenon is not surprising for another reason: such a mechanism limits excessive trabecular excursions that may otherwise damage the tissues. Similar damage-preventing boundary mechanisms limit excessive distention of other tissues in the vascular system.

1.8.2.3 Persistent SC Closure Necessarily Increases Resistance to Aqueous Outflow

The inner wall of SC progressively meets the outer wall as IOP increases. Apposition of SC walls causes physical compression of the aqueous valves with resultant closure of their lumen (Fig. 1.6) [32]. In these progressively increasing regions of contact, there is also no SC lumen. Aqueous cannot physically cross SC endothelium into the canal lumen in regions where the lumen is absent. Resistance to flow necessarily increases when the area available for flow decreases. After aqueous flows into SC through entry sites, it must then move circumferentially in SC to aqueous exit sites at collector channel ostia. Reduction of SC diameter physically reduces space available for circumferential aqueous flow. Reduction of SC lumen size therefore necessarily increases resistance to flow.

1.8.2.4 Small IOP Changes Cause TM Movement

Trabecular tissues move in response to small IOP changes. For example, when IOP increases from hypotony to 5 mm Hg the juxtacanalicular space enlarges and SC endothelial cells distend into the lumen of SC [35]. Trabecular tissues not only move outward into the canal, but also exhibit distortion of individual SC endothelial cells. Similarly, when pressure is greater in SC than in the anterior chamber, the entire trabecular meshwork collapses into a solid sheet of tissue. Striking tissue excursions occur when the pressure in SC is 5 mm higher than in the anterior chamber [37], a finding made even more apparent when pressure is SC is 8 mm higher than in the anterior chamber (Fig. 1.4) [35]. We may conclude that small IOP changes induce large changes in configuration of trabecular tissues. Furthermore, these same studies demonstrate that all of the TM tissues participate in the IOP-induced configuration changes.

1.8.2.5 IOP Decreases Normally Cause Trabecular Tissue Recoil

Trabecular tissues recoil in response to reductions in IOP [34, 35]. At physiologic pressure, all studies demonstrate distention of SC endothelium with related distention of the trabecular lamellae. These same studies report that reduction

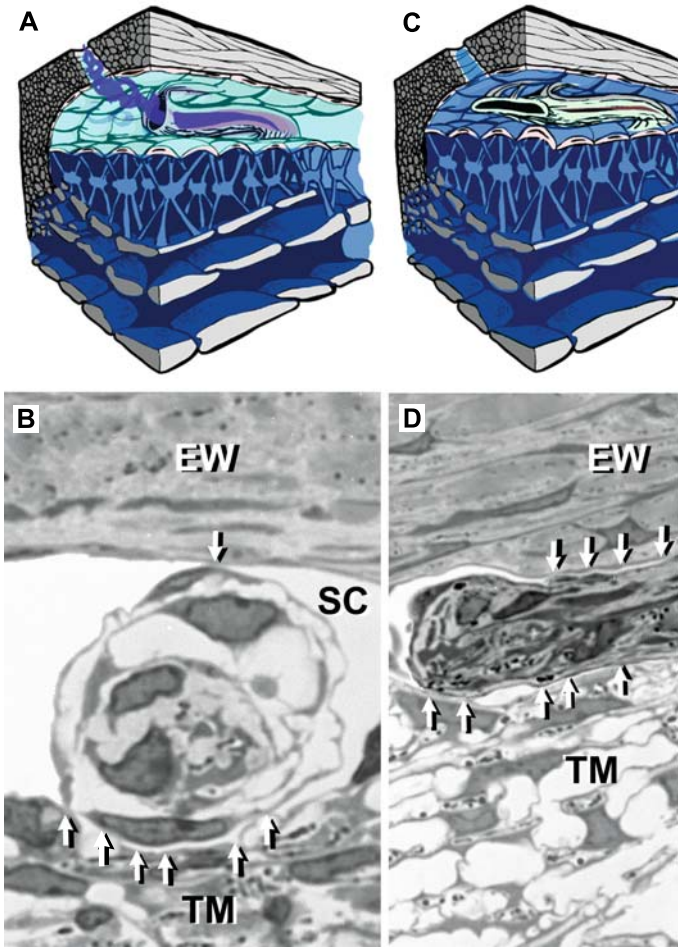


Fig. 1.6 Aqueous vein (70 long) with various degrees of compression against Schlemm's canal (*SC*) external wall (*EW*) by trabecular meshwork (*TM*) at IOP of 25 mm Hg. *White arrows* designate areas of compression. Minimal compression (**A,B**). Marked compression with lumen closure (**C,D**). Rhesus macaque eye

of pressure results in systematic recoil of these same tissues [34, 35]. This recoil response occurs at both the tissue and cellular level. Schlemm's canal endothelial distension decreases resulting in the cells undergoing a change from a plate-like to a round configuration with development of deep nuclear notches and folds. Juxtacanalicular cell nuclei and cytoplasmic elements change from a stellate to a round configuration. The juxtacanalicular space and intertrabecular spaces decrease. Cell processes in the spaces become thicker and less elongated. Trabecular lamellae recoil resulting in reduced intertrabecular spacing and reduced distention into SC. The lumen of SC concurrently enlarges.

1.8.2.6 Trabecular Tissue Excursions Are Limited by Stiffening or by SC Closure

Progressive tissue stiffening necessarily limits the vigor of IOP-induced distention and recoil in response to transient IOP changes. As IOP increases, progressive SC closure also necessarily reduces the possible range of TM excursions

in response to oscillatory pressure transients because the tissue cannot move further outward. Flow can only persist when the trabecular tissues can recoil sufficiently vigorously to allow separation of SC walls. Reduction of the excursion range thus progressively reduces the ability of trabecular tissues to drive the aqueous pump.

1.8.2.7 Reduction of SC Wall Apposition Improves Outflow in Living Primates

Pilocarpine causes contraction of the ciliary muscle, thus placing tension on the scleral spur rotating the spur both inward and posteriorly [14]. Scleral spur rotation dilates SC, permitting increased circumferential flow. Even modest SC wall separation provides a large conduit for aqueous flow [43]. If such a modest SC wall separation is present, circumferential flow can occur and a localized trabeculotomy should greatly enhance outflow; however, Barany et al.'s study [7] of living primates notes that a localized trabeculotomy has only a modest effect on outflow. By contrast, in the same eyes pilocarpine instillation causes a marked improvement in outflow.

The findings indicate that the canal is functionally segmented [7]. Extensive canal wall apposition limits circumferential flow in response to a localized SC opening. After a localized trabeculotomy, pilocarpine affects the whole circumference of SC [7] and causes a further marked reduction in resistance.

The results are consistent with the drug's ability to reduce canal wall apposition around the entire canal circumference. The results also indicate that there is normally extensive apposition of the canal walls. These findings indicate that both vigorous intrinsic trabecular tissue recoil and optimal positioning of scleral spur are essential to optimize pressure control mechanisms.

1.8.2.8 Trabecular Tissue Stiffening Prevents SC Expansion or Blood Reflux

Experimental stretching of trabecular tissues induced by a pressure of 25 mm Hg closes SC to a potential space (Figs. 1.4B, 1.6) [35]. Experimental stiffening of the tissues in that configuration prevents trabecular meshwork recoil and prevents SC expansion or dilation (Fig 1.4C). Intraocular pressure reduction to zero in the still-living eye causes some reflux of blood into SC; however, the lumen of SC remains so narrow that only a two- to three-cell layer of red blood cells is able to enter the canal. While the red cells are visible histologically, no blood is apparent at the dissecting microscope. In contrast, when SC expands and fills with blood before fixation, the canal is so widely dilated that blood is easy to see in the canal without any magnification (Fig. 1.4A). The experimental fixation of the tissues at physiologic pressure with subsequent reduction of pressure to allow blood to flow into SC parallels the clinical observations of Schirmer's gonioscopy where filling is absent [46] in eyes with poor outflow facility, and Kronfeld's aqueous withdrawal test in eyes with advanced glaucoma in which no visible blood enters SC [40].

1.8.3 Laboratory Evidence: Pump Failure Mechanisms in Enucleated Eyes

1.8.3.1 Enucleated Eye Studies Identify Structural Changes That Limit Pulsatile Flow

The aqueous pump model envisions continuous ocular IOP transients, any of which are able to provide a driving mechanism for aqueous flow, just as the venous and lymphatic systems are each driven by such transients. It is difficult to envision a situation where the cardiac pulse, respiration, eye movement, and blinking are all absent; therefore, enucleated eye studies cannot easily duplicate normal conditions. Such studies can, however, identify structural responses to IOP changes that must also affect the ability of IOP transients to induce tissue movement in the living eye. Closure of SC is just such a response.

Grant and Trotter's comparison of facility of outflow in living eyes with tonography (C = 0.233) and enucleated eyes with cannulation (C = 0.27) demonstrates comparable flow rates [20]. They

Table 1.3 Studies by Morton Grant and associates. Resistance mechanisms in normal and glaucomatous eyes involve Schlemm's canal (*SC*) wall apposition. *L* living, *E* enucleated, *N* normal, *G* glaucoma, *R* resistance, *TM* trabecular meshwork, *IOP* intraocular pressure. (See text and figures for references)

Reference	Species	L or E	N or G	Technique to reduce resistance to flow	Study type	Conclusions: resistance mechanism
[21]	Human	E	N	Removal of tissue in reach of cystitome (tissue undefined)	Microsurgery measure R, no histology	Tissue in reach of cystitome (TM only)?
[22]	Human	E	G	As above	As above	As above
[12]	Human	E	N	Reduce IOP	Measure R, no histology	SC wall apposition
[12]	Human	E	N	Move SS backward	Measure R, no histology	SC wall apposition
[13]	Human	E	N; G	Remove SC external wall	Measure R, no histology	SC wall apposition
[35]	Human	E	N	Removal of tissue in reach of cytitome (TM and SC walls)	Microsurgery, measure R, histology	TM or SC wall apposition
[35]	Human; monkey	E; L	N	Reduce IOP	Histology	SC wall apposition
[54]	Monkey	E	N	Move SS backward	Measure R, histology	SC wall apposition
[52]	Human	E	N	Move SS backward	Measure R, histology	SC wall apposition
[53]	Human	E	N	Move SS backward	Measure R, histology	SC wall apposition
[44]	Human	E	N	Microsurgery reduce IOP	Measure R, no histology	SC wall apposition

point out, however, "these same results might also be explained by coincidental mutually compensatory differences in the methods and in the eyes" [20]. Goldmann further emphasizes, "One must not overestimate agreement because of differences between the living and enucleated eye. The aqueous humor of an enucleated eye flows out through the bisected episcleral veins and conjunctival veins in which pressure must be zero" [19]. In addition, "the episcleral and conjunctival venous system collapses in the enucleated eye" [20]. In contrast, in the living eye, both aqueous and episcleral veins are continuously open. Furthermore, a normal backpressure of ~8–9 mm Hg forms an interface with the pressure in the aqueous vein–SC unit.

Nevertheless, the absence of ocular pulse transients does not preclude passive fluid movement through the outflow system just as fluid moves through the cardiac and lymphatic systems after death. The trabecular tissues are capable of distending with pressure, as are the aqueous valves and the collapsed aqueous and episcleral veins. Grant and Trotter point out that such studies are important to provide insights into passive structural boundaries or limitations imposed on flow [19].

1.8.3.2 Trabecular Meshwork as the Site of Resistance?

The foundation for much of our understanding of aqueous outflow resistance comes from the correlative microsurgery and perfusion studies of Morton Grant and associates. Textbooks often

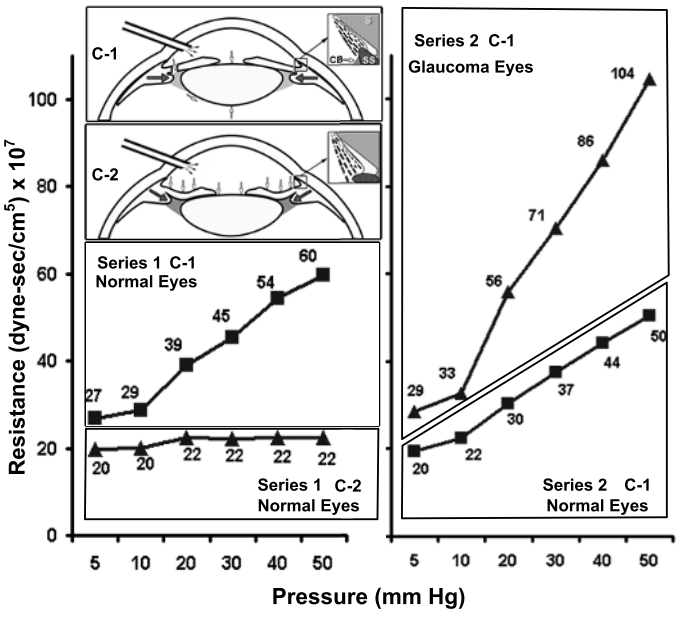


Fig. 1.7
Schlemm's canal (*SC*) configuration determines variable resistance characteristics of normal and glaucomatous eyes. Condition 1 (*C-1*) with iridectomy; pressure gradients equalize between anterior and posterior chamber. Schlemm's canal is not held open and variable resistance is present in both series 1 and 2. The variable resistance is much greater in glaucoma eyes. Condition 2 (*C-2*); no iridectomy. Reverse pupillary block forces the lens posteriorly, thus forcing the ciliary body (*CB*) and scleral spur (*SS*) posteriorly resulting in TM movement away from SC external wall. Holding SC open eliminates the variable resistance found under C-1 in both normal and glaucoma eyes. (From [12]; series-1 data derived from Fig. 2; series-2 data derived from Fig. 1)

cite Grant's early studies indicating that 75% of normal aqueous outflow resistance [21] and the abnormal resistance in glaucoma [22] are in the trabecular tissues; however, subsequent studies of Grant and associates paint a much different picture. These subsequent studies point to SC wall apposition as the explanation for much of normal resistance and for the abnormal resistance in glaucoma as summarized in Table 1.3.

Histologic confirmation that tissue removal is limited to the trabecular meshwork is absent from Grant's initial studies [21, 22]; however, our subsequent work [36] demonstrates that the resistance-reducing effect found in his original studies not only involves disruption of trabecular tissues, but also disruption of SC outer wall and collector channel ostia. Because of the evidence of extensive tissue removal, our report observes that conclusions from the earlier studies require modification [36].

Although Grant's earlier studies clearly localize resistance to the outflow region, the studies cannot discriminate whether resistance is in the trabecular tissue, a result of SC wall apposition, a result of collector channel ostia occlusion or some combination thereof [36].

1.8.3.3 Resistance Increases with Increasing IOP in Normal Eyes

The human aqueous outflow system experiences inertia-free flow [12]. If structural elements in the outflow system were part of a geometrically fixed system, then outflow resistance would not change with increasing flow or pressure under conditions of inertia-free flow [12]. However, perfusion studies demonstrate that outflow resistance increases markedly with increasing IOP [12]; therefore, structural elements in the outflow system must not be structurally fixed but rather are physically altered to account for the increasing resistance with increasing IOP [12]. The external wall of SC is a stable structure, whereas constituents of the trabecular meshwork are compliant and distend outward into SC [13]. Experimental findings of increasing resistance with increasing pressure, consideration of trabecular tissue characteristics, and the requirement that changes in tissue configuration must explain increasing resistance led Ellingsen and Grant to the following assessment: increasing resistance with increasing pressure found in their enucleated eye experi-

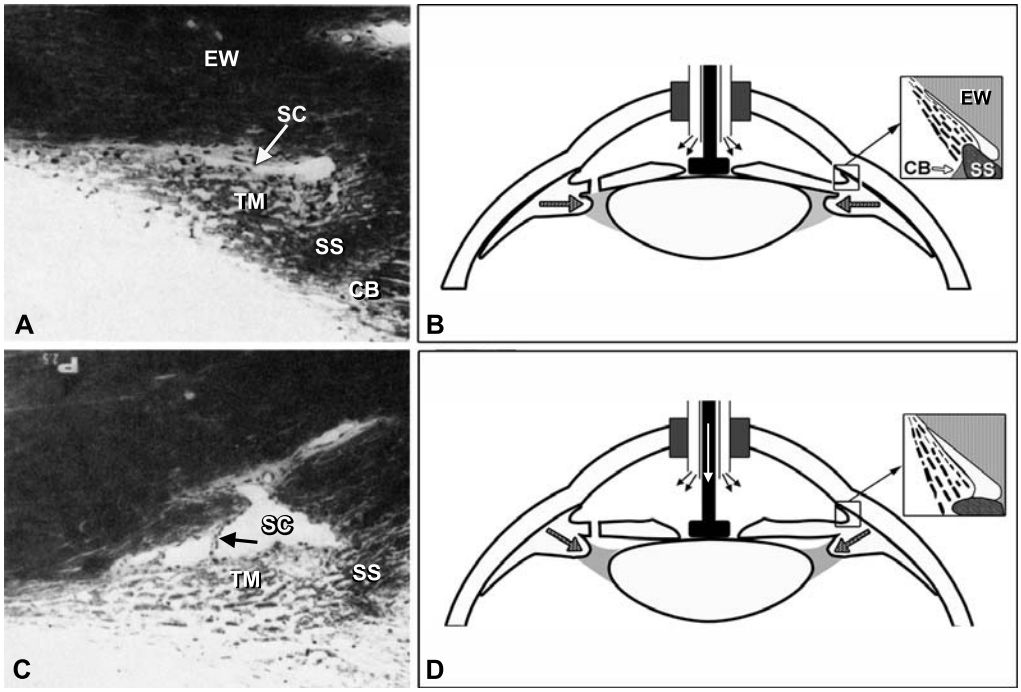


Fig. 1.8 Lens depression dilates Schlemm's canal. **A, B** No lens depression. **A** The trabecular meshwork (*TM*) is in extensive apposition to Schlemm's canal (*SC*) external wall, causing closure of SC lumen (*arrow*). **B** Corneal perfusion fitting contains lens-depression device. Ciliary body (*CB*) and SS rotate forward contributing to SC closure. **C** With lens depression as depicted in **D**, the CB and scleral spur (*SS*) rotate posteriorly, pulling the trabecular tissue attachments away from SC external wall (*EW*). The TM distends and SC lumen is large. *Arrow* demonstrates aqueous valve in SC. (**A** and **C** from [53])

ments results from progressive apposition of the trabecular tissues to the unyielding external wall of SC [12]. Departure from the authors' previous view that the resistance is localized to the trabecular meshwork may be partially explained by the authors' awareness (pers. commun.) of a clearly articulated contemporary clinical report describing SC wall apposition as a mechanism leading to elevated IOP [49].

1.8.3.4 SC Wall Separation Decreases Resistance to Aqueous Outflow

If SC wall apposition causes the increasing resistance with increasing IOP, then reduction of SC wall apposition will lessen the resistance increase. In fact, all studies examining the issue demonstrate that experimental separation of SC walls lessens the IOP-induced resistance increase caused by increasing IOP [12, 13, 11, 44, 52, 53, 54]. The studies therefore lead to the conclusion that SC wall apposition is the cause of the variable resistance in normal and glaucomatous eyes.

Experiments leading to Ellingsen and Grant's initial conclusion involve their study of the effects of SC wall separation (Fig. 1.7) [12]. Without iridotomy, reverse pupillary block forces the iris against the crystalline lens. The lens–iris diaphragm moves backward, pulling the scleral spur backward and inward. Trabecular tissue attachment to the scleral spur and ciliary body causes them to move away from the external wall of SC. Their studies then compare resistance increases in the eyes perfused with and without an iridotomy. Separation of SC inner wall from the external wall results in a larger SC lumen

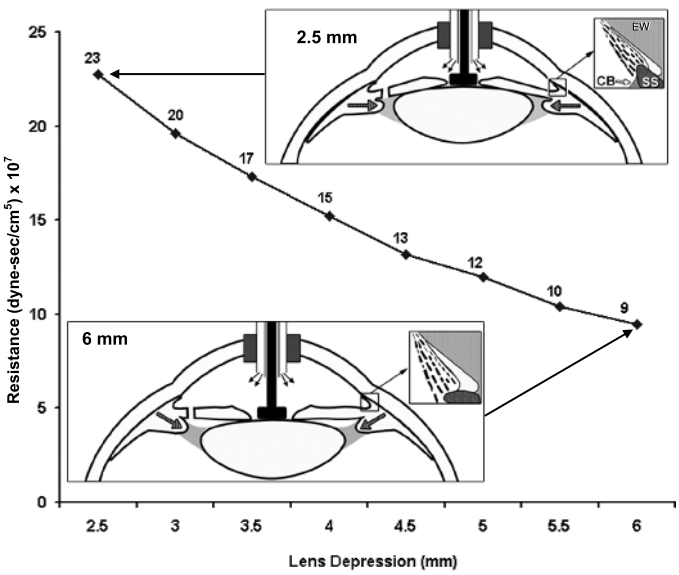


Fig. 1.9
Lens depression that dilates SC correlates with marked reduction in outflow resistance. Lens depression rotates ciliary body (*CB*) and scleral spur (*SS*) backward away from SC external wall (*EW*). (Data from Fig. 2 of [54])

and increased region for aqueous transfer to SC. The separation resulting in a larger lumen also facilitates increased circumferential flow. Separation of the walls of SC greatly reduces resistance, which led Ellingsen and Grant to conclude that SC wall apposition is the mechanism responsible for the variable resistance in normal eyes and the abnormal increase in variable resistance found in glaucomatous eyes [12].

Van Buskirk embarked on a series of studies, motivated [54] by the data of Ellingsen and Grant [13], suggesting the following: "under ordinary circumstances there is little or no circumferential flow in SC, with the walls supposedly in apposition" [54]. Studies by Van Buskirk and Grant [54], and Van Buskirk [52, 53], employ another technique that induces SC wall separation to examine the effects on outflow resistance (Fig. 1.8).

A special fitting closes a corneal trephine opening and allows perfusion. The same fitting contains a device that permits quantitative increases of lens depression toward the back of the eye. Backward movement of the lens creates tension on the zonules to rotate the scleral spur posteriorly and dilate the canal, a finding documented histologically [53]. Resistance markedly decreases with SC wall separation (Fig. 1.9) [52, 54].

Calculations also indicate that aqueous flows < 10° circumferentially around the canal on each side of a localized 30° (one clock-hour) trabeculotomy opening. When lens depression separates the walls of the canal, aqueous flows circumferentially a total of 35° on each side of the site with a corresponding reduction in resistance [54]. At a low IOP of 2.5 mm Hg, where there is no SC wall apposition, lens depression improves outflow facility by only 1%, whereas at 25 mm Hg with more extensive SC wall apposition, lens depression improves aqueous outflow by 89%. In fact, as IOP increases and SC wall apposition progressively increases, separation of SC walls by lens depression becomes progressively more effective with a remarkably high correlation coefficient of 0.97 [52].

Van Buskirk's later studies further emphasize that SC wall separation reduces outflow resistance. The experiments again involve lens depression to cause SC wall separation and also now involve quantitative histologic evidence that SC wall separation correlates with reduced outflow resistance [53]. In the studies, resistance changes correlate with lens depression and thus with the degree of apposition between SC walls (Fig. 1.9).

Rosenquist et al.'s experiments further examine the issue of resistance resulting from SC wall

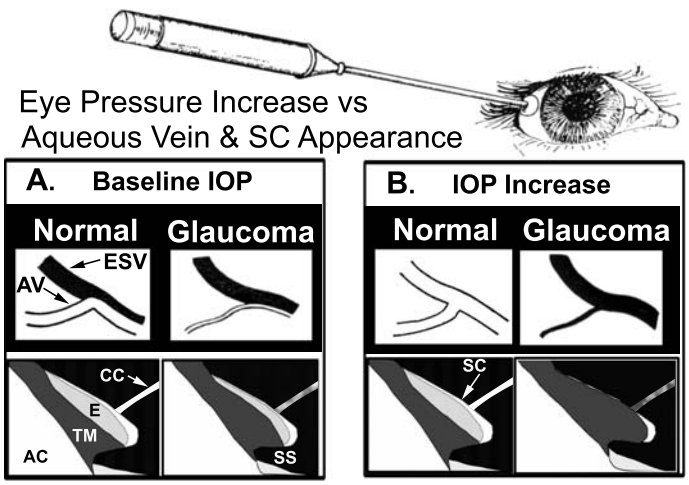


Fig. 1.10
A Status of aqueous veins (*AV*), episcleral veins (*ESV*), and trabecular meshwork (*TM*) at baseline intraocular pressure (*IOP*) and **B** conditions of IOP increase in normal and glaucomatous eyes. In normal eyes, the scleral spur (*SS*) retains a posterior position holding the TM way from Schlemm's canal (*SC*) allowing large TM excursions (*E*), thus providing aqueous access to the collector channels (*CC*) and AV. In glaucoma eyes, the scleral spur rotates forward, and SC is small. Both TM excursions and pulsatile AV flow are limited. An IOP increase causes the TM to close SC, stopping flow into CC and AV. *AC* anterior chamber. (**A** and **B** upper panels from [4])

apposition [44] using the well-documented technique [53] of differences in IOP as the variable to alter SC wall separation. At 7 mm Hg IOP there is little SC wall apposition, whereas at 25 mm Hg IOP SC walls are more extensively appositional [53]. The study examines the effect of sequential internal trabeculotomies on outflow resistance in eyes perfused at these two different pressures. Sequential trabeculotomy has a much greater effect in reducing resistance in eyes perfused at 25 mm Hg IOP. There are much greater areas of SC wall apposition at 25 mm Hg, providing further evidence of SC wall apposition as the cause of the variable resistance associated with lack of circumferential flow.

1.8.3.5 SC Wall Separation Causes Resistance Reduction after Microsurgery

Ellingsen and Grant's work demonstrates that removal of SC external wall causes greater than 50% reduction in aqueous outflow resistance and the reduction is almost equivalent to removal of SC inner wall. They point out that if the sum of resistances eliminated from removal of either SC inner or outer wall is in excess of 100%, the explanation must be a synergy causing the sum to be greater than the individual parts. They conclude that stretching of SC inner wall causes it to come into apposition with the unyielding outer wall and that an intact and unyielding outer wall is necessary for normal resistance [13].

1.8.3.6 SC Wall Apposition Causes the Abnormal Resistance in Glaucoma Eyes

The conclusion follows from the experimental work of Ellingsen and Grant (Fig. 1.7), who reason as follows: "Forcible retro displacement of the lens–iris diaphragm tends to stabilize facility of outflow (inverse of resistance) by its traction on the scleral spur and trabecular meshwork, while intraocular pressure acting directly upon the aqueous outflow channels tends to reduce facility of outflow in the absence of this stabilizing force" [12]. If glaucomatous eyes experience the same type of resistance increase with IOP that is present in normal eyes, but the magnitude of the resistance increase is greater, the same resistance mechanism is likely to be present. Their work demonstrates that the same type of IOP-induced resistance increase is present in glaucomatous

eyes, but the magnitude of the resistance increase is much greater [12]. From this evidence, they point out that SC wall apposition provides a rational explanation for the excess resistance in glaucomatous eye.

Summary for the Clinician

- Trabecular tissues stretch and intermittently close SC in normal eyes. The position of the scleral spur and intrinsic control of trabecular tissue distention and recoil determine the normal extent and persistence of SC closure.
- Both trabecular tissue stiffening and trabecular tissue resting against SC external wall limit the ability of the tissues to undergo excursions in response to IOP transients. A reduction in trabecular tissue excursions by either mechanism decreases the efficiency of pump responses. Escape of aqueous to SC and circumferential flow in the canal are also prevented.
- Schlemm's canal wall apposition both prevents escape of aqueous to SC and prevents circumferential flow within the canal to collector channel ostia.
- Experimental trabecular meshwork stiffening prevents SC from expanding. Intentional reflux of blood into SC results in entry of an inadequate volume of blood to be visible clinically.

1.9 Clinical Evidence of Pump Failure Mechanisms in Glaucoma

Ascher points out that SC and the aqueous veins act as a physiologic unit [4]. Examination of this physiologic unit in the context of current knowledge permits new insights into glaucoma mechanisms. Glaucomatous eyes have well-documented clinically visible outflow abnormalities [4]. Traditional concepts of the trabecular tissues as a rigid structure prevent development of a coherent explanation for these abnormalities [4]. These glaucoma abnormalities also exhibit a gradation of findings, at present limiting their use as clinical prognostic tool. Ascher points out, however, that we must not expect sharp dividing lines in a progressive disease such as glaucoma, but may instead use the observations and their gradations as a means to understand the glaucoma process.

1.9.1 Pulsatile Aqueous Flow Decreases in Glaucoma Eyes

Kleinert [38] reports the presence of 196 aqueous veins in 111 normal subjects. He further notes pulsatile flow in 28% of the identified aqueous veins. By contrast, only 6% of glaucoma eyes exhibit pulsatile flow in the aqueous veins. Furthermore, no pulsatile flow is present in eyes with pressure readings higher than 28 mm Hg. In glaucoma eyes, pilocarpine and adrenergic agents each cause an increase in pulsatile flow with a concurrent reduction in IOP toward normal.

1.9.2 Pulsatile Aqueous Flow Stops As IOP Increases in Glaucoma Eyes

Kleinert's [38] clinical studies mirror the many laboratory studies of Grant and colleagues, which localize the normal resistance [12, 13, 32, 35, 53, 54] and abnormal resistance in glaucoma [12] to a problem of SC wall apposition. Kleinert's clinical studies [38] also look at how raising intraocular pressure influences outflow (Fig. 1.10). An ophthalmodynamometer presses on the side of the eye to raise intraocular pressure. In normal eyes pulsatile aqueous flow increases in the aqueous veins even when a force as high as 150 g raises intraocular pressure.

In glaucoma eyes, markedly lower force (as low as 38 g) suffices to stop pulsatile aqueous flow into the aqueous veins. The eyes are not able to compensate for the pressure increase, leading to the nomenclature of the "compensation maximum test" [38]. When high intraocular pressure causes aqueous flow to stop in the aqueous veins, the veins fill with blood. Pressure in the aqueous veins must drop for blood to enter them. In these glaucoma eyes then, aqueous vein pressure and flow fall concurrently with increasing intraocular

pressure. As in enucleated eyes with inertia-free flow, we may conclude that a structural mechanism is present between the anterior chamber and the aqueous veins that stops aqueous flow as IOP increases. We now know that IOP-induced stretching of trabecular tissues causes occlusion of SC [12, 52–54], and increases resistance [12, 13], thus preventing aqueous flow. Kleinert's [38] clinical observations therefore provide confirmatory evidence for laboratory conclusions that trabecular tissue apposition to SC external wall is a mechanism causing abnormal resistance in glaucoma.

1.9.3 Pulsatile Aqueous Flow Stops with Episcleral Venous Pressure Increases

1.9.3.1 Aqueous Influx Phenomena in Aqueous Veins: A Sign of Normal Flow

In normal eyes, intentional occlusion of a more distal large recipient episcleral vein causes aqueous flow from the aqueous vein into the small proximal upstream episcleral veins [4]. More robust pulsatile flow into the vein accompanies the aqueous vein pressure rise. This more robust or vigorous flow is recognizable because pulse waves of blood-tinged aqueous develop a greater amplitude, velocity, and different character. Because of the new higher pressure, the aqueous vein becomes more tense with aqueous and develops a "glass rod" appearance [3, 9, 18, 51].

The small proximal episcleral veins, previously at a slightly higher pressure than the aqueous veins, fill with aqueous in seconds. A mechanism at the level of SC thus rapidly increases pulse pressure in the aqueous vein to a level above that of the upstream episcleral tributaries driving aqueous into these tributaries. The only way aqueous pressure can increase is if a flexible regional mechanism is present in the aqueous vein–SC system that rapidly responds to the new venous pressure conditions. More vigorous pulsatile flow is a manifestation of this regional mechanism.

1.9.3.2 Pulsatile Aqueous Influx Stops in Glaucoma Eyes

In glaucomatous eyes, the blood influx phenomenon, rather than the aqueous influx phenomenon, is the typical response [3, 4, 9, 18, 51]. The blood influx phenomenon occurs when recipient episcleral vein occlusion results in blood flowing from the small more proximal episcleral veins into the aqueous vein. The aqueous vein fills rapidly with blood in a retrograde fashion until blood reaches the scleral origin of the aqueous vein. In glaucoma eyes, the normal mechanism providing an immediate more robust pulsatile aqueous discharge and slight increase in aqueous pressure is thus dysfunctional or absent. Pilocarpine separates the walls of SC, allows greater trabecular meshwork excursions, increases pulsatile flow, and causes the blood influx phenomenon to change to an aqueous influx phenomenon [4].

1.9.4 Pilocarpine: Pulsatile Aqueous Flow Increases When SC Expands

Both laboratory and clinical studies support the conclusion that trabecular tissues progressively move outward and cause collapse of Schlemm's canal and increasing resistance. Clinical consequences are a reduction in forceful pulsatile flow and the inability of blood to reflux into SC [4]. In glaucoma eyes, pilocarpine concurrently expands SC, improves pulsatile flow, and reduces intraocular pressure [1, 4, 10, 25]. Pilocarpine responses thus support other laboratory and clinical observations pointing to SC wall apposition and reduction of pulsatile flow as a mechanism causing abnormal resistance in glaucoma.

1.9.5 SC Blood Reflux: Measure of Trabecular Tissue Movement

1.9.5.1 SC Blood Reflux: An Expansile SC Requires Compliant Trabecular Tissue

At physiologic pressure, the lumen of SC is a narrow space in normal eyes (Figs. 1.1, 1.4, 1.6, 1.8)

Table 1.4 Blood reflux into Schlemm's canal (*SC*) provides a measure of trabecular meshwork compliance. Compliance confers the ability of the trabecular meshwork to induce pulsatile flow in response to IOP transients. *TM* trabecular meshwork

Technique	Reference	SC blood reflux	Comments and mechanisms
Goniolens	[40]	Absent	SC closure in glaucoma
Goniolens	[15]	Absent	Pathognomonic of glaucoma
Flanged goniolens	[48]	Reduced or absent	TM sclerosis, SC inexpansile
Suction goniolens	[39, 41]	Slow and non-uniform	TM sclerosis
Suction goniolens	[39, 41]	Slow SC emptying	TM sclerosis
Aqueous removal	[39, 41]	Absent	Irreversible SC wall apposition/adhesion
Suction goniolens	[45, 46]	Rapid and complete	TM normal
Suction goniolens	[49]	Rapid and complete	TM normal
Suction goniolens	[49]	Slow and patchy	TM degeneration
Suction goniolens	[49]	Absent	Irreversible SC wall apposition/adhesion

[32, 35]. Experimentally, however, in the normal eye blood refluxes into SC when episcleral venous pressure rises above intraocular pressure (Fig. 1.4A) [30–32, 37]. From experimental work in living eyes, we know that reversal of pressure gradients causes the highly compliant trabecular meshwork to collapse thus greatly enlarging or expanding the lumen of SC [30, 31, 35, 37]. Because a column of blood fills the large SC space, blood in the widely dilated canal is easily visible gonioscopically. In contrast, experimental fixation of the trabecular meshwork in a distended configuration prevents trabecular meshwork collapse and thus prevents SC dilation (Fig. 1.4C). Only a thin layer of one or two red cells thick enters SC (Fig. 1.4C). Such a thin red-cell layer, equivalent to the thickness of a blood smear on a slide, is not clinically visible.

1.9.5.2 SC Blood Reflux Abnormalities: Measure of Glaucoma Severity

Clinically, reversing the normal pressure gradient between the anterior chamber and SC causes blood to reflux into SC as summarized in Table 1.4. Either reducing intraocular pressure or raising episcleral venous pressure causes pressure reversal [4, 40]. Globe compression followed by release [40] or aqueous withdrawal [40] lowers intraocular pressure. Jugular compression or a goniolens that compresses the episcleral veins [46, 48, 49] raises episcleral venous pressure. Rapid filling of SC is strong evidence of a normal outflow system [40, 45, 46]. Such filling may begin in 5–10 s and finish in 15–30 s [46]. Correspondingly, rapid elimination of blood occurs following restoration of normal pressure gradients.

As glaucoma process progresses, there is a gradation of findings [4, 40, 45, 46, 48, 49] as summarized in Table 1.5. Suson and Schultz [49] summarize the findings and implications as follows: initially in eyes with ocular hypertension rapidity of SC filling slows, but the canal fills and outflow facility remains near normal. "Blood-filling defects of the canal gradually appear with increasing frequency and severity, closely paralleled by deteriorating outflow facility. It is reasonable to believe…the initial reduction of outflow facility…was due to compression of the inner wall against the outer wall of SC with restriction of the effective filtration area. Subsequent aggravation of the impaired facility most likely resulted from damage to SC inner wall…and its adhesion

Table 1.5 Clinical manifestations of aqueous pump failure in glaucoma. *IOP* intraocular pressure, *SC* Schlemm's canal, *TM* trabecular meshwork, *ESV* episcleral veins

Clinical technique	Clinical observation	Normal	Elevated IOP	Early glaucoma	Advanced glaucoma	Significance
Slitlamp exam	Spontaneous pulsatile aqueous flow	Often seen vigorous, forceful	Sluggish	Uncommon	Flow absent	TM movement reduced by: trabecular sclerosis; SC wall apposition
Increase IOP by: ophthalmo-dynamometry or digital pressure	Pulsatile aqueous flow	Vigorous pulsatile flow + + +; stroke volume increase + + +	Pulsatile flow + +; stroke volume increase + +	Pulsatile flow +; stroke volume increase +	Pulsatile flow absent	
	Aqueous vein flow stops (compensation maximum)	Aqueous flow persists even with extreme IOP ↑	Stops with marked IOP ↑	Stop with moderate IOP ↑	Stops with minimal IOP ↑	SC walls collapse together preventing further flow
	Blood reflux into aqueous veins	Variable	Frequent	Usually	Always	SC collapse: no pressure in aqueous veins
Gonioscopy: ESV compression or aqueous withdrawal	SC blood reflux rapidity, uniformity and reversibility	SC rapid uniform filling; rapid SC emptying	Slow SC filling, slow SC emptying	Slow SC filling, patchy SC filling	SC blood filling absent	TM distends, TM stiffens, SC closes, no recoil, SC closure, irreversible
Aqueous vein compression	Pulsatile flow (aqueous influx into ESV, aqueous influx phenomenon) or blood influx into aqueous veins	Aqueous vein pulsations more vigorous, aqueous fills proximal anastomosis of ESV	Less vigorous aqueous vein pulsations, blood may fill aqueous vein	Blood commonly fills aqueous vein	No aqueous vein pulsations, blood always refluxes into aqueous veins (blood influx phenomenon)	Pulsatile flow less vigorous; increasing TM stiffness and SC wall closure reduce TM movement necessary for pulsatile flow

to the outer wall, demonstrated gonioscopically as blood filling defects." In advanced glaucoma, blood fails to reflux into SC even with very aggressive measures to reduce pressure gradients [40].

Investigators interpret the inability to reflux blood as evidence of irreversible trabecular tissue stiffening or adhesion to the external wall of SC in advanced glaucomas [30, 38, 40]. Chronic IOP elevation may cause an undesirable cycle of chronic compression of trabecular tissue against SC external wall and further IOP elevation [40]. This consideration suggests that earlier detection and treatment of ocular hypertensives may reduce the progression and severity of the aqueous outflow system disease process [40].

Summary for the Clinician

- Clinical evidence of pump failure in glaucoma involves a progressive decrease in vigor of pulsatile flow into the aqueous veins as the disease stages worsen.
- Pilocarpine contracts the ciliary muscle, pulls on scleral spur, dilates SC, increases the stroke volume of pulsatile flow, and reduces IOP in responsive glaucomatous eyes.
- Blood refluxes into SC, filling it rapidly and uniformly in normal eyes. Similarly, a reduction in pressure causes a rapid emptying of SC. These findings demonstrate flexibility of trabecular tissues allowing them to move rapidly in response to transient pressure-gradient changes.
- In progressive stages of the glaucoma process, blood reflux into SC slows and blood reflux into SC is less uniform leading to patchy or absent filling in more advanced disease.
- In advanced glaucoma, SC fails to fill with blood even in response to measure that markedly reverse pressure gradients. Clinicians propose that the lack SC filling results from trabecular stretching, sclerosis, and eventual irreversible changes that leave the TM in permanent apposition to SC external wall.

1.10 Conclusion

This chapter provides a summary of evidence that supports the presence of a pumping mechanism that returns aqueous to the vascular system. The aqueous pumping mechanism controls normal flow and pressure. The pumping mechanism fails in glaucoma. Clinical and laboratory evidence point to reduced trabecular movement and persistent SC closure as mechanisms causing pump failure. An intrinsic abnormality of the composition of trabecular tissues may alter normal distention and recoil. Extrinsic factors that may also lead to SC closure are altered shape of the limbal region, altered flexibility of the limbus at the corneoscleral junction, and alterations in ciliary body tension.

Summary for the Clinician

- In this model the aqueous outflow system acts as a mechanical pump. The pump fails in glaucoma. Clinically visible functional changes accompany pump failure pointing to mechanisms causing the failure.
- Pump failure results from trabecular tissue stiffening and SC lumen closure.
- The proximate cause of pump failure is structural involving persistent trabecular tissue apposition to SC external wall.
- Reversing the cause of pump failure requires restoration of normal structural relationships providing a new target for medical or precisely directed surgical approaches.

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Chapter 2

Risk Calculators: Evidence-Based Care of Ocular Hypertension and Glaucoma Patients

2

Steven L. Mansberger and Emily L. Patterson

Core Messages

- The Ocular Hypertension Treatment Study showed that intraocular pressure (IOP) reduction by 20% decreased the probability of developing visual field defects or optic disc deterioration in patients with high IOP. Risk factors were age, cup-to-disc ratio, visual field severity (pattern standard deviation), central corneal thickness, and diabetes (protective).
- The Early Manifest Glaucoma Trial demonstrated that treatment with ALT plus betaxolol in patients with early glaucoma reduced their risk of progression by half. The baseline risk factors for progression included age, disc hemorrhages, pseudoexfoliation, bilaterality of disease, and visual field severity (mean deviation).
- The Collaborative Normal-Tension Glaucoma Study showed a slower rate of progressive visual field loss in low-tension glaucoma patients who reduced their IOP by 30% by any means than in patients who received no treatment. Risk factors included disc hemorrhage, female gender, African-American race, and vasospasm.
- The Collaborative Initial Glaucoma Treatment Study showed no difference between treatments of newly diagnosed glaucoma patients with topical hypotensive medication vs trabeculectomy surgery. Risk factors included age, diabetes, African-American race, and visual field severity.
- Integrating information from studies is important to determine the patients most at risk of worsening glaucoma, but may be difficult because of the different risk factors identified by different studies.
- The Advanced Glaucoma Intervention Study found that lower IOP is associated with slower progression of visual field defects in patients with advanced glaucoma. It also found that the performing laser before trabeculectomy was favored for African-American patients. The risk factors for the patients in the ATT treatment sequence were baseline visual field score, male gender, and baseline visual acuity. The risk factors for those in the TAT treatment sequence were baseline visual field score and diabetes.
- Clinical decision making may depend on information from the best available evidence, but may also include information from biased and inaccurate sources.

- Evidence-based medicine improves the quality of clinical decision making by evaluating and integrating the best scientifically tested information available.
- Risk calculators can benefit individual ophthalmologists by allowing them to individualize complicated algorithms and improving the accuracy of their assumptions about patient prognosis.
- Risk calculators can benefit patients by offering information that may enhance their understanding of their disease and improve compliance.
- Society at large may benefit from use of risk calculators if more rational and cost-effective decisions are made by the providers using these tools.
- Disadvantages of risk calculators include built-in inaccurate assumptions about patient behavior and slow clinician acceptance of such models.

2.1 Introduction

A busy private-practice ophthalmologist starts her Thursday morning glaucoma clinic full of optimism and ambition. She spent Wednesday evening at an educational dinner devoted to evidence-based medicine and applying the results of clinical trials, and she is certain she is now ready to care for her patients, armed with facts.

Her first patient is a 60-year-old man with ocular hypertension. His intraocular pressure (IOP) is 26 mm Hg OU, and his cup-to-disc ratios are 0.7. She performs pachymetry, and finds his cornea thickness to be 540 μm OU. His standard achromatic automated visual fields are normal with a pattern standard deviation of 1.9. He has no significant past medical history.

Her next patient is a 50-year-old woman complaining of difficulty reading and no past ocular history. Her exam includes a normal anterior segment with an open angle, an IOP of 24 mm Hg, and glaucomatous cupping with a notch in the inferior temporal quadrant of both eyes. Further testing reveals a corneal thickness of 510 μm and dense superior arcuate visual field defects in both eyes with a mean deviation of 8.0 dB and a PSD of 3.5 dB.

The ophthalmologist wonders which glaucoma trial will offer valuable evidence for deciding how to treat these patients, what is the risk of significant visual field loss and blindness, and what information she needs to decide how best to treat her patients.

2.2 Evidence from Recent Randomized Clinical Trials

Investigators designed recent randomized controlled clinical trials to help with the management of glaucoma patients. These studies examine a large spectrum of glaucoma – from ocular hypertension to early glaucoma, to severe glaucoma. The Ocular Hypertension Treatment Study determined the efficacy of ocular hypotensive treatment in ocular hypertension patients [8, 13]. The Collaborative Initial Glaucoma Treatment Study [16] and the Early Manifest Glaucoma Treatment Study [14] examined treatment of early or newly diagnosed glaucoma patients; The Collaborative Normal-Tension Glaucoma Study (NTGS) [4] examined mild to moderate glaucoma in patients with normal intraocular pressure; and the Advanced Glaucoma Intervention Study [23] investigated surgery or laser in patients with moderate to severe glaucoma.

These studies guide clinicians in their treatment of glaucoma patients, examining the full range of glaucoma from preperimetric glaucoma to advanced glaucoma. We discuss the highlights of these trials herein, according to their ability to help with risk assessment.

2.2.1 Preventing or Delaying Glaucoma: The Ocular Hypertension Treatment Study

The Ocular Hypertension Treatment Study (OHTS) randomized patients with IOP of 24–32 in one eye and 21–32 in the contralateral eye to observation or to IOP reduction by 20% with any available medical treatment [7]. The probability of developing reproducible visual field defects or optic disc deterioration was 4.4% in the treated group and 9.5% in the untreated group [8, 13]. The OHTS also identified baseline factors that predicted the development of POAG, including older age, larger vertical cup-disc ratio, higher IOP, greater pattern standard deviation on perimetry, and thinner central corneal measurement. A history of diabetes was protective for developing glaucoma.

2.2.2 Treating Newly Diagnosed Glaucoma: the Early Manifest Glaucoma Trial and the Collaborative Initial Glaucoma Treatment Study

The Early Manifest Glaucoma Trial (EMGT) randomized patients with early glaucoma either to argon laser trabeculoplasty plus betaxolol ($n = 129$) or to monitoring without immediate treatment ($n = 126$) [15]. These were newly diagnosed glaucoma patients, found during a community glaucoma screening. The rate of progression was 45% in the treated group vs 62% in the untreated group. The treatment reduced intraocular pressure approximately 20% and decreased the risk of worsening glaucoma by 50% [14]. The study identified elevated IOP, exfoliation, bilateral disease, worse mean deviation with perimetry, and older age as baseline risk factors for glaucoma progression. Corneal thickness was not found to be a risk factor. During follow-up, disc hemorrhages increased the risk of progression.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) is another study investigating patients with early glaucoma. It enrolled 607 patients with newly diagnosed open-angle glaucoma and randomized them to treatment with topical ocular hypotensive medication or trabeculectomy surgery [20]. The 5-year outcomes reported in the CIGTS demonstrated that both medications and surgery resulted in reduced intraocular pressure, and both groups of patients had similar low rates of visual field progression [16]. Only 11% of patients treated medically vs 14% of patients treated with surgery had significant progression during follow-up. Medically treated patients were less likely to develop cataracts, suffer non-cataract-related visual acuity loss, or complain of ocular side effects. Risk factors for progressive visual field defects in this study include baseline visual field, age, African-American race, and diabetes [16].

2.2.3 Treating Moderate to Advanced Normal Tension Glaucoma: the Collaborative Normal-Tension Glaucoma Study

The Collaborative Normal-Tension Glaucoma Study (NTGS) randomized 240 patients with glaucoma and intraocular pressures less than 20 mmHg, to treatment or no treatment. The patients had to have documented progression or a specific visual field defect. The treatment included medications, laser, or surgery to reduce intraocular pressure at least 30%. The rate of progressive visual field loss was slower in the treated group than in a group that did not receive treatment when the analysis adjusted for the effect of cataracts. Risk factors for progression of visual field defects in the untreated patients of CNTGS were migraines, female gender, vasospasm, disk hemorrhage, and African-American race [4].

2.2.4 Treating Uncontrolled Glaucoma: the Advanced Glaucoma Intervention Study

The Advanced Glaucoma Intervention Study (AGIS) was a randomized controlled clinical trial designed to evaluate the clinical course of medically uncontrolled open-angle glaucoma by two surgical treatment sequences. Of 591 patients,

789 eyes were treated at 11 clinical centers between 1988 and 1992 and randomized to a treatment sequence of argon laser trabeculoplasty, trabeculectomy, and trabeculectomy (ATT sequence); or trabeculectomy, argon laser trabeculoplasty, and trabeculectomy (TAT sequence). The main outcome measures of the study were visual acuity and visual field, although intraocular pressure (IOP), complications of treatment, time to treatment failure, and need for adjunctive medications were among the many factors evaluated. For visual acuity, The study also found that the ATT sequence was favored for African-American patients, whereas the TAT was better for whites for a visual acuity and visual field outcome [22]. Multivariate regression analysis revealed several factors associated with visual field progression. The risk factors for the patients in the argon laser trabeculoplasty–trabeculectomy–trabeculectomy (ATT) treatment sequence were baseline visual field score, male gender, and baseline visual acuity. The risk factors for those in the trabeculectomy–argon laser trabeculoplasty–trabeculectomy (TAT) treatment sequence were baseline visual field score and diabetes [23].

2.2.5 Integrating Information from Studies

These studies uncover identifiable risk factors for progressive glaucoma with consistencies and inconsistencies (see Table 2.1). Most studies agreed that older age, African-American race, elevated IOP, and worse visual field are risk factors. In contrast, they also found that hypertension, smoking history, and family history of glaucoma were not risk factors. Finally, several discrepancies occur for diabetes, gender, central corneal thickness, and, among other factors, for their association with progressive glaucoma.

How do we adjudicate these disparate results? One reason for these differences in risk factors may be the result of different stages of glaucoma having different risk factors for progression. For example, ocular hypertension patients may have different risk factors for progression in comparison with a glaucoma patient who has likely undergone treatment. Another explanation is that the studies did not assess similar risk factors; AGIS and CIGTS did not measure corneal thickness. Recent retrospective studies have shown corneal thickness to be predictive of progressive glaucoma [9, 18]. The EMGT included only optic disc hemorrhages, and not other optic disc features, as a potential explanatory variable for progressive glaucoma [14].

These studies provide important information guiding the treatment of ocular hypertension and glaucoma. Future studies may comprehensively examine the risk factors most predictive for progressive glaucoma. It may be possible to develop algorithms to identify a patient who is most likely to become worse, and an ophthalmologist may decide to treat this patient more aggressively.

2.3 How Do Clinicians Use This Important Information to Take Care of Patients?

Balas and Boren show that new knowledge from randomized controlled trials requires an average of 17 years to be incorporated into clinical practice [2]. The authors feel that the delay is created because knowledge fails to reach most clinicians, and when clinicians have access to the knowledge, they have insufficient tools and incentives to promote a best practice approach [2]. Clinicians make their decisions regarding treatment based on three major sources of knowledge: published results; third-party influences; or personal experience.

Clinicians may value these sources of information differently in their decision making; some may place the highest value on published information, integrating published information into their practices, even if this information is obtained from unreliable sources. Others may feel that personal experience has the highest importance, only changing their practice when they have a personal experience that warrants a change. Most clinicians are probably less rigid, using a combination of sources to make decisions.

Making decisions based on each of these sources of information creates limitations and barriers. For example, reviewing published information in journals requires funding to access them, time to critically read the study for strengths and weak-

Table 2.1 Recent large randomized controlled trials and the baseline risk factors for the development and progression of glaucoma from multivariate regression analysis. *OHTS* Ocular Hypertension Treatment Study, *EMGT* Early Manifest Glaucoma Trial, *CIGTS* Collaborative Initial Glaucoma Treatment Study, *NTGS* Collaborative Normal-Tension Glaucoma Study, *AGIS* Advanced Glaucoma Intervention Study. *X* significant association with development of glaucoma or glaucomatous progression *N/A* not applicable. The analysis did not include this risk factor or the study design did not allow for determination of an association with this factor

Study	OHTS	EMGT	CIGTS	NTGS	AGIS
Outcome	Visual field/ optic disc	Visual field/ optic disc	Visual field	Visual field	Visual field
Risk factor					
IOP	X	X			
Age	X	X	X		X
Cup:disc ratio	X	N/A			N/A
Disc hemorrhage				X	N/A
Exfoliation	N/A	X			N/A
Bilaterality	N/A	X			N/A
Diabetes	X (protective)		X		X[a]
Hypertension					
Migraine/vasospasm				X	N/A
Smoking history					
Family history of glaucoma					
African-American		N/A	X	X	
Gender				X (female)	X[b] (male)
No. of interventions	N/A	N/A			X
Visual acuity					X[b]
Visual field severity	X (pattern standard deviation)	X (mean deviation)	X (CIGTS visual field score)		X(AGIS visual field score, protective)
Central corneal thickness	X		N/A	N/A	N/A

"Protective" means that the presence of the risk factor decreases the risk of glaucoma or glaucomatous progression

[a] For AGIS trabeculectomy–argon laser trabeculoplasty–trabeculectomy sequence only

[b] For AGIS argon laser trabeculoplasty–trabeculectomy–trabeculectomy sequence only

nesses, and statistical knowledge to understand the results. Even a single ophthalmology journal "contains a large volume of information, making it difficult for a busy clinician to keep up with new information".

Some clinicians rely on published results contained within the glossy and colorful magazines, termed "throwaways." The publisher sends these free magazines to most clinicians' offices, which eliminates the problem of accessing the articles. The articles are short in length, enabling a busy clinician to read them quickly; however, they contain preliminary, unproven therapies that lack rigorous peer review and consensus. In other

words, these forms of published results may create treatment decisions based on inappropriate information. Finally, even when a journal published an innovative change to clinical care, this change still requires promotion and consensus building to become integrated into practice.

The second source of information is third-party influences; these include clinical guidelines released in published journals and books. One example is the American Academy of Ophthalmology's Preferred Practice Patterns publications [1]. A committee of experts creates these publications based on consensus, their knowledge, and clinical experiences. The recommendations are subjective, vary by expertise of the panel, and may not be based on the best available evidence. Other forms of third-party information, such as clinical conferences, may be limited by the accuracy of the information, as well as credibility and consistency. In summary, third-party influences guide clinical decisions but may not represent the best available evidence.

The third and most subjective source of information for clinical decision making is personal experience. Clinicians attain personal experience from their clinical training and experience. They are the time-honored methods for creating a knowledge base and shaping one's clinical decision making; however, clinical training and experience can vary between training programs. In addition, decisions can be altered by recent personal experiences. For example, after 11 September 2001, Americans believed that they were more likely to be involved in a terrorist attack in an airplane than to have a car accident, and many avoided flying for several months. The same bias towards decision making may occur when an ophthalmologist encounters an ocular hypertensive patient who has developed severe visual field loss after a short period of follow-up. He is biased toward aggressively treating his next ocular hypertensive patient.

Evidence-based medicine (EBM) is a philosophy of decision making which incorporates these three sources of knowledge to determine the current best evidence from clinical acumen and scientific research to make decisions about the care of individual patients [21]. It integrates best practice approaches into clinical experience. It makes medical literature more clinically applicable [5]. It is difficult to practice EBM when the results of randomized controlled trials are complex. Risk assessment may help to simplify complex medical research results towards the care of individual patients.

2.4 Implementing Information from Clinical Studies into Clinical Care of Patients

2.4.1 A Current Risk Calculator: The Devers Ocular Hypertension to Glaucoma Risk Calculator

We developed The Devers Ocular Hypertension to Glaucoma risk calculator [3, 17] from the results of the OHTS Study [8, 13]. We took the natural log of the hazard ratios of the OHTS multivariate proportional hazard model to create beta coefficients for each covariate such as corneal thickness. The beta coefficients are multiplied by the corresponding values of the covariates to determine a sum (or g(x)). This g(x) is subtracted from the g(x) of an average OHTS ocular hypertensive patient, and takes the exponential of the difference to create a hazard ratio [10]. This hazard ratio is multiplied by the mean probability of developing glaucoma of 9.5% over 5 years for the OHTS participant [13] to create an absolute risk or probability of glaucoma (with a maximum of 99%). For example, if the odds ratio of a representative patient is 2.0, the mean probability of glaucoma in 5 years is 19% (2.0 multiplied by 9.5%).

Figure 2.1 shows a printout for the 60-year-old ocular hypertension patient in the Introduction. His risk factors include: no diabetes; a corneal thickness of 540 μm; cup-to-disc ratio of 0.7; pattern standard deviation of 1.9; and an intraocular pressure of 26 mm Hg. He has a 41.2% probability of developing glaucoma in 5 years.

2.4.2 Benefits to Eye Care Providers

Trying to decide whether to treat the above patient is complex without a risk calculator. The OHTS multivariate regression contains six vari-

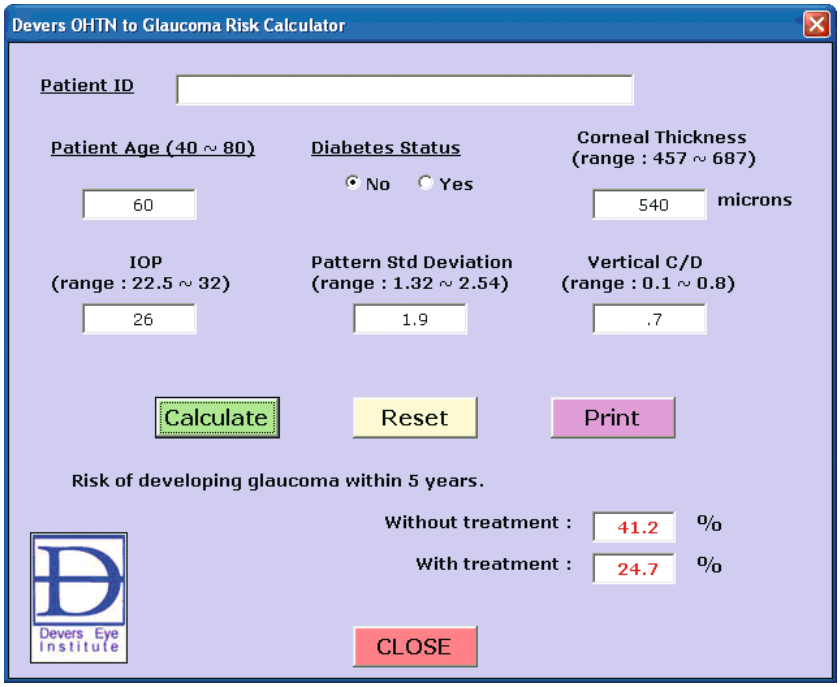

Fig. 2.1 The Devers Ocular Hypertension to Glaucoma risk calculator (Microsoft Excel version). This program shows that the ocular hypertension patient in the introduction has a risk of developing glaucoma of 41% and this decreases to 24.7% with treatment. *IOP* intraocular pressure

ables that are predictive of developing glaucoma from ocular hypertension: age; corneal thickness; IOP; PSD; diabetes status; and vertical C/D. Even if one divides the continuous variables of age, corneal thickness, IOP, and PSD into thirds and uses nine different combinations for C/D (0.0–0.8), 1458 (3×3×3×3×2×9) different combinations of variables exist for ocular hypertension patients. This creates a large number of different combinations of variables for any one ocular hypertension patient.

We performed a survey of ophthalmologists to estimate their ability to predict the risk of glaucoma in ocular hypertensive patients. Ophthalmologists had the benefit of an oral review and written handouts summarizing the OHTS results. We found that ophthalmologists tended to underestimate the risk when compared with the actual risk found by the risk calculator. They also had a large range of predictions, sometimes differing from the actual risk by 40%. In general, this difficulty in determining risk and the variability in the estimates will result in under-treatment of ocular hypertensive patients. In addition, ophthalmologists will have different treatment recommendations for the same ocular hypertension patient.

This difficulty creates a barrier to applying data from large clinical trials, such as the OHTS, to individual patients. The Institute of Medicine recommends that clinicians practice evidence-based medicine by using the results of large randomized clinical trials [12]. Using an available and easily understood risk calculator may decrease the barrier of complexity by simplifying the risk estimate of glaucoma.

2.4.3 Benefits to Patients

A risk calculator may provide benefits to patients regarding compliance. The OHTS risk calculator provides clinicians with an individualized estimate of susceptibility to developing glaucoma

in 5 years for a patient; thus, risk calculators encourage treatment to be patient centered rather than population based. The Health Belief model indicates that providing information regarding susceptibility helps improve patient compliance [6]. In other words, patients are more likely to adhere to therapy if they have a more definitive expectation of risk, rather than something vague, such as "higher or lower" risk; thus, risk calculation may strengthen the physician–patient relationship and enhance compliance.

Estimates of risk should include a discussion with the patient of the benefits of treatment, because patients will be more motivated to be compliant if they understand that treatment is beneficial. For the OHTS study, patients should understand that their chance of developing visual field loss should drop by approximately 60% with treatment [23]. A patient with a risk of 30% of developing glaucoma over 5 years can decrease his risk to 12% with ocular hypotensive treatment. In this example, a risk calculator maximizes compliance by providing estimates of susceptibility to developing glaucoma from ocular hypertension, as well as by quantifying the benefits of treatment.

2.4.4 Benefits to Society of a Risk Calculator

Risk calculators may simultaneously save money and decrease blindness. For example, some providers treat all ocular hypertensive patients based on the OHTS study results. This produces excess costs to society. The 5-year cumulative probability of developing glaucoma was 9.5% in the untreated group and 4.4% in the treated group. This results in a relative risk reduction of 54% [(9.5 - 4.4) ÷ 9.5] and an absolute risk reduction of 5.1% (9.5 - 4.4). In this example, the number needed to treat (NNT) is 20 (1/0.051) persons to prevent one person from developing glaucoma. If one uses visual field loss (an outcome more likely to be associated with decreased quality of life) as the criterion for glaucoma, the NNT increases to 42 persons! The main reason for these high NNT values is low risk of developing glaucoma for the majority of ocular hypertension patients.

The excess 5-year cost to prevent one ocular hypertensive patient from developing glaucoma is $54,000 with an NNT of 20 and $113,000 with an NNT of 42 (conservatively assuming effective monotherapy with a $20-per-month beta-adrenergic antagonist and two extra office visits per year). Substituting an $80 prostaglandin analog for treatment increases the cost to $126,000 with an NNT of 20 and $264,600 with an NNT of 42. Clinicians need to consider these costs as well as side effects, efficacy, and convenience when choosing an ocular hypotensive medication for treatment.

Clearly, providers should avoid treating every ocular hypertension patient. A risk calculator can help select those patients who will most benefit from treatment because of their high risk of developing glaucoma. It can also determine which patients have a low risk of developing glaucoma and should not be treated. Finally, when a calculator determines a borderline risk, the provider's experience and the patient's input can provide guidance regarding whether to treat.

2.4.5 Disadvantages of Risk Calculators

A recent study suggests that in a critical care setting, clinicians may not change their treatment based on a risk calculator [24]. This randomized, clinical trial showed that even when a risk model predicted an ICU patient would die within a week, doctors rarely used this information to obtain an end-of-life recommendation from the family [24]. The authors of the study suggested that the doctors were unwilling to apply results from the calculator due to "inertia" and "lack of incentives" with the current situation, not because of any perceived flaws in the risk model itself. Presumably, implementation of risk assessment would differ between a critical care setting and an ophthalmologist's office. But the point remains that simply providing a risk assessment tool does not guarantee adoption by clinicians.

Risk assessment and calculation has several other limitations. Risk calculators are based on the best available information; thus, their use should be restricted to patients who are similar to those included in the study. For example, with regard to a risk calculator based on the OHTS,

ophthalmologists should not assume that eyes with secondary causes of ocular hypertension, such as pseudoexfoliation or pigmentary dispersion syndrome, will have similar risk factors to the OHTS study population. Also, clinicians need to understand that a risk calculator provides a mean risk based on a group of patients with similar characteristics. Rare combinations in OHTS, such as a cup-to-disc ratio less than 0.2, an intraocular pressure above 29 mm Hg, or an age of above 70 years, will result in larger confidence intervals around individual estimates and therefore less precise estimates [11].

In addition, a risk calculator should be validated in a separate sample of ocular hypertension patients. The OHTS patients may not accurately represent a typical ocular hypertension patient in an eye care provider office and they may have a lower or higher probability of developing glaucoma. These differences may occur because the OHTS patients received free medications and clinical visits, were reliable visual field takers, and were apparently compliant with their medications and follow-up. These characteristics are typical of research study patients, but uncommon in the clinical realm; thus, validation in additional patient populations and everyday clinical settings would enhance the ability to generalize the risk calculators such as the Devers OHTN to Glaucoma risk calculator [3].

The OHTS Cox proportional hazard model [8] was created using the characteristics from both the observed participants (untreated) and the participants who were randomized to ocular hypertensive medications (treated). Using information for treated patients to determine the risk in an untreated population usually results in lower risk ratio than would have been obtained if the multivariate Cox proportional hazard model had included only untreated participants. Also, it is unclear if the OHTS analysis controlled for all significant interactions in the data. When significant interactions are excluded from the model, this decreases the predictive ability of the model, increasing the confidence intervals of the estimates; thus, the risk calculator of the current study may underestimate risk in untreated patients, and, if significant interactions were not controlled for, result in higher confidence intervals.

Another manuscript highlights the caveats of risk calculators, in general and specifically, for the Devers OHTN to Glaucoma risk calculator [17]. Two variables of the current risk calculator require further mention. The relevance of diabetes as a protective factor has been questioned because the OHTS entrance criteria created a highly selected population of diabetics, who are unlikely to be representative of most diabetic patients with ocular hypertension [8]. An investigator should exercise caution when applying the results to diabetic patients. Also, PSD is highly variable and needed to be averaged over multiple baseline visual fields [8]. This variability would create larger confidence intervals for individual estimates. Future analyses may compare the predictive value of risk calculators with and without including diabetes and PSD; however, using PSD and diabetes in the risk calculator should not have a significant effect on the risk estimates. The risk calculator demonstrates a difference of 6.0 and 2.7%, respectively, in the risk of glaucoma when one changes diabetic status and alters PSD by two standard deviations (while keeping the remainder of the characteristics at the OHTS averages). This suggests that even if diabetes and PSD create variation (or higher confidence intervals) in the risk calculator results, the variation in the risk calculator estimate is less than the 40% difference of the surveyed ophthalmologists (see above in Benefits to Eye Care Providers).

2.4.6 Future Risk Calculators

Table 2.1 highlights the variables significantly associated with glaucomatous progression in ocular hypertension and glaucoma patients. We have developed a risk calculator for ocular hypertension. The Devers Ocular Hypertension to Glaucoma risk calculator will not be the final model and will need to be adjusted by future studies in different populations. Investigators may use the results from the European Glaucoma Prevention Study [19] to validate the equation predicting glaucoma, the magnitude of the beta coefficients for the covariates, and to determine smaller confidence intervals for the predictive values.

Clinicians need risk calculators to be created from studies such as the Early Manifest Glau-

coma Trial, the Collaborative Initial Glaucoma Treatment Study, and the Advanced Glaucoma Intervention Study. For example, the second patient in the Introduction could undergo treatment using medications or surgery, but CITGS indicates that while visual field loss would be similar between treatments, quality of life and visual acuity would be more likely to be preserved with medications rather than with surgery. Also, she has none of the risk factors for progressive glaucoma from the CITGS, AGIS, or EMGT, also suggesting that the ophthalmologist should start with medical treatment.

Like the above example, risk calculators could identify the patients at highest risk for glaucomatous progression. These patients could be monitored closely and treated more aggressively when compared with a patient who is unlikely to progress. Finally, risk calculators could identify those who would benefit from a specific type of treatment, such as ocular hypotensive medications, argon-laser trabeculoplasty, and surgery. Overall, this may decrease the risk of blindness in glaucoma patients.

Summary for the Clinician

- Reducing intraocular pressure is efficacious to delay or prevent glaucomatous visual field and optic disc progression. Assessing risk factors for progressive glaucoma is important to identify those ocular hypertension and glaucoma patients most likely to develop worsening glaucoma. Currently, we have a risk calculator for determine the probability of developing glaucoma from ocular hypertension. Future calculators examining risk factors for progressive glaucoma in patients with early and moderate glaucoma may identify the patients most likely to progress as well as the most efficacious treatment; however, risk assessment and risk calculators are new, and they require future research to determine their benefits.

2.4.7 Conclusion

A number of randomized, controlled clinical trials have been completed in recent years, yielding valuable information for the management of ocular hypertension and glaucoma patients. The first patient in the Introduction has a high risk of developing glaucoma without treatment. The second patient could undergo treatment using medications or surgery, but CITGS indicates that while visual field loss would be similar between treatments, quality of life and visual acuity would be more likely to be preserved with medications rather than with surgery. Utilizing the data from these studies can be difficult, however, as the results are derived from specific patient populations and outcomes are not easily compared. A risk calculator is one tool to assist clinicians in integrating and applying the data from well-designed clinical studies. While risk calculators have some limitations, they provide benefits to patients, clinicians, and to society as a whole.

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Chapter 3

Dynamic Contour Tonometry

3

Evelin Schneider, Hartmut E. Kanngiesser, Christoph Kniestedt

Core Messages

- Intraocular pressure is a major risk factor in the pathogenesis of glaucoma
- Goldmann applanation tonometry is the present gold standard of IOP measurement; however, Goldmann tonometry depends on corneal thickness and on other mechanical parameters of the cornea.
- Dynamic contour tonometry measures transcorneal pressure with minimal deformation of the cornea. This principle measures pressure instead of force.
- Dynamic contour tonometry allows measuring the ocular pulse amplitude and calculates diastolic IOP from several pulse amplitude cycles.
- Various mutually contradictory correction tables have been proposed for applanation tonometry. Dynamic contour tonometry is obviously independent of corneal thickness.
- Dynamic contour tonometry is especially suitable for taking IOP in LASIK eyes.
- Dynamic contour tonometry requires measuring periods of 4–5 s and is difficult in the incompliant patient or in nystagmus.
- The value of dynamic contour tonometry in corneal diseases, such as keratokonus or corneal scars, or in childhood glaucoma, has still to be determined.

3.1 Intraocular Pressure

3.1.1 IOP Measurement in Glaucoma Diagnosis

Glaucoma is not a single clinical disease. The diagnosis "glaucoma" summarizes a large amount of diseases with various physiologic mechanisms. Glaucoma eyes show a number of ocular conditions, including elevated intraocular pressure (IOP), which result in damage to the optic nerve and loss of visual field. These ocular conditions are very complex and closely connected among one another.

A relative elevation of IOP, resulting from reduced drainage from the eye, obstructed or physically damaged drainage structures, plays an outstanding role in the pathogenesis of glaucoma. But as in any organic system, the response to the deviation of one physiologic parameter, such as IOP, varies with the qualities of this special system. In glaucoma, apoptosis of retinal ganglion cells is not just a simple consequence of high intraocular pressure. Intermediate and contributory factors, such as ischemia (due to insufficient blood flow to the optic nerve), decreased axoplasmatic flow, free radicals, excitatory amino acids, such as glutamate and hyperglycemia with the formation of advanced glycation end products (AGEs), determine the damage caused by a relative elevation of IOP in the eye. The distribution of these factors among eyes with and without glaucomatous damage explains their varying susceptibility to elevated IOP; hence, an increase in IOP causing optic nerve damage in one eye may be tolerated by another eye without any pathologic consequences. This condition is called "ocular hypertension." On the other hand, a combination of disadvantageous conditions may cause glaucomatous damage, although IOP is within the statistically "normal" range, which is called "normal-tension glaucoma."

As a consequence of these considerations, the diagnosis of glaucoma cannot be based exclusively on IOP measurements. In diagnosing and screening glaucoma, tonometry is indispensable but not sufficient, resulting in a high percentage of false positives and false negatives if considered the only determining factor. The examination has to be completed by ophthalmoscopy of the optic disc and the surrounding nerve fiber layer as well as by visual field testing in order to detect glaucomatous damage. Additionally, gonioscopy is necessary for the differentiation between the various kinds of glaucoma.

On the other hand, elevated IOP is more than a risk factor for glaucoma. It necessarily causes damage to retinal ganglion cells when exceeding a certain limit which has to be estimated individually for every patient. Accurate IOP measurement is not only one of the basic methods in glaucoma diagnosis, it is also fundamental in adequate follow-up and successful treatment of glaucoma patients.

A comparison of different tonometry techniques regarding practicability, accuracy, physical principles, and possible sources of error is therefore of practical interest.

3.1.2 Principles and Problems of IOP Measurement Methods

Intraocular pressure is maintained by a constant production of aqueous, about 2 µl/min. The pressure that results from the dynamic balance of aqueous production and drainage from the eye is equally transmitted to its outer layers, sclera and cornea, and can be measured there. Indirect IOP measurement is the principle of non-invasive tonometry and involves a number of fundamental problems. First of all, most common tonometers work with deformation of the eye's surface. They either apply a standard force to measure the resulting deformation of the globe or they produce a standard deformation to determine the required force. This principle does not allow IOP measurement in the undisturbed eye. The variable nature and flexibility of cornea and sclera imply a varying resistance to deformation of the globe. Beyond this, deformation of the globe causes aqueous displacement and the resulting changes in IOP, again, depend on the flexibility of the ocular coat; therefore, all techniques of indirect IOP measurement only supply an approximation of original IOP.

Maklakoff tonometry was introduced in 1885. It is based on the applanation of a variable area of the corneal surface. Previously introduced cocaine anesthesia of the cornea allowed direct corneal application of Maklakoff's tonometer. The constant applanation force, caused by the tonometer's weight, resulted in the flattening of a variable area of the corneal sphere. The contact area was marked with aniline pencil and the applanated area became visible through aniline going into solution when touching the tear film.

According to the Imbert–Fick Law, published in 1888, the pressure within the globe is equivalent to the inflicted force, divided by the flattened area. This relationship is only valid for tension-free, thin membranes. The effects of capillary pressure of the tear film and of the rigidity force of the bent cornea were neglected.

Schiøtz tonometry largely replaced Maklakoff tonometry after 1905. Following the principle of indentation tonometry, IOP was now measured by the distance a plunger sank into the globe when the tonometer was put on the corneal surface. This distance was transmitted and displayed on a graduated scale. Additional weights could be supplemented in order to measure different ranges of IOP.

Just like Maklakoff tonometry, this technique causes variable ocular deformation and is therefore highly dependent on the rigidity of the cornea. Schiøtz assumed constant rigidity, following Hook's Law, and introduced "elasticity constants" for extrapolation back to zero aqueous displacement. Extrapolation curves finally revealed a more complex, non-linear correlation between applied force and aqueous displacement when extra weights were added to the tonometer.

The Goldmann tonometer was introduced in 1955 as the first modern applanation tonometer [10]. It worked with a considerably reduced deforming force, which, for the first time, was applied to the cornea horizontally and not vertically. In addition, a constant diameter of 3.06 mm of the corneal surface was applanated and the required force was measured. This procedure reduced the error resulting from variable rigidity of

the globe to a minimum. Being much more accurate, Goldmann tonometry superseded both, Schiøtz and Maklakoff tonometry, which are rarely applied today.

Nevertheless, corneal applanation still makes this method dependent on corneal properties, adhesion of the tear film, and the effects of aqueous displacement. The most important condition for accurate IOP measurement is the exact applanation of the given area which has to be adjusted at the slit lamp, an inherently subjective process.

Most common tonometers work with the principle of corneal applanation.

Dynamic contour tonometry is the first measuring technique which does not cause considerable deformation of the eye. The Pascal tonometer was designed to measure IOP with less aqueous displacement and less dependence on corneal properties.

3.1.3 Comparison of Common Tonometers

Goldmann applanation tonometry (GAT) has been the gold standard in IOP measurement for a long time. It is performed at the slit lamp. Local anesthetic and fluorescein must be administered before examination. The tonometer prism is advanced close to the patient's cornea, and then observed through the oculars of the slit lamp, using blue light. When the prism touches the cornea, two green semicircles are seen. The appositional force between prism and cornea has to be altered using the thumb wheel until the inner aspects of the circles are just in contact and the correct area is applanated. The IOP is then read off the analog scale on the thumb wheel.

The GAT readings are affected by corneal properties, easiest shown by central corneal thickness. Besides this, the operator's subjective impression biases the adjustment of the force and GAT detects a single value of the strongly fluctuating IOP. Applanation of thick corneae in common requires more appositional force and results in higher GAT readings than applanation of thin corneae.

Several portable tonometers, such as Draeger and Perkins tonometer, work with the principle of Goldmann applanation tonometry. They can be used when the patient cannot be positioned properly at the slitlamp and the patient can assume a lying or sitting position. The results do not significantly deviate from Goldmann IOP readings.

Tonopen is a small portable applanation tonometer. It has to be calibrated before examination and a sterile cover has to be put over the tip. After local anesthesia, the tonopen is gently tapped against the cornea. A beep indicates correct applanation and the pressure reading is displayed.

The very small measuring tip of this device makes it easier to use with corneal abnormalities. On the other hand, it reduces the reliability of a single measurement. To obtain valid readings, four to six measurements have to be taken and the final averaged reading is displayed together with a confidence indicator.

Non-contact tonometry does not touch the eye but uses a puff of air to flatten the cornea. The time needed to flatten the cornea to give maximum reflection of a light beam is inversely proportional to IOP.

This method does not require local anesthesia or fluorescein application and includes no risk of infection. New generations of non-contact tonometers with auto focus for correct positioning of the sensor tip in front of the patient's cornea allow very quick and simple measurements; however, the puff of air applied to the cornea causes discomfort to most patients. Devices with automatic puff control have been designed to reduce the amount of air pressure for each measurement and to optimize patient comfort.

Non-contact tonometry is inferior to Goldmann applanation tonometry regarding the accuracy and reliability of IOP readings.

Langham's pneumotonograph (PTG) [18] generates a constant air flow through a probe covered by a membrane that touches the cornea. It provides the examiner with continuous IOP measurements. The pressure underneath the membrane increases gradually until it reaches the counterforce of the cornea. In this equilibrium, the device indirectly calculates the pressure in the anterior chamber. For this conversion, the tonometer uses a non-linear correction formula that never has been published and still defies scientific debate.

3.2 Dynamic Contour Tonometry

3.2.1 Physical Methodology

Dynamic contour tonometry (DCT) is a continuous (dynamic) and direct tonometric principle. It reads the IOP at the interface between the sensitive tonometer tip and the surface of the cornea.

Pressure in liquids and gases is defined as constantly distributed forces acting perpendicular to all boundaries (law of hydrostatic pressure by Blaise Pascal *1623, †1662). Direct measurement requires interface forces between the rigid tip and the semi-rigid corneal tissue that ideally equal the forces generated by the pressure in the eye. These interface forces are uniformly distributed and act perpendicularly to the interface.

The DCT tip touches the corneal center and slightly forces the cornea into its own concave curvature until pressure equilibrium is obtained on both sides of the cornea. The pressure sensor has the same curvature as the tonometer tip and measures the IOP on the external surface of the cornea.

The following three hypothetical steps illustrate the underlying principle of contour tonometry:

1. The entire globe is floating in a container filled with casting resin as shown in Fig. 3.1. The cornea behaves like an elliptic shell that reacts stiffly to stretch but fairly flexibly to bend. Nevertheless, the forces during bending and buckling may not be neglected. The pressure in the casting resin precisely equals pressure, P, within the eye. Forces, F, which are generated by pressure, P, act uniformly at both sides of the cornea. The interface forces between the liquid resin and the globe equal IOP. The globe remains its shape almost irrespectively from pressure differences over the cornea [23]. It stays close to its original contour under living conditions. The resin shall now cure without shrinking or other changes. It forms a hollow space of rigid material that surrounds the globe. The interface forces still act as before but now between rigid wall and semi-rigid globe. A pressure sensor that is integrated in the wall has the same contour as the piece of wall that it replaces and measures true pressure, p, without distortion through the cornea.

Obviously, such a tonometer has no practical sense.

2. The second step leads to a more practical but still hypothetic approach (Fig. 3.2). A tube filled with casing resin is placed onto the cornea with an appositional force just strong enough to tighten the gap between the tube and the cornea. Again, the resin is under pressure, P, and cures under constant conditions without any kind of shrinking. After removal of the cornea, it forms the inverse contour of the cornea; however, in contrast to the first theoretical model, and as it will be explained in the third step, the contour of the cornea is now different from its shape in the unloaded state. A pressure sensor is now integrated in the center of the resin. It has exactly the same curvature as the piece of resin for which it stands. If the tip touches the cornea with the same appositional force as used previously to hold the tube, the same force distribution as before curing of the resin is reestablished. As a consequence, the pressure sensor reads pressure, P, transcorneally.

3. For the third step we use a tip with a bigger diameter, as shown in Fig. 3.3. The tip has a diameter very similar to that of Goldmann's Applanation Tonometer tip, but with the surface curvature and an integrated central pressure sensor, as was clarified in step two.

The appositional force may now been selected over a wide range. It influences only the diameter of "contour matching," where the surface of the cornea is matched to the shape of the tip but only marginally affects the force distribution over the contour match area. In a similar manner, the IOP, the corneal radius and thickness, or other corneal properties influence mainly the diameter of contact. This explains the minimal measurement error over a wide range of corneal properties.

Figure 3.3 explains the contour change of the cornea during contour tonometry. The forces, F, that are homogeneously exerted by the intraocular pressure, P, generate tangential tensions inside the cornea. If the contour match area (A_C), defined by the diameter, d, is considered separately, the forces, F, act on both sides of the cornea and, thus, this part of the cornea around the apex is free of any tensions. However, in the vicinity of area A_C, the forces, F, act only from inside and generate tangential tensions that spread as con-

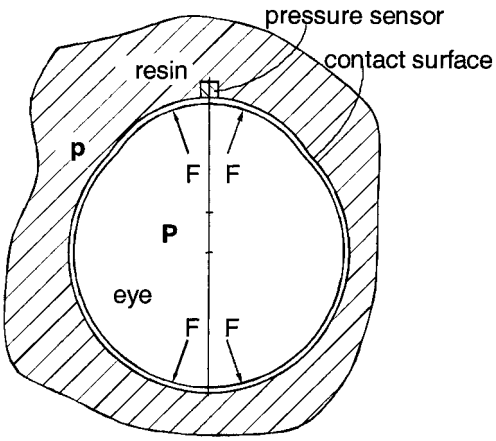

Fig. 3.1 Hypothetical device for transcorneal pressure measurement (step 1). *P* = intraocular pressure, *F* = Force generated by intraocular pressure

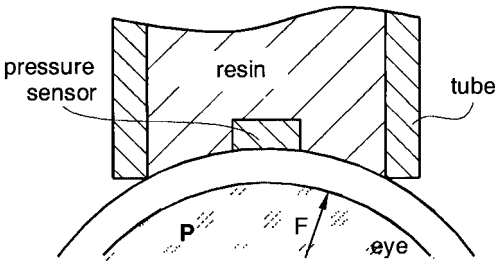

Fig. 3.2 Hypothetical device for transcorneal pressure measurement (step 2). *P* = intraocular pressure, *F* = Force generated by intraocular pressure

centric pulling forces into the rim of the cornea and flatten the corneal contour across A_C. The radius of curvature, R_C, will increase relatively to the normal and force-free situation ($R_C' = R_C + \Delta R$).

Theoretically, each individual cornea calls for a custom-made contour-matched tip to fulfill these contour-matching conditions; however, in vitro measurements that are presented below resulted in a "standard contour" that provides reliable measurements of true IOP for a fairly wide range of corneal dimensions and properties. The lack of a precise reference necessitates a study on cannulated eyes to confirm these results with similar precision in an in vivo setup.

The actual Dynamic Contour Tonometer tip has a centrally located piezo-resistive pressure sensor with an active diameter of less than 0.25 mm². The resolution is better than 0.1 mmHg over a range of more than 300 mmHg. The contour of the tip has a radius of 10.5 mm. The appositional force has a constant low value of 9.81 mN (1 g), assuring only marginal provocation of the eye.

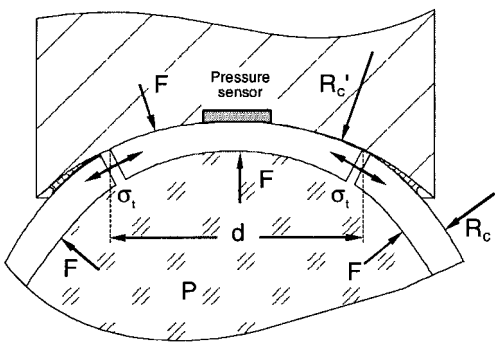

Fig. 3.3 Dynamic contour tonometer; contact area $\mathbf{A_C}$ with contour diameter **d**, *P* = intraocular pressure, *F* = Force generated by intraocular pressure

3.2.2 Measurement Procedure

A practical implementation of DCT has been realized in the PASCAL Dynamic Contour tonometer (Ziemer Ophthalmic Systems AG, Port, Switzerland). The PASCAL is a slit-lamp mounted device, used in much the same way as a Goldmann tonometer (Fig. 3.4)

Installed into the optical axis of the slit lamp, PASCAL gives the user a view of the contact interface between cornea and tonometer tip (Fig. 3.5). A transparent pressure-sensing tip with a contoured contact surface, called the sensor tip, is applied to the center of the patient's cornea with a small, constant force. This force is generated by a spring-loaded actuator (called "cantilever"). The

Fig. 3.4 Dynamic contour tonometer measurement at the slit lamp

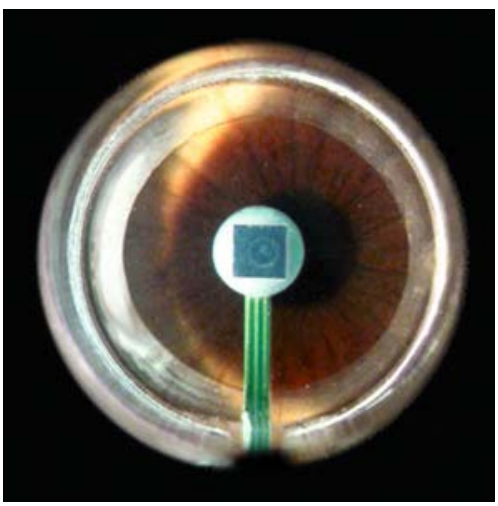

Fig. 3.5 View through sensor tip. *Dark circular area* represents area of direct contact between cornea and tip. *Little bluish square* represents pressure sensor

piezo-electric pressure sensor built into the contoured contact surface of the sensor tip generates an electrical signal which is proportional to the IOP (Fig. 3.6). As an audible feedback indicating proper eye contact, the main unit generates an audio signal whose pitch is proportional to the IOP detected. The pressure signal, which is modulated by pulsatile ocular blood flow, is detected for a period of about 5 s (corresponding to approximately five to ten heartbeats); then the tonometer is pulled away from the eye, thereby terminating the measurement.

PASCAL software computes IOP and its variation (modulation) caused by cardiac pulsation (%, OPA) from the digitized pressure-dependent electrical signal and from the baseline signal level corresponding to atmospheric pressure. These signals are stored and processed by a microprocessor situated in the body of the tonometer, and the PASCAL software computes IOP and its variation (modulation) caused by cardiac pulsation (OPA) from the digitized pressure-dependent electrical signal and from the baseline signal level corresponding to atmospheric pressure. These signals are stored and processed by a microprocessor situated in the body of the tonometer, and the numerical results are displayed on an LCD display screen. Besides the numerical values for IOP and OPA (in mmHg), a quality score, Q, is also computed and displayed for each measurement. The score is computed from an evaluation of the number of valid data points, noise level, presence of artifacts, and regularity and shape of pulsations. Q provides a useful indicator for the trustworthiness of the result and reduces the probability of obtaining erroneous reading due to artifacts and poor data quality. No operator action is required besides switching the tonometer on and centering the sensor tip on the patient's cornea; hence, it is not possible for the operator to influence the measurement and the result.

By definition, the "IOP" displayed by the PASCAL tonometer is the diastolic IOP. The difference between diastolic and systolic IOP is also obtained and shown as OPA, providing an indication for the range of pressure to which the optic nerve is exposed. The pressure curve with its characteristic fluctuations may be printed, together with the numerical result, on an optional

Fig. 3.6
Sensor tip with concave surface and embedded pressure sensor

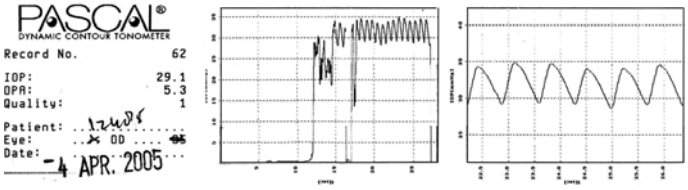

Fig. 3.7
Printout of a typical pressure curve

printer for documentation purposes and for further examination (Fig. 3.7).

Inspection of individual pressure curves reveals characteristic features that may vary from patient to patient. The ocular pulse amplitude in healthy eyes typically is in the 1.5–3 mmHg range and equal (within ± 10%) in both eyes. A more elastic cornea, high ocular perfusion, and high systemic blood pressure may give rise to an elevated OPA (values up to 7 mmHg are frequently encountered; extremes up to 10 mmHg are rarely seen). Stiffer corneas and reduced perfusion may yield OPA values below 1.5 mmHg. A large difference between left and right eye are a strong indicator for a stenosis or fistula in the sinus cavernosus.

3.2.3 Absolute and Relative Accuracy

To demonstrate the concordance of contour tonometry with intracameral manometry, an in vitro study [12] has been performed. Sixteen freshly enucleated human eyes were de-epithelialized. An intubation needle was placed in the anterior chamber. The corneas were dehydrated with Dextrane 20% from both sides of the cornea until stable central corneal thickness (CCT) values were achieved. The CCT was monitored using ultrasound pachymetry. Corneal radius (CR) and astigmatism (AS) were measured using a keratometer. The tube in the anterior chamber was connected to a pressure transducer and to a bottle system filled with balanced salt solution. The pressure in the eye was then artificially altered between 5 and 58 mmHg in 15 consecutive steps by changing the height of the bottle in relation to the eye. The mean of each of five consecutive measurements taken at each pressure setting with DCT, Goldmann applanation tonometry and pneumatonometry, was compared with the direct manometric readings from the pressure transducer. The DCT readings were strongly correlated to manometrically obtained pressure with a linear regression of ($y = 1.00x + 0.34$, $R^2 = 1$, $P < 0.001$). Averaged (between five consecutive readings for each eye at each pressure step) DCT measurements on human cadaver eyes exhibited a constant bias of $+0.58 \pm 0.085$ mmHg (mean ± 95% CI) relative to the corresponding manometric readings (Fig. 3.8). The 95% limit of agreement for these averaged measurements was ± 0.98 mmHg.

To determine the variability in repeated measurements, five consecutive readings at identi-

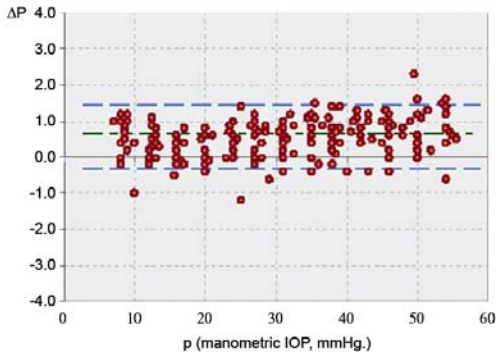

Fig. 3.8 Bias of tonometer readings against manometric IOP (cadaver eyes). Difference ΔP of contour tonometer reading (mean of five consecutive measurements) and manometric IOP is plotted against manometric IOP. *Dashed line:* mean bias; *dotted line:* 95% prediction interval of tonometer bias. *DCT* dynamic contour tonometry

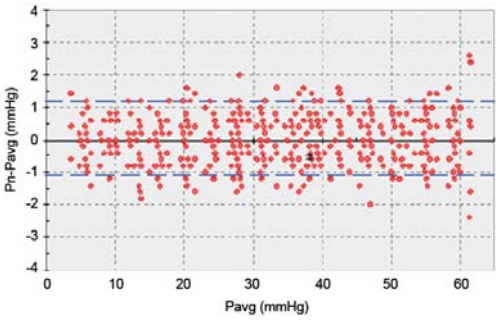

Fig. 3.9 Variability of repeated measurements with contour tonometer (cadaver eyes). Difference of individual measurements from mean of five consecutive repeat measurements is plotted against mean of five measurements. *Dashed line:* 95% limit of agreement of all measurements

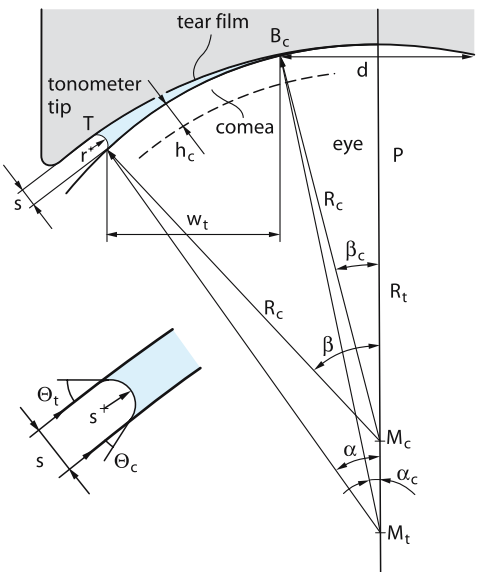

Fig. 3.10 Geometric parameters used for describing the interaction of contour tonometer tip, tear film, and cornea. In the calculations, β_C and θ_t are substituted by the mean wetting angle α

cal conditions each were taken on 16 eyes at eight different manometric pressures and plotted (Fig. 3.9) against their averages. The 95% limit of agreement for repeat measurements was ± 1.14 mmHg.

To study the relationship between corneal geometry (CCT and CR) with the expected systematic measurement error, **ΔP***, as the difference of the tonometer reading and the true IOP at different pressures, the contact diameter, d, for each of the 1200 individual measurements taken on our set of cadaver eyes was computed. The relationship between corneal elasticity and **ΔP*** was not investigated, because the measurement of corneal elasticity is beyond the scope of this study.

From the geometrical setup shown in Fig. 3.10, the contour match diameter using the force equilibrium is described by:

$$F_{iop} + F_c + F_r + F_{ap} = 0$$

where

$\mathbf{F}_{iop}$ is the force exercised by effective IOP, acting on the tonometer's contact surface, $\mathbf{F}_c$ is the capillary force or adhesion force created within the tear film, caused by negative capillary pressure within the tear film, $\mathbf{F}_r$ is the rigidity force responding to deformation of the cornea, and $\mathbf{F}_{ap}$ is the appositional force applied externally to the

tonometer (e.g., in case of the Goldmann Applanation Tonometer set by the adjustment of the thumb wheel).

The two forces with negative sign, $\mathbf{F}_c$ and $\mathbf{F}_{ap}$, attract tip and cornea, whereas the forces with positive sign, $\mathbf{F}_{iop}$ and $\mathbf{F}_t$, push tip and cornea away from each other.

A complex set of geometrical calculations and the use of iterative solving techniques lead to a non-explicit formulation for contour match diameter, d.

$$d = F(F_{ap}, P, R_c, R_t, h_c, \Theta, \gamma, v_t)$$

where
P is the true IOP, $\mathbf{R}_c$ is radius of curvature of the cornea, $\mathbf{R}_t$ is radius of curvature of the tonometric tip, $\mathbf{h}_c$ is thickness of the cornea, and Θ is the mean wetting angle between tear film/cornea and tear film/tip, γ is the surface tension of the tear film air boundary, and $\mathbf{v}_t$ is the volume of the tear film.

The radius of curvature of the tip is $\mathbf{R}_t = 10.5$ mm, the appositional force used for the measurements was $\mathbf{F}_{ap} = 1.0$ g, and Θ and γ are material constants. Equation (2) thus reduces to

$$d = F(R_C, h_C, P)$$

Then we plotted observed individual measurement deviations ($\Delta P = p - P$) against the corresponding calculated value of d. A second-order least-squares fit of the data points thus obtained furnished a polynomial describing the theoretical measurement error as a function of contour match diameter:

$$\mathbf{\Delta P^*} = (m \cdot \mathbf{d}^2) + (n \cdot \mathbf{d}) + q$$

with
$m = 0.0632 (p_m < 0.0001), n = -0.6399 (p_n = 0.0002)$, and $q = 1.961$ ($p_q = 0.0006$). The 95% limit of agreement of the experimental points with the polynomial is ± 1.3 mmHg.

With these coefficients, **ΔP*** was calculated for an array of IOP values, corneal radii, and corneal thicknesses. The result is displayed in Fig. 3.11. Computed **ΔP*** is shown at different levels of true IOP ranging from 5 to 30 mmHg. Areas where **ΔP*** is less than 0.5 mmHg are green. The inter-

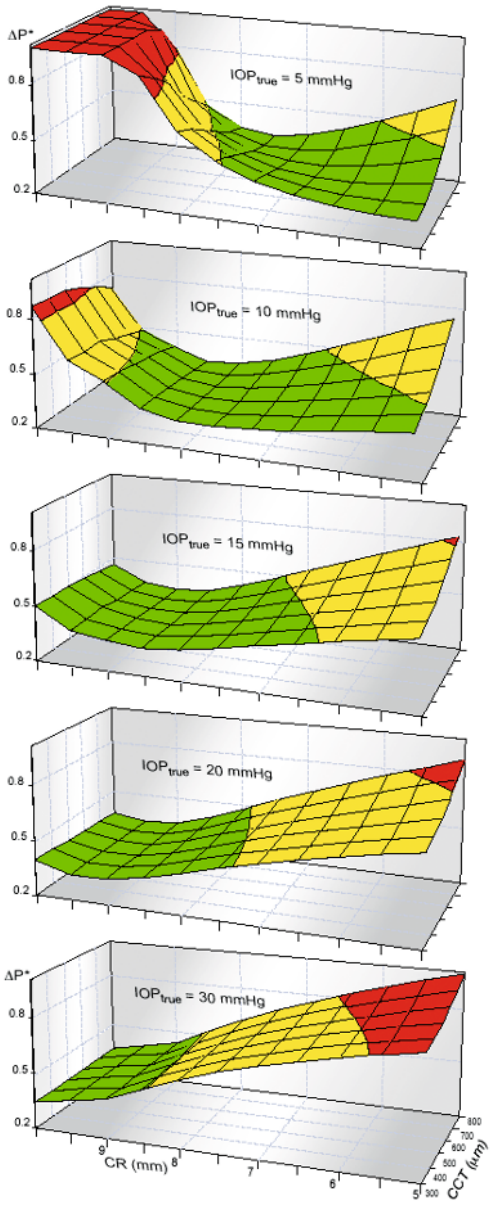

Fig. 3.11 Theoretical pressure measurement error ΔP* of contour tonometer, plotted against corneal radius (*CR*) and corneal thickness (*CCT*) for five selected values of true IOP (P=5, 10, 15, 20, 30 mmHg). Areas where $\Delta P^* < 0.5$ mmHg: *green*; $0.5 > \Delta P^* > 0.8$ mmHg: *yellow*, $\Delta P^* > 0.8$ mmHg: *red*. (Areas where $\Delta P^* > 1$ were cut off in the topmost graph)

mediate range $0.5 > \Delta P^* > 0.8$ mmHg is yellow, and ranges for which ΔP^* exceeds 0.8 mmHg are shown in red. Values for ΔP^* exceeding 1 mmHg were cut off in the graph for $P = 5$ mmHg.

In conclusion, the systematic error of DCT remains less than 0.8 mmHg for a wide range of corneal properties and IOP values (CCT = 300–700 µm, CR = 6.5–9.5 mm, and IOP = 10–30). On cadaver eyes the systematic error seems to be not relevant and never underestimates true IOP.

3.3 Clinical Application of Dynamic Contour Tonometry

3.3.1 Dynamic Contour Tonometry or Applanation Tonometry with Correction Factor?

The differences between GAT and DCT essential for the daily use are summarized in Table 1.

Numerous studies have been conducted to determine a correlation factor to define "real" IOP in eyes with unusually thin or thick corneas. Argus [32] introduced a correction formula assuming 578 µm as normal. Stodtmeister [30] published correction nomograms for applanation tonometry performed on corneas of different thickness than 580 µm. Ehlers et al. [4] compared CCT to a correction factor, derived from manometric IOP and applanating IOP, whereas Wolfs and Klaver [34] have plotted CCT to manometric values directly. Orssengo and Pye [22] recently proposed a new nonlinear correlation formula. Its accuracy and clinical application has not yet been proven with an independent manometric study. The fact that normal corneal thickness is assumed to vary widely between 450 and 600 µm raises the question: At which CCT level should one start using the nomograms? Using a linear regression model, Kniestedt et al. [17] have found a significant correlation between GAT and CCT with 0.25 mmHg change per 10 µm variation in corneal thickness in a glaucoma population of 258. Dynamic contour tonometry did not show a significant linear correlation to CCT.

A review of the literature shows variations between 0.11 mmHg [27] and 0.71 mmHg [25] for every 10-µm CCT change. These studies applied different study designs to different race and diagnosis groups; therefore, it is not surprising that they showed different mean corneal thicknesses. The fact that inhomogeneous patient samples of different corneal thicknesses, rigidities, and hydration conditions result in a wide range of correlation factors leads to the assumption that a linear correlation between applanation tonometry and the entire range of possible CCTs cannot exist. Kniestedt et al. [17] addressed this issue with a piecewise regression model and found that with thin corneas (< 535 µm) the slope between CCT and IOP is significantly steeper than with normal or thick corneas. Taking only the slopes below and above the cut-off points at 20-µm steps, the correlation was always stronger and significant between thin CCT (500, 520, 540 µm) and IOP for GAT. Surprisingly, the slopes above the cut-off points turned out to be negative; however, this phenomenon was not significant due to larger measurement errors on thick corneas. The reason for the higher measurement errors on thick corneas has not yet been clarified. It is possible that thick corneas result in higher errors per se since corneal rigidity is increased, or thick corneas may represent a non-homogeneous group, some of which may be inherently thick while some may be thickened by subclinical edema; the latter would correspond to the negative correlation between relatively thick CCT and GAT as has already been observed by Simon et al. [29].

3.3.2 DCT in LASIK Eyes

Laser in situ keratomileusis (LASIK) has become the most popular and frequently used technique of refractive surgery. A refractive alteration is induced to the cornea by laser ablation of the corneal stroma. In myopic LASIK, this procedure results in a variable reduction of central corneal thickness (CCT), a flattening of the corneal surface and a profound change of corneal mechanics. As a consequence, applanation tonometry underestimates IOP in eyes after myopic LASIK.

Table 3.2 shows the results of several studies on the mean reduction of CCT and IOP readings using GAT, non-contact tonometry and tonopen pre- and post-LASIK. This raises the question

Table 3.1 Comparison of dynamic contour tonometry and Goldmann applanation tonometry. *IOP* intraocular pressure, *OPA* ocular pulse amplitude

Dynamic contour tonometry	Goldmann applanation tonometry
▪ **Principle**	
Measurement and transformation of IOP into electrical signals by a piezo element, which is applied to the cornea with a constant force	Measurement of the force required for applanation of a constant area on the corneal surface
▪ **Results**	
Dynamic measurement of systolic IOP, diastolic IOP, and OPA, indication of a quality score	Static and analog measurement of mean IOP, OPA, and quality of measurement can only be estimated
▪ **Source of error**	
- Low-quality readings	- Influence of corneal biomechanics, such as central corneal thickness and elasticity, lead to falsely high or low readings in non-standard eyes with thick or thin corneae (LASIK eyes) or eyes with corneal pathologies (scars, edema) - Operator bias, analog scale
▪ **Applicability**	
No readings or unreliable low-quality readings in eyes with very low IOP or OPA, or patients with inadequate cooperation, poor vision, or nystagmus	An estimate of IOP by experienced operators is still needed, even in cases where DCT fails
▪ **Preparations before measurement**	
- Application of local anesthetic Lamp - Installation of a disposable tip cover - Insertion of the tip into the tip carrier	- Application of local anesthetic and fluorescein - Tip disinfection - Insertion of the tip into the tip carrier
▪ **Care and maintenance**	
- Calibration and system check at regular intervals - Occasional cleaning - Replacement of batteries	- Calibration and system check at regular intervals - Occasional cleaning

Table 3.2 Results of several studies on the mean reduction of central corneal thickness (*CCT*) and IOP readings using Goldmann applanation tonometry (*GAT*), non-contact tonometry (*NCT*), and tonopen pre- and post-LASIK

Reference	GAT (mmHg)	NCT (mmHg)	Tonopen (mmHg)	CCT (µm)
[7]	– 1.9			– 76.6
[5]	– 2.5			– 73.0
[37]	– 3.8	– 2.3		– 53.7
[24]		– 2.8		– 46.7
[9]	– 1.5	– 1.4	– 1.3 (central)	– 75.5
[3]	– 2.9 (after 1 month)	Not significant		– 77.1
[35]	– 0.1 (not significant)	– 1.1	Not significant	– 32.0
[21]	– 3.7	– 4.3		– 77.4

Table 3.3 The mean reduction of DCT readings, GAT readings, and CCT (post-LASIK minus pre-LASIK)

Reference	DCT (mmHg)	GAT (mmHg)	CCT (μm)
[2]	– 1.0 (not significant)	– 3.3	– 85
[28]	Not significant	– 4.9 (after 1 week) – 5.4 (after 4 weeks)	– 78
[13]	+ 0.6 (not significant)	– 3.0	– 90
[33]	– 1.2 (not significant)	– 4.3	– 90

as to whether DCT, which measures IOP without considerable corneal deformation, is a more appropriate device for accurate IOP reading in LASIK eyes.

Several studies compared DCT and GAT readings before and after LASIK. The mean reduction of DCT readings, GAT readings, and CCT (post-LASIK minus pre-LASIK) is listed in Table 3.3. According to these studies, DCT is not significantly influenced by changes in CCT after LASIK, whereas GAT readings are significantly reduced. This must be considered in clinical practice. The attempt to correct GAT readings using correction tables will not furnish more reliable results [13]. Dynamic contour tonometry, on the other hand, represents a reliable and accurate tool for the measurement of IOP in LASIK eyes.

3.3.3 DCT in Clinical Practice: Experiences, Advantages, and Disadvantages

In a clinical study [26], DCT and Goldmann tonometry were evaluated in view of their agreement, independence of corneal properties, and applicability to different groups of patients.

In order to determine the influence of corneal geometry on both methods, eyes with presumed standard distribution of IOP were carefully selected. Both glaucoma eyes and eyes with a history of intraocular inflammation or trauma were excluded from the study. Eyes with astigmatism >2 dpt were not included to avoid inaccurate GAT.

Measurements were performed in the following sequence: GAT at the slit lamp (Haag-Streit, Switzerland), DCT at the slit lamp (Swiss Microtechnology AG, Port, Switzerland), pachymetry (OLCR, Haag-Streit, Switzerland), and keratometry (Alcon).

Comparing both techniques, a median difference of 1.8 mmHg and a mean unsigned difference of 2.86 mmHg was found, with higher average results in DCT compared with GAT, which is in good agreement with the current literature [14, 15].

Falsely low GAT readings, particularly in the present study, may not explain the median difference. The mean GAT result in this study was 15.61 mmHg (median = 16.0 mmHg), which is in agreement with mean IOP in healthy eyes as described in the literature [8, 11, 17, 30, 33]. On the other hand, DCT is calibrated against manometric pressure and equally claims to measure true IOP [12, 15, 16]. Obviously, there is a difference of calibration between both methods, with either GAT generating too low readings [6], or DCT generating too high readings.

This study is quite conclusive concerning the influence of corneal properties on IOP measurements.

Corneal curvature did not influence IOP readings significantly in both GAT and DCT. In contrast, a clear correlation between CCT and GAT readings was found (Figs. 3.12, 3.13).

Assuming a linear correlation between GAT and CCT, a 4.5-mmHg difference per 100-μm deviation from mean CCT was calculated. The mean CCT of this study was 551.43 μm. The influence of CCT on GAT readings has been described by several authors [6, 30, 32, 31, 36].

In the evaluation of a new measurement technique, the agreement between the new and the old instrument is of great interest. Since considerable deviations in the results between the two instruments might occur in some cases, the operator

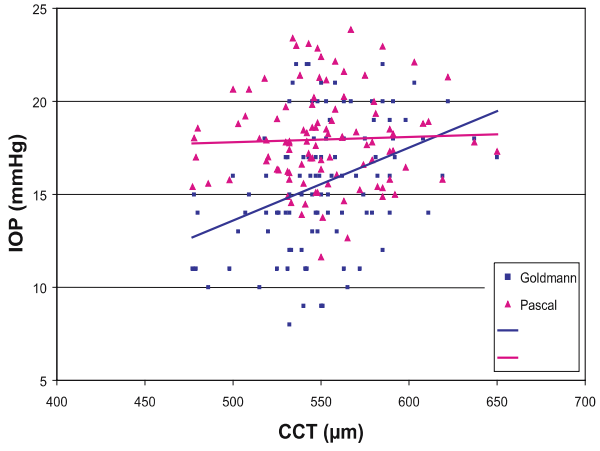

Fig. 3.12 Influence of CCT on IOP measurements. GAT is significantly influenced by CCT ($R=0.375$, $P=0.000$). The DCT measurements are CCT independent ($P=0.756$). *CCT* corneal thickness, *DCT* dynamic contour tonometry, *GAT* Goldmann applanation tonometry

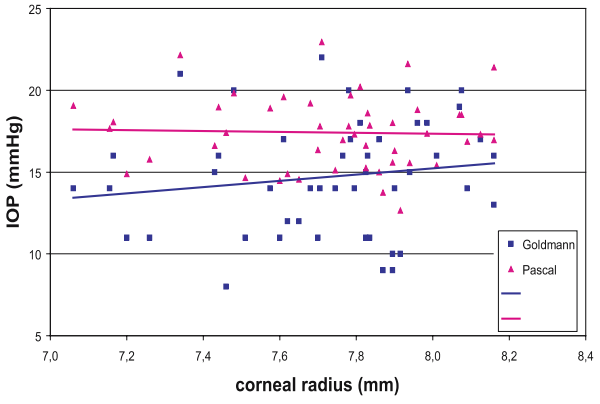

Fig. 3.13 Influence of corneal curvature on IOP measurements. Neither GAT ($P=0.749$) nor DCT ($P=0.762$) are significantly influenced by corneal curvature.

is often concerned with the question of whether they actually measure the same parameter.

From Fig. 3.14 it is obvious that DCT and GAT are clearly correlated, which should be expected for two instruments claiming to measure the same parameter. We can also see the general deviation of DCT towards higher values, which is discussed above, as well as the distribution of results and the remarkable disagreement between DCT and GAT.

In order to illustrate the agreement between the two methods, a Bland-Altman analysis was performed. Figure 3.15 shows a mean difference of 2.34 mmHg between DCT and GAT, with a standard deviation of 2.49 mmHg. Considering the intra-observer variability of both methods and the assumed calibration difference, which will have to be studied in more detail, a mean deviation of 2.34 mmHg seems acceptable, although disagreement of >5 mmHg can be observed in a fair amount of measurements, as is seen in Fig. 3.15. For eyes with low IOP, DCT readings are considerably higher than GAT results, whereas this effect is reduced and inverted with increasing IOP.

Hence, the question arises as to whether this results from underestimation of IOP by GAT in eyes with thin corneae; therefore, GAT measurements were adjusted for CCT (Fig. 3.16). This transformation results in a lower standard deviation of 2.19 mmHg, indicating a higher agreement between GAT and DCT; however, there is still remarkable disagreement between the two instruments which cannot be explained by the effect of CCT on GAT alone. The influence of other factors, such as corneal rigidity, has to be taken into consideration.

The effect of different amounts of disagreement for different IOP levels is also reduced after adjustment for CCT, but can still be observed.

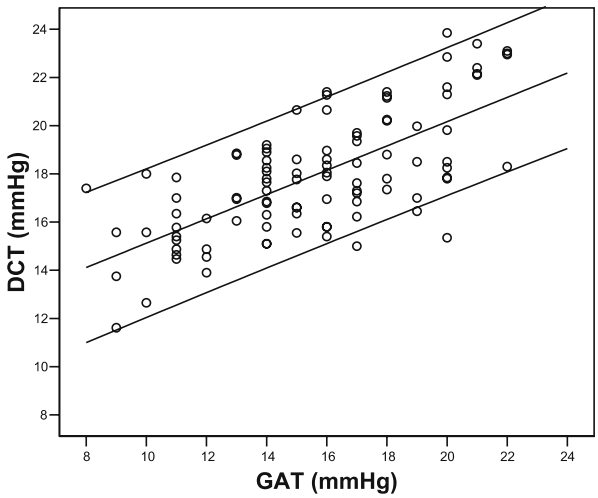

Fig. 3.14
Pearson correlation of IOP measurements obtained by Goldmann and Pascal tonometer (R=0.693, P=0.000). *Diagonal lines* represent the 95% prediction intervals.

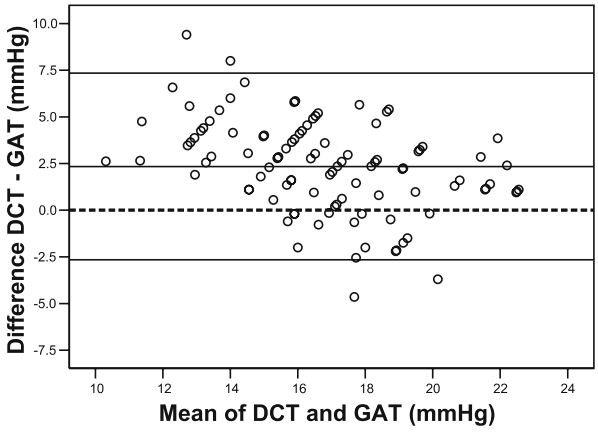

Fig. 3.15
Bland-Altmann graph, not adjusted for CCT. The mean difference between DCT and GAT is + 2.34 (± 2.49 SD). In cases with low IOP, DCT tends to result in markedly higher results than GAT. With increasing IOP, this effect is reduced and finally inversed.

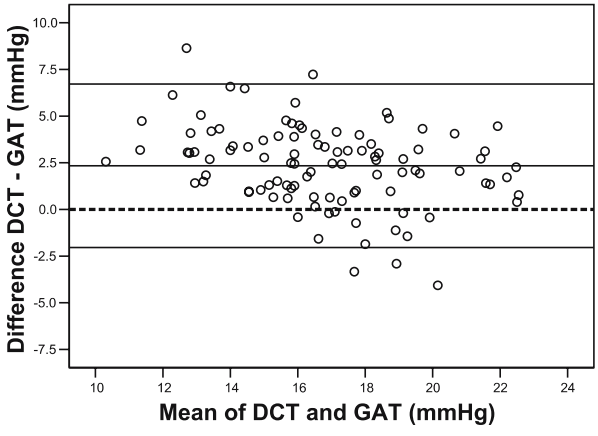

Fig. 3.16
Bland-Altman graph, adjusted for CCT. Correction of GAT measurements for CCT results in better agreement between the two measurements (2.19 SD) and reduces the difference in agreement for different IOP levels.

One explanation could be a possible tendency of DCT to equalize low and high IOP measurements.

The usefulness of both techniques in clinical practice is of considerable interest. For DCT, the tonometer tip has to be positioned on the patient's cornea for at least 4–5 s. If the patient is not able to prevent eye movements during that time, IOP measurement is disturbed, resulting in lower reading quality. In nine patients with poor fixation of the contralateral eye, nystagmus, or lack of cooperation, repeated DCT measurements could not achieve a better quality than Q4–Q5, and hence reliable DCT readings could not be achieved. On the other hand, GAT allows reliable and reproducible estimation of IOP by experienced examiners, even in difficult cases; therefore, DCT seems to be advantageous for cooperative patients with sufficient ocular fixation, especially post-LASIK patients with altered corneal properties.

No information is yet available on the usefulness of DCT in cases with corneal disease such as keratokonus, scarred corneas, corneal edema, or congenital glaucoma. In these cases, GAT usually results in unreliable measurements [19, 20]. A correlation to direct anterior chamber IOP measurements should be achieved to validate DCT in these special situations.

Comparison of DCT and GAT measurements to direct anterior chamber IOP measurements will also carry on the observations and conclusions obtained from this study. The difference in measurement results between the two instruments as a possible consequence of difference in calibration, of disagreement due to the influence of CCT, and other possible, yet still undefined, corneal properties, and the varying amount of disagreement at different IOP levels, need further investigation. Intracameral IOP measurements will be useful to find out which of both techniques comes closer to the measurement of "true" IOP.

For clinical use, the influence of CCT on GAT readings and the deviation of DCT towards higher IOP reading should be considered. In summary, DCT seems to provide a method of measuring IOP independent of central corneal thickness.

Summary for the Clinician

- Dynamic contour tonometry is a valuable method of measuring IOP independent of corneal parameters. Its clinical applicability has been proven by the development of the PASCAL tonometer. The present advantages over Goldmann applanation tonometry are IOP readings in corneas with major deviations of corneal thickness, and especially in LASIK eyes. The assessment of DCT in corneal diseases, such as keratokonus or corneal scars, and in childhood glaucoma, still needs further investigation.

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Chapter 4

Effect of Corneal Thickness on Applanation Tonometry, Pneumotonometry, and Tonopen Measurements

4

Lutz E. Pillunat, Markus Kohlhaas, Andreas G. Böhm, Eberhard Spoerl

Core Messages

- Goldmann applanation tonometry depends significantly on corneal thickness. By setting 550 µm as a mean for corneal thickness, a correction factor for every 20 µm should be applied, i.e., a correction factor of 1 mmHg/20 µm
- Goldmann applanation tonometry does not depend on corneal curvature or axial length.
- Pneumotonometer readings are inaccurate compared with Goldmann applanation tonometry and depend on corneal curvature.
- Tonopen readings are inaccurate and are independent of corneal thickness, axial length, and corneal curvature.

4.1 Influencing Factors in Applanation Tonometry

Intraocular pressure (IOP) represents a fundamental parameter for ocular health and disease. Intraocular pressure is not only important in the diagnosis and management of glaucoma, but also in the assessment of the postoperative course of all intraocular surgical interventions. For almost 50 years applanation tonometry, according to Goldmann, represents the gold standard for the evaluation of IOP [7, 8].

It has been reported that IOP measurements using the Goldmann applanation tonometer are affected by corneal thickness, corneal curvature, and axial length [16, 17]. Normally hydrated, thicker corneas lead to higher readings and thinner corneas to lower readings. The clinical significance of these observations has been demonstrated in studies which have shown a lower corneal thickness in some cases of normal-tension glaucoma and a higher corneal thickness in ocular hypertension and some refractory glaucoma cases [1–4].

Empirical studies suggest a correction factor for applanation IOP readings of 0.19–1 mmHg per 10-µm deviation from the average corneal thickness [2, 3, 13–15]. Those studies were based on comparisons of individuals and groups of patients with different corneal thicknesses without knowledge of the real IOP. There has been only one paper, published by Ehlers, using a manometric controlled closed system where the actual IOP was known. However, this work was done only in a small series of eyes; therefore, the aim of the present study was to examine the effect of corneal thickness, corneal curvature, and axial length on Goldmann applanation tonometry, pneumotonometry, and tonopen in a manometric controlled closed system in an in vivo model with larger subject numbers of patients.

4.2 Approach to a Clinical Study

In a masked prospective clinical trial 125 eyes of 125 consecutive patients scheduled for cataract surgery were examined. Thirty-three patients were men and 92 women, with a mean age of

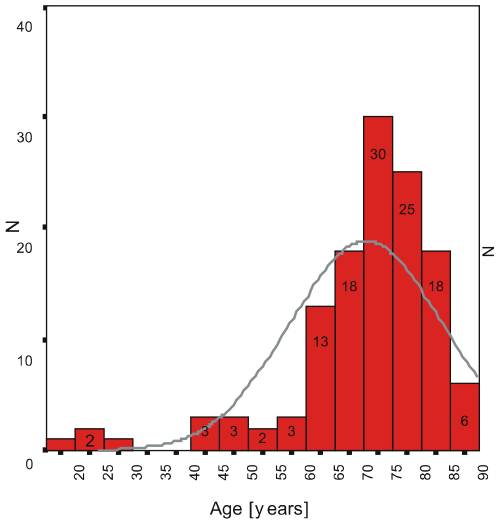

Fig. 4.1 Distribution of age ($n = 125$) (according [9])

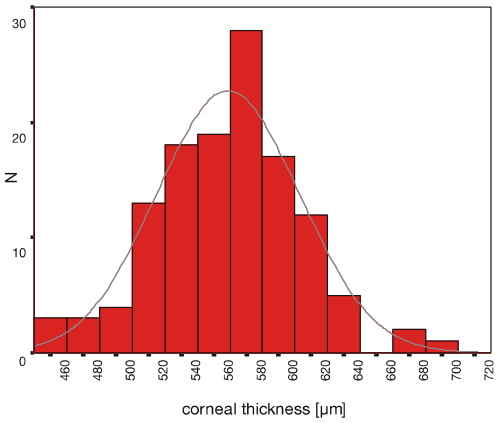

Fig. 4.2 Distribution of central corneal thickness ($n = 125$) (according [9])

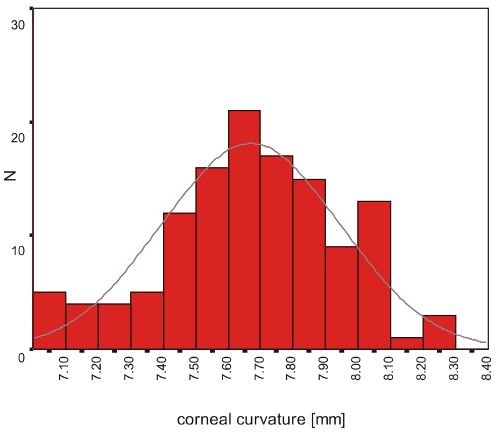

Fig. 4.3 Distribution of corneal curvature ($n = 125$) (according [9])

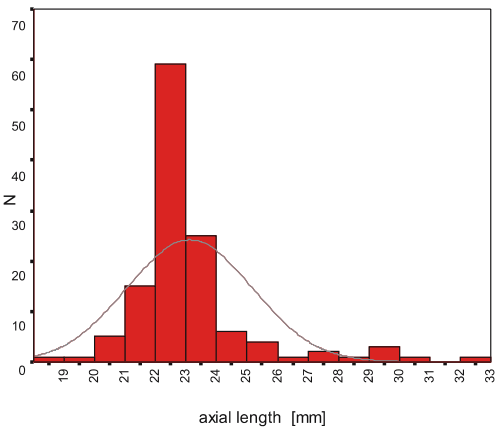

Fig. 4.4 Distribution of axial length ($n = 125$) (according [9])

72.9 ± 13.2 years (age range 18–91 years; Fig. 4.1). No eye had previous intraocular surgery or had a pathology other than cataract. All subjects received an ophthalmological clinical exam including evaluation of the anterior segment with a slit lamp. Patients with any corneal abnormality, e.g., scars or Fuchs dystrophy, were excluded.

All patients signed an informed consent before entering the study. The study was approved by the institutional ethics committee of the medical department of the University of Dresden.

Preoperatively keratometry was performed using the "Zeiss" keratometer and the axial length was measured by A-scan ultrasonography (Sonomed 2500, Technomed). After peribulbar anesthesia an eyelid retractor was placed and then a cannula was passed into the anterior chamber at the temporal limbus. The central corneal thickness was measured by the first investigator using the ultrasonic pachymeter DGH-500 Pachette. Then the opening of the cannula of 0.8 mm permitted access to the aqueous humor. The cannula

was connected to an adjustable saline (BSS) reservoir. The IOP was directly calibrated by a water column at three different IOP levels (20, 35, and 50 mmHg). After each IOP level was reached, the cannula was closed after 1 min to maintain a closed system during the actual IOP measurements. The precorneal film was stained with fluorescein solution and IOP was measured with the Perkins applanation tonometer, by pneumotonometry and tonopen, in a randomized fashion at each IOP level by the second investigator. To maintain masking, the first investigator measured the central corneal thickness and the second investigator measured the IOP without knowing the corneal thickness. All parameters (IOP, corneal curvature, axial length, and corneal thickness) were measured three times and means were calculated.

For statistical analysis single and multiple linear regression analysis was performed using SPSS 11.0 (SAS Institute, Chicago, Ill.). Significance levels were evaluated by the Student's *t*-test.

4.3 Results of a Clinical Study

Mean central corneal thickness was 569 ± 44 µm (mean ± standard deviation) ranging from 462 to 705 µm (Fig. 4.2), corneal curvature was 7.72 ± 0.27 mm (range 7.07–8.32 mm; Fig. 4.3), and axial length was 23.62 ± 2.05 mm (range 18.84–32.93 mm), respectively (Fig. 4.4).

In applanation tonometry at 20 mmHg the IOP readings varied from 16 to 27 mmHg (mean 20.86 ± 1.99 mmHg), at 35 mmHg from 31 to 42 mmHg (mean 35.74 ± 1.97 mmHg), and at 50 mmHg from 45 to 55 mmHg (mean 50.5 ± 2.01 mmHg). There was a strong correlation between IOP and corneal thickness at all IOP levels: at 20 mmHg ($r^2 = 0.831$; $p < 0.0001$); at 35 mmHg ($r^2 = 0.783$; $p < 0.0001$); and at 50 mmHg ($r^2 = 0.753$; $p < 0.0001$). In tonopen readings there was a significant offset of the measurements at 20 mmHg by – 3.6 mmHg – i.e., the mean measured IOP was 16.4 mmHg ($p < 0.001$). There was no correlation between corneal thickness and IOP readings at all IOP levels. In pneumotonometry there was a significant offset of 4.6 mmHg, i.e., the measured IOP at the IOP level of 20 mmHg was 15.4 mmHg ($p < 0.001$). There was no significant correlation between IOP readings and corneal thickness.

In applanation tonometry there was no correlation between IOP and corneal curvature at 20 mmHg ($r^2 = 0.12$; $p = 0.407$), at 35 mmHg ($r^2 = 0.18$; $p = 0.336$), and at 50 mmHg ($r^2 = 0.09$; $p = 0.869$), and no correlation between IOP and axial length at 20 mmHg ($r^2 = 0.09$; $p = 0.659$), at 35 mmHg ($r^2 = 0.09$; $p = 0.862$), and at 50 mmHg ($r^2 = 0.08$; $p = 0.347$). The tonopen readings were independent of corneal curvature, but in pneumotonometry there was a significant correlation at all IOP levels with corneal curvature ($p < 0.008$) at all IOP levels.

The correlations in applanation measurements between IOP and corneal thickness, corneal curvature, and axial length are shown exemplarily in Figs. 4.5, 4.6, and 4.7 for the level of 35 mmHg. The correlation between corneal thickness and the difference between real IOP and IOP measured by applanation tonometry at 35 mmHg is shown in Fig. 4.8.

Regression analysis showed similar equations describing the relationship between IOP and central corneal thickness (CCT) for the three different IOP levels. Implementing the data of all three different IOP levels (20, 35, and 50 mmHg) regression analysis revealed the equa-

Table 4.1 The Dresdner correction table shows the dependence of the applanation intraocular pressure reading on corneal thickness in applanation tonometry [9]

Corneal thickness (µm)	Correction value (mmHg)
475	+3.19
500	+2.13
525	+1.07
550	0.02
575	–1.04
600	–2.10
625	–3.16
650	–4.21
675	–5.27
700	–6.33

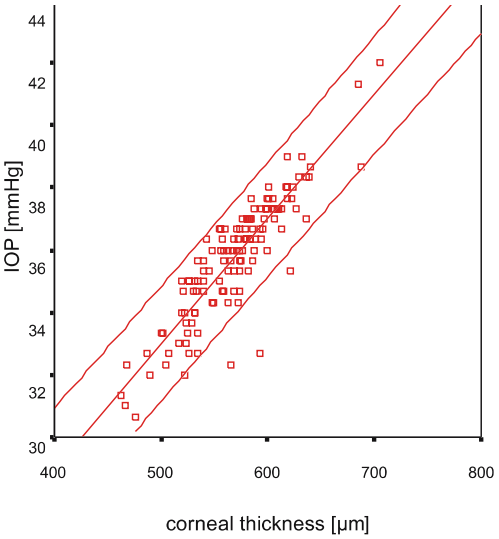

Fig. 4.5 Correlation between central corneal thickness and intraocular pressure using applanation tonometry at a preset IOP level of 35mmHG (regression line and 95% confidence interval, $n = 125$) in applanation tonometry

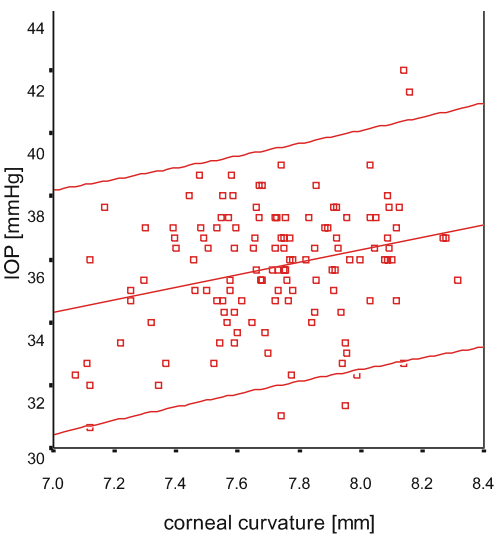

Fig. 4.6 Association between corneal curvature and intraocular pressure (regression line and 95% confidence interval, $n = 125$) in applanation tonometry at a preset IOP level of 35mmHG

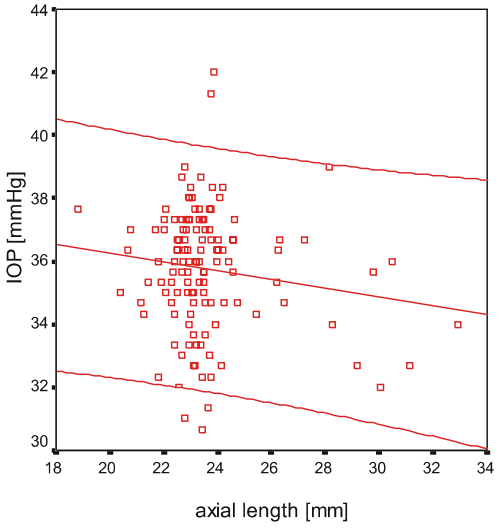

Fig. 4.7 Association between axial length and intraocular pressure (regression line and 95% confidence interval, $n = 125$) in applanation tonometry at a preset IOP level of 35mmHG

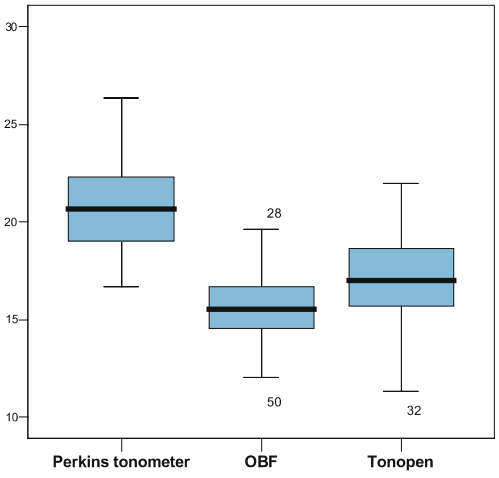

Fig. 4.8 Intraocular pressure measurements with three different tonometers at an IOP level of 20 mmHg. Pneumotonometry (*OBF*) and Tonopen showed a significant offset from "true" IOP.

tion $\Delta IOP = (-0.0423 \times CCT) + 23.28$. All four equations are shown in Fig. 4.9. Using the latter equation, correction values for applanation IOP readings were calculated for different corneal thicknesses Table 4.1). Using this equation ΔIOP is 0 at a central corneal thickness of 550 µm.

A deviation of ± 10 µm from a central corneal thickness of 550 µm resulted in a measurement error of ± 0.4 mmHg. In other words, a deviation of ± 25-µm corneal thickness from 550 µm was related to a difference of approximately ± 1 mmHg.

4.4 Pitfalls and Solutions for Tonometric Measurements

The IOP measurements by applanation tonometry were linearly correlated to central corneal thickness at different IOP levels. There was no correlation between IOP readings and corneal curvature and axial length. To our knowledge, the present study is the largest study proving the correlation between IOP readings obtained by applanation tonometry and corneal thickness using an in vivo model where the real IOP was known and the actual deviation could be measured.

There have been various studies examining the correlation between IOP readings by applanation tonometry and corneal thickness. Over all reported studies the measurement error ranged from 0.19 to 1 mmHg per 10-µm deviation from the average corneal thickness [2, 3, 13–15, 17]. In the present study the measurement error was 0.4 mmHg per 10 µm from 550 µm. In contrast to the present study, those studies used previously classified eyes as normal or ocular hypertensive based on IOP readings. A proportion of the ocular hypertensive eyes might actually have a normal IOP but a false-high IOP reading due to a thick cornea. This might lead to an underestimation of the effect of corneal thickness on IOP measurement and might be responsible for the discrepancy between population studies and our results. The scattering in tonopen readings and in pneumotonometric measurements was higher and therefore there was a lack in accuracy of the measurements resulting in a remarkable offset from the true IOP. Tonopen readings, however, seem to be independent from corneal curvature, axial length, and CCT, but the measurements are not more than an estimate.

In a study performed by Ehlers et al. a manometric controlled closed system was used to examine the correlation between corneal thickness and IOP measured by applanation tonometry. Those experiments were performed in a small number of 29 patients [5]. Ehlers reported an error between real IOP and IOP measured by applanation tonometry of ± 0.71 mmHg per 10-µm difference in corneal thickness. In comparison with Ehlers data we obtained a smaller correction factor with ± 0.4 mmHg per 10 µm. This difference between the studies might be caused by the different sample sizes (29 vs 125) and the fact that, in contrast to our study, in Ehlers study corneal curvature effected IOP readings. Another important difference between both studies seems to be that in Ehlers study the real IOP and the measured IOP were the same at a thickness of 520 µm, in our study at a thickness of 550 µm. This is an offset of 30 µm between both studies, which is most likely caused by the use of different techniques for the measurement of corneal thickness. Ehlers used an optical pachymeter, which provides lower readings compared with ultrasound pachymetry, which was used in the present study.

In a paper by Orssengo and Pye a mathematical model examining the influence of corneal properties on the measurements of IOP obtained by applanation tonometry was presented [12]. Their calculations were based on a normal corneal thickness of 520 µm. Using their model they reported good agreement with Ehlers data; however, at lower IOP levels the calculated model showed lower correction values compared with Ehlers reported results, suggesting that the correction factor obtained by Ehlers data is too high. This seems to be in good agreement with our results. Besides these differences, the problem of inaccurate applanation readings might be much more complex.

Another attempt of in vivo measurements with direct intracameral IOP readings was performed by Feltgen and coworkers. In their study no correlation between corneal thickness and IOP readings was observed. They concluded that no recalculation of IOP according to corneal

thickness was necessary [6]; however, in contrast to Ehlers study and to the present study, they used an open system, not a closed system. As an open system allows the aqueous humor to leave the eye, the IOP is lowered during the measurement. This might explain the difference between their results and the results of Ehlers and the present study.

In contrast to other studies, we could not detect an effect of corneal curvature and axial length on applanation IOP readings [1, 2, 15, 18]. In our series we examined consecutive patients scheduled for cataract surgery; therefore, the distribution of corneal curvature, corneal thickness, and axial length was random and not influenced by the investigators. Compared with other empirical studies by Mark et al. [11] and Mark [10], our study population showed not a wide scattering of corneal curvature (7.07–8.32 mm) with a mean ± standard deviation of 7.72 ± 0.27 mm and axial length (18.84–32.93 mm) with 23.62 ± 2.05 mm, respectively. It is possible that this distribution might have caused the lack of correlation between IOP readings and corneal curvature and axial length; therefore, a study with a similar design with a wider scattering of these parameters seems to be necessary to answer the question as to whether corneal curvature or axial length might have an effect on IOP measurements obtained by applanation tonometry; however, according to our data, even if there is an effect of corneal curvature and axial length on applanation IOP readings, which was not detected by our study, the effect should be minimal in comparison with corneal thickness. On the other hand, the distribution was spread enough to find a significant correlation between pneumotonometer (OBF) readings and corneal curvature.

The mean corneal thickness in our study with 569 ± 44 µm (range 462–705 µm) was higher compared with previously reported mean corneal thicknesses in the general population [13, 18]. Dependent on the technique used, mean corneal thickness has been reported to be 530 ± 29 µm for optical pachymetry and 544 ± 34 µm for ultrasound pachymetry [3]. As mentioned previously, we used ultrasound pachymetry to determine the corneal thickness, which reveals higher readings as optic pachymetry. Additionally, the mean age of our study population was high, with 72.9 ± 13.2 years, and it is known that corneal thickness tends to be higher in older patients [17].

4.5 Conclusion

In conclusion, the present study demonstrates that thin corneas lead to an underestimation and thick corneas to an overestimation of applanation IOP. Corneal curvature and axial length do not have a significant effect on IOP readings obtained by applanation tonometry. A deviation of 25 µm in corneal thickness from 550 µm results in a difference of 1 mmHg between real IOP and measured IOP by applanation tonometry. As corneal thickness affects IOP readings obtained by applanation tonometry, we suggest for the time being that IOP readings be corrected by corneal thickness according to the "Dresdner correction table" to get a good approximation of the real IOP value in each given patient (Table 4.1). In recent studies there were hints that the rigidity of the whole eye might be of importance for calculating or measuring IOP. Furthermore, a new instrument, the Pascal contour tonometer, seems to measure IOP independently from corneal thickness. But as long as these tonometers are not evaluated and widely spread, Goldmann applanation tonometry will be the worldwide standard for the future. Therefore, the Dresden correction table gives valuable assistance for calculating the true IOP; however, further studies are needed to validate the scale and demonstrate its value for the management of glaucoma.

Summary for the Clinician

- Experimental studies were performed in order to evaluate the effect of corneal thickness on applanation tonometry, on tonopen readings, and on pneumotonometry in an in vivo study. In a masked prospective clinical trial 125 eyes of 125 patients undergoing phacoemulsification were examined. Corneal curvature was measured by Zeiss keratometry and axial length by ultrasound pachymetry. By cannulating the anterior chamber prior to surgery, IOP was set to 20, 35, and 50 mmHg in a closed system by water column. After measuring the corneal thickness, IOP was taken with the Perkins applanation tonometer, the pneumotonometer (OBF), and the tonopen in a randomized order. For statistic analysis single and multiple linear-regression analysis was performed using SPSS 11.0. Significance levels were evaluated by the Student's *t*-test.
- The difference between measured and real IOP was significantly dependent ($p < 0.0001$) on corneal thickness in applanation tonometry. The association between IOP and corneal curvature or axial length was not statistically significant ($p > 0.05$). The pneumotonometric measurements were significantly correlated with corneal curvature ($p < 0.08$) but not correlated with corneal thickness. Tonopen readings were independent of corneal curvature, axial length, and corneal thickness. Tonopen readings and OBF readings, however, delivered inaccurate readings compared with the Goldmann data when compared with the real IOP.
- Corneal thickness significantly affects IOP readings taken by applanation tonometry according to Goldmann's principle. A correction of IOP readings by corneal thickness according to the Dresdner correction table might be helpful to get a better idea of the real IOP value. Tonopen readings were independent of corneal properties but showed a high measurement offset, which was also true for OBF readings.

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Chapter 5

Electrophysiology in the Diagnosis of Glaucoma

5

Thomas Meigen and Michael Bach

Core Messages

- Among the electrophysiological procedures in ophthalmology, pattern ERG (PERG) recordings are the most useful test for an early detection of glaucoma at this time.
- PERGs are recorded in response to contrast-reversing checkerboard patterns. In early stages of glaucoma steady-state PERGs to checkerboard patterns with small check sizes (around 0.8°) are preferentially reduced in amplitude.
- Due to a sizeable interindividual amplitude variability, this amplitude change in glaucoma is best assessed by a PERG ratio, where the PERG amplitude to small checks is normalized by the PERG amplitude to large checks in the same patient.
- In a prospective study the PERG ratio was shown to identify eyes at risk before manifest field damage; thus, PERG recordings under appropriate recording conditions may help to identify patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur.
- A selective stimulation of ganglion cells in the magnocellular stream of the visual system seems less promising, as earlier hypotheses about a preferential damage of magnocellular ganglion cells in earlier stages of glaucoma could not be validated.
- Recently, new methods to study the effect of glaucomatous ganglion cell damage on cortical potentials (VEPs) have been presented that may improve the early detection (S-cone VEP) and the follow-up of glaucoma (mfVEP) in the future.

5.1 Introduction

5.1.1 Glaucomatous Damage of Ganglion Cells

Ganglion cells are inner retinal neurons that receive inputs from bipolar and amacrine cells and that subserve the transmission of visual information via the optic nerve to the visual cortex. It is known that ganglion cell death in glaucoma is a multi-factorial mechanism of apoptosis [20]; however, it is still unknown how the different factors (e.g., mechanical compression by elevated intraocular pressure, vascular dysfunction, or neurotrophic deprivation) interact in the manifestation of glaucomatous atrophy of ganglion cells. Significant loss of ganglion cells will inevitably result in visual disability; however, there is built-in redundancy within the visual system, so that a larger number of neurons can be lost without becoming manifest on standard tests of visual function. Approximately 25–30% of the ganglion cell fibers can be lost before significant visual field defects are observed [52]; thus, an early detection of glaucoma is complicated by the fact that no visual impairment is perceived by the patients in this early stage.

The search for an early indicator for glaucomatous damage to the ganglion cells was inspired for several years by the dichotomy of magnocellular and parvocellular streams within the visual system [61, 62]. These two sub-systems can be activated selectively by appropriate visual stimuli, e.g., motion stimuli are processed by the magnocellular system, while isoluminant stimuli with a color contrast but no luminance contrast are processed by the parvocellular system [61, 62]. These sub-divisions of the visual system became relevant for glaucoma diagnosis after Quigley et al. [83] described that large nerve fibers of the magnocellular stream are preferentially damaged in early glaucoma. For more than a decade,

research on early diagnosis was dominated by this „magnocellular damage paradigm." Meanwhile, this paradigm had been challenged by new experimental data and there is evidence that magnocellular damage in early glaucoma is only marginally greater – if at all – than parvocellular damage. Crawford et al. [26] quantified the effect of experimental glaucoma in monkeys by the reduction in metabolic drive as indicated by cytochrome oxidase histochemistry. The detrimental effect of experimental glaucoma did not appear to be any greater for the magnocellular system than for the parvocellular system in the LGN or in the visual cortex. Yücel et al. [103] quantified LGN nerve fiber loss in a primate glaucoma model and reported that neurons in the parvocellular layers undergo even more shrinkage than neurons in magnocellular layers. Recently, Spry et al. [88] compared a variety of psychophysical tests to evaluate ganglion cell loss in early glaucoma. They stress the importance of ganglion cell sub-populations with lower levels of redundancy for the explanation of early ganglion cell loss in glaucoma. Moreover, the deficits in blue–yellow color perception as exploited by short-wavelength perimetry in early glaucoma [84] cannot be explained with a preferential damage of the „color-blind" magnocellular subsystem.

Summary for the Clinician

- Approximately 25–30% of the ganglion cell fibers can be lost before significant visual field defects are observed.
- A „preferential magnocellular damage" can no longer be used as a model for the pathological changes in early glaucoma.

5.1.2 The Importance of Early Detection of Glaucoma

Elevated intraocular pressure (IOP) is a well-known risk factor for glaucoma that had once been used as a synonym for glaucoma but had been out of focus during the past decade due to a concentration on molecular mechanisms, genetical risk factors, and neuroprotective strategies in basic research. Recently, two clinical studies have demonstrated the importance of an elevated IOP on the progression of glaucoma.

The Early Manifest Glaucoma Trial (EMGT) was designed to determine the efficacy of IOP lowering by a combination of betaxolol therapy and argon laser trabeculoplasty in subjects with documented glaucomatous damage [35]. The EMGT confirmed the role of IOP as a major risk factor and showed that each mmHg of IOP lowering was associated with an approximate 10% decrease in risk of glaucoma progression. The Ocular Hypertension Treatment Study (OHTS) tested patients with an elevated IOP between 24 and 32 mmHg in at least one eye, but normal visual fields and normal optic nerves [51]. Patients with IOP lowering of 20% below baseline and less than 24 mmHg were less likely to convert to glaucoma over 5 years (4.4 %) than patients without treatment (9.5%); thus, an early identification of patients at risk is essential to delay glaucoma progression.

For a patient with an elevated IOP of 25 mmHg the risk to develop manifest glaucoma is only about 1% per year; however, a comparison of different studies shows a large variation between 0.4% and 17.4% for this percentage, probably due to differing study populations with different risk factors or degrees of pressure elevation [4, 33, 48, 78, 99]. One important confounding factor for a closer correlation of IOP and glaucomatous progression is the central corneal thickness, which can affect IOP measurement by Goldmann applanation tonometry. The Ocular Hypertension Treatment Study (OHTS) verified within their pool of 1636 subjects that an increased central corneal thickness was more common among patients with ocular hypertension (OHT) [23]. The OHTS data suggest that many OHT patients may have little more than thickened corneas that result in their misclassification on the basis of Goldmann tonometry. This finding demonstrates the importance of identifying glaucomatous damage to the ganglion cells at an early stage, before irreversible retinal damage and visual field loss has occurred, while sparing patients who have „just" an elevated IOP or a thickened cornea. There exist well-developed psychophysical and morphological techniques

Table 5.1 Electrophysiological techniques for glaucoma management

Method	Abbreviation	Useful in glaucoma	Comment
Electroretinogram	ERG	Standard paradigm: No PhNR: Possibly	Useful in detecting retinal diseases
Electrooculogram	EOG	No	Function of the pigment epithelium
Multifocal ERG	mfERG	Standard paradigm: No Specialized paradigms: Possibly	Useful in detecting localized retinal damage
Pattern ERG	PERG	Yes	Early indicator of glaucoma damage
Visual evoked potential	VEP	Standard paradigm: No S-cone VEP: Possibly	Function of the entire visual pathway, dominated by the center
Multifocal VEP	mfVEP	Possibly	Promise of objective perimetry

to monitor the course of glaucoma to assess therapeutic efficacy, but early detection could well profit from electrophysiological techniques, as will be seen.

Summary for the Clinician

- Recently, two clinical studies have demonstrated the importance of an elevated intraocular pressure on the progression of glaucoma.
- The large proportion of patients with ocular hypertension that will never develop glaucoma demonstrates the need to identify those eyes at risk before irreversible retinal damage and visual field loss has occurred.

5.1.3 Electrophysiological Procedures in Ophthalmology

Electrophysiological procedures allow a recording of surface potentials that are generated by the neurons of the visual system in response to flash and pattern stimuli. Compared with imaging techniques in ophthalmology (e.g., optical coherence tomography, fluorescein angiography, or ultrasound sonography), the electrophysiological methods are *functional* tests, as the evoked surface potentials are by-products of signal processing within the visual pathway. Compared with psychophysical procedures in ophthalmology (e.g., perimetry, visual acuity testing, or color vision testing) the electrophysiological methods allow an objective *localization* of functional deficits, as the type of the recording enhances the contribution of specific neurons along the visual pathway (e.g., photoreceptors, bipolar cells, ganglion cells, or optic nerve). During past decades a sophisticated framework of electrophysiological test procedures has been put forth for separate functional testing of the different neural structures along the visual pathway (Table 5.1). Although most of these procedures are not suited to detect glaucomatous damage of retinal ganglion cells (Table 5.1, third column), they play an important role in the differential diagnosis to exclude other disorders of the visual system (Table 5.1).

- The scotopic and photopic flash-ERG is driven by photoreceptors and bipolar cells and is used to diagnose diseases of the outer retina such as retinitis pigmentosa [66].
- The electro-oculogram (EOG) measures changes in the standing potential of the eye in a sequence of dark and light adaptation intervals and is a functional test of the retinal pigment epithelium, e.g., in Best's maculopathy [68].

- The pattern ERG (PERG) reflects ganglion cell activity and is an important tool to study pathological changes of the inner retina such as glaucoma [8].
- The visual evoked potential (VEP) is recorded over the occipital pole of the head and is used for functional testing of the optic nerve and the first processing steps within the visual cortex [73].

One of the most fascinating developments in the field of ophthalmological electrophysiology during the past decade was the introduction of multifocal recordings by Sutter [90] and Sutter and Tran [91]. This method allows a simultaneous recording of local ERG, PERG, and VEP responses from more than 100 regions within the visual field [67]. As multifocal recordings bridge the gap between standard electrophysiological procedures and perimetry, this method is often denoted as „objective perimetry".

However, neural responses to any stimulus are processed by all stages of the visual pathway from the photoreceptors to the visual cortex. This has four important implications for the electrophysiological diagnosis of glaucoma.

- The isolation of inner and outer retinal ERG contributions by applying flash and pattern stimuli is less complete than might be expected from the simplifying classification mentioned above, e.g., Viswanathan et al. [97] blocked the action potentials of retinal ganglion and amacrine cells and demonstrated that the photopic negative response (PhNR), a late component in the photopic fullfield flash-ERG around 90 ms, is generated by the inner retina. By applying this promising new PhNR technique, several groups found a reduction of the PhNR component in glaucoma patients [25, 27, 29, 98]. Since the currently available data on PhNR from different laboratories are somewhat conflicting, we do not cover the PhNR here.
- The PERG responses may be reduced as a consequence of photoreceptor or bipolar dysfunction, when ganglion cells do not receive an appropriate input; thus, the integrity of the earlier processing steps must be validated, e.g., by scotopic and photopic flash-ERG recordings or by multifocal ERG recordings (Table 1), before an abnormal PERG response can be traced back to a specific ganglion cell dysfunction.
- No pattern stimulus can be reversed in contrast without an associated local luminance modulation; thus, responses from luminance mechanisms within the outer retina may potentially be superimposed on pattern specific responses. This superposition of inner and outer retinal contributions in the processing of pattern stimuli led to controversies about the neural origin of the PERG.
- Ganglion cell activity generates the neural input for further processing along the visual pathway; thus, glaucomatous damage of ganglion cells may have a significant impact on VEP or multifocal VEP responses (Table 5.1). The advantage of using the VEP for glaucoma detection is that – in contrast to PERG recordings – no signal intrusion from luminance mechanisms of photoreceptors and bipolar cells is expected in cortical recordings; however, active VEP electrodes are placed over the occipital cortex in a larger distance to the pathological site of glaucoma-caused damage when compared with PERG electrodes.

In the following sections we review the current contributions of the different electrophysiological recording procedures to the early detection of glaucoma. We focus mainly on PERG data, where a glaucomatous damage of ganglion cells can be observed most directly. The reminder of the chapter summarizes glaucomatous changes to VEP and multifocal VEP (mfVEP) recordings.

Summary for the Clinician

- Ganglion cell function can be observed in pattern (PERG) recordings.
- Multifocal recordings bridge the gap between standard electrophysiological procedures and perimetry.

5.2 Early Detection of Glaucoma Using PERG Recordings

5.2.1 PERG Recordings

The PERG is recorded in response to contrast-reversing checkerboard patterns where the mean luminance is constant in time. The retinal potentials are recorded with corneal electrodes. Various types of electrodes may be used, such as gold

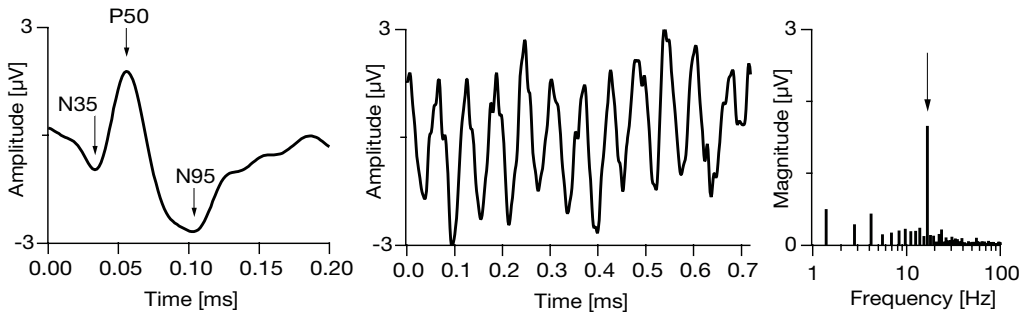

Fig. 5.1 Pattern ERG (PERG) waveform. **a** A transient PERG is obtained at slow stimulation rates. The waveform is characterized by a small negative component at approximately 35 ms (N35), followed by a larger positive component between 45 and 60 ms (P50) and a larger negative component at a 90–100 ms (N95). **b** At faster stimulation rates the so-called steady-state PERG is evoked. The waveform becomes roughly sinusoidal and Fourier analysis is required to determine the amplitude (right).

foil electrodes [1] or conductive fiber electrodes, like the DTL electrode [28]; however, it is important that the electrode does not degrade the optical image on the retina, as reduced retinal contrast leads to marked reduction of the PERG [36, 104]. With an appropriate technique, a high stability and reproducibility with an inter-session coefficient of variation down to 10% can be obtained [74]. A more detailed description of the PERG recording procedure can be found in the ISCEV standard [8].

With low temporal frequencies of less than 6 reversals per second (rps) a transient PERG is obtained (Fig. 5.1a). The waveform is characterized by a small negative component at approximately 35 ms (N35), followed by a larger positive component between 45 and 60 ms (P50) and a larger negative component at about 90–100 ms (N95). At higher temporal frequencies above 10 rps the successive waveforms overlap and the so-called steady-state PERG is evoked (Fig. 5.1b). The waveform becomes roughly sinusoidal and Fourier analysis is required to determine the amplitude and temporal phase shift relative to the stimulus [11].

5.2.2 Neural Origin of PERG Responses

The search for an electrophysiological indicator of glaucomatous damage is related to finding stimulus conditions that isolate signals from retinal ganglion cells, if possible without any intrusions from photoreceptor or bipolar cell activity. Meanwhile it has been validated that PERG recordings approach this optimum closely. The way in which this validation process was performed is an example for the cross-fertilization of basic research and clinical application that can be found in ophthalmological electrophysiology. The clinical diagnosis benefits from the development of new testing procedures, whereas the interpretation of the evoked responses has been clarified by specific changes under well-defined pathological conditions.

As each pattern reversal of a checkerboard is associated with local luminance increments and decrements, the outer retina adds to the activity of the inner retina during pattern stimulation, as was demonstrated by current source-density studies in cats and primates [17, 86, 106]. If the ERG would be a linear function of the stimulus intensity, the responses to luminance increments and decrements during a pattern stimulation would be exact mirror images and would cancel out; however, the ERG also contains nonlinear components [16, 24]. In addition, the PERG may contain lateral interaction components as bipolar cells, amacrine cells, and ganglion cells collect contrast information within their receptive field with center-surround antagonistic organization [57, 71].

The superposition of luminance specific and lateral interaction specific PERG components led to intense and controversial discussions about

the neural origin of the PERG. Spekreijse [87] found that the cortical VEP responses clearly depended on spatial contrast, whereas the retinal PERG responses seemed to be dominated by the luminance properties of the stimuli. The Arden group challenged this view and showed that a pattern specific subcomponent can be identified by applying extensive computer averaging and artifact rejection [2, 3].

A more pragmatic way to clarify whether the PERG is a veridical ganglion cell response is to monitor full-field flash-ERG changes and PERG changes after transection of the optic nerve. Maffei and Fiorentini [64], and Maffei and coworkers [65], demonstrated in cat and monkey that the PERG was progressively reduced at a rate consistent with ganglion cell degeneration, whereas the full-field flash ERG remained unchanged; however, differing results were found in pigeon, where a preservation of the P50 component of the PERG response was observed after transection of the optic nerve [21, 81]. In humans, only few PERG data of patients were reported where the completeness of a traumatic or surgical optic nerve section could be verified. Harrison et al. [34] reported one such case and found that the PERG response was reduced but not extinguished. In patients with optic nerve atrophy the degree of degeneration is difficult to quantify and the results of corresponding PERG studies were contradictory [2, 7, 30, 72, 85]. The most comprehensive reports on PERG abnormalities in patients with optic nerve diseases have been published by Holder [38–40]. Holder concluded that the N95 component of the transient PERG is generated by ganglion cells, whereas the P50 component reflects a mixture of inner and outer retinal contributions [39].

Summary for the Clinician

- Each pattern stimulus activates both inner and outer retinal neurons.
- Due to a close interaction of basic research and clinical application, it could be validated that PERG responses are generated by ganglion cells.

5.2.3 PERG Changes in Glaucoma

5.2.3.1 Historical Review

The first paper to report PERG recordings in a glaucoma patient was published by May et al. in 1982 [70]. In 1983 two papers appeared, one from Bobak et al. [22] and the first of Wanger and Persson's seminal work with 11 patients [101]. This was the starting point for a continuous stream of studies on PERG changes in glaucoma and ocular hypertension [5, 9, 14, 19, 31, 58, 63, 75, 77, 79, 80, 82, 93, 100, 102]. All but one of these papers report PERG amplitude reduction in glaucoma without significant effects on latency. The one exception is a study by van den Berg et al. [96], who did not find a correlation between visual field loss and PERG amplitude, which can in hindsight be understood as a consequence of the experimental design applied. In order to reduce interindividual variability the authors used the fellow eyes as reference; however, the incidence of glaucoma in the fellow eye of a glaucomatous eye is very high, and PERG reduction seems to precede obvious visual field loss. It is likely, therefore, that in van den Berg's study [96] PERG amplitudes were also reduced in the reference eye, thus eliminating differences during interocular comparison and leaving the effect of glaucoma on PERG amplitudes undetected.

5.2.3.2 Check-Size Specific Reduction

PERG to large stimulus checks is spared in early glaucoma. This is illustrated in Fig. 5.2, where recordings from a normal individual, a patient with early glaucoma, and a patient with advanced glaucoma are depicted [9]. In the left column, ERG responses to a flash stimulus show little change in glaucoma. In contrast, the PERG to small check sizes (0.8°, center column) is affected in early and late glaucoma, whereas the PERG to large stimulus checks (16°, right column) is relatively normal in early glaucoma, but markedly reduced in the advanced stage of the condition.

The check-size specific effect is shown in Fig. 5.3 in further detail. On the left, there are findings from 15 glaucoma eyes [9], whereas

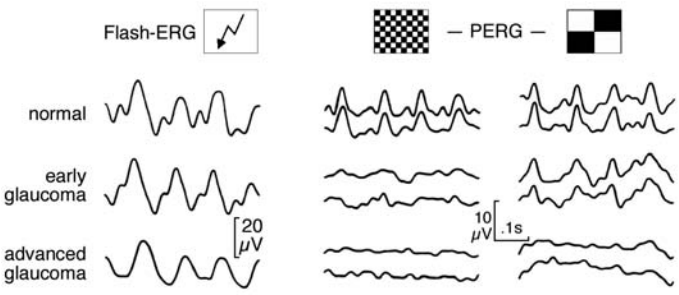

Fig. 5.2
ERG and PERG in glaucoma. The flash ERG (left column) is relatively little affected, even in advanced glaucoma. In early glaucoma (center row), there is a sizable reduction of the PERG to 0.8° checks and little reduction for 16° checks. In advanced glaucoma (bottom row), the PERG to any check size is reduced. (From [5], with permission, modified after [9])

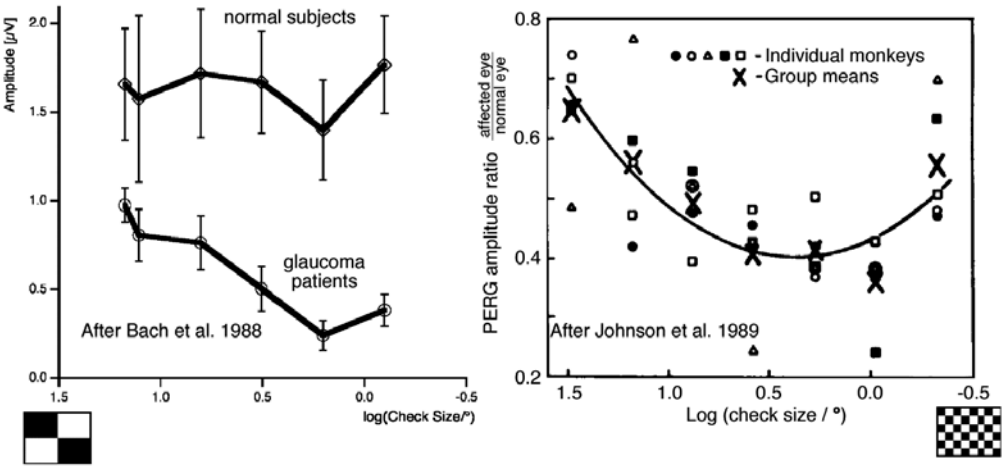

Fig. 5.3 Check-size-specific PERG changes in glaucoma. Left: human data from normal individuals and glaucoma patients (From [5], with permission, modified after [9]). Right: Non-human primates with experimentally induced glaucoma. (From [5], with permission, modified after [50])

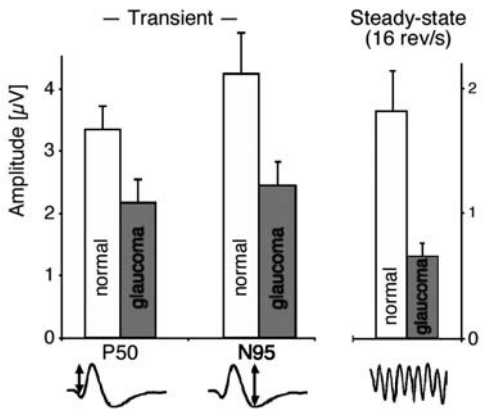

Fig. 5.4
P50 vs N95, transient vs steady-state stimulation with 0.8° checks in normal eyes (white bars) and glaucomatous eyes (gray bars). Transient stimulation (left two bar pairs) allows discrimination between the P50 and the N95 component. The relative effect of glaucoma is virtually identical. In steady-state stimulation at 16 rps (right bar pair) the relative glaucoma effect is most pronounced. (From [5], with permission)

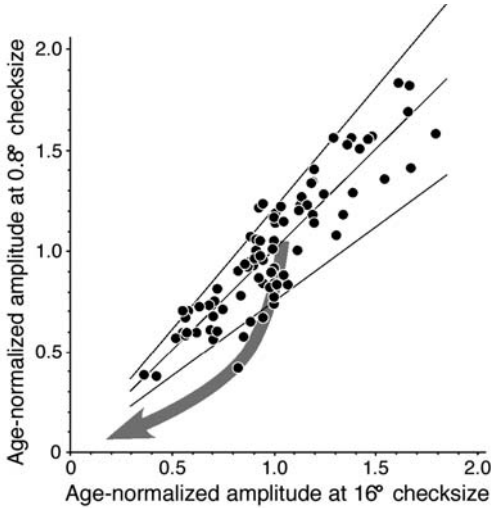

Fig. 5.5 PERG amplitudes to 0.8° checks vs amplitudes to 16° checks from 85 normal eyes. A wide scatter of amplitude between individuals is seen. The course of disease is likely to follow the arrow. (From [5], with permission)

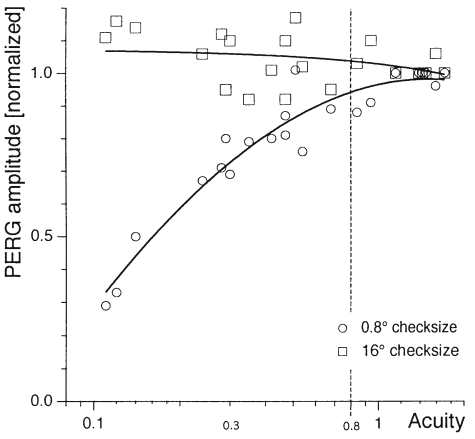

Fig. 5.6 Effects of dioptric defocus on the PERG amplitude in ten eyes of visually normal subjects either at best correction or with various values of defocus. Based on these findings, we only view PERG results in glaucoma as valid when the visual acuity is ≥ 0.8, as indicated by the dashed vertical line. (From [5], with permission)

results from experiments with experimentally induced glaucoma in monkeys are depicted on the right [50]. Both experiments show that the PERG to large checks is relatively little affected in early glaucoma, with increasing effect with decreasing check size. There is also an indication that with very small checks (< 0.5°) the glaucoma effects become smaller again as reported by Trick et al. [93]. These differential effects of check size have useful implications when using the PERG in early diagnosis of glaucoma, as is detailed in the following section.

5.2.3.3 P50 vs N95, Steady-State vs Transient Responses

In a group of 8 normal control eyes and 23 eyes of 12 glaucoma patients, the PERGs to transient stimulation and to steady-state stimulation were compared. Figure 5.4 shows that in the transient response, both the P50 and the N95 component were affected rather similarly by glaucoma. In contrast, the steady-state response is relatively much more affected by glaucoma, and rapid stimulation at 16 rev/s showed a much more pronounced amplitude reduction than did transient stimulation, when compared in the same glaucoma patients (right side of Fig. 5.4) [14]. When reversal rates become higher than 18 rev/s, returns are diminishing for normal/glaucoma discrimination in the PERG [37], probably because of decreasing signal-to-noise ratio.

These frequency-dependent effects have also been shown by Trick [92] and correspond well with psychophysical work that showed more glaucomatous effects at higher temporal frequencies [47, 59, 94]. Altogether, this evidence suggests that steady-state PERG recording at temporal frequencies between 10 and 20 rps is most efficacious to detect incipient glaucoma damage.

Summary for the Clinician

- Glaucomatous damage of ganglion cells leads to specific PERG changes (Table 5.1), mainly when PERGs are recorded with small check sizes (around 0.8°) and under rapid pattern-reversal conditions (“steady state”).

5.2.4 The "Freiburg" PERG Paradigm

5.2.4.1 Basic Paradigm

While the group differences in the PERG amplitude between normal controls and glaucoma patients are highly significant, it is still questionable whether a useful risk assessment can be performed on an individual basis. To tackle this problem, the Freiburg group arrived at the following paradigm: Firstly, steady-state stimulation of 16 rev/s is employed. This frequency is believed to be in the optimum range, because there is less glaucoma sensitivity at lower (e.g., 8 rev/s) and higher rates (e.g., 18 rev/s, probably because of decreasing signal/noise ratio, [14, 37]). The exact reversal rate also depends on the equipment, as aliasing by the frame rate of the stimulus monitor must be avoided [12].

Secondly, two check sizes, 0.8° and 16° were combined. This reduces the effect of interindividual variability (PERG amplitude varies by a factor of three between individuals). Recalling Fig. 5.3 we note that the PERGs to 0.8° checks are strongly affected by glaucoma, whereas the PERGs to 16° checks are not. Since the interindividual variability is multiplicative, such that an individual with a large 0.8° PERG will also have a large 16° PERG, it makes sense to compute the ratio as follows:

$$\text{PERG-ratio} = \frac{\text{PERG amplitude to 0.8° checks}}{\text{PERG amplitude to 16° checks}}$$

In Fig. 5.5 the scatter of a normal control population is seen (data extended from [7]). There is a high correlation between the amplitudes to 0.8° and 16° check size. In glaucoma, initially the 0.8° response is reduced, then later the 16° response. Consequently, an untreated or treatment-resistant glaucoma eye will likely follow the hypothetical curve indicated by the curved arrow in Fig. 5.5. A constant PERG ratio corresponds to the 45° line in Fig. 5.5. For individual diagnosis, the lower and upper lines indicate the 5 and 95% confidence interval for the PERG ratio, respectively. The PERGs from individual eyes that fall below the lower confidence line are at risk of developing glaucoma.

5.2.4.2 The Problem: Reduced Acuity

Any degradation of retinal imaging (e.g., cataract or defocus) leads to amplitude reduction [10]. Dioptric defocus is the more problematic case here, since it affects the PERG evoked by 0.8° checks and not the PERG evoked by 16° checks [9], thus changing the PERG ratio in the same manner as glaucoma would. This is illustrated in Fig. 5.6: Visual acuity was reduced by dioptrical defocus, covering a decimal acuity range from 0.1 to 1.6. Increasing defocus markedly reduces PERG amplitude when 0.8° checks are employed but has no significant effect with a 16° check size. Wide-angle scattering, as occurs with cataracts, also affects the 16° response, leading to less marked effects on the PERG ratio. The effects are easily understood when the low-pass nature of defocus and the PERG's linear contrast-amplitude characteristic are taken into account [36, 104].

To avoid false-positive results, the Freiburg group performs PERG glaucoma testing only on eyes with a visual acuity ≥ 0.8, tested at the PERG-stimulus distance of 57 cm with a semi-automatic procedure [6]. While optical correction can be optimized, many glaucoma patients have beginning media opacities, thus precluding PERG testing.

5.2.4.3 PERG in OHT: Longitudinal Studies

In order to test the utility of the PERG as an early glaucoma indicator, longitudinal studies have been performed to test whether the PERG identifies eyes with elevated IOP that later develop manifest glaucoma. There is a relative scarcity of such studies, largely due to the need of long-term investment of sizeable resources and the loss of patients to follow-up. In an early study, the Freiburg group addressed the problem by selecting high-risk eyes (e.g., glaucoma in the patient's other eye, family history) and recorded the history of 29 eyes in 18 individuals for 1–3 years [79]. Initially, in 12 of these eyes the PERG was abnormal, and 5 of these eyes did develop glaucomatous field defects. In contrast, none of the eyes with initially normal PERG developed glaucomatous field defects.

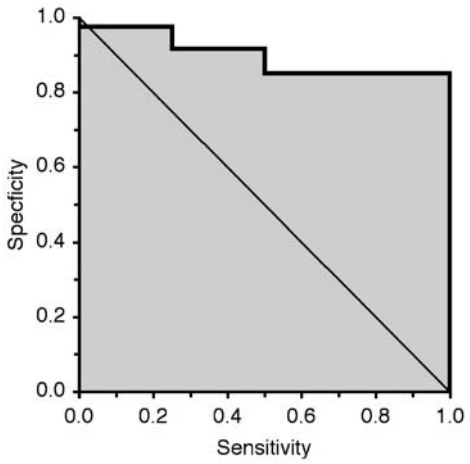

Fig. 5.7 Sensitivity/specificity analysis of the PERG as glaucoma predictor. The 4 of 124 eyes which did develop glaucoma define the "true-positive" cases. Only PERG measurements at the beginning of the longitudinal study are included in this figure. (From [5], with permission)

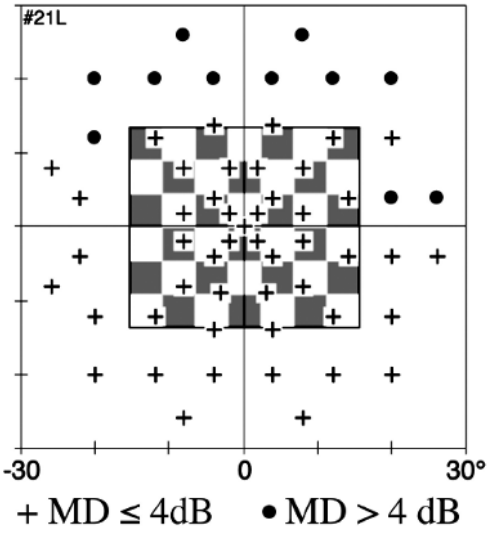

Fig. 5.8 A visual field from the left eye of a glaucoma patient. Black discs denote pathologic field locations with MD > 4 dB. The checkerboard pattern in the center represents the size of a typical PERG stimulus. Even though there is no field defect in the region covered by the PERG stimulus, the PERG response is often abnormal. This suggests that the PERG picks up non-focal damage in glaucoma. (From [5], with permission)

In a more recent prospective study [95], the Freiburg group recorded the history of 124 eyes of 67 patients with initial IOP > 24 mmHg and no apparent visual field damage for up to 8 years (mean follow-up time 5.9 years). Over this time, four eyes of four patients developed manifest glaucoma. This low incidence was expected, but made it difficult to assess the predictive value of the PERG. By varying the pathology threshold of the PERG ratio (defined above), the sensitivity and specificity of the technique can be compared. The sensitivity/specificity analysis (also known as receiver operating characteristics analysis) are shown in Fig. 5.7. For a sensitivity of 100%, there was a high specificity of 85%. While this may be a chance high value (only four true positives), the data suggest that the PERG is of value in defining eyes that are at higher risk of developing manifest glaucoma.

5.2.4.4 PERG May Reveal "Panretinal Ganglion Cell Damage" in Glaucoma

In hindsight it was unexpected for the PERG to detect glaucoma changes so effectively, considering that the stimulus covers only the central 15°, whereas early field defects arise typically in the more peripheral Bjerrum area. There was already indirect evidence that the PERG reflects diffuse, non-focal damage to the ganglion cells [13], but to test this more directly the Freiburg group looked at the PERG in eyes that had no field damage within the retinal area covered by the PERG stimulus. An example of such a field is seen in Fig. 5.8. In 13 of 18 such eyes (from 16 patients) with a normal field in the stimulated area, we obtained a pathological PERG [15]. This suggests that the PERG picks up a „panretinal" damage mechanism, which affects the ganglion cells before reliable field damage is observed. It is intriguing to investigate the spatial extent of the

glaucoma-induced PERG reduction with multifocal techniques, which allow one to record independent responses from a large number of visual field locations simultaneously. In general, this is an ambitious approach, as PERG amplitudes from a 15°×15° patch are already small, and will be further reduced if even smaller patches are used for stimulation; therefore, mfPERG studies are hampered by small responses and there are only three reports so far on mfPERGs and glaucoma [56, 60, 89]. These studies report, as expected, that mfPERG amplitudes are reduced in glaucoma patients and furthermore indicate that the PERG reduction does not appear to be in a topographical relationship to the visual field loss observed in these patients. While these data support the above interpretation that the PERG is affected „panretinally" in glaucoma, they also indicate that glaucoma detection does not benefit from the spatial resolution provided by the multifocal approach at the expense of reduced signal-to-noise ratio; therefore, while the mfPERG might have the potential to enhance our knowledge of the pathophysiology of glaucoma, we would at this time not consider it useful to aid in the early detection of glaucoma.

Summary for the Clinician

- In order to reduce the interindividual amplitude variability, a PERG ratio can be calculated where the PERG amplitude to small checks is divided by the PERG amplitude to large checks in the same patient.
- In a prospective study the PERG ratio was shown to identify eyes at risk before manifest field damage.
- As the PERG ratio is affected by visual acuity, the "Freiburg PERG-paradigm" can only be applied on eyes with a visual acuity ≥ 0.8.

5.3 VEP Recordings in Glaucoma

5.3.1 Conventional VEP Recordings in Glaucoma

Any neural signal that reaches the visual cortex must have passed the layer of ganglion cells in the retina; thus, cortical VEP recordings offer another electrophysiological test of ganglion cell function. In glaucoma patients a delayed latency and/or a reduced amplitude of the major positive VEP component near 100 ms (P100) were reported by different studies [22, 69, 76]. Parisi [76] performed a simultaneous recording of PERG and VEP responses from normal subjects, patients with primary open-angle glaucoma (POAG), and patients with ocular hypertension (OHT). Besides PERG amplitude changes, VEP amplitudes were significantly reduced in POAG eyes, whereas in OHT they were similar to controls. Moreover, the retino-cortical signal transmission time, as assessed by the difference between VEP and PERG latency, was longer in POAG patients and inversely related to PERG amplitude; thus, retinal ganglion cell degeneration is accompanied by a slowed signal transmission in the visual pathway that can be assessed by VEP recordings.

None of the above-mentioned VEP studies tested the prognostic value of VEP amplitudes and latencies for an early detection of glaucoma. Recently, a „blue-on-yellow" VEP method had been presented as a functional test of the blue-sensitive S-cone pathway [59] that may be used for early detection of glaucoma. This S-cone pathway is affected in glaucoma before standard subjective perimetry as has been shown by psychophysical findings [49, 88]. Horn et al. [46] recorded blue-on-yellow VEPs in a group of patients with pre-perimetric glaucoma and showed that VEP progression of glaucomatous optic nerve damage was associated with a significant prolongation of the VEP latency 2 years before morphological changes were evident.

The VEP recordings depend on both retinal activity and the neural conduction along the post-retinal visual pathway; thus, VEP amplitude and latency measures may be confounded by factors independent of glaucomatous damage of retinal ganglion cells. Parisi [77] compared PERG and VEP data with nerve fiber layer (NFL)

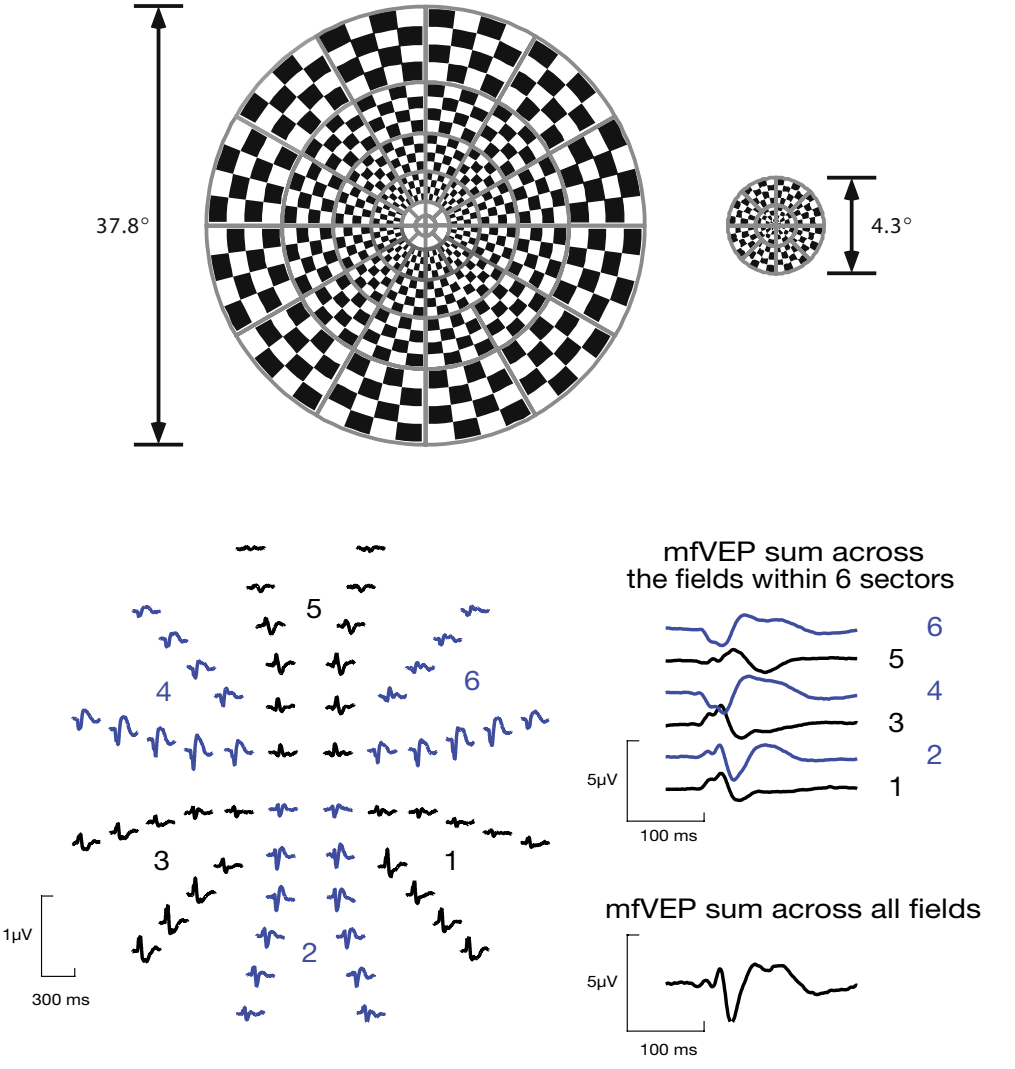

Fig. 5.9 Multifocal VEP (mfVEP) recordings. Top: "Dartboard" stimulus with 60 stimulus fields, each containing a checkerboard pattern that is reversed in contrast to evoke a local mfVEP for the corresponding part of the visual field. Bottom: Grand mean mfVEP traces across 30 visually normal subjects. The waveform of mfVEP traces varies very strongly which can be seen in the mfVEP sum across the stimulus fields in different sectors (1–6) of the visual field. The main reason for this variability is the individual folding of the cortical surface.

thickness data as assessed by optical coherence tomography in glaucoma patients. While amplitude and latency were abnormal for both PERG and VEP recordings, only PERG changes were correlated with NFL changes, whereas no correlations between NFL and VEP parameters were found.

Summary for the Clinician

- In glaucoma patients a delayed latency and/or a reduced amplitude of the major positive VEP component near 100 ms (P100) were reported by different studies.
- The "S-cone VEP" may help to improve the early diagnosis of glaucoma.

5.3.2 Multifocal VEP Recordings in Glaucoma

Baseler et al. [18] were the first to record a multifocal VEP (mfVEP). They scaled the size of local checkerboard patterns inversely to the cortical magnification factor for the corresponding eccentricity to activate a similar number of cortical neurons for all parts of the stimulated visual field. In contrast to multifocal ERG recordings the waveform of mfVEP traces varies very strongly even for normal subjects (Fig. 5.9). This variation can be found both when comparing different field locations in the same subject and when comparing the same field location between different subjects. The variation ranges from amplitude differences and inversions of polarity to nearly flat waveforms which might be misinterpreted as objective evidence for a scotoma [45, 55]. The main reason for this variability is the individual folding of the cortical surface as some cortical VEP generators may not project a signal onto a pair of recording electrodes, although visual function is normal in that part of the visual field. Consequently, a latency analysis is difficult in mfVEP recordings as a specific mfVEP peak (e.g., > 120 ms) may be interpreted as either a delayed component or a polarity-inversed component without increased latency.

During the past years many improvements have been introduced in the mfVEP recording and analysis procedures that helped to overcome the problem of interindividual variability and false scotomas. By performing multichannel recordings the chance to pick up a signal from at least one pair of electrodes can be increased significantly [44, 53]. An arrangement of several electrodes placed close (about 4 cm) to a common reference point near the inion has been shown to minimize the number of false scotomas. A reduction of mfVEP magnitude variability was achieved in different ways. Klistorner and Graham [54] found a correlation of mfVEP amplitudes and spontaneous EEG magnitudes and proposed the common shielding of intracortical mfVEP and EEG potentials as the source for this correlation. Klistorner and Graham [54] showed that the mfVEP can be normalized by the EEG magnitude which may reduce interindividual amplitude variability [54].

Hood et al. [43] presented a method to detect monocular scotomas by an interocular comparison of mfVEP responses within the same subject. As both eyes project to the same cortical surface, a flat mfVEP trace in one eye cannot be traced back to an unfavorable location of the generator when the stimulation of the other eye evokes a significant mfVEP for the same field. Of course, this methods fails if both eyes are involved in a pathological process. For the more general case of binocular involvement in glaucomatous defects Hood et al. [45] developed a method to detect mfVEP magnitude losses by analyzing the signal-to-noise ratio for each stimulus field which helps to avoid the misinterpretation of pure noise responses [105]. The calculation of the signal-to-noise ratios reduces interindividual variability in a similar way as the EEG-scaling method mentioned above [54]. The specificity of the scotoma detection will be enhanced if the criteria for scotoma detection are extended from the analysis of single stimulus fields to spatial patterns of neighboring visual field locations; however, such a pooling of mfVEP data across stimulus fields reduces the spatial resolution of the method [32, 41].

The above-mentioned improvements of the mfVEP recording and analysis strategies have helped to establish the mfVEP methods as a new

tool for the diagnosis of glaucoma. Hood et al. [42] demonstrated that Humphrey visual fields (HVF) and monocular mfVEPs show a comparable number of defects in patients with early to mild glaucomatous damage. With the addition of the interocular test, the mfVEP showed more abnormalities than HVF; however, although there were abnormalities detected by the mfVEP that were missed by the HVF, the reverse was true as well. Goldberg et al. [32] reported that mfVEP testing detected scotomas in nearly all cases of glaucoma where field defects had been established on subjective testing. They also found that about 60% of the subjects with glaucoma who had a fellow eye with a normal visual field demonstrated abnormal mfVEPs in that eye. As it is very likely that the fellow eye of a glaucomatous eye will develop glaucoma in the future, the mfVEP defects may indicate an increased sensitivity of the mfVEP method to detect early glaucomatous damage when compared with static perimetry; however, until the power of the mfVEP for an early detection of glaucoma has been validated by longitudinal studies, the major field of application for mfVEPs might be the follow-up of the course of the disease where mfVEPs may supplement static perimetry.

Summary for the Clinician

- In recent years the multifocal VEP (mfVEP) has been established as a new tool for the diagnosis of glaucoma.
- mfVEPs may supplement static perimetry in the follow-up of glaucoma in the future (Table 5.1).

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Chapter 6

Adherence and Persistence in Glaucoma

6

Gail F. Schwartz

Core Messages

- Patients' health may be jeopardized and health care resources may be wasted by failures in patient adherence or persistence. Patient adherence is defined as the extent to which patients' behaviors correspond with providers' recommendations. Patient persistence is defined as the extent to which a recommended therapy is continued over time.
- Patients with chronic conditions, such as glaucoma, that require lifelong treatment and follow-up care are particularly susceptible to low adherence and poor persistence.
- A large body of research has documented that both adherence and persistence are significant problems among glaucoma patients.
- Potential barriers to adherence and persistence with treatment regimens can be classified as patient demographics, behavioral factors, treatment regimen characteristics, situational factors, and health care system issues.
- Several approaches may be taken by ophthalmologists to improve the extent to which patients observe recommendations over time.

6.1 Introduction

The benefits of medical care are overwhelmingly related to how closely patients follow providers' recommendations over time. Failures in patient adherence, i.e., the extent to which patients' behaviors correspond with providers' recommendations [41] and persistence i.e., the extent to which a recommended therapy is continued over time [29], may jeopardize patients' health and lead to wasted health care resources [11, 40]. In recent years, the term "adherence" has replaced what traditionally was referred to as "compliance" [18]. This shift has occurred because adherence may better recognize the importance of patients' responsibility and involvement in their care. For consistency, "adherence" is used throughout this chapter to describe the extent to which patients' behaviors correspond with providers' recommendations, even though many of the studies discussed used the term "compliance." Although adherence and persistence both reflect patients' behaviors relative to recommended treatment regimens, persistence allows for some degree of nonadherence; thus, a patient whose medication is prescribed twice daily but who takes it only once daily is persistent with therapy, although the level of adherence is 50%.

Low adherence and poor persistence are particularly vexing to practitioners who treat patients with chronic conditions, such as glaucoma, that require lifelong treatment and follow-up care. In order to manage these issues in everyday-practice settings, ophthalmologists need to be able to identify patients who are nonadherent and/or not persistent, as well as those who are at risk for such behaviors. Unfortunately, accurate and affordable measures of adherence and persistence are lacking [11], and the literature concerning who might be at risk is confusing. In fact, it has been suggested that motivating factors affecting adherence may be different for each condition and even for each patient–physician pair [40]. Such variability might explain, in part, the fact that physicians have been found to be unable to accurately predict which of their glaucoma patients would have low (<50%) vs high (>90%)

rates of adherence with ocular hypotensive medication regimens [15].

This chapter reviews literature published since 1990 concerning rates of adherence and persistence in patients with glaucoma. In addition, factors that may affect such behaviors are discussed. Where data for patients with glaucoma are unavailable, information is provided from studies of patients with other chronic conditions. Finally, approaches that ophthalmologists might consider to improve patient adherence and persistence are proposed.

6.2 Adherence

Since 1990 the primary methods used to measure medication adherence in glaucoma patients have been (a) patient self-report via either a self-administered questionnaire or a structured interview by trained personnel, and (b) calculation of medication-possession ratios and average days without therapy. Methods and findings of ten adherence studies in glaucoma management are summarized in Table 6.1 [9, 10, 13, 16, 17, 22, 26, 28, 38, 39].

Table 6.1 Summary of adherence studies. *ICD-9* International Classification of Diseases, ninth revision, *n* number, *OAG* open-angle glaucoma, *OH* ocular hypertension, *POAG* primary open-angle glaucoma, *UK* United Kingdom, *USA* United States. (Adapted with permission from [30])

Reference	Study design	Adherence measure(s)	Adherence findings
[13]	Method: standardized questionnaire administered by interview (USA) Sample: patients from glaucoma subspecialty practices ($n = 230$)	Patient report of how often they forgot to instill their eyedrops	Never or almost never missed a dose: 85%
[39]	Methods: structured interview; hierarchical cluster analysis of reasons for nonadherence (USA) Sample: consecutive POAG patients treated in an academic-based glaucoma practice ($n = 48$)	Patient report of missed doses and barriers to medication adherence	Never missed a dose in previous 14 days: 92% Identified 71 distinct barriers to adherence: Situational/environmental factors: 49% Medication regimen factors: 32% Patient factors: 16% Provider factors: 3%
[38]	Methods: focus groups and in-depth interviews (USA) Sample: patients had seen 2 or more ophthalmologists for glaucoma and were taking ≥ 2 topical ocular hypotensive drugs	Patient report of nonadherence and reasons for nonadherence	All patients in focus group reported some level of nonadherence Forgetfulness the main reason for nonadherence Few nonadherent due to side effects Cost not a reported factor in nonadherence Many patients instilled eyedrops incorrectly Some patients want regimens to be easier

Table 6.1 (*continued*)

Reference	Study design	Adherence measure(s)	Adherence findings
[16]	Method: prospective study; open questionnaire administered by interview (Greece) Sample: patients with chronic glaucoma referred to a glaucoma clinic ($n = 100$)	Patient report of frequency of missed doses of eyedrops and reason(s) for missing doses Clinically significant nonadherence: missed > 2 doses/week	Clinically significant nonadherence: 44% Voluntary nonadherence: 29% Involuntary nonadherence: 15% Reasons for nonadherence: Lack of visual symptoms without treatment and/or Blurring of vision with treatment: 34% Forgetfulness: 28% Inconvenient frequency: 16% Medication unavailable: 15% No one available to instill drops: 5% Nonadherence more frequent in: Those using drops up to 2 times/day vs those using drops > 4 times/day Men vs women Judged very capable of instilling eyedrops accurately: 53%
[28]	Methods: 12-week, randomized, observer-masked, crossover study of 2 formulations of a topical beta-blocker; standardized patient-preference questionnaire administered by interview (USA) Sample: POAG or OH (n 202)	Patient report of frequency of missed doses of ocular hypotensive medication	Never forgot medication: 78%; 68% Never or rarely forgot medication: 98%; 96%
[17]	Methods: computerrecords review; structured telephone interview; compared cases (nonadherent patients) and controls (adherent patients; USA) Time frame: 2 years Sample: patients with ICD-9 code for glaucoma or glaucoma suspect; $n = 438$ interviewed	Follow-up visit adherence: Adherent: seen at least every 6 ± 2.5 months	Visit nonadherence associated with: Being a glaucoma suspect vs a defined glaucoma case Dissatisfaction with waiting time in clinic Not having been prescribed an ocular hypotensive drug Not taking an ocular hypotensive medication as prescribed

Table 6.1 (*continued*)

Reference	Study design	Adherence measure(s)	Adherence findings
[26]	Methods: mailed questionnaire; hospital and practice dispensing data for subset of patients (UK) Time frame: 12 months for dispensing data Sample: patients > 55 years of age with repeat prescriptions for a topical beta-blocker in 3 clinical practices; $n = 86$ reports; $n = 55$ pharmacy dispensing records	Patient report of frequency of missed drops	Frequently or occasionally missing drops: 24% Reports of never missing drops associated with belief that drops were "vital" as opposed to "important" Insufficient eyedrops for 51% (of 55 with dispensing data) Average shortfall in nonadherent patients: 85 days
[10]	Method: retrospective cohort study (USA health maintenance organization) Time frame: 12 months following the index prescription Sample: patients newly initiated on any topical ocular hypotensive medication to treat OAG ($n = 616$)	Nonadherent: did not fill sufficient prescriptions for ≥ 80% of days Days without therapy: cumulative number of days during which ocular hypotensive therapy was not available	Nonadherent: 25% Average days without therapy in nonadherent group: 104 days Average days without therapy in adherent group: 7 days Nonadherence most strongly related to < 2 visits with an ophthalmologist during the study period
[22]	Method: patient interview (USA) Sample: clinic patients taking eyedrops for glaucoma ($n = 100$)	Patient report of whether doses ever missed and reasons for missing	Not strictly adherent: 59% Increasing daily frequency of eyedrops associated with increasing rate of nonadherence Reasons for nonadherence: Forgetfulness Away from home Inconvenient timing/frequency Side effects

Table 6.1 (*continued*)

Reference	Study design	Adherence measure(s)	Adherence findings
[9]	Method: retrospective cohort study (New Jersey Medicaid Program) Time frame: 12 months Sample: patients newly initiated on any topical ocular hypotensive medication ($n = 2440$)	Total nonadherence: absence of a filled prescription for any ocular hypotensive medication in the 12 months following the index prescription Days without therapy: cumulative number of days during which ocular hypotensive medication was not available in the 12 months following the index prescription	Total nonadherence: 23% Average days without therapy in overall sample: 112 days Nonadherence most strongly related to use of medication requiring > 2 instillations/day, initial therapy with a single ocular hypotensive agent, and presence of multiple other drugs in the patient's overall regimen

Articles are ordered chronologically beginning with the most recently published. Articles were included on the basis of a search of MEDLINE using the PubMed search service with the key words glaucoma, ocular hypertension, adherence, and compliance and the time frame of 1990 through 2004

Rates of medication adherence measured by patient self-report have been quite variable, but several studies have reported rates of 85% or greater. In a 12-week, randomized, observer-masked crossover study of two formulations of a topical beta-blocker, 98 and 96% of patients responded that they never or rarely forgot their medication [28]. Similarly, 92% of 48 patients from an academic-based glaucoma specialty practice reported never missing a dose of their ocular hypotensive therapy during the preceding 2 weeks [39], and 85% of 230 patients seen in glaucoma subspecialty practices reported never or almost never missing a dose [13]. In contrast, all members of a focus group that included 21 patients who had seen at least two ophthalmologists and who were taking at least two topical ocular hypotensive agents acknowledged some level of nonadherence [38]. Other studies have found substantial but not universal nonadherence. For example, 59% of clinic patients instilling eyedrops for glaucoma agreed with the statement that they had "not strictly adhered with the medical regimen prescribed by their doctor" [22], 44% of patients with chronic glaucoma reported missing more than two doses per week [16], and 24% of patients prescribed a topical beta-blocker reported frequently or occasionally missing doses [26]. Variability in reported adherence rates may reflect differences in patient groups studied as well as the fact that patient self-reports are subject to recall bias and that patients sometimes overestimate adherence to meet what they believe to be provider expectations [18].

Two retrospective cohort studies conducted in the United States estimated nonadherence using medication-possession ratios and average days without therapy [9, 10]. Among 2440 patients newly initiated on any topical ocular hypotensive agent, 23% did not fill any prescription in the 12 months following the index prescription. In the overall sample, patients were without therapy for an average of 112 days [9]. Similar findings were reported in a more recent year-long study of 616 patients beginning ocular hypotensive therapy: 25% of patients did not fill sufficient prescriptions for at least 80% of days, and nonadherent patients were without therapy for an average of 104 days [10].

Summary for the Clinician

- Rates of patient adherence with ocular hypotensive medication and follow-up instructions have been found to be variable but generally lower than is clinically desirable.

6.3 Persistence

As with adherence, methods of measuring persistence are not standardized. Methods and findings of 11 persistence studies are summarized in Table 6.2 [2, 4, 6, 23-25, 27, 31, 34, 35, 42]. Note that while few recent studies of medication adherence compared agents, most persistence studies have used comparative designs.

Several retrospective cohort studies [4, 23-25, 31, 34] of managedcareplan pharmacyclaims data have used survival analysis methods (Cox regression) to calculate persistence rates and to control for length of follow-up and patient characteristics [14]. Persistence estimates have varied but generally have been found to be relatively low. Figure 6.1 [23] shows a representative plot of a survival function for time to discontinuation of therapy based on data for 2850 patients prescribed an ocular hypotensive drug. Overall, 39% of patients discontinued the index drug within 21 months. There were substantial differences in risks of discontinuation across classes of drugs, however. Patients treated with beta-blockers, a carbonic anhydrase inhibitor, or an alpha-2 adrenergic agonist were from 1.62 to 2.10 times more likely to discontinue the index therapy than were those treated initially with a prostaglandin ($P \leq 0.02$ for all comparisons).

Other research also has shown that persistence is enhanced among patients treated with a prostaglandin [4, 6, 25, 31, 34, 35]. For example, a recent retrospective cohort study [25] of 28,741 patients initially dispensed any of seven ocular hypotensive agents found that 33% of patients treated with a prostaglandin and 19% of those treated with any of the six other therapies had not discontinued their initial regimen after 12 months. A study of 1474 primary open-angle glaucoma suspects initially treated with a prostaglandin or beta-blocker demonstrated similarly low persistence: during 12 months of follow-up, 39 and 25%, respectively, had not discontinued therapy (Fig. 6.2) [31]. Using various research designs, mean and median times on therapy have been shown to be longer in those patients treated with a prostaglandin compared with those receiving other classes of drugs [4, 6, 34, 35]. It is notable, though, that variability in persistence existed within the prostaglandin class [24].

Table 6.2 Summary of persistence studies. (Adapted with permission from [30])

Reference	Study design	Drugs studied	Persistence findings
[25]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 12 months Sample: patient dispensed any index drug ($n = 28{,}741$)	Initial treatment with any of 7 ocular hypotensive agents Comparison: selected prostaglandin vs all other drugs	Prostaglandin vs other drugs: No discontinuation: 33 vs 19% No discontinuation or change: 23 vs 13%
[31]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 12 months Sample: POAG suspects dispensed either index drug ($n = 1474$)	Initial treatment with a beta-blocker or a prostaglandin	Prostaglandin vs beta-blocker: No discontinuation: 39 vs 25% No discontinuation or change: 30 vs 18%

Table 6.2 (*continued*)

Reference	Study design	Drugs studied	Persistence findings
[24]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 12 months Sample: patient dispensed any index drug ($n = 4356$)	Initial treatment with any of 3 topical prostaglandin analogs	Variability in persistence within the prostaglandin class
[27]	Method: naturalistic, prospective study (France) Time frame: 1 year Sample: patients with POAG or OH ($n = 549$ eyes)	Second-line therapy with a beta-blocker or a prostaglandin as monotherapy or as part of combination therapy	Monotherapy prostaglandin vs beta-blocker: No discontinuation: 84 vs 69% Mean time on therapy: 326 vs 292 days Combination therapy; with prostaglandin vs without prostaglandin: No discontinuation: 80 vs 44% Mean time on therapy: 340 vs 237 days
[6]	Method: retrospective chart review (Europe) Time frame: 2 years Sample: patients with POAG or OH ($n = 260$)	Initial treatment with a beta-blocker or a prostaglandin	Prostaglandin vs beta-blocker: Median time on therapy: 21.8 vs 10.8 months
[2]	Method: decision-analytic model (European chart review; French costs) Time frame: 3 years Sample: 10,000 hypothetical patients/group	Initial treatment with a beta-blocker or a prostaglandin	Prostaglandin vs beta-blocker: Mean time on therapy: 20.5 vs 13.4 months
[23]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 21 months Sample: patients dispensed any index drug ($n = 2850$)	Initial treatment with any of 5 ocular hypotensive agents	Overall: No discontinuation: 61% No discontinuation or change: 43%

Table 6.2 (*continued*)

Reference	Study design	Drugs studied	Persistence findings
[42]	Method: prospective, multicenter, historical controlled trial (USA) Time frame: up to 6 months Sample: glaucoma or OH patients switched to a prostaglandin from other monotherapies ($n = 3179$)	Initial monotherapy with any of 18 ocular hypotensives; switch to a prostaglandin	No discontinuation of prostaglandin after switch: 78%
[35]	Method: prospective chart review (USA) Time frame: 1 year Sample: OAG or OH patients switching from or adding to beta-blocker therapy ($n = 148$)	Initial treatment with a beta-blocker; switched to a prostaglandin or added a prostaglandin or alpha-adrenergic agonist	Prostaglandin + beta-blocker vs alpha-agonist + beta-blocker: Mean time on therapy after switch/add: 11.2 vs 9.4 months
[4]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 2 years Sample: patients dispensed any index drug ($n = 1330$)	Initial treatment with any of 7 ocular hypotensive agents	Range: Prostaglandin vs alpha-blocker at 1 year: No discontinuation or change: 64 vs 37% Prostaglandin vs alpha-blocker at 2 years No discontinuation or change: 57 vs 31% Prostaglandin vs carbonic anhydrase inhibitor: Median time on therapy: 553 vs 120 days
[34]	Method: retrospective cohort study (USAmanaged care plan pharmacyclaims data) Time frame: 18 months Sample: patients dispensed any index drug ($n = 1006$)	Initial treatment with any of 6 ocular hypotensive agents	Overall: No discontinuation: 38% No discontinuation or change: 20% Range: Prostaglandin vs beta-blocker: Mean time to discontinuation: 216 vs 183 days Mean time to discontinuation or change: 193 vs 176 days

Articles are ordered chronologically beginning with the most recently published. Articles were included on the basis of a search of MEDLINE using the PubMed search service with the key words glaucoma, ocular hypertension, persistence, and persistency, and the time frame of 1990 through 2004

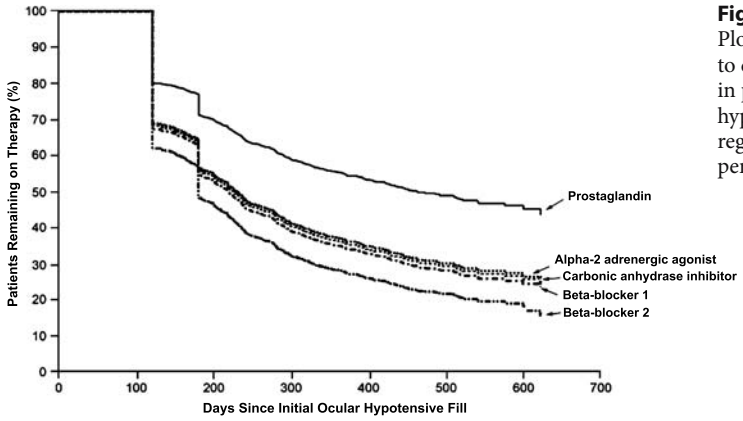

Fig. 6.1
Plot of survival function for time to discontinuation of therapy in patients prescribed an ocular hypotensive drug: adjusted Cox regression model. (Adapted with permission from [23])

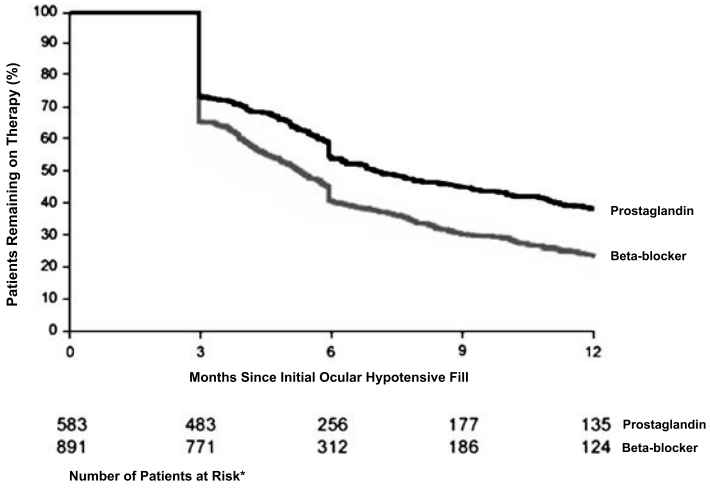

Fig. 6.2
Plot of survival function for time to discontinuation of therapy in patients with ocular hypertension: adjusted Cox regression model. (Adapted with permission from [31])

Summary for the Clinician

- Rates of patient persistence with ocular hypotensive medication have been found to be relatively low, but persistence is higher among those treated with a prostaglandin.

6.4 Barriers to Adherence and Persistence

On balance, research has documented that both adherence and persistence are significant problems among glaucoma patients. The question of why patients fail to adhere and persist with treatment regimens raises complex issues. A taxonomy of obstacles to adherence in glaucoma patients developed by Tsai et al. [39] and a conceptual framework of factors affecting antihypertensive medication adherence proposed by Krousel-Wood et al. [18] have been adapted to aid in systematically assessing barriers to both adher-

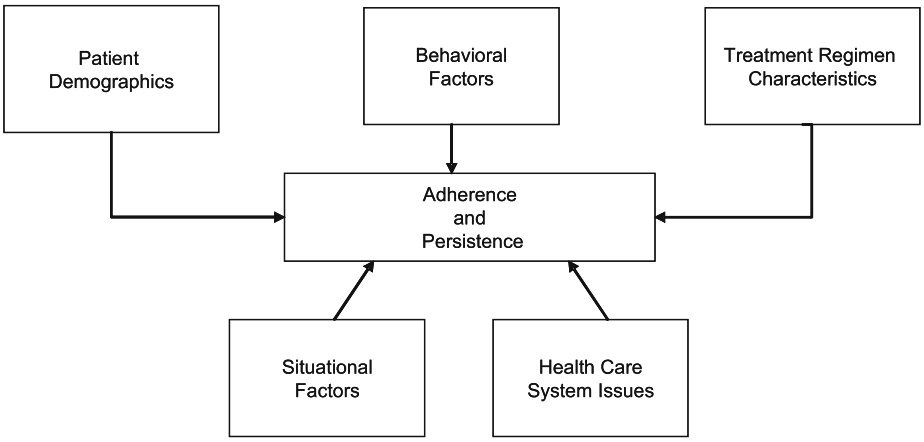

Fig. 6.3 Conceptual framework of factors affecting ocular hypotensive medication adherence and persistence

ence and persistence (Fig. 6.3). Potential barriers are classified as patient demographics, behavioral factors, treatment regimen characteristics, situational factors, and health care system issues.

6.4.1 Patient Demographics

Differences among patient characteristics such as age, race, and gender have been associated with adherence and persistence. Nonadherence has been found to be more common in male chronic glaucoma patients [16], and persistence with antihypertensive medications has been shown to be lower among men [20]. In hypertensive patients, nonwhite race has been associated with both lower adherence [21, 32] and poorer persistence [1]. A higher rate of medication adherence has been shown in older patients with hypertension [21], but persistence with antihypertensive therapies has been found to be both positively [3, 5, 20] and negatively [1] associated with age.

6.4.2 Behavioral Factors

Behavioral factors that affect adherence and persistence in glaucoma include memory (forgetfulness); knowledge, motivations, and health beliefs; skill in instilling eyedrops; and treatment for comorbidities [39]. Several researchers [16, 22, 38] have identified forgetfulness as a major reason for medication nonadherence in glaucoma patients. Contributing to forgetfulness is the fact that the chronic and often asymptomatic nature of glaucoma makes it difficult for patients to remain motivated to adhere and persist with treatment regimens over time [39].

Glaucoma suspects might be expected to be motivated to adhere and persist with clinicians' recommendations in order to avoid progression to glaucoma; however, these patients have been found to be more likely than those with diagnosed glaucoma to be nonadherent with follow-up visit instructions [17]. In addition, 12-month medication persistence rates for glaucoma suspects are similar to rates for the overall group of patients newly prescribed ocular hypotensive agents (Figs. 6.1 [23] and 6.2 [31]).

The impact of beliefs concerning the importance of lifelong care is reflected in the finding that glaucoma patients who reported never missing drops tended to believe that eyedrops were "vital" as opposed to "important" [26]. Unfortunately, even when patients are motivated to instill eyedrops, they often lack the skills to do so correctly [16, 38].

The effect of comorbidities on medication adherence and persistence is unclear. Nonadherence in glaucoma patients has been associated with the use of a large number of nonocular

hypotensive prescriptions before the initiation of ocular hypotensive therapy [9]. In contrast, persistence has been shown to be higher in hypertensive patients taking drugs for concurrent disorders [5, 7].

6.4.3 Treatment Regimen Characteristics

Treatment regimen characteristics affecting adherence and persistence include the dosing schedule and medication-related side effects. Frequency of instillation has been found to be negatively related to adherence in patients with glaucoma [8, 9, 16, 22]. For example, therapy with an agent requiring more than two instillations per day has been associated with total nonadherence (filling no prescription for any glaucoma medication over a 12-month period) in patients newly initiated on a topical ocular hypotensive [9]. A meta-analysis of eight studies (11,485 observations) of medication adherence with antihypertensive therapies found that average adherence for once-daily dosing was significantly higher than for multiple daily dosing (91 vs 83%, respectively; $p < 0.001$) [12]. In asthma, refill persistence has been found to be greater in patients prescribed two drugs in a single inhaler compared with those prescribed the same drugs in two separate inhalers [36].

Patients with glaucoma remain free of symptoms until the later stages of the disease; however, treatment may result in ocular or systemic side effects in some patients. Both adherence and persistence are likely to be compromised if the patient decides that the cost of a medication regimen in terms of side effects outweighs the often intangible, long-term benefits of therapy. Patients make the final decision about whether or not to use a prescribed medication as directed over time, and they are less likely to do so if an agent's tolerability is poor [18, 19, 37].

6.4.4 Situational Factors

Situational factors, such as major life events and changes in routine on weekends, have been suggested as negatively impacting medication adherence [39]. In clinical settings, patients have reported that having no one available to instill eyedrops [16] and being away from home [22] make it difficult for them to adhere with their medication regimen.

6.4.5 Health Care System Issues

Health care system issues that impact adherence and persistence include provider-related factors, such as physician–patient communication and patient satisfaction with the provider [39], as well as access to services and the cost of care and medications. In glaucoma patients, nonadherence with follow-up visit instructions has been associated with dissatisfaction with clinic waiting times [17]. Among patients treated for hypertension, lower medication adherence has been associated with lack of information from the provider, lack of a primary care provider, and lack of clinic follow-up [33, 41]. Problems scheduling appointments and unreimbursed medication costs also may negatively affect adherence [18] and, presumably, persistence.

Summary for the Clinician

- Both adherence and persistence are significant problems among glaucoma patients.
- Potential barriers include patient demographics, behavioral factors, treatment regimen characteristics, situational factors, and health care system issues.

6.5 Improving Adherence and Persistence

Some factors, such as demographic characteristics, that affect adherence and persistence cannot be altered by treating clinicians, but clinicians can attempt to influence other factors. The following are several approaches that might improve the extent to which patients observe recommendations over time [30].

6.5.1 Improve Motivation and Knowledge by Reinforcing the Importance of Adherence and Persistence

Maximizing treatment benefits over the long term requires that the patient understand the recommended medication and follow-up regimens as well as the interrelationships among adherence, persistence, and disease control. Ophthalmologists enter into conversations with glaucoma patients that often continue for many years. Such conversations must regularly stress the benefits of ocular hypotensive therapy and ongoing follow-up, and should emphasize the active role that the patient must take in minimizing disease progression.

6.5.2 Provide Literature to Read at Home

The patient may be better able to understand and retain information provided during the office visit if the same messages are repeated and their importance is reemphasized in literature read at home.

6.5.3 Write Down All Drop Directions; Consider an Easy-to-Read Chart

Providing the patient with written drop directions and an easy-to-read chart detailing the dosing schedule may enhance adherence. A copy of all written materials given to the patient should be retained in the medical record.

6.5.4 Regularly Evaluate the Treatment Regimen

Given the association between the complexity of the medication regimen and reduced adherence, the ophthalmologist should consider prescribing the simplest feasible regimen. At follow-up visits, questions concerning potential side effects that might reduce adherence and persistence should be asked and changes to the regimen should be considered if problems arise. The ophthalmologist and technician should be alert to visible ocular side effects, such as hyperemia, that may compromise adherence and persistence.

6.5.5 Improve Patient Skills by Monitoring Drop Instillation Techniques

The following practices are advisable: consider having a patient new to ocular hypotensive therapy start with a practice bottle of artificial tears; have a technician observe the patient instilling drops in the office at each visit to help the patient develop and retain skills that will minimize wastage; provide clear instructions concerning the timing and spacing of drops. Depending on the regimen, consider prescribing a device to administer the drop.

6.5.6 Question Patients Concerning Adherence and Persistence

At each visit, a technician should ask when the patient last filled a prescription, how much medication remains in the bottle at home, and how long a bottle of medication usually lasts. Patients also should be asked how many doses they missed in the previous month and when the last drop was instilled. (The latter question sometimes yields different answers if asked more than once during the same visit.)

6.5.7 Help Patients Fit the Treatment Regimen Into Their Routines

Patients often are better able to remember to instill their eyedrops if they develop cues such as drinking their morning coffee, teeth brushing, or taking other medications. Patients having difficulty with forgetfulness can be asked to keep a calendar and check off when they instill drops. Patients who work might consider keeping an extra bottle of medication at the work site.

6.5.8 Consider Health System Issues

Ophthalmologists need to be sensitive to cost and access issues, as patients may be embarrassed to admit that they cannot afford to pay for medication or follow-up visits. In patients for whom paying for medication is difficult, a referral to one of the patientassistance programs offered by pharmaceutical companies may help improve adherence and persistence. It also can be useful to start patients with samples to accustom them to taking therapy and to encourage them to refill prescriptions. For those with pharmacy benefits, physicians should be familiar with the coverage, provide 90-day refills if possible, and offer reliable patients a generous number of refills.

Summary for the Clinician

- Ophthalmologists can use several approaches to improve patient adherence and persistence.

6.6 Conclusion

Glaucoma is a chronic and often asymptomatic condition that requires adherence and persistence with medication and follow-up regimens to reduce the risk of progression. Low adherence and poor persistence are major barriers to controlling glaucoma, and both adherence and persistence are affected by many factors, some of which can be influenced by treating physicians. Clinicians need to distinguish between problems of efficacy vs those of adherence and persistence in order to achieve the best possible patient outcomes and to avoid making unnecessary and costly changes in therapy.

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Epidemiology and Related Fields

Chapter 7

Glaucoma Care in Developing Countries of Asia

7

Paul J. Foster and Ravi Thomas

Core Messages

Impact of glaucoma

- 73 million people worldwide are affected by glaucoma.
- Half are Asian, most in developing countries.
- Worldwide, most glaucoma is undiagnosed.
- Angle closure is more likely to cause blindness than primary open-angle glaucoma (POAG).

Management of POAG in developing nations

- Unselected medical therapy of ocular hypertension (OH) is not justified.
- Pending verification by additional research, medical treatment of some subgroups with OH may be justified.
- Medical therapy of established POAG is justifiable in individual cases, although it is not viable as a public health intervention.
- Laser trabeculoplasty is unlikely to contribute to management of POAG.
- Primary surgery is an appropriate first-line method of managing POAG provided that the diagnosis is confirmed and surgery is of good quality.
- Anti-scarring treatments, such as mitomycin C (MMC), enhance success rates in glaucoma surgery.
- Potential side effects of MMC emphasize that high-quality surgical training is essential if their widespread use is to be recommended.
- Incidence of complications from use of MMC can be reduced by altering the method of application and surgical technique.

Diagnosis of primary angle-closure glaucoma (PACG)

- 75% of PACG in Asia is asymptomatic.
- Traditional classification of PACG according to symptoms and IOP does not engender a logical approach to management.
- Physical signs of tissue damage at key sites (trabecular meshwork and optic nerve) should be sought.
- The mechanism responsible for angle closure should be identified.
- Management is determined by mechanism and extent of damage to tissue, and risk to vision.

Management of PACG in developing nations

- Laser or surgical iridotomy/iridectomy remain the cornerstones of management of early disease
- High presenting IOP (>35 mmHg), extensive PAS (>6 clock hours), or glaucomatous optic neuropathy are indicators that PI will not fully control disease
- Symptomatic angle closure responds to laser iridoplasty as well as systemic acetazolamide
- Angle-closure patients with any visually significant cataract should be considered for lens extraction as a method of managing their angle closure prior to laser iridotomy/iridectomy.
- Lens extraction and laser iridoplasty offer method of managing residual appositional angle closure after PI.
- Public health interventions, such as screening and prophylactic treatment, are probably justified for PACG (unlike POAG).

Government and industry

- Improvements in education, skills, and resources would help enhance care.
- Some Asian countries suffer from inefficient health care systems.

The development of domestic manufacturing of generic medicines in developing Asian nations presents political obstacles but offers a solution to supply of affordable medication.

7.1 The Problem

Currently, the World Health Organization ranks glaucoma as the second largest cause of blindness worldwide, behind cataract [67]. While sophistication and efficacy of cataract surgery has increased, in many parts of the world most research into glaucoma focuses on etiological issues, or diagnostic methods reliant on sophisticated and expensive equipment; however, for the populations of the developing countries of Asia (defined by per capita income < $9386 in 2005 [2]), access to adequate preventive or therapeutic glaucoma care remains elusive. Many of the issues related to blindness are inextricably linked to poverty. Loss of sight from glaucoma is permanent. This state of affairs is unlikely to be reversed in the foreseeable future. The size of the problem will only increase as populations continue to increase in age. The only hope of making a significant impact on the increasing number of people suffering from glaucoma in the large, densely populated countries of Asia, such as India and China, will be from low-cost interventions using robust, available technologies that are safe.

The first steps in dealing with a problem are recognizing its existence and understanding the causes. Epidemiological research over the past decade has quantified the absolute and relative proportions of glaucoma in many Asian populations. The "Quigley model" of pooled population prevalence data worldwide suggested that 66.8 million people were affected by primary glaucoma, and another 6 million by secondary glaucoma. Nearly half of this number (29.8 million) were believed to be East Asians [62]. There were believed to be approximately 6.7 million people bilaterally blind from primary glaucoma.

In Asia, there are four major groups of people in whom glaucoma prevalence should be considered: East Asians (China, Japan, Korea, Taiwan, etc.); South Asians (India, Pakistan, Bangladesh, and Nepal); Southeast Asians (Thai, Malay, Vietnamese, Indonesians); and the newly settled European immigrants to Australia and New Zealand. It is becoming increasingly apparent that glaucoma has differing characteristics in each of these different groups. The precise reasons for these differences are not fully understood. Furthermore, each nation in Asia will have unique political and economic characteristics that influence the way that effective health care is delivered.

7.2 Primary Open-Angle Glaucoma

Among South and East Asian people, primary open-angle glaucoma (POAG) does occur at approximately the same frequency as in European people and is probably the most common form of glaucoma in these populations [20, 32, 65, 73]. One important regional difference that appears consistent is that mean intraocular pressure (IOP) is lower than in other racial groups, and that POAG in East Asian people develops at lower IOP levels [28, 31, 73]. This observation has not been satisfactorily explained. The situation in Southeast Asians is not well understood, although it appears that POAG is the most common variety of glaucoma, with PACG being less common than in Chinese [14].

7.3 Primary Angle-Closure Glaucoma

7.3.1 Defining Primary Angle-Closure Glaucoma

Clear and meaningful descriptions of the incidence and prevalence of primary angle-closure glaucoma (PACG) have been hindered by the anachronistic classification scheme based around symptoms that is widely used in most textbooks

Table 7.1 Classification of angle closure and associated glaucoma using parallel schemes specifying disease stage and mechanism of closure

Disease staging
Stage 1: Angle closure suspect/narrow angle an anatomical predisposition to closure
Stage 2: Angle closure; partial or total closure of the angle with synechiae and/or raised IOP
– Non-ischemic
– Ischemic: with tissue injury, such as iris whorling or stromal atrophy, often history of symptoms
Stage 3: Angle closure with glaucomatous optic neuropathy
Mechanism of closure
– Pupil block
– Anterior non-pupil-block, including plateau iris and peripheral iris crowding
– Lens related
– Factors behind the lens

and persists in some research publications. This "traditional" classification of angle closure uses the term glaucoma indiscriminately. The diagnosis is made primarily on the basis of symptoms, with secondary emphasis on IOP and gonioscopic findings. As symptoms are not a typical feature of angle closure in Asian people, and in neither Europeans nor Asians have symptoms been proven to be a reliable guide to the risk of visual loss, the description of cases as either acute, subacute/intermittent, or chronic angle closure does not give a clear idea of the stage of the disease or risk to vision. A modified classification for epidemiological studies has divided the natural history of angle closure into three stages: firstly, an anatomically narrow angle (or primary angle-closure suspect: PACS) with no other abnormality. Secondly, a similar angle appearance (PACS) with evidence of closure of the angle (either synechiae and/or a raised IOP), termed primary angle closure (PAC). The final stage is angle closure combined with glaucomatous optic neuropathy (GON) manifesting with structural damage to the neuroretinal rim of the optic disc, combined with a reproducible visual field defect. These conditions are classified as primary angle-closure glaucoma (PACG) [29]. This scheme has also begun to find acceptance in clinical usage [7]. It is likely that the classification of angle closure will be further revised in the coming years, placing less emphasis on symptoms and towards a scheme using parallel specifying the mechanism causing closure, and location and severity of tissue damage sustained as a consequence (Table 7.1).

Acute angle closure used to be considered a form of glaucoma, although with the growing acceptance that glaucoma implies a characteristic form of optic neuropathy, this is increasingly out of step with current opinion and practice. The accounts of visual prognosis in those suffering a symptomatic episode of PAC (i.e., acute angle closure) suggest that 60–75% recover without any optic disc or visual field damage [11, 22, 23]. One retrospective study of IOP control following symptomatic angle closure in Singaporeans showed that 42% were successfully treated by laser iridotomy alone. The remaining 58% were judged to require treatment; 33% underwent trabeculectomy [10]. This indicates that the prognosis may less optimistic when measured in years instead of months; however, in a study of European people living in Rochester, Minnesota, the probability of becoming blind in one eye from PACG was 4% after 5 years among patients not blind at diagnosis [25]. What is becoming clear is that with prompt, appropriate management the symptomatic phase of the disease will avert catastrophic visual loss in the majority of cases. The real challenge to preventing blindness lies in

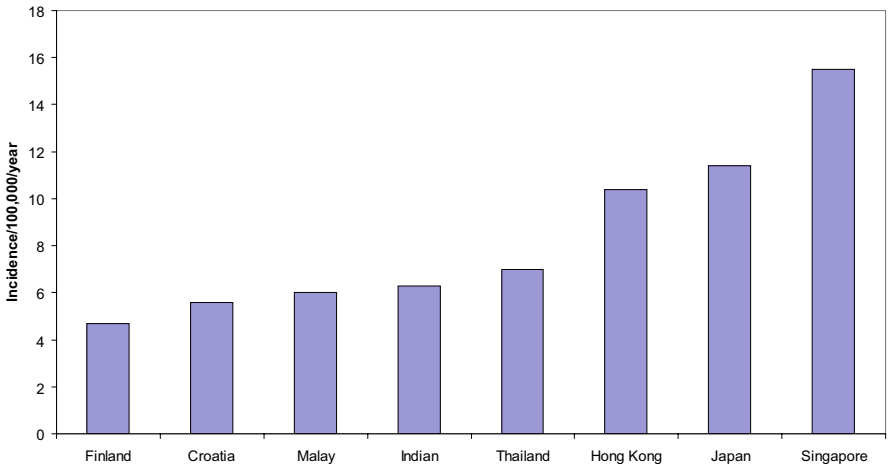

Fig. 7.1 A histogram showing age- and sex-standardised incidence of symptomatic angle-closure in different countries. Incidence is higher among East Asian people, than in Caucasians

tackling the longer-term, asymptomatic "chronic" form of angle closure.

7.3.2 Incidence of Primary Angle Closure

The incidence of symptomatic ("acute") angle closure has been studied in several countries: Finland [77]; Japan [34]; Israel [21]; Thailand [34]; Singapore [72, 87]; and Hong Kong [44]. Age- and gender-standardized incidence ranges from 4.7 cases/100,000 population/ year in Finland to 15.5 cases/100,000 per year among Chinese Singaporeans. This is illustrated graphically in Fig. 7.1, showing East Asian people (Japanese, and Chinese from Singapore and Hong Kong) having the highest rates. South and Southeast Asians (Indian, Thai, and Malay people) have lower rates of angle closure.

The studies described above do not answer important questions about incidence of disease without symptoms. As 75% of angle closure in Asian people occurs without symptoms, the inferences which can be drawn from these data are severely limited, as they apply to a minority of cases. Data on progression from narrow angles, to angle closure (synechial or appositional), to PACG are extremely scarce. Two recent publications from Vellore in southern India give an important insight into the natural history of angle closure. Normal subjects and people with narrow drainage angles were enrolled from a population survey. Among the people with narrow drainage angles 22% (95% CI: 9.8, 34.2) had developed synechial (64%) or appositional angle closure (36%) over a period of 5 years [79]. The people with established angle closure at the time of the population survey were advised to undergo laser iridotomy. Eight of 28 people examined (28%, 95% CI: 12, 45) had progressed to PACG over 5 years. One of 9 patients who underwent LPI progressed compared with 7 of 19 who refused LPI [82]. There is an urgent need for more data on natural history and progression of angle closure; however, in the context of the existing body of knowledge, the prophylactic effect of laser iridotomy appears strong in Indian people.

7.3.3 Prevalence of Primary Angle Closure

Prevalence rates of primary angle closure (PAC) are relatively high in the Asia-Pacific region. A study in rural Taiwan found 17 people suffering

Table 7.2 Population prevalence of angle closure and associated glaucoma in Chinese Singaporeans and Mongolian people. *PAC* primary angle closure, *PACG* PAC with glaucomatous optic neuropathy. (From [30])

	All occludable angles	PAC	PACG
Mongolia (rural)	6.4% (4.3, 8.5)	2.0% (1.3, 3.1)	0.8% (0.4. 1.7)
Singapore (urban)	6.3% (4.9, 7.6)	2.2% (1.4, 3.1)	0.8% (0.4, 1.2)

Rates given for the population aged 40 years and older
Age and gender structure of both populations is very similar
All occludable angles category includes those with PAC and PACG
PAC category includes those with PACG 95% confidence intervals, given in parentheses

from PAC (3.0%). Two of these 17 people (12%) were blind in both eyes [15]. Table 7.2 gives age- and gender-standardized prevalence of occludable drainage angles, PAC, and PACG for populations of Singapore and Mongolia aged 40 years and older [30]. In Mongolia, 91% of glaucoma cases were previously undiagnosed, whereas in Singapore, 79% of cases of PACG had been diagnosed previously. While PACG is acknowledged as a major cause of ocular morbidity in East Asian populations, the situation for people living on the Indian subcontinent is less clear. It has been widely believed that PACG is more common than among European people [16]; however, two recent population surveys have provided conflicting data. In Vellore, southern India, the prevalence of PACG was 4.3% among people aged 30–60 years. All the PACG cases detected were of the chronic type, making PACG about five times as common as POAG [39]; however, in neighboring Hyderabad, PACG and occludable angles without glaucoma were found with prevalence of 0.7 and 1.4%, respectively, in participants 30 years of age or older. The prevalence of these two conditions considered together increased significantly with age. Most (83%) of those with PACG had asymptomatic disease [18]. The difference in prevalence of PACG between the people for Hyderabad and Vellore are, in large part, explicable on the grounds of differing definitions and diagnostic methodology. What can be gleaned from these studies is that PACG is probably more common in India than in European people and, as in the rest of Asia, is generally asymptomatic. Further data from India, using standardized definitions, would be helpful in verifying the results of these two projects.

7.3.4 Risk Factors

Angle closure is rare before the age of 40 years, after which prevalence rises. Female gender is recognized as a major predisposing factor toward development of PAC. The prevalence of narrow drainage angles, PAC, and PACG all tend to be higher in women than in men [4, 9, 71, 73]. People suffering angle closure had shorter axial lengths than did unaffected people [51]. Chinese people suffering "acute" angle closure have shorter axial lengths than did those affected by "chronic," asymptomatic angle closure. Both groups had shorter axial lengths than people classified as normal [50, 76]. Similar findings have been reported in India [35, 74].

A shallow anterior chamber depth (ACD) is widely considered the leading anatomical risk factor for angle closure. The ACD correlates with demographic risk factors. Women have shallower ACD than men, and ACD is shallower in older people than in the young [5, 27, 52, 88]. There is evidence to support the belief that mean ACD in populations is inversely proportional to the rate of angle closure [6, 24, 27]; however, this theory is not proven conclusively. A study comparing ultrasound biometry in African-Americans, European Americans, and Taiwanese Chinese concluded that there was no significant difference between Chinese and the other two groups in terms of their ACD and axial length. This may

suggest that other ocular biometric parameters should be sought to explain the excess of PACG in Chinese people [17]; however, in any given population, the shallowest anterior chambers are found in those individuals with the highest risk of angle-closure glaucoma, namely elderly women. The recent recognition that ACD has a different dose-response curve in different population will have relevance for identifying the disease if screening programs are ever proven viable [12].

The onset of symptomatic, acute angle closure has been linked to meteorological factors [72]. Case series have also suggested an association between upper respiratory tract infections, antitussive agents [44], as well as nebulized bronchodilators, possibly pointing toward an autonomic mal-coordination as a trigger for acute attacks.

7.4 Impact of Glaucoma on Patients and Access to Care

Among Indian people, PACG caused blindness in at least one eye of 42% of sufferers [18]. POAG caused blindness in at least one eye of 18% of those affected [20]. In China it is estimated that 9.4 million people aged 40 years and older have glaucomatous optic neuropathy with 5.2 million (55%) being blind in at least one eye and 1.7 million (18.1%) blind in both eyes. PACG is believed to be responsible for the vast majority (over 90%) of bilateral glaucoma blindness in China [30]. Research in developed countries, where populations suffer mainly POAG, shows that only about half of all cases of glaucoma have been identified and have received any treatment [57, 85]. In Hyderabad, southern India, only 7% of those with POAG had been previously diagnosed compared with 33% of those with PACG (although only 8% had previously received an iridotomy) [18, 20]. A similarly disappointing finding was identified in Mongolia where 9% of glaucoma cases were previously diagnosed (no cases of POAG had been diagnosed before, vs 14% of PACG cases) [28]. In Guangzhou city, China, different rates of previous diagnosis were identified in PACG and POAG cases: 48 and 7%, respectively (He, unpublished data). It is unclear whether glaucoma has a strong socio-economic gradient. A higher predilection for those of lower socioeconomic status may be expected in PACG, as most sufferers are less educated and affluent hypermetropic people [18]. Myopia is a risk factor for POAG [56]. More of these people are of higher socioeconomic status [86]; therefore, the most visually destructive form of the disease (PACG) may affect the poorest, most disadvantaged people. Table 7.3 summarizes the proportion of cases previously diagnosed.

7.5 Medical Therapy

The Ocular Hypertension Treatment Study and Early Manifest Glaucoma Treatment Study have shown the benefit of medical treatment in ocular hypertension (OH) and POAG, respectively [41, 48]; however, recommendations from these studies do not apply equally to all nations, especially in developing countries. The "number needed to treat" (NNT) indicates the number of people that must be treated to achieve the desired end point (prevent onset or progression of glaucoma). For the representative patient recruited in OHTS the NNT is 20 (reciprocal of the absolute risk reduction of 5%). Functional (field) defects occurred in only 50% of patients in the OHTS. At best, such an intervention would prevent the occurrence of early glaucoma, not blindness. This comes with a high (and lifelong) monetary cost. Combining this with lost-opportunity costs would be a persuasive argument against treating all OH in many developing countries. A refinement would be to identify subgroups where the absolute risk is higher, and the NNT low enough to justify treatment [69, 80]. It might be appropriate to treat people with higher IOPs or thinner corneas [37]. Identifying people with IOP > 25 mmHg and corneal thickness < 556 would reduce the NNT to about 6. The NNT for the prevention of progression of early glaucoma is five to six [48]. Because progression is usually slow and the incidence of bilateral blindness relatively low [63], an appropriate strategy in developing countries may be to concentrate on cases at higher risk: bilateral early POAG and higher IOP or those with pseudoexfoliation [61]. This strategy will lower the NNT and make the decision to treat more acceptable.

The decision to detect and treat depends on the available resources and is inextricably linked to public health issues. Population attributable risk (PAR) percentage addresses the issue of whether an intervention is justifiable on public health grounds [66], and quantifies the risk in a population associated with a predisposing factor that may potentially be eliminated with treatment. The calculation of PAR(%) is based on the assumption that such factors increase the risk of a disease, over and above any existing baseline risk in the population. Taking OH as an example, PAR percentage indicates the amount of POAG in the population that could be prevented by treating all OH in the entire population. Assuming a 3% prevalence of OH and using the results of the Ocular Hypertension Treatment Study, the proportion of POAG in the population which could be prevented is around 8.5%. This is far below what would considered for public health intervention (threshold might be around 20%; J.P. Muliyil, pers. commun.). This is highly unlikely to compete with cataract, other systemic diseases, or issues such as sanitation, clean drinking water, and immunization. Performing a similar calculation using the Early Manifest Glaucoma Trial study data, a PAR(%) for preventing progression of early POAG would be around 20%. This makes a more persuasive argument; however, given the slow progression of most POAG, the low incidence of blindness, low per capita income in developing countries, and the logistical realities, it is unlikely to spur many health policymakers into action.

7.6 Laser Treatment

Laser peripheral iridotomy (PI) remains the definitive method of managing most cases of PAC prior to the onset of glaucomatous optic neuropathy [60, 70]. Peripheral iridotomy combined with supplementary medical and laser treatment is often successful even when early glaucomatous damage has occurred to disc and field [78]. In Asian eyes, PI alone may be insufficient for the long-term IOP control following acute angle closure; 58% of such eyes required additional methods of management including trabeculectomy [10]. There is little doubt over the benefit of a PI for the fellow eye of one which has already suffered symptomatic angle closure [8].

In people who have not suffered symptomatic (acute) PAC, the question of whether to perform prophylactic PI is controversial [33]. Currently, there are no clinical trials to support this decision, and the best available information that guides a logical choice of management comes from studies of natural history of angle closure. One such study in southern India found that one-fifth of all people with anatomically narrow angles (22%, 95% CI: 9.8, 34.2) developed raised IOP and/or PAS over 5 years [79]. Primary angle-closure suspects (PACS) had shorter axial lengths and thicker lenses, but biometric parameters could not identify those who progressed to PAC [35, 79]. Compared with those with open angles, the relative risk for the progression of PACS to PAC was 24.2. None of the patients who progressed developed glaucoma (disc or field changes) and none had an acute attack; however, the numbers of people in this study were relatively small, and the true rate of these events could be as high as 6% [69]. Among the people with PAC, only one of nine eyes (11.1%, 95% CI: 0, 32%) that received PI progressed to PACG; however, among 19 eyes of people who declined treatment, 7 (37%, 95% CI: 15, 59%) suffered progression. The difference between these two rates is not statistically significant, probably as a consequence of the small numbers of people involved, although considering all existing evidence for the benefit of PI, this result should be considered clinically significant. Assuming that PI is 100% effective in preventing disease, the NNT to prevent progression to PACG is around 4. The PAR(%) gives an indication of the feasibility of public health initiatives to control PACG. Estimates of PAR are derived from relative risk and prevalence of the risk factor. This also has to be modified to reflect the relative efficacy of treatment in preventing disease. Realistic projections of PAR for angle closure vary from 26 to 56% (Thomas, unpublished data). In the public health context these are good to very good. Research is underway to verify the presumed efficacy of prophylactic treatment in high-risk populations. Research is underway to assess the risks and benefits [59].

Laser iridoplasty, in which contraction burns are applied to the peripheral iris to reverse

appositional angle closure, is now recognized as an important tool in managing people with acute angle closure. Iridoplasty within 48 h of an "acute" episode led to good IOP control without medication in 21 of 30 eyes (70%, 95% CI: 50–90%) over a mean follow-up of 33 months [45]. In a randomized trial comparing iridoplasty against topical medical treatment used in cases of symptomatic primary angle closure presenting within 48 h of onset, argon laser iridoplasty reduced IOP faster in the first 2 h [47]. This is considered important in view of the likelihood that the longer the angles remain closed, the greater the risk of synechial closure at a later stage. The theory is sound but the outcome measure (control of IOP at day 1 after laser) was eventually similar in both groups. It is important to stress that patients in these studies received a laser iridotomy within 48 h of presentation. Current expert opinion suggests that if IOP is not promptly controlled by medical means, the patient should be considered for laser iridoplasty. In cases of asymptomatic angle closure due to plateau iris (in which a PI has been performed), iridoplasty changed the angle width from 0 to between 20 and 30°. The effects persisted for a mean of 79 months. In three cases closure occurred between 5 and 9 years. Re-treatment opened the angle in all three cases [68]. Lack of instruments and infrastructure limit the application of this therapy to the populations of developing countries. Paracentesis has been suggested as a method of controlling IOP in acute angle closure [46]. The technique is invasive and studies report on small numbers. Although paracentesis may be an option for emergency management in developing countries when IOP cannot be medically controlled and a laser is not immediately available, at this time it should be considered experimental.

There are no recent articles which deal with argon laser trabeculoplasty (ALT) in developing countries. Agarwal et al. showed that ALT as a primary procedure successfully controlled IOP in 65% (95% CI: 48, 82%) of 30 Asian Indian eyes with POAG over a 5-year follow-up [3]. If the ten eyes that were lost to follow-up are assumed to have failed (worst-case scenario), the success rate would fall to 50%. This is comparable to mid-term results of existing trials from the developed world [36]. In India few glaucoma specialists use ALT [83].

7.7 Surgery

Surgery carries greater inherent risks but may offer a more effective method of managing glaucoma in developing countries. A single intervention clearly has major advantages in terms of compliance and lower long-term costs. The relative performance of surgery against laser and medication for IOP control is still the subject of debate. The Moorfields Laser, Medicine, Surgery (LMS) trial showed surgery to be superior to medicine and laser [54]. The Collaborative Initial Glaucoma Treatment Study has demonstrated the equivalence of medicine and surgery [49]. Specialists in developed counties (correctly) apply the results to maintain the current algorithm of medical treatment, laser, and then surgery. In a developing country, the opposite policy is often applied. Primary surgery is an acceptable alternative for the developing world provided, of course, that the diagnosis is confirmed and surgery is of good quality [83]. The problem of lower success rates in certain populations should be offset by the primary use of mitomycin C (MMC); however, the potential side effects emphasize that high-quality training in the use of antimetabolites is essential if their widespread use is to be recommended [64]. One recent, major advance that offers tangible benefits to glaucoma care in developing countries is the demonstration that incidence of complications can be reduced by altering the method of application and surgical technique [42, 43].

Lens extraction is a logical choice in the management of angle closure as it will, in one procedure, eradicate pupil block, lens-induced angle closure, and will often benefit non-pupil-block mechanisms such as plateau iris and peripheral iris crowding. In a prospective pilot study in 18 Chinese patients who presented with symptomatic angle closure, all underwent phacoemulsification with posterior chamber intraocular lens implantation following medical control of IOP. There was a 10-mmHg decrease in IOP on the seventh postoperative day IOP [55]. The small sample size and short follow-up limit extrapola-

tion of these data, and more research is needed before the role of lens extraction can be decided. The determining factor in the success of lens extraction is the stage of the disease at which it is performed. At a relatively early stage, prior to the formation of synechiae > 180°, or significant functional damage to trabecular meshwork not affected by synechiae, lens extraction alone works well. In the presence of glaucoma coexistent with a clinically significant cataract, a combined cataract/glaucoma surgery would be the ideal approach for both POAG as well as PACG. A recent evidence-based update addressed some important related issues [40]. Although it is widely believed that glaucoma and cataract surgery separated in time are superior to a simultaneous procedure, there was insufficient evidence to confirm this. There is a moderate amount of evidence to show that the use of MMC in combined cataract and glaucoma surgery reduces IOP by 2–4 mmHg. In addition, two-site combined surgery lowers IOP by 1–2 mmHg compared with one-site surgery. In the review, the strength of supporting evidence was moderate, and the amount of IOP lowering was not considered significant enough for us to warrant advice on change in practice (single site or twin site). There was weak/insufficient evidence for phacoemulsification lowering IOP more than nucleus expression techniques, when combined with a filtering procedure. The magnitude of the difference in IOP lowering (1–2 mmHg) is again not sufficient to advise to change whatever technique surgeons in developing countries are currently using. The results of trabeculectomy performed with a manual small-incision cataract surgery are reported to be equivalent to that of trabeculectomy combined with phacoemulsification [81]. Seventy-eight eyes underwent triple phacoemulsification and 86 eyes underwent Blumenthal triple procedure with the intra-operative use of mitomycin C in all cases. Both groups had a 50% reduction in IOP during a mean follow-up of 17 months. Target IOP was achieved in 76% (95% CI: 66, 85) patients in the phacoemulsification group and 73% (95% CI: 63, 82) in the Blumenthal group. The retrospective design and a short (and differential) follow-up period for the two techniques are limitations. The Blumenthal technique is probably more cost-effective technique compared with phacoemulsification, particularly where developing countries are concerned. An important, additional advantage is that this technique may be specifically advantageous in a setting where there are more mature, brown, and black cataracts.

7.8 Political Considerations

Government policy has considerable impact on the health care services it provides. In India it has been debated whether current policy is appropriate [19]. In 1976 India became the first country in the world to start a national program for control of blindness. All surveys in the country have shown that cataract is the most common cause of blindness and all prevention of blindness programs have been "cataract-oriented"; however, limited and narrow focus in training may have produced suboptimal outcomes in many cases. The recognition of this fact has led to efforts to improve skills among ophthalmologists [84].

Efficiency in provision of health care varies considerably between different Asian nations. One indicator of capacity of the system is number of doctors. China has 300 doctors per 100,000 people, higher than even Australia with 260. By comparison, India has 48 [1]. Remarkably, this great advantage of human resources does not translate into greater productivity. Taking cataract surgical rate (CSR, expressed as case/million year^{-1}), Australia's CSR is 6300, India's is 3100, and China's CSR is only 500 [26]. The reasons for these disparities are complex but do point to underlying problems in health care provision as a whole in some Asian countries. There is a long-standing tendency for migration of doctors and nurses to occur toward richer countries, mainly the U.S., U.K., and Canada. Many reasons for this are cited, but there are "push" and "pull" influences [13]; both need to be addressed in order to prevent loss of skilled workforce from poorer countries.

7.9 The Pharmaceutical Industry

More than a third of the world's population has no access to essential drugs. Most of those people live in Asia. Several factors determine the acces-

sibility of drugs in developing countries. One of the important determinants of access to drugs is the international patent system. A global patent regime devised in 1994 has been set out in the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement. Strong protectionist legislation will inevitably limit access for the poor to medication. A step forward for the many millions in developing countries has been the recognition of the primacy of public health over the interests of patent proprietors, outlined in the "Doha Declaration on the TRIPs Agreement and Public Health," adopted by the WTO Ministerial Conference in 2002 [75]. An alternative to reliance on supplies of medication from industrialized countries is to develop domestic manufacturing. India has built a large pharmaceutical industry through an array of measures in support of domestic firms, and has become the world's leading producer of generic versions of patented drugs; however, the implementation of the World Trade Organization patent regime in 2005 is driving a transformation of the industry. Key elements of the present shake-up include the return of "big pharma" companies on a large scale and the emergence of several Indian firms that aim to become fully fledged research-based multinationals [53]. There is a growing recognition of the need to provide an appropriate balance between access rights and patent rights [58].

Summary for the Clinician

- Glaucoma ranks second only to cataract in the magnitude of blindness caused worldwide. Importantly, blindness from glaucoma remains irreversible. Most of those blinded by glaucoma live in Asia. Primary angle-closure glaucoma (PACG) is more visually destructive than primary open-angle glaucoma (POAG). PACG is typically asymptomatic. Medical therapy of established cases of POAG is probably justified in individual cases, but not as a public health strategy given the costs of, and limited access to, medication in the developing world. Primary surgery offers a viable method of managing glaucoma cases in the developing world, but requires high-quality surgery, and consequently, adequate training and quality control systems. Screening for angle-closure and early prophylactic treatment may prove useful in prevention of blindness programmes, but requires further trials before it can be widely recommended. Lens extraction may prove a useful method of managing cases of angle-closure.

7.10 Conclusion

Primary angle-closure glaucoma is a leading cause of blindness in the developing countries of Asia. This is a great humanitarian loss, as most blindness caused by angle closure is largely preventable with existing medical technology. The disease is more visually destructive than both POAG and secondary glaucoma. Large-scale, early detection and prevention of PACG offers probably the biggest, immediately achievable goal in prevention of blindness worldwide; however, this would require recognition of the problem and concerted will to act at governmental, health service, and NGO levels.

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Chapter 8

Health Economics, Cost-Effectiveness, and Glaucoma Care

8

Anja Tuulonen and Harri Sintonen

Core Messages

- The gap between possibilities of treatment and resources available is broadening all the time.
- Much more could be done for the patients than we can afford; therefore, choices have to be made and priorities set.
- It is important to adopt the most cost-effective clinical practices. We need monitoring and more data on (a) what we produce in terms of activity, case mix, and outcome, (b) how we produce, i.e., what criteria we use to abandon and adopt new treatments and technologies, (c) how much we produce relative to our peers, and (d) to whom we deliver care.
- Cost-utility analysis is presently regarded as the best method of economic evaluation in health care. It is a special case of cost-effectiveness analysis in which health effects are measured in terms of change both in length and quality of life.
- The economic evaluation of glaucoma is in its infancy.

8.1 Health Economics

8.1.1 Basics

Since the first publications in the 1950s and 1960s, health economics as a discipline has developed rapidly. Health economics has been divided into eight categories [47] which are presented in Table 8.1. The table also shows the distribution of articles published in these categories in the main health economic journals up to mid-1999 [30]. This chapter limits the discussion mainly to issues related to economic evaluation (category E in Table 8.1).

According to Maynard, the purpose of health economics is to protect individual citizens by reducing premature death and taxes [29]; the former can be achieved if scarce resources are targeted efficiently to produce health, i.e., increases in the length and quality of life; the latter can be achieved if such efficiency results in the removal of useless old procedures and the prevention of the adoption of useless new interventions, even if these are championed by powerful interest groups who are not focused on the evidence base [29].

In the course of their work, clinicians make many decisions about the care of individual patients.Clinicians are, however, also asked to participate in decisions for large groups of patients. For these groups, clinicians need to weigh not only the benefits and risks but should also consider whether these benefits are worth the resources consumed [12, 33]. If resources are used for one purpose, they cannot be simultaneously used for something else, thus creating opportunity costs in terms of health benefits foregone elsewhere.

The joint outcome of separate decisions should be in accordance with the overall objectives of the system [48]. When health care is provided to the entire population, finite resources and opportunity costs must also be considered. Clinicians, increasingly more in everyday life, are called upon to convince society that the benefits of their interventions justify the costs. It is important to become aware that focusing on local autonomy

Table 8.1 The activities of health economics in eight categories as described by Williams [47] and an analysis of 736 articles published in the two main health economics journals, the "Journal of Health Economics" and "Health Economics," up to the mid-1990s. (From [30])

	Category	Article (% of total)
A	What influences health? Occupational hazards, consumption patterns, education, income	11
B	What is health? What is its value? Perceived attributes of health, health status indexes, value of life, utility scaling of health	21
C	Demand for health care Influences of A + B on health care seeking behavior, barriers to access (price, time, psychological, formal), agency relationship, need	13
D	Supply of health care Costs of production, alternative production techniques, input substitution, markets for inputs (work force, equipment, drugs, etc.), remuneration methods and incentives	21
E	Microeconomic evaluation at treatment level Cost-effectiveness and cost-benefit analysis of alternative ways of delivering care (e.g., choice of mode, place, timing or amount) at all phases (detection, diagnosis, treatment, aftercare, etc.)	15
F	Market equilibrium Money prices, time prices, waiting lists, and non-price rationing systems as equilibrating mechanisms and their differential effects	8
G	Evaluation at whole-system level Equity and allocative efficiency criteria brought to bear on E + F, inter-regional and international comparisons of performance	10
H	Planning, budgeting, and monitoring mechanisms Evaluation of effectiveness of instruments available for optimizing the system, including the interplay of budgeting, work-force allocations, norms, regulation, etc., and the incentive structures they generate	12
	Overview	2

(i.e., a clinician making a decision about a single patient in isolation from any consideration of the effects on the whole health care system) could result in effects that may be harmful for the larger system of health care.

Despite the fact that there is now good evidence that many interventions are both clinically effective and cost-effective, ignorance about how to translate this evidence into practice is considerable [28]. Even if data are available about the costs and benefits of interventions, practitioners and regulators often adopt interventions which are demonstrably not cost-effective, and while doing this they enhance the perception of under-funding [28]. Typically, physicians practice in a fragmented, isolated tradition and do not have good enough administrative information available by which they could monitor (a) what they produce in terms of activity, case mix, and outcome, (b) how they produce, i.e., what criteria they use to abandon and adopt new treatments and technologies, (c) how much they produce relative to their peers, and (d) to whom they deliver care [29].

8.1.2 Role of Micro-Economic Evaluation

It is inescapable that health care systems operate in a decentralized manner, since a vast amount of information is needed to make individual treatment decisions for millions of people [48]. If a decentralized system is to work properly, each decision maker needs to be able and *willing* to take all the costs and benefits into account when deciding what to do. The fundamental problem facing all health care systems is how to make the system more cost-effective. To reach this objective, two approaches are available. The broader one is concerned with changing the system, and the narrower one with making the existing system work better [48].

The gap between possibilities of treatment and resources available is broadening all the time. Much more could be done for the patients than we can afford; therefore, choices have to be made and priorities set. Health care is not about "ordering treatments à la carte."

Instead, rationing occurs "when anyone is denied (or simply not offered) an intervention that everyone agrees would do them some good and which they would like to have" [28]. From the viewpoint of our well-being, it is desirable that the inevitable choices would be made in such a way that the health status of population would be maximized with the resources available. To achieve that we have to choose and use the most efficient procedures and technologies in health care, i.e., such procedures and technologies for which the ratio between health status change (effectiveness) attained and costs incurred is maximized.

8.2 Efficacy, Effectiveness, and Efficiency

Efficacy is the outcome of an intervention in ideal settings, whereas *effectiveness* describes outcome in everyday practice. Although the best evidence of efficacy can be reached by randomized controlled trials, for economic evaluation they are often "small and tight" due to relatively small sample sizes, tight inclusion and exclusion criteria (i.e., selected patients compared with "usual" patients), protocol-driven costs, such as frequent tests and visits, as well as short follow-up considering all costs and outcomes in the course of chronic diseases.

Economic evaluation of health care procedures and technologies is about assessing their *efficiency*: the health effects produced by them are weighed against the sacrifices or costs required in attaining them. Efficiency is thus defined as a relationship between health effects and costs.

Especially economic evaluation of pharmaceuticals (pharmacoeconomics) has recently gained a lot of attention due to the fact that the proportion of total health care expenditure spent on pharmaceuticals has increased substantially in recent years. For example, in Finland the expenditure on pharmaceuticals has in recent years grown approximately 10% per year in real terms. The most important single reason for that is the trend towards using new, more expensive pharmaceutical preparations. It is, however, equally important to build knowledge about the cost-effectiveness of new surgical techniques and technologies since rapidly emerging and expensive technologies often enter clinical practice without adequate evaluation of their cost-effectiveness, especially in diagnostics.

8.2.1 Methods of Economic Evaluation

Economic evaluation deals with establishing the efficiency of the *whole treatment process* compared with another treatment process. In the evaluation process, several different methods can be used. They differ in terms of how health effects are measured. The measurement and evaluation of costs take place in the same way in all methods. The principle in economic evaluation is to report the resources (e.g., the required health care personnel and facilities, diagnostic and therapeutic equipment) used separately from their unit costs (e.g., cost per surgical and diagnostic intervention, visits, hospitalization) [24]. This helps us to interpret the results of a study from one setting to another, as unit prices are known to vary by location. Charges should be separated from costs since they may bear little resemblance to economic costs [14].

8.2.1.1 Cost-Minimization Analysis

If it is known that treatments lead to the same clinical outcomes, cost minimization analysis can be used. In this approach one is looking for the treatment alternative that produces *identical* clinical outcomes at the least cost. Unfortunately, the cases are relatively rare where clinical outcomes across alternatives are virtually the same.

8.2.1.2 Cost-Effectiveness Analysis

When health effects are measured by simple indicators in "natural" or physical units (such as lives saved, life-years, or seeing-years gained, years of blindness avoided, painless/healthy days gained), or numerous disease-specific clinical measures (e.g., changes in visual acuity, intraocular pressure, or visual field indices), and they are related to costs, we are referring to cost-effectiveness analysis. The cost-effectiveness can only be shown in relation to a defined alternative [24]. A treatment is never cost-effective in itself.

The problem with this method often is that the indicators describe health effects inadequately and narrowly. Difficulties arise if, for example, the main therapeutic effect of the alternatives to be compared is different (e.g., one may have an effect mainly on length of life, another on its quality) or if the side effects of the alternatives are different in amount or severity. Then the comparability across alternatives is difficult, even impossible. The efficiency criterion is the additional cost per additional unit of effectiveness (so-called marginal or incremental cost-effectiveness ratio).

8.2.1.3 Cost-Utility Analysis

Cost-utility analysis is presently regarded as the best method of economic evaluation in health care. It is a special case of cost-effectiveness analysis in which health effects are measured in terms of change *both in length and quality of life*. These changes are aggregated into a single index number by weighting length of life with people's "exchange rate" between quality and length of life. This exchange rate is elicited from population, or from patients with evaluation studies. This allows measuring effectiveness in terms of a change in Quality-Adjusted Life Years (QALYs).

QALYs are composed of the same principle as the total points in ski jumping: points for the length of the jump (length of life) and points for its style (quality of life). The total points (QALYs) can be increased by improving style (quality of life) and/or lengthening the jump (life). The changes in QALYs are related to changes in costs. The efficiency criterion of cost-utility analysis is thus marginal or an incremental cost-utility ratio (or, in fact, the ratio between change in costs and change in QALYs).

To be able to compare the efficiency of different interventions in terms of cost-utility for the same disease (or even different interventions for different diseases) against each other requires the measurement of changes in quality of life with a generic (non-disease-specific) instrument. This means that one uses the same instrument for measuring quality of life regardless of what disease has brought about the changes in quality of life. In addition, the instrument must produce a single index number for quality of life that reflects a plausible exchange rate between quality and length of life on a 0–1 scale.

A good example of such an instrument is the 15D in the sense that in most of the important properties (comprehensiveness, reliability, validity, discriminatory power, responsiveness to change) it compares favorably with other instruments of that kind, i.e., the Canadian Health Utilities Index (HUI), the EQ-5D (formerly the EuroQoL), and the SF6D (derived from the SF-36) [20, 38, 39]. The 15D instrument includes 15 dimensions with five levels on each: mobility; vision; hearing; breathing; sleeping; eating; speech; elimination; usual activities; mental function; discomfort and symptoms; depression; distress; vitality; and sexual activity [39].

Cost-effectiveness in eye care has also been measured in terms of cost per Disability Adjusted Life Year (DALY) [22]. DALYs measure burden of disease in terms of both premature death and disability. DALYs are the sum of the years of life lost through premature mortality and years of life with lived with disability [34].

8.2.1.4 Cost-Benefit Analysis

If health effects are measured and valued in monetary terms and they are weighed against costs, we are dealing with cost-benefit analysis. The advantage of this form of analysis is that *both the costs and benefits are measured in the same units*. It is then possible to examine the efficiency of even a single pharmaceutical, i.e., whether its monetary benefits are greater than the monetary costs. The biggest problem of this type of analysis is the evaluation of health effects in monetary terms: all valuation methods are more or less disputable. The efficiency criterion is cost-benefit ratio or net benefit.

8.2.1.5 Decision Analytical Modeling

The use of decision-analytical modeling to estimate the cost-effectiveness of health care interventions is becoming widespread [2]. Ideal study design for economic evaluation include a randomized study design, measures of outcome, quality of life and costs, "usual" patients, "usual" treatment protocol, non-expert (in addition to expert) clinical experience, long follow-up, follow-up of drop-outs, and large sample size. Sometimes the length of follow-up in the clinical trial may be too short for the purposes of economic evaluation. Modeling studies have been undertaken making projections of long-term outcomes from short-term trial data [12]. Modeling can be used to extrapolate cost and effectiveness estimates over a longer time horizon using available epidemiological and natural history data.

Economic modeling is a relatively cheap and effective way of synthesizing existing data and evidence available on the costs and outcomes of alternative interventions. For example, Markov models have a long history of use in health care service decision-making and are particularly suited to the modeling of progression of chronic disease over time. In Markov modeling the disease in question is divided into distinct states and transition probabilities are assigned for movements between these states over a discrete time period (cycle). By attaching estimates of resource use and health outcome consequence to the states and transitions in the model, and then running the model over a large number of cycles, it is possible to estimate the long-term costs and outcomes associated with a disease. Markov models are particularly suited for the calculation of QALYs [2]. Cost-utility analysis based on Markov models may be sensitive to parametric uncertainty. Probabilistic sensitivity analysis is recommended especially in cases where model parameters are based on limited number of observations [27].

Interpretation of modeling studies is limited because of the assumptions that often have to be made due to inadequate evidence [24]. Clinical and epidemiologic studies never give all relevant information, but that is no reason for not investigating what such studies can offer to assist the decision-making process. It appears more useful for decision makers to have some information on potential cost-effectiveness than to have no information at all. A decision is necessary regardless of whether the economic evaluation is performed [24]. A model, even if partly based on assumptions, can provide important information on potential scenarios. It has also been stated that all models are wrong – also our current mental models of thinking – since they always remain imperfect and incomplete in their attempt to represent and analyze the real world [40]. We should, thus, not worry about whether or not to use a model, but rather which model to use. As long as the modeling helps us to promote health care into the right direction, it may be useful.

8.2.2 Guidelines for Economic Evaluation

To improve the quality and comparability of economic evaluations, various parties have compiled methodological guidelines and recommendations for carrying out economic evaluations of pharmaceuticals. The best known and most detailed guidelines are the Australian "Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee" and the Canadian "Guidelines for Economic Evaluation of Pharmaceuti-

Table 8.2 Users' guides for economic analysis for clinical practice. (From [12])

1. Are the results valid?

- To be valid, economic evaluations require evidence of the effectiveness of the alternatives being compared
- Economic evaluations are more valid if effectiveness data reflect normal clinical practice as closely as possible

Did the analysis provide a *full* economic comparison of health care strategies?

Were the costs and outcomes properly measured and valued?

- Were the physical quantities of resources consumed or released reported separately from their prices or unit costs?
- Were data on costs and outcomes appropriately integrated? When making comparisons between alternatives in terms of cost per life year gained or cost per QALY gained, it is important to compute the incremental cost-effectiveness ratio of one therapy over another. This is because the most relevant information relates to the extra benefit that would be gained compared with any extra cost

Was appropriate allowance made for uncertainties in the analysis?

Are estimates of costs and outcomes related to the baseline risk in the treatment population?

2. What were the results?

What were the incremental costs and outcomes of each strategy?
Do incremental costs and outcomes differ between subgroups?
How much does allowance for uncertainty change the results?

3. Will the results help in caring for my patients?

Are the treatment benefits worth the harms and costs?
Could my patients expect similar health outcomes?
Could I expect similar costs?

cals" [5, 6]. The Australian guidelines define the information that the authorities require for making decisions on subsidizing pharmaceuticals, whereas the Canadian guidelines describe how to make a good economic evaluation. Users' guides for economic analysis for clinical practice have also been published (Table 8.2) [12].

All guidelines emphasize that the evaluation should be made from the societal perspective. This means that when studying efficiency, all costs, i.e., the value of all resources required by the treatment process, are taken into account regardless of who incurs them or pays for them. The information needed in economic evaluation can be collected in different ways and the guidelines also describe how to behave in different situations. The simplest evaluation can be done on desktop based on existing information and literature. The other extreme is an evaluation for which a large, long-term, randomized, economic–clinical trial is organized for collecting simultaneously effectiveness and cost data from the treatment alternatives under comparison.

8.3 Economic Evaluation and Glaucoma Care

Glaucoma has received very little attention from health economists for the time being [24]. There are a number of published articles, almost exclusively dealing with microeconomic evaluation, with very few addressing the questions in the other seven categories of health economics listed in Table 1. The majority of economic articles have addressed costs [9, 24]. Such studies are, however, of little help for clinical decision making. A few cost-effectiveness studies have been

published, but thus far (cost)-utility in glaucoma care has been studied superficially at best.

8.3.1 Cost-Effectiveness Analyses of Screening for Glaucoma

In 1983 Gottlieb et al. designed a model to evaluate the cost-effectiveness of various screening methods in subjects aged 40–79 years [19]. They evaluated screening, diagnostic and follow-up costs, and introduced a measure of Quality Adjusted Years of Vision (QAYV). Net effectiveness was measured in terms of vision saved as a result of screening. A variety of sensitivity analyses was performed. The authors concluded that (a) the cost per year of vision saved was the lowest in the age group 55–70 years, (b) screening targeted only at the age group over 70 years was probably not cost-effective, (c) tonometry was more cost-effective in the younger than in the older groups, and (d) screening targeted to high-risk groups, e.g., first-degree relatives of glaucoma patients, was more cost-effective than screening of general population.

In a Canadian study, modeling was used to project effectiveness and costs (year 1994) for the screening procedure over 12 different scenarios [3]. The selection of different scenarios analyzed was broad and seemed to take into account a reasonable range of possible outcomes. The study population model included all people aged 40–79 years. The authors used opinion-based estimates of the effectiveness of glaucoma treatment, i.e., treatment is 50% effective in the prevention of blindness (varied ± 20% in a sensitivity analysis). Years of blindness avoided were predicted using a decision type of model. The authors concluded that there is no proof that treatment of glaucoma would prevent blindness. Even when treatment efficacy was assumed to be as high as 50%, the cost-effectiveness of most glaucoma screening programs considered would not be competitive.

Tuck and Crick carried out an economic analysis in London to assess the cost-effectiveness of different modes of screening/case-finding for glaucoma defined in terms of various combinations of three main tests (ophthalmoscopy, tonometry, and perimetry) with associated referral criteria (relatively lax or relatively severe) [42]. No specific mode of screening was regarded as a comparator. Resource utilization was not fully reported separately from the unit costs. The cost analysis (year 1992 converted to 1995) covered only the costs of diagnosis and not the costs of subsequent treatment and monitoring. Indirect costs were not considered. The cost per true positive for each screening mode was calculated as the measure of cost-effectiveness. The authors concluded that glaucoma screening of people over 40 years could be justifiable. The best balance between sensitivity and costs was to use ophthalmoscopy and tonometry routinely on patients over the age of approximately 40 years, together with perimetry either routinely or in glaucoma high-risk groups. Screening was most likely to be economic when conducted in conjunction with overall eye examinations.

8.3.2 Pharmacoeconomic Studies in Glaucoma

A recent review reported 232 hits using the keywords "glaucoma and costs/cost analysis and epidemiology and medical management." Thirty-six articles reporting original results were considered suitable for analysis [37]. Finally, 17 articles related to costs could be found in the reference list of the review.

In general, the drug costs represent a small proportion of all the costs. A recent review reported that in glaucoma approximately half of glaucoma costs are associated with direct medical costs [37]. In cost analyses costs have been reported in different ways, such as yearly cost of glaucoma medications [32, 49], the cost of treatment per month [8], daily cost of therapy [32], and treatment costs based on DRG prices and drug consumption costs based on defined daily dose (DDD) [4].

With the introduction of new glaucoma medications, the increases in costs have been huge. For example, in 1998–2002 in one region in Italy, the total costs of glaucoma medication increased fivefold. During the same period the number of patients receiving glaucoma therapy doubled while the population and the number of ophthal-

mologists in the area remained unchanged [10, 45]. When the drug prices are rising faster than the total spending in health care, the long-term consequences to the system are significant. The impact of third-party coverage for health care costs [13], especially medications, has not been explored in glaucoma care.

Kobelt [23], Kobelt and Jönsson [25], and Kobelt et al. [26] performed an international modeling study in nine countries and reported the transposition from first-line treatment to second-line products. The study was based on retrospective chart review in different countries and calculated only costs, not outcome. The Markov model was used and costs per patient during 1–2 years were reported for France, the U.K., and Germany. The costs with the new treatments were lower than with previous therapy [25]. Higher frequency of treatment changes were associated with higher costs [26]. Similarly, Denis et al. reported that drug treatment changes were one of the two explanatory factors for the bulk of total cost variance [11]. Another independent contributor was the presence of glaucoma instead of ocular hypertension. Recently, cost-effectiveness comparisons of prostaglandins and beta-blockers have also been reported [7, 46].

8.3.3 Other Cost Studies in Glaucoma

Albright reported that the number of laser trabeculoplasties performed in 2000 was 57% less than the number of procedures in 1992 [1]. Simultaneously the average charge per procedure has also markedly decreased. Also a reduction in the use of surgical procedures to treat glaucoma, especially as first-line therapy, has been reported in the literature [36, 37, 41].

Iskedjian et al. investigated in a longitudinal, retrospective study the costs of primary open-angle glaucoma [21]. The authors calculated the yearly costs in different stages of glaucoma. Differences between mean yearly costs were statistically significant between mild, moderate, and severe glaucoma. Similar results were reported from the Netherlands where patients in academic hospitals had more severe glaucoma and treatment was more expensive than in non-academic hospitals [35]. In a pilot study, the costs of the telemedicine and conventional visits of glaucoma care were reported to be equal, but telemedicine application saved traveling costs [43].

8.4 Future

8.4.1 Future Challenges in Health Economics

Despite increased levels of investment in health services research and health economics, health care delivery is still characterized by problems that have been known and unresolved for decades [13, 29]. In their drive for reducing death and taxes, health economists have had little success in reducing a series of problems, such as medical practice variations, differences in health between different groups, medical errors, cost-effective care, and patient outcomes. For example, in glaucoma care a large observational study of the treatment strategies for newly diagnosed patients in nine countries on three continents revealed striking variations in the use of both drugs and surgical interventions among countries [23].

Why have we failed? The physicians determine the pattern of care that is delivered and in no country is this systematically measured and managed. Both generic health-related quality-of-life instruments and QALY calculations have been used extensively, but no health care system has used routinely such measures to quantify the success of its investments [29].

All systems have intrinsically optimal rates to growth which may be far less than the fastest possible growth. Almost everyone believes – with minimal evidence – that more health care is always better [13, 16, 17, 45]. The highest spending country (the United States) does not have measurably better outcomes [31]. Evidence has begun to emerge that greater expenditure can be associated with poorer health outcomes [15].

In everyday practice, the challenge lies in trade-off between over-consumption of care and too little care. The current legal and cultural environments exert tremendous pressure to do more [15]. Missing a rare – or in case of glaucoma, early – diagnosis may be regarded as much worse than over-testing. With the shift of spectrum of

detected disease, newly detected cases will generally be milder cases and outcomes will seem to improve. This in turn creates stimulus to do even more. With more to do, there is more worry, more unnecessary treatment, more mistakes, and more costs [15].

8.4.2 What Kind of Information Do We Need About Glaucoma Care?

Since the economic evaluation of glaucoma is in its infancy, there is a long list of questions to be addressed, with a few of them listed here:

1. In glaucoma care, we do not know what the impact of high resource utilization (e.g., early diagnosis and treatment, frequent visits and testing, several examination methods) have on important outcome, i.e., prevention of glaucoma-induced visual disability.
2. In diagnostics and follow-up, it is not known how many tests are enough and what number represents over-testing, and how often we should take these tests during the follow-up.
3. When more care and resources will be provided, which patients should receive additional care, i.e., what should be the threshold for initiating and intensifying treatment using different examination methods?
4. We do not have enough evidence to decide whether screening for glaucoma would be cost-effective. There are currently at least two ongoing studies using Markov modeling on this issue, one in Finland and one in Scotland.
5. What leads the everyday clinical decision-making process in glaucoma care is a black box. For instance, how does the concept of "free" medication affect treatment selection. It is known that how providers are funded and who gets paid does matter, e.g., fee for service leads to over-production [13]. It is important to realize that every policy may threaten someone's interests also in glaucoma care.
6. The cost-effectiveness of laser therapy compared with medication needs to be assessed. It is unclear why the use of laser trabeculoplasty has dramatically decreased despite its comparable efficacy to medications.
7. We need future estimates of need for services. Since the stage of glaucomatous damage is often asymmetric between the patient's two eyes, the effect of better and worse eye on quality of life and costs may be different and needs to be assessed.

Economic evaluations in glaucoma encounter several challenges. The quality of life in glaucoma patients is affected only very late during the disease process [8, 44]. A recent evidence synthesis states that no studies were found that assessed the treatment of ocular hypertension using delay of progression to severe visual impairment as an end point [18]. If glaucoma-induced visual disability – not a very frequent event – is used as an outcome measure, very large sample sizes are required for economic evaluations.

There is a need to ensure that further evidence of the cost-effectiveness of competing therapies is produced efficiently and that the evidence is translated into practice. One of the main challenges of the decade is in getting ophthalmologists to adopt the most cost-effective practices. It is not how much we spend but *how* we spend [31]. It is no longer enough that an intervention is clinically effective; it needs to be cost-effective as well if we are to make the most of our finite resources.

Summary for the Clinician

- Clinicians make many decisions about the care of individual patients which form large groups of patients; for the latter, clinicians need to weigh not only the benefits and risks but should also consider whether these benefits are worth the resources consumed. It is no longer enough that an intervention is clinically effective; it needs to be cost-effective as well if we are to make the most of our finite resources. In everyday practice the challenge lies in trade-off between over-consumption of care and too little care.

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Therapy – Surgery

Chapter 9

Future of IOP-Lowering Medication for Glaucoma Therapy

9

Paul L. Kaufman and B'Ann True Gabelt

Core Messages

- Glaucoma therapies utilizing compounds that alter the actin cytoskeleton are very promising for the future. They act via a mechanism not targeted by current glaucoma therapies to enhance aqueous humor outflow via the trabecular meshwork (TM).
- Other classes of compounds that are promising for development as topical drop therapies and may act by enhancing aqueous outflow via the trabecular route include steroid antagonists, and adenosine agonists and antagonists.
- Gene therapy targeting the TM will eventually be used to express proteins or peptides that can alter the actin cytoskeleton and interactions of cells with the extracellular matrix.
- Topical drop therapy to enhance outflow via the uveoscleral route will be accomplished by new prostaglandin (PG) analogs targeting the EP receptor subtypes in addition to the FP receptor subtype.
- Other classes of compounds that may be developed as topical drop therapies and affect uveoscleral outflow as well as other aqueous dynamics pathways include serotonin agonists and nitrovasodilators. Gene therapy to enhance uveoscleral outflow will include increased local production of PGs, extracellular matrix degrading enzymes, and ciliary muscle (CM) relaxants.
- The long-term use of inflow suppressants may eventually decline due to the unfavorable effects on outflow pathways which could eventually lead to outflow obstruction.
- New classes of compounds that may be developed as topical drop therapies to suppress aqueous humor formation include opioids and cannabinoids.
- Prolonging contact with the cornea for enhancing drug delivery may be accomplished by entrapment and encapsulation of the drug in liposomes, niosomes, nanoparticles, microparticles and contact lenses, and incorporation of bioadhesives into the vehicle solutions, as well as combinations of these approaches.
- Continuous intraocular pressure (IOP) monitoring may soon be available via contact lenses fitted with strain gauges and transmitters.

Note: Due to the citation limitation, in most cases when multiple citations are available, only the most recent representative citation or review article is listed since other relevant citations may be found within it.

9.1 Introduction

One of the primary goals of glaucoma therapy is to control intraocular pressure (IOP). IOP reduction by just a few mmHg can have a significant effect on disease progression. The first line of therapy in lowering IOP is usually pharmacological in the form of topical eye drops. Over the course of time, most patients will use more than one medication, singly and in varying combinations, experimenting with differing classes of compounds with varying mechanisms of action.

The goal of the current chapter is to look at what lies ahead in the next 20 years for IOP-lowering drug therapy, rather than to dwell on the numerous possible formulations and combinations that can be made using currently available medications. Enhancing outflow and suppressing inflow will likely remain the general mechanisms of action targeted by future therapies as they have been in the past; however, since long-term use of drugs that reduce IOP by decreasing aqueous humor formation may have a negative effect on the eye [24], enhancing outflow may become the preferred therapeutic approach.

9.2 Outflow Enhancement

9.2.1 Trabecular Outflow

9.2.1.1 Basic Structure

The angle of the anterior chamber is bounded anteriorly by the corneal endothelium, and posteriorly by the root of the iris and ciliary body. At the apex of the angle lies the TM, suspended between Descemet's membrane and the anterior portion of the CM (Fig. 9.1). The TM commences just posterior to the point where Descemet's membrane terminates. This transition zone is identified gonioscopically as Schwalbe's line, but is less easily seen histologically. The TM continues posteriorly until it joins the scleral spur and CM. The inner portion of the meshwork (that closest to the anterior chamber) is called the uveal meshwork, and the outer portion closest to Schlemm's canal constitutes the corneoscleral meshwork, which is itself separated from the endothelial lining of Schlemm's canal by the juxtacanalicular tissue, or endothelial meshwork [30]. There is, however, no sharp dividing line between the portions. Some of the meridional CM fibers insert into the TM.

The TM harbors 60–80% of the resistance to aqueous outflow with the remainder residing in the CM, sclera, collector channels, and intrascleral aqueous veins. Current evidence suggests the juxtacanalicular or subendothelial region adjacent to Schlemm's canal is the primary location of resistance to aqueous humor drainage within the TM. Quantitative morphological studies revealed a significant increase in extracellular material in the subendothelial region of the meshwork adjacent to Schlemm's canal in glaucomatous eyes compared with age-matched normal controls. In eyes with primary open-angle glaucoma (POAG), material derived from (or adhering to) the thickened sheath of the elastic-like fibers predominates and presumably contributes to the increase in outflow resistance. Factors influencing the formation of sheath-derived plaques may also contribute to optic nerve fiber loss before or in conjunction with IOP elevation. Cell number diminishes at these sites in POAG and pigmentary glaucoma, but it is difficult to correlate cell loss with increased resistance to outflow [30].

Cytoskeletal and junctional proteins may be especially important in the maintenance and modification of outflow resistance. Agents that interfere with dynamics of the actin cytoskeleton (Fig. 9.2) alter the cell shape, contractility, and adhesion to neighboring cells, and to the extracellular matrix in culture, and decrease trabecular outflow resistance in the living monkey eye by expanding the areas available for fluid drainage (reviewed in [19]).

9.2.1.2 Myosin Light-Chain Kinase Inhibitors

Recent studies have revealed a number of novel agents that reduce outflow resistance in the living monkey or rabbit eye and/or the enucleated porcine and human eye, probably by cytoskeleton-related mechanisms [2, 19]. With some agents, the lowered resistance is accompanied by, and perhaps caused by, changes in cellular contractility in the TM (e.g., cellular relaxation)

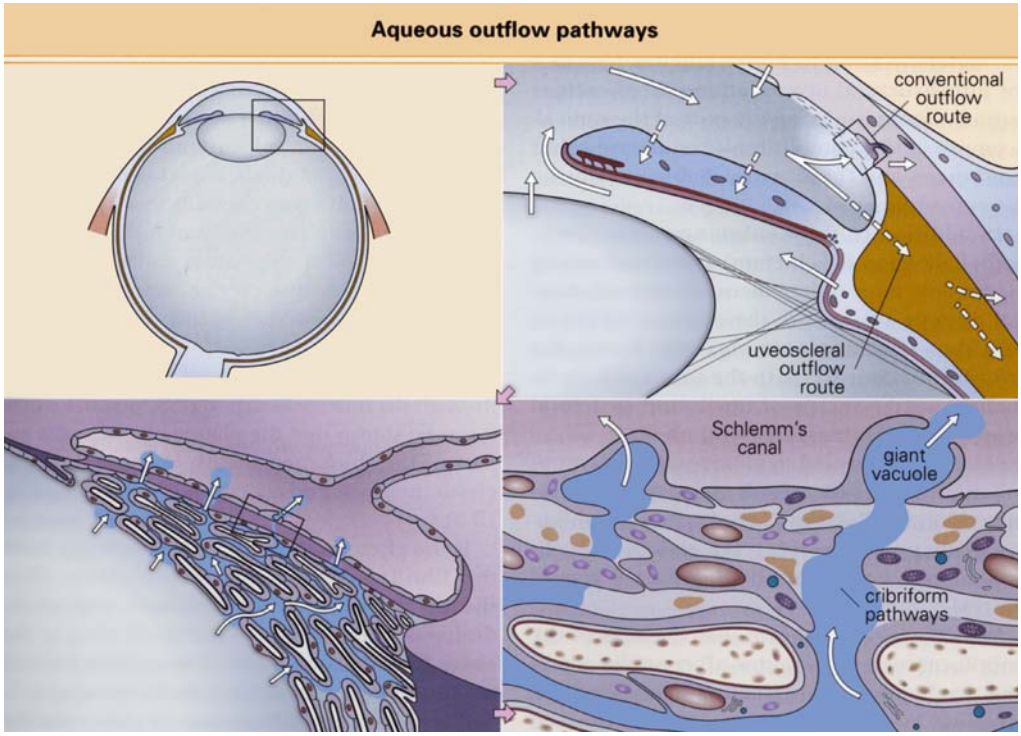

Fig. 9.1 Aqueous outflow pathways. The aqueous humor leaves the anterior chamber via the trabecular meshwork and Schlemm's canal (the so-called conventional outflow route) or via the ciliary muscle and sclera into the orbit, the so-called uveoscleral outflow route. (From [29])

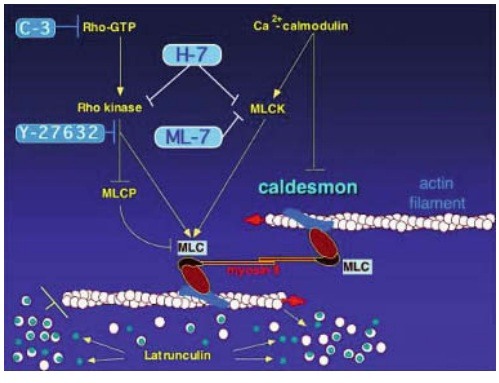

Fig. 9.2 Pathways targeting actomyosin contractility to enhance aqueous humor outflow through the TM. *MLCK* myosin light chain kinase, *MLCP* myosin light chain phosphatase, *MLC* myosin light chain. (From [11])

without apparent cell–cell separations. H-7, a serine–threonine kinase inhibitor, inhibits actomyosin-driven contractility and induces general cellular relaxation by inhibiting myosin light chain kinase or Rho kinase. Although H-7 does not directly affect actin polymerization, the inhibition of contractility leads to deterioration of the actin microfilament bundles and perturbation of its membrane anchorage at matrix adhesion sites in human TM and other cultured cells [19]. In living monkeys, H-7 administered intracamerally or topically increases outflow facility and decreases IOP. Multiple topical doses of 2–5% are effective in decreasing IOP without adversely affecting corneal thickness. Morphological studies in the living monkey eye show that H-7 expands the intercellular spaces in the juxtacanalicular meshwork, accompanied by removal of extracellular material. The inner-wall cells of Schlemm's canal become highly extended, yet cell–cell junctions are maintained (Fig. 9.3) [42]. H-7 also increases outflow facility in human [2] and pig eyes in vitro.

Summary for the Clinician

- Due to the lack of specificity of H-7 to inhibit actomyosin contractility and the high concentrations needed, it is unlikely that this compound, per se, will be further developed in the future; instead, it has served as a tool for investigating prospective mechanisms and identifying characteristics to be targeted for further development.

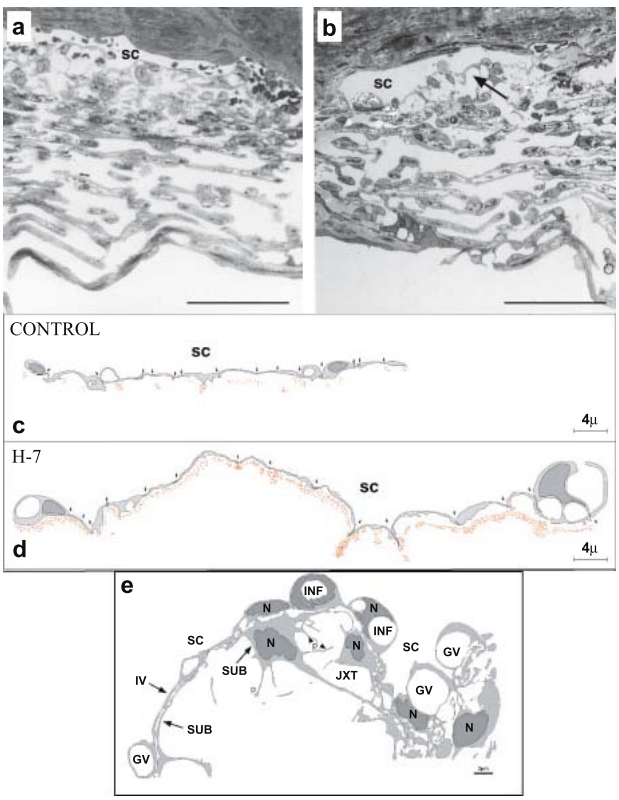

Fig. 9.3 Morphology after perfusion of monkey eyes in vivo with H-7 or LAT-B. Light micrographs of vehicle (**a**) and H-7 (**b**) treated eyes shows expanded intercellular spaces (*arrow*), extended IW cells, and maintained cell–cell junctions after H-7 (*bar* = 50 μm). Drawings depict 15-cell stretches (cell–cell junctions marked by *arrows*) along the Schlemm's canal (*SC*) of control (*C*) and H-7-treated (**d**) eyes. The location of individual gold particles is represented by *red dots*. (From [42] with permission) **e** A long "montage" of transmission EM images, depicting the inner wall IW–JXT regions of the TM following LAT-B. Massive "ballooning" of the JXT region is shown along with retention of close contact between IW and SUB, the irregular diameter of P of IW cells, and the prominent GV. It is difficult to state whether LAT-B increased GV prominence due to the apparent variability in the prominence of GV in the vehicle-treated eye, as well as their non-homogeneous distribution along the canal's wall. *GV* giant vacuoles, *INF* membrane infoldings, *IW* inner wall, *JXT* juxtacanalicular region, *OW* outer wall, *P* cellular processes, *SC* Schlemm's canal, *SUB* sub-canalicular cells, *TM* trabecular meshwork

9.2.1.3 Rho Kinase Inhibitors

Compounds which are more selective in targeting the Rho kinase pathway also show promise for future therapeutic development. Pharmacological studies show that H-7-induced cellular relaxation in the TM and subsequent enhancement of outflow facility may be partially related to its Rho kinase inhibition. A more specific ROCK inhibitor, Y-27632, induces reversible changes in cell shape and decreases in actin stress fibers, focal adhesions, and protein phosphotyrosine staining in human TM cells and Schlemm's canal cells, altering flow pathways through the juxtacanalicular tissue and increasing outflow facility two- to threefold in monkey eyes in vivo [47]. A derivative of Y-27632, Y-39983, also decreases IOP, and increases outflow facility and optic nerve head blood flow, as reported in monkey and rabbit studies recently conducted in Japan [18].

9.2.1.4 Latrunculins

A more potent and very promising group of compounds for future development have been isolated from marine sponge macrolides, such as latrunculins A and B. These compounds alter cell shape and disrupt microfilament organization by sequestering G-actin, leading to disassembly of actin filaments. Latrunculins A and B increase outflow facility and decrease IOP in living monkeys (Fig. 9.4; Table 9.1) [19] and in pig eyes in vitro. A preliminary morphological study in the living monkey eye shows that latrunculin B induces massive "ballooning" of the juxtacanalicular region, leading to a substantial expansion of the space between the inner wall of Schlemm's canal and the trabecular collagen beams (Fig. 9.3). No detrimental effects on tight junctions and cell–cell and cell–extracellular matrix adhesions are observed in the TM [48], although latrunculins interfere with cell–cell adhesions in cultured

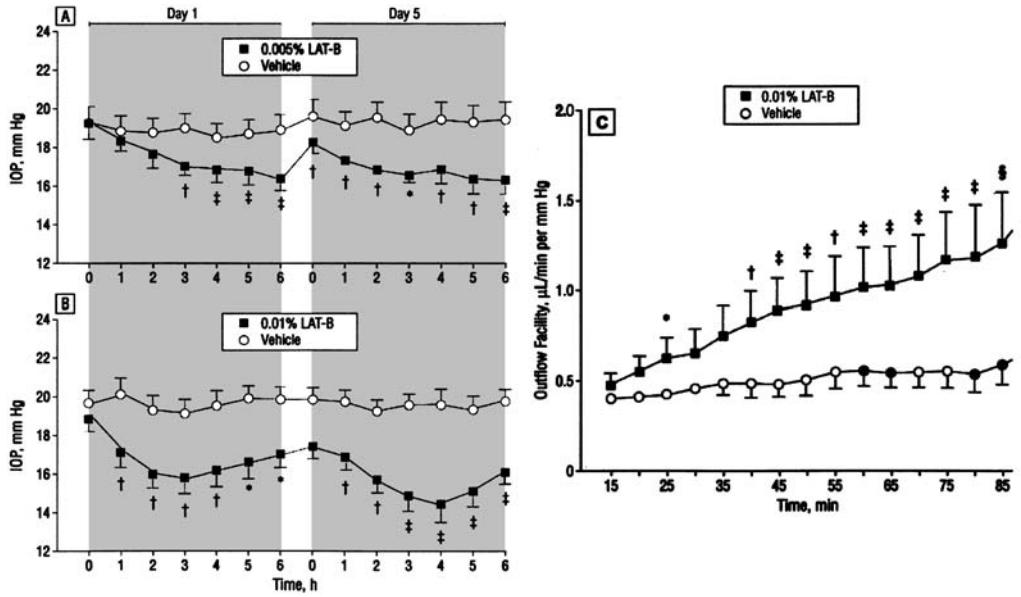

Fig. 9.4 Effects of Latrunculin (LAT) B on IOP and outflow facility in monkeys. **A,B** 0.005/0.01% Lat-B and vehicle (4×5 or 2×10 µl) were administered to opposite eyes topically twice daily for 4.5 days. Intraocular pressure (*IOP*) was measured before and after the first (on day 1) and ninth (on day 5) treatment. **C** Outflow facility was measured by two-level constant pressure perfusion for 90 min on day 9 (2 h after the fifteenth treatment with 0.01% LAT-B once or twice daily). Data are expressed as mean ± SEM: $n = 8$ (IOP); $n = 7$ (outflow facility). The IOP difference between eyes corrected for baseline was tested for differences vs 0.0 by the two-tailed paired *t*-test: * $p < 0.01$; † $p < 0.005$; ‡ $p < 0.001$. Outflow facility difference between eyes was tested vs 0.0 by the two-tailed paired *t*-test: * $p < 0.05$; † $p < 0.03$; ‡ $p < 0.05$; § $p < 0.01$. (From [34])

Table 9.1 Effect of Latrunculin B (*LAT-B*) on outflow facility in monkeys. (From [34])

	Outflow facility (μl/min mmHg^{-1})		LAT-B/vehicle
	LAT-B	Vehicle	
90 min	0.93 ± 0.19	0.51 ± 0.08	1.75 ± 0.13**
First 30 min	0.58 ± 0.10	0.43 ± 0.05	1.35 ± 0.14*
Second 30 min	0.89 ± 0.19	0.51 ± 0.08	1.69 ± 0.14***
Third 30 min	1.19 ± 0.28	0.57 ± 0.11	2.00 ± 0.14***

Following 15 doses of 0.01% LAT-B/vehicle, outflow facility was measured by two-level constant pressure perfusion for 90 min. No baseline outflow facility was determined, but all monkeys were selected from those that had similar baseline facilities in both eyes per previous studies. Data are mean ± SEM for seven animals. Ratios are unitless. Difference between eyes was tested for ratios ≠ 1.0 by the two-tailed paired *t*-test: * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$

TM cells. Multiple topical treatments with low doses of latrunculin-B are effective in increasing outflow facility, relaxing the iris sphincter and CM without adversely affecting the cornea in nonhuman primate eyes.

Latrunculin A or B may also be useful in treating steroid-induced glaucoma. Concurrent administration of latrunculin A prevents the dexamethasone-induced reorganization of the actin cytoskeleton in human TM cells and reverses existing dexamethasone-induced reorganization [26]. Latrunculin and actin depolymerizing agents may also affect outflow facility by activation of matrix metalloproteinases as a result of actin cytoskeletal reorganization and changes in cell morphology [43].

9.2.1.5 Steroid Antagonists

The aqueous humor of control and POAG patients has levels of cortisol in excess of what is in the general circulation, due to the activity of 11β-hydroxysteroid dehydrogenase 1 in the ciliary epithelium where it may be involved in regulating aqueous secretion. The cortisol levels could also reduce aqueous outflow facility to a level that is detrimental in susceptible individuals. In the normal population, 34–42% of patients treated with topical or systemic corticosteroids are termed "steroid responders," and develop moderately to markedly elevated IOP after several weeks. This contrasts to patients with POAG, 90% of whom are considered strong steroid responders. The oral administration of the glucocorticoid biosynthesis inhibitor metyrapone to glaucoma patients or the 11β-hydroxysteroid dehydrogenase inhibitor carbenoxolone to ocular hyperpertensive patients [39] elicit small, transient reductions in IOP.

Topically applied 3α, 5β-tetrahydrocortisol (3α, 5β-THF), an intermediate metabolite of cortisol, decreases IOP and increases outflow facility in glaucomatous human eyes, and 3α, 5β-THF antagonizes dexamethasone-induced cytoskeletal reorganization in normal human-cultured TM cells. Interestingly, cultured TM cells from patients with POAG metabolize cortisol predominantly to 5β-dihydrocortisol (5β-DHF), which potentiates the facility-decreasing and IOP-increasing effects of dexamethasone. These cells produce relatively little 3α, 5β-THF from cortisol.

Possible mechanisms for steroid-induced elevation of IOP have been proposed and include: accumulation or deposition of extracellular matrix material; decreased protease and stromelysin activities; reorganization of the TM cytoskeleton; increased nuclear size and DNA content; decreased phagocytic capacity; and changes in the synthesis of specific proteins. The progressive induction of one major steroid product in human TM cells matches the time course of clinical steroid effects on IOP and outflow facility. This molecule, known as myocilin (MYOC), appears to be a secreted glycoprotein with aggregation- and

extracellular matrix-binding groups interacting with extracellular components such as fibronectin [8].

Alluded to previously, LAT-A can reduce or prevent the formation of actin networks in TM cells exposed to dexamethasone. Other compounds are currently being developed to be effective in reducing IOP in the steroid glaucoma model; these may have broader application for glaucoma IOP-lowering therapy in general.

9.2.1.6 Adenosine Agonists/ Antagonists

Adenosine is a common signaling molecule often associated with cellular responses to stressful situations. Ischemia, in many tissues including the eye, can lead to rapid increases in adenosine concentration. Intravenous infusion of exogenous adenosine into healthy human subjects causes an ocular hypotensive effect and significantly increases choroidal and optic nerve head blood flow [35]. The vasodilatory effects of adenosine in vascular beds is mediated primarily by adenosine A1 and adenosine A2 receptors. The ocular hypotensive effect is presumably due to activation of the adenosine A1 receptors which is correlated with an increase in outflow facility in nonhuman primates. Stimulation of the adenosine A1 subtype in TM cells in vitro results in secretion of matrix metalloproteinase (MMP)-2 which could contribute to extracellular matrix remodeling and enhancement of outflow facility. Other functional adenosine receptor subtypes (A2A and A3) are also present on TM cells. All three subtypes, upon stimulation, produce similar responses of Ca^{2+} release and cell volume changes, making it unlikely that differential effects of adenosine subtype selective agonists on aqueous humor outflow are mediated through TM cells alone.

In ocular hypertensive patients, adenosine levels are elevated compared with normotensives and correlate with IOP [7]. The elevated levels of adenosine may be due primarily to the reduction in ocular blood flow identified in glaucomatous individuals and may represent an adaptive response to enhance blood flow and decrease IOP by increasing outflow facility. Ciliary epithelium contains stores of ATP which, upon release, may be degraded to adenosine by ecto-adenosine triphosphatase. Delivery of adenosine downstream to TM and Schlemm's canal inner-wall cells could represent a mechanism for regulating outflow [6]. Conversely, stimulation of the adenosine A2 and A3 receptors is known to increase IOP; thus, elevated adenosine levels could possibly contribute to the elevation in IOP. The functional adenosine receptor subtypes in glaucomatous and normal eyes needs to be evaluated to help clarify this issue.

Summary for the Clinician

- Future development of glaucoma therapies targeting adenosine receptors would likely utilize adenosine A1 agonists and/or adenosine A3 antagonists.

9.2.1.7 Gene Therapy

Another approach to increase aqueous humor outflow (trabecular outflow) is to use gene therapy to inhibit or enhance the molecular pathways involved in regulating trabecular cell contractility or to block cellular interactions with the extracellular environment that enhance actomyosin contractility and the formation of actin stress fibers. The recent discovery of TM-specific promoters may allow more specific targeting of this tissue [13]. Delivery of genes to the anterior segment of the living primate eye using viral vectors has not yet been successful due to the accompanying inflammatory response which precludes assessment of the effect of the expressed transgene on aqueous humor dynamics. Glaucoma is a chronic disease; thus, long-term expression of the transgene will be required for any gene therapy approach for this disease.

Once the vectorologists can modify their constructs to eliminate these confounding issues (not a trivial matter), some of the genes that will be of therapeutic interest for anterior-segment gene therapy may include the following:

Rho kinase and C3. Rho kinase, targeted for pharmacological therapy, as described above

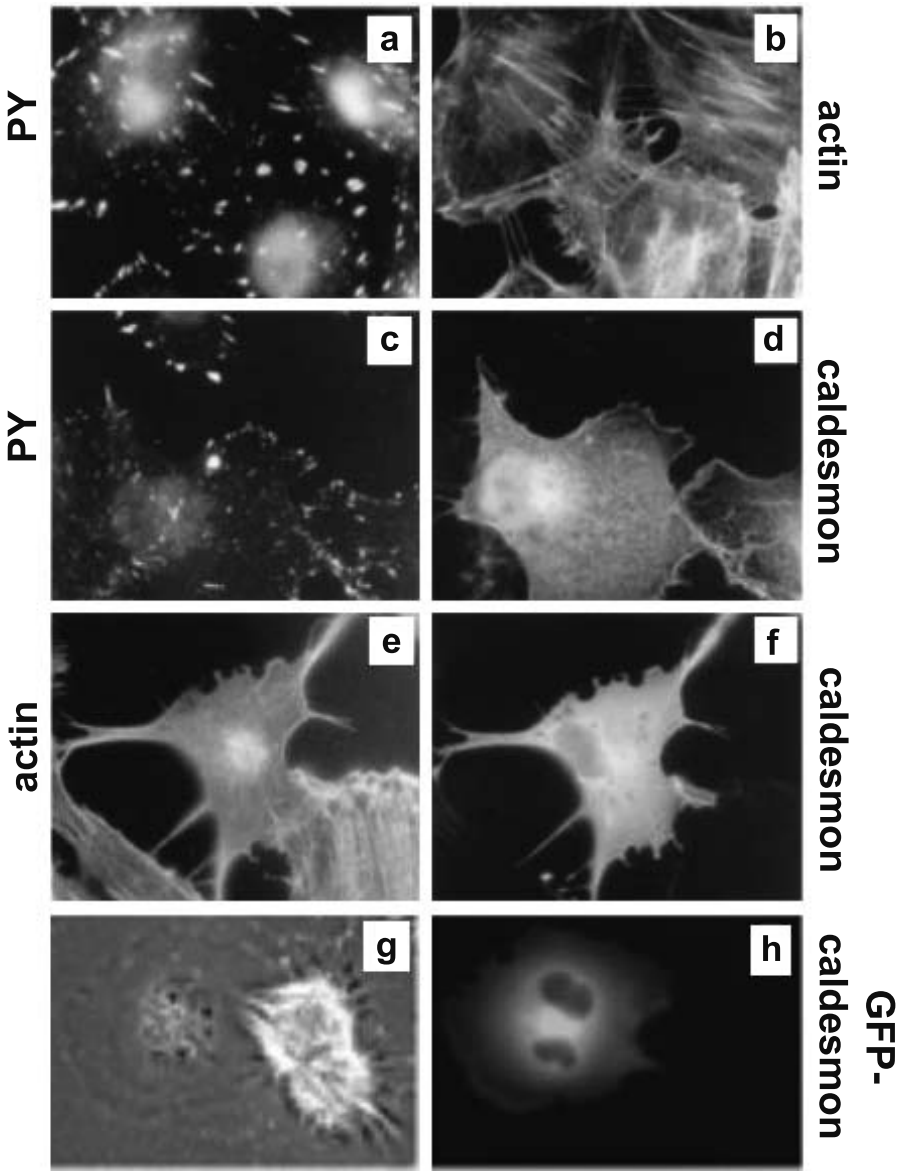

Fig. 9.5 Caldesmon gene therapy in vitro. **A–F** Effect of caldesmon overexpression on focal adhesions and the actin cytoskeleton of SV80 cells. **A,B** Cells in control culture. **C–F** Cells transfected with full-length caldesmon. Staining for focal adhesions was performed with anti-phosphotyrosine (*PY*) antibody (**A,C**); for actin with FITC-phalloidin (**B,E**); and with antibody to visualize transfected caldesmon (**D,F**). Note that focal adhesions (**A,C**) in cells expressing full-length caldesmon (**C**) are much smaller than those in nontransfected cells (**A**). Stress fibers are abundant in nontransfected cells (**B**) but disappear in cells expressing full-length caldesmon (**E**). Some caldesmon-transfected cells show an increase in the formation of long processes (**E,F**) **G,H**. Caldesmon prevents development of traction forces in cells attached to an elastic silicone-rubber substrate. Cells were plated onto a fibronectin-coated silicon-rubber film 7 h after transfection with green fluorescent protein (GFP)–caldesmon. **G** Phase-contrast images of substrate-attached cells and wrinkles they produce. **H** Green fluorescent protein fluorescence images of the same fields show that cells expressing full-length GFP–caldesmon cannot deform the substrate, whereas cells expressing truncated caldesmon readily form wrinkles. (From [15])

for H-7, and rho kinase inhibitors, such as Y-27632 and Y-39983, may also be inhibited by a gene therapy approach. The GTPase Rho, which activates Rho kinase, can be inhibited by proteins, including the dominant negative Rho A (RhoN19) and C3 transferase (a botulinum exoenzyme known to inactivate Rho and disrupt actin filaments and cellular adhesions). Overexpression of C3 transferase can increase outflow facility in monkey-organ-cultured eyes in vitro [27].

Construction of a dominant negative Rho vector will allow targeting of a specific Rho protein and may have different effects than the C3 protein. Dominant negative Rho transduced into human TM cells and organ-cultured human eyes results in reductions of actin stress fibers, focal adhesions and intercellular junctions, and small increases in outflow facility [38].

Caldesmon. Another intracellular protein involved in regulating actomyosin contractility is caldesmon. This protein has been studied mainly in smooth muscle cells and acts by blocking the interaction of actin with myosin, inhibiting actin-activated myosin ATPase activity. Caldesmon affects several actomyosin-based processes, including the movement of actin filaments over myosin heads in vitro.

In nonmuscle cells in culture, caldesmon overexpression leads to suppression of cellular contractility, manifested by a reduced capacity to develop traction forces applied to the underlying extracellular matrix (Fig. 9.5) [15]. This relaxation of the cells resembles in many ways the effect of H-7 on the contractility of cells. Overexpression of caldesmon in human TM cells in vitro following adenoviral vector transduction results in a loss of actin stress fibers and focal adhesions. Outflow facility is enhanced in human and monkey anterior segment organ cultures following transduction with adenoviral vectors carrying nonmuscle caldesmon [10]. It is important that caldesmon overexpression prevent focal adhesion and stress fiber formation, even if the cells express constitutively active Rho [15], showing that caldesmon is operating downstream from the Rho signaling pathway (Fig. 9.2).

α-Catenin. Another protein to target using gene therapy to potentially enhance outflow facility is α-catenin. α-Catenin is a protein found exclusively in cell–cell adhesion complexes (adherens junctions) where it plays a key role in linking cadherins (transmembrane proteins that directly mediate adhesions between neighboring cells) to the actin cytoskeleton [41]. Blocking normal α-catenin function disrupts cell adhesion. Vectors containing a dominant negative version of α-catenin are currently under construction and will be tested for their effects on the cytoskeleton and cell junctions of human TM cells and for their outflow facility effects in organ-cultured anterior segments.

Hep II. Among the signaling pathways that maintain the actomyosin cytoskeleton in vivo are integrin-mediated mechanochemical signaling events via the extracellular matrix. Included in the matrix proteins identified in the TM are laminin, fibronectin, types I, III, IV, V, VI, and VIII collagen, chondroitin, dermatan and heparan sulfate proteoglycans, hyaluronic acid, and a small amount of keratan sulfate. Fibronectin is distributed throughout the TM along the trabecular beams and is especially prevalent in the juxtacanalicular tissue next to Schlemm's canal. It is also found in the basement membrane of the inner wall of Schlemm's canal. The other major components of the basement membrane on the inner wall of Schlemm's canal are laminin and type-IV collagen. During aging and glaucoma, the expression of some matrix proteins is altered. For example, fibronectin levels are upregulated. In contrast, laminin levels are reduced in glaucomatous eyes. Myocilin, a protein that is upregulated during glaucoma, may also be a component of the extracellular matrix. Myocilin is secreted into the media of human TM cells treated with glucocorticoids and is found in the extracellular matrix of TM cells in culture as described previously [8].

Two domains of fibronectin can affect the organization and the contractility of the actin cytoskeleton. They are the central cell binding domain and a heparin-binding domain called the Hep-II domain. Both these domains contain a binding site for members of the integrin receptor family. In addition, Hep-II domain contains a binding site for another family of cell surface receptors called the syndecans, which are cell surface heparan sulfate proteoglycans. All the members of the syndecan family bind fibronectin.

Using recombinant integrin-binding domains from fibronectin to block integrin-fibronectin interactions, it has been shown that a binding domain called Hep II significantly lowers IOP in human eye organ cultures. Treatment of human TM cells with the Hep-II domain disrupts cell–cell junctions and causes a disruption of the cadherin/β-catenin complex of cell–cell junctions, and subsequently, a disassembly of actin filaments [12]. This suggests that gene therapy that interferes with cell–extracellular matrix mediated signaling events could be an approach for modulating aqueous humor outflow in vivo.

Summary for the Clinician

- Gene therapy approaches to enhance outflow through the TM will likely target pathways which alter the TM cytoskeleton and TM interactions with the extracellular matrix.

9.2.2 Uveoscleral Outflow

9.2.2.1 Basic Structure

The anterior chamber and the spaces within the TM are continuous with those between the CM bundles (Fig. 9.1). Water and larger molecules from the anterior chamber can pass into and through the CM via its anterior face, and from there, into the suprachoroidal space to be carried away, some perhaps by the choroidal vessels, but most actually *through* the sclera into the orbit. Indirect measurements in young, health-conscious humans, although incorporating some assumptions, indicate that uveoscleral outflow may routinely account for nearly 50% of total aqueous drainage. This decreases somewhat with age (reviewed in [11]). Aqueous draining via the uveoscleral route takes 2 h or more before it reaches the general circulation.

This system likely evolved to protect the eye in several ways during inflammation. The TM may become compromised by inflammation or obstructed by inflammatory debris, and the choroid may be overloaded with debris and extravasated proteins that must be removed from the eye. In this situation, prostaglandins would be released and, as autacoids or hormones that are synthesized, released, and locally acting, would induce the production of matrix metalloproteinase enzymes that would break down some of the extracellular matrix in the uveoscleral pathways to allow greater flow via this route. Since the eye has no lymphatics, uveoscleral outflow may serve as an analog to an intraocular lymphatic drainage system. Redirection of aqueous outflow from the trabecular to the uveoscleral pathway would both rid the eye of excess proteins and maintain physiological IOP [19].

9.2.2.2 Prostaglandin Analogs

Prostaglandin (PG) analogs are the most potent and efficacious topical ocular hypotensive agents currently known for the treatment of human glaucoma. The most effective PGs for lowering IOP in humans are derivatives of $PGF_{2\alpha}$-isopropyl ester (ie), modified structurally to enhance ocular penetration and specifically activate the FP-prostanoid receptor. Side effects of early analogs included ocular irritation, conjunctival hyperemia, and headache; these have been largely eliminated with latanaprost, a 17-phenyl-substituted isopropylester prodrug derivative of $PGF_{2\alpha}$-ie, which maintains an ~30% IOP reduction with once daily topical application of a 30-μl drop of 0.005% solution in ocular hypertensive patients with starting IOP of ~26 mmHg. Other analogs with similar IOP-lowering efficacy, but slightly higher prevalence of side effects, include 0.03% bimatoprost and 0.004% travoprost.

A new $PGF_{2\alpha}$ derivative, AFP-168, has been developed in Japan. Its affinity for the FP receptor and IOP-lowering response in monkeys exceed those of latanoprost, and it has less stimulating effect on melanogenesis in melanoma cells [46]. This compound is currently in clinical trials in Japan.

Other PG subtypes are being targeted for future anti-glaucoma drug development as well. The EP2-receptor agonist, butaprost, increases uveoscleral outflow approximately twofold in normotensive cynomolgus monkeys without an effect on outflow facility [32]. These findings

are in agreement with the enlargement of the uveoscleral pathway observed after long-term treatment (1 year) of normotensive cynomolgus monkeys with bimatoprost, latanoprost, sulprostone (EP3/EP1 agonist), or AH13205 (EP2 agonist). Similar morphological changes are observed in all groups as well as in the contralateral untreated eyes. Uveoscleral outflow pathways are enlarged and appear organized. More myelinated nerve fiber bundles are found. Changes in the TM are also noted [40].

The selective EP4 receptor agonist ONO-123A may represent a novel anti-glaucoma drug that directly enhances pressure-dependent outflow, perhaps indicating an effect on the TM. In monkeys a single topical dose increases outflow facility by 43% [23]; however, further studies, including multiple treatments, are needed before claims can be made that this receptor subtype acts through mechanisms different than all other PG subtypes to date.

Summary for the Clinician

- Drugs targeting different PG subtypes will be forthcoming, although the mechanism of action will still likely be via an enhancement of uveoscleral outflow.

9.2.2.3 Serotonin Agonists/ Antagonists

Serotonin (5-HT) receptors were identified in ocular tissues of the anterior segment of the eye in several species, including human. These findings suggest that 5-HT might play a role in regulating aqueous humor dynamics and IOP.

There are conflicting reports on the effects of 5-HT receptor subtype ligands on IOP in various species and as a consequence of activity at other classes of receptors [31].

Of particular interest, one study demonstrates that 5-HT_2 agonists, but not 5-HT_2 antagonists or 5-HT_{1A} agonists, are involved in locally mediated control of IOP in conscious cynomolgus monkeys [31]. The mechanism by which a selective 5-HT_2 agonist, R-DOI, lowers IOP in normotensive monkeys is primarily by increasing uveoscleral outflow [33].

Summary for the Clinician

- The 5-HT2 receptor stimulation represents another pathway for IOP-lowering drug therapy development that is currently being pursued; however, the possibility of an overlapping effect via PG-related mechanisms must first be ruled out.

9.2.2.4 Nitric Oxide

Nitric oxide (NO) synthases are detected in ocular structures involved in fluid (aqueous humor) drainage from the anterior portion of the eye (CM and TM) as well as in layers of the retina and its circulation supply. Nitric oxide has the potential to be involved in both protective and damaging functions related to glaucoma. Inhibition or enhancement of its production in selected locations in the eye could be used to therapeutic advantage.

In human glaucoma eyes there are dramatic reductions in staining indicative of NO synthase activity in CM and outflow pathways compared with control eyes unrelated to general ocular decrease, the use of multiple glaucoma therapies, or the severity of the disease [4].

Nitric oxide-mimicking nitrovasodilators can act at various sites in the anterior segment of the eye to potentially decrease IOP by increasing outflow facility, decreasing episcleral venous pressure, decreasing aqueous humor flow, and relaxing the CM to potentially increase uveoscleral outflow. In human eyes the TM and CM are enriched sites of NO synthesis. Topical and intracameral administration of nitrovasodilators to monkey eyes in vivo decreases IOP and possibly increases outflow facility, respectively; however, the outflow facility increase is devoid of a clear-cut dose-response relationship, making the mechanism for the IOP lowering unclear. Nitrovasodilators relax TM and CM strips precontracted with carbachol in vitro. The IOP

and aqueous humor formation are decreased in isolated pig eyes perfused with nitrovasodilators [44], suggesting mechanisms independent of ocular vasculature.

Summary for the Clinician

- Development of nitrovasodilators for topical drop glaucoma therapy has not yet been initiated. This class of compounds has the potential to alter both aqueous humor inflow and outflow.

9.2.2.5 Gene Therapy

Gene therapy has the potential to alter the extracellular environment to enhance aqueous outflow via the uveoscleral route. Overexpression of PG synthesizing genes is being targeted for this type of therapeutic approach. Genes for all prostanoid receptors are expressed in human postmortem TM. Prolonged treatment of human TM cells with latanoprost or $PGF_{2\alpha}$ ethanolamide increases expression of genes for IGF-1 and fibroleukin. IGF-1 can increase the level of matrix metalloproteinase (MMP) enzymes in TM cells that can degrade components of the extracellular matrix. The protease activity of fibroleukin may also be active against extracellular matrix elements [50].

The MMP upregulation via gene therapy is another approach to enhance outflow through the TM and CM. It is one mechanism by which PGs are believed to enhance uveoscleral outflow through the CM. The TM also expresses a spectrum of MMPs. MMPs directly control outflow resistance in organ culture. MMP-3 (stromelysin) in an adenoviral vector construct transduces and shows expression in human TM cells in vitro and rat TM, iris, and uveoscleral pathways in vivo [22].

In the eye there are multiple sites of action for nitrovasodilators or NO donors as described above.

Selective stimulation of the endothelial form of NO synthase (NOS-3) could increase blood flow to the retina. It may also be possible that overexpression of NOS-3 in the anterior segment could potentially increase outflow facility, uveoscleral outflow, and decrease aqueous humor formation.

Stimulation of the neuronal and inducible forms of NOS (NOS-1 and NOS-2, respectively) most likely should be avoided since NO produced via these enzymes is often associated with the formation of highly destructive peroxynitrite.

Summary for the Clinician

- The gene therapy approach to enhance aqueous outflow via the uveoscleral route may advance rapidly as soon as vectorologists can develop vectors that produce long-term expression in the anterior segment without inducing inflammation. Genes that will be targeted for overexpression will likely include those whose products relax the CM and break down its extracellular matrix.

9.3 Inflow Suppression

Long-term use of drugs that decrease IOP by decreasing aqueous humor formation could have a negative effect on the eye. Some patients who have well-controlled IOP with timolol show evidence of reduced pressure control with continued administration. In cynomolgus monkeys treated with topical timolol for over 7 months, underperfusion of the TM results in meshwork densification, activation of meshwork endothelial cells, and increased extracellular material within the cribriform region. Unilateral aqueous flow suppression in monkeys with timolol (β1,2 antagonist) + dorzolamide (carbonic anhydrase inhibitor) and redirection of aqueous outflow in the same eye with topical $PGF_{2\alpha}$-ie (enhanced uveoscleral outflow) significantly decreases outflow facility [24]. Humans receiving oral acetazolamide over a several-week period demonstrate restoration of IOP but reduction in tonographic outflow facility.

Even though aqueous flow suppression is not the optimum approach for IOP reduction, it will continue to be a mechanism that can be targeted

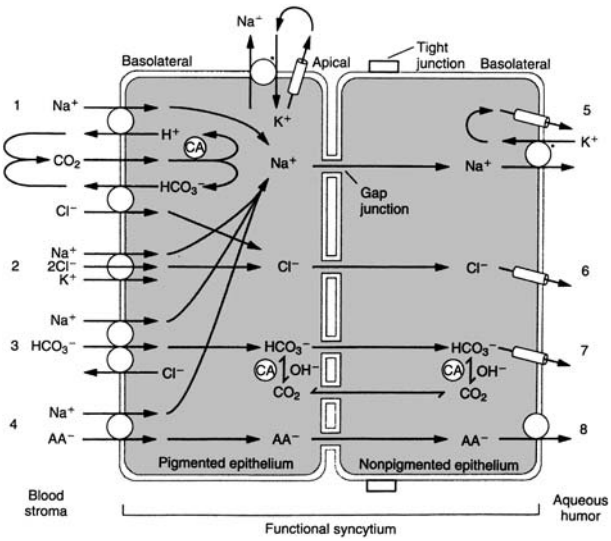

Fig. 9.6 Possible secretory pathways in the ciliary processes. *AA* ascorbic acid, *CA* carbonic anhydrase. (From [49])

for glaucoma therapy development at least for the immediate future.

9.3.1 Basic Structure

The ciliary processes consist of a central core of highly vascularized connective tissue stroma and a specialized double layer of epithelium that covers the stromal core. The inner epithelial layer (nonpigmented epithelium, NPE) is in direct contact with the aqueous humor, and the outer pigmented epithelium (PE) lies between the NPE and the stroma (Fig. 9.6).

Three physiological processes contribute to the formation and chemical composition of the aqueous humor: diffusion; ultrafiltration; and active secretion. Under normal conditions active secretion accounts for 80–90% of total aqueous humor formation. The active process of aqueous humor secretion is mediated by selective transport of certain ions and substances across the basolateral membrane of the NPE against a concentration gradient. Two enzymes abundantly present in the NPE that are involved in this process are sodium-potassium adenosine triphosphatase (ATP) and carbonic anhydrase. Sodium-potassium ATPase provides the energy for the metabolic pump, which transports sodium into the posterior chamber. As a result of active transport, aqueous humor in humans exhibits increased levels of ascorbate, some amino acids, and certain ions such as Cl^-. There is also passive transport of HCO_3^-.

Carbonic anhydrase is abundant in the basal and lateral membranes and cytoplasm of the pigmented epithelium and NPE of the ciliary processes. Inhibition of the production of HCO_3^- also leads to an inhibition of the active transport of Na^+ across the NPE, thereby reducing active aqueous humor formation (reviewed in [9]).

9.3.2 Opioids

Opioid receptors can modulate various functions in the eye. The kappa opioid receptor agonists, bremazocine and dynorphin A, lower IOP bilaterally following unilateral topical administration by suppressing aqueous humor formation in rabbits. The IOP and aqueous flow suppression are antagonized by the relatively selective kappa opioid receptor antagonist, nor-binaltorphimine (nor-BNI). However, species differences may exist, since the IOP-lowering response in monkeys following topical administration of bremazocine, could be completely blocked by maintaining the mean arterial pressure by simultaneous intravenous infusion of angiotensin II. Also, there is no effect of bremazocine on outflow

facility in monkeys, in contrast to rabbit studies [37].

Summary for the Clinician

- The efficacy of other opioid subtypes in modulating aqueous humor dynamics in primates has yet to be determined. Derivatives must be developed which minimize central and systemic effects.

9.3.3 Cannabinoids

A number of well-done studies show that in normal people, smoking a marijuana cigarette reduces IOP by ~24%, an effect comparable to other glaucoma medications. However, the duration of action of smoked or ingested marijuana, Δ9-THC or other cannabinoids, is unacceptably short – approximately 3.0–3.5 h. Decreased blood pressure, decreased optic nerve blood flow, and short duration of the IOP-lowering effect are significant actual and potential problems irrespective of the psychotropic effects. Another issue is whether cannabinoids can work topically. Δ9-THC, the supposedly active compound, applied topically, whether in single or multiple doses, whether once or four times daily, does not lower IOP.

The demonstration of a wide distribution of cannabinoid CB1 receptors in the human anterior eye segment and retina suggest that cannabinoids may influence several physiologcial functions in the human eye. The CB1 mRNA levels were significant in the human retina, ciliary body, and iris. Cannabinoid subtype selective compounds are currently being identified and studied.

Small reductions in IOP after topical administration of WIN 55,212-2, an aminoalkylindole with CB1 activity, to normal monkeys are attributed to reductions in aqueous humor flow [5]. Larger reductions in IOP are produced in glaucomatous monkeys after multiple topical treatments. In human glaucoma resistant to conventional therapies, topical WIN decreases IOP within the first 30 min [36]. WIN had no effect on in vitro monkey or dog CM resting tension or the contractile response to carbachol. Conversely, induction of bovine CM contraction in vitro by an endogenous and a synthetic cannabinoid results from CB1 receptor activation [28].

The cannabinoid HU-210 suppresses cell proliferation and cell viability in differentiating pheochromocytoma cells, in association with altered distribution of microtubules and microfilaments. The potential of an effect on the actin cytoskeleton suggests that one target may be outflow through the TM. Intracameral injection of HU-210 into monkey eyes in vivo produced a dose-dependent decrease in IOP but inflammation and corneal toxicity have delayed mechanistic studies.

Some endogenous cannabinoids, known to decrease IOP following topical application, may be hydrolyzed to arachidonic acid and thus act via PG pathways.

9.4 Drug Delivery

The main aim of pharmacotherapeutics is to attain effective drug concentrations at the intended site of action for a sufficient period of time to elicit a response. Major problems contributing to poor bioavailability with current ocular therapeutics include precorneal loss factors such as tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and relative impermeability of the corneal epithelium. Various approaches, such as viscosity enhancement, use of mucoadhesives, particulate drug delivery, vesicular drug delivery, prodrugs, and controlled release systems, such as Ocuserts, are being explored.

9.4.1 Vesicular Drug Delivery

Vesicular systems not only help in providing prolonged and controlled action at the corneal surface, but also help in providing controlled ocular delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface. In vesicular dosage forms, the drug is encapsulated in lipid vesicles, which can cross cell membranes. In ophthalmics, ve-

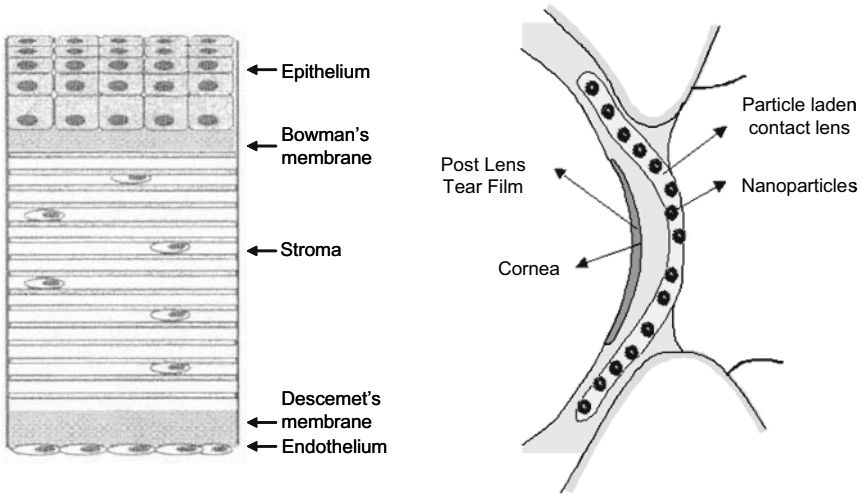

Fig. 9.7 The cornea (*left*) and particle-laden contact lens (*right*). (From [14, 45])

sicular drug delivery (reviewed in [21]) systems include liposomes and niosomes.

Liposomes are microscopic vesicles with a diameter ranging from 80 nm to 10 μm and are composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. These vesicles can entrap both hydrophilic and hydrophobic drugs. Positively charged liposomes seem to be preferentially captured by the negatively charged corneal surface but may cause initial irritation. Liposomes used in combination with bioadhesive polymers, collagen matrices, gel-forming solution, and gangliosides prolong the residence time of the preparation in the precorneal region; however, these combinations have short half-lives, limited drug capacity, and problems with sterilization that must be overcome before they can be used clinically.

Niosomes are non-ionic surfactant vesicles and are also bilayered structures that can entrap both hydrophilic and lipophilic drugs. They have the advantages of liposomes but are lower in cost, and have greater stability and ease of storage. Surfactants also act as penetration enhancers.

Nanoparticles are polymeric colloidal particles, ranging from 10 nm to 1 μm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed. They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membranes) or nanocapsules (solid matricial spheres). Nanocapsules show a better effect, possibly because the drug is in a non-ionized form in the core and can diffuse at a greater rate into the cornea. Nanocapsules also have better bioadhesive properties.

Encapsulation of drug in microspheres can prolong drug concentration in the aqueous humor by twofold.

9.4.2 Contact Lenses

Another form of encapsulated drug delivery is via soft contact lenses laden with drug formulations in nanoparticles dispersed in the lens material. Contact lenses made with the particle-laden hydrogels release therapeutic levels of drug for a few days. The drug delivery rate can be controlled by varying the loading of nanoparticles in the gel. Drug will diffuse from the particles, travel through the lens matrix, and enter the post-lens tear film (Fig. 9.7). This type of lens has advantages over soaked contact lenses in that more drug can be incorporated into the lens and release is continuous for longer periods of time. Also, it takes a few hours to load lenses with drug from aqueous solutions with a large fraction of the drug that is left in the solution going to waste.

Further development of particle-laden lenses for drug delivery is likely to be forthcoming [14].

9.4.3 Penetration Enhancers

Current topical drop therapy has begun to utilize penetration enhancers (reviewed in [20]) or absorption promoters to transiently increase the permeability characteristics of the cornea. Classes of penetration enhancers include calcium chelators (e.g., EDTA), surfactants (e.g.,. Brij), bile acids and salts (deoxycholate), preservatives (e.g., benzalkonium chloride), glycosides (e.g., Saponin), fatty acids, azone, cytochalasins, and ionophores. Caution must be exercised in the use of these agents since they themselves can penetrate the eye and may therefore produce unknown toxicological effects.

9.4.4 Bioadhesives

The capacity of some polymers to adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye by non-covalent bonds forms the basis of ocular mucoadhesion. Clearance time of bioadhesive polymeric systems is much slower since it now depends on the rate of mucus turnover rather than the tear turnover rate. The most commonly used bioadhesives are macromolecular hydrocolloids with numerous hydrophilic functional groups capable of forming hydrogen bonds. These do not cross biological membranes. Some examples of polymers used in ophthalmics for their mucoadhesive properties include: hyaluronic acid; hydroxypropyl methylcellulose; chitosan; DEAE-dextran; and polyacrylic acid derivatives (e.g., carbopols, polycarbophils, and carboxymethylcellulose; reviewed in [20]).

Mucoadhesive polymers, such as chitosan, have been used to coat nanoparticles to increase the time associated with the ocular mucosa and consequently prolong the penetration of drug into the ocular structures. Additional studies are needed to investigate the interaction and internalization of these particles and their toxicity following repeated administration. Other properties that make chitosan a good candidate for ocular drug delivery include its biodegradability, ocular tolerance, good rheological properties, and adaptability for designing different delivery systems (reviewed in [1]).

Receptor-mediated bioadhesion may also be accomplished with the use of lectins. Lectins are proteins that recognize and bind to sugar complexes attached with high specificity to proteins and lipids. Drug delivery to the eye may be prolonged by conjugation to lectins that adhere to the corneal and conjunctival epithelia, which is covered by mucin. Lectin-binding sites exist on the corneal and conjunctival epithelia of human and other species. The use of lectins in drug targeting is an area that will likely grow in years to come (reviewed in [3]).

9.4.5 Ocular Inserts

Ocular inserts placed in the cul-de-sac of the eye have the advantage over liquid formulations of prolonged retention and controlled release, allowing effective drug concentration in the eye over an extended time period with more accurate dosing and decreased risk of systemic side effects. However, ocular inserts have not been widely used in ocular therapy due to the foreign-body sensation that occurs. Ocular inserts prepared from mucoadhesive thiolated polymers are well tolerated by patients and may represent a promising new solid device for ocular drug delivery [17].

Summary for the Clinician

- Prolonging contact with the cornea for enhancing drug delivery may be accomplished by entrapment and encapsulation of the drug in liposomes, niosomes, nanoparticles, microparticles, contact lenses, and incorporation of bioadhesives into the vehicle solutions. Combinations of bioadhesive and nanoparticles are also promising approaches. Use of penetration enhancers may have undesirable toxicological effects.

9.5 IOP Monitoring

In contrast to the single point-in-time aspect of our current IOP measurement techniques, continuous monitoring of IOP would greatly improve managing glaucoma, testing of drugs that could lower IOP, and basic research into mechanisms of glaucoma. Increased IOP and wide diurnal IOP variations are considered major risk factors for glaucoma progression.

9.5.1 Contact Lenses

In humans, an IOP change of 1 mmHg causes a change of central corneal radius of curvature of approximately 3 μm. A soft contact lens has been developed with an embedded microfabricated strain gauge that allows measurement of changes in corneal curvature that correlate with IOP [25]. Incorporation of a telemetry chip and an antenna into this device will allow for wireless power and data transfer. Extended testing in humans will then be feasible.

9.5.2 Implantable Sensor

A completely encapsulated IOP sensor equipped with telemetric signal and energy transfer integrated into the haptics of an intraocular lens is being developed [16]. This approach will remain limited to patients who need intraocular surgery. Other telemetry-based sensors have been used in animal studies, but these have required some component to be implanted under the skin as well as into the eye.

Summary for the Clinician

- Continuous monitoring of IOP via a contact lens or implantable sensor may allow for better regulation of IOP during glaucoma therapy; however, a contact lens would need to be removed for topical drop therapy administration.

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Chapter 10

Filtering Bleb Imaging with Confocal Laser Technology (Rostock Cornea Module)

10

Rainer Guthoff, Günther Schlunck, Thomas Klink, Franz Grehn

Core Messages

- Long-term success of trabeculectomy depends particularly on intensive postoperative care about filtering bleb (FB) development.
- Standardized biomicroscopic FB evaluation is the basis for identification of impending FB failure.
- In this context, FB confocal in vivo microscopy with the Rostock Cornea Module (RCM) can give supplementary semiquantitative information about the presence of microcysts, cellular infiltrates, and the arrangement of stromal fibers.
- The distribution and character of blood vessels can be seen more precisely than by slit-lamp microscopy.
- The knowledge of FB histopathology helps in understanding the FB information obtained by confocal in vivo microscopy.
- As stromal patterns and infiltrating cells are visualized, this technique holds promise in the detection of structural alterations before they are accessible to conventional slit-lamp biomicroscopy.

10.1 Introduction

The aim of trabeculectomy is to lower the intraocular pressure (IOP) in otherwise uncontrolled glaucoma in order to avoid glaucoma progression. The maintenance of an IOP low enough to prevent glaucoma progression (target IOP) depends on a functioning filtering bleb (FB). The early postoperative healing period is crucial for the future FB function and therefore for the success of trabeculectomy. An unwanted strong FB wound healing can be inhibited by antimetabolites in this early stage; therefore, proper biomicroscopic evaluation of FB appearance is the most important tool [3, 19]. The FB appearance depends on the initial conjunctival situation, the course of surgery including the intraoperative use of antimetabolites, the postoperative stage, and the extent of wound healing. Classifications of characteristic FB findings were introduced to categorize FB features early and reproducibly, and to estimate the risk of failure more easily [19, 26]. Nevertheless, the proper time for intervention to prevent FB scarring can be missed, as the meaning of various FB features is unclear and FB assessment depends on the investigators' experience [3, 5, 15, 18, 19, 21]; therefore, additional methods for FB analysis are needed to determine the individual risk of FB failure.

The recently available laser scanning system (Heidelberg Retina Tomograph HRT II, Heidelberg Engineering, Germany) combined with a lens system [Rostock Cornea Module (RCM), licensed by Heidelberg Engineering] allows confocal in vivo microscopy of FB with high-resolution, uniform illumination and a lack of distortion (Fig. 10.1A). For the meaningful use of the information obtained by this technique it is essential to know the clinical FB appearance as well as FB histology, which stands behind the clinical picture. On this basis confocal in vivo FB microscopy may serve as an additional tool for FB evaluation.

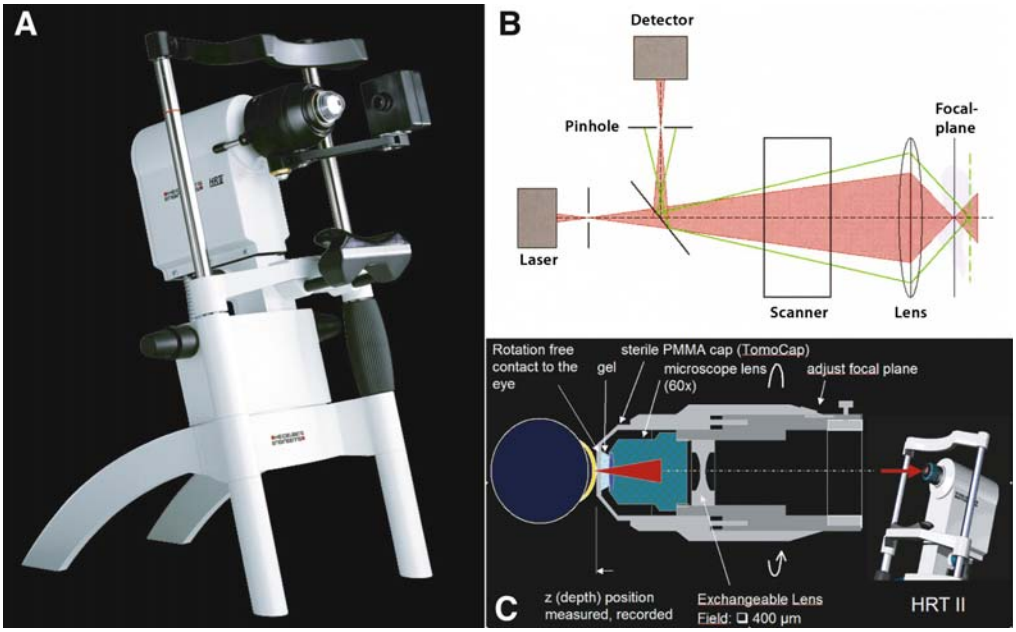


Fig. 10.1A The Heidelberg Retina Tomograph HRT II combined with Rostock Cornea Module. The video monitoring system allows for exact positioning (source: Heidelberg Engineering Inc.). **B** Principle of confocality [22]. **C** The external hydraulically operated Rostock Cornea Module (RCM) is mounted on the HRT II. The lens system is coupled to the eye with a PMMA cap. (Source: Heidelberg Engineering Inc., Heidelberg, Germany)

10.2 Confocal In Vivo FB Microscopy with the RCM/HRT II Based on the Laser-Scanning Technique

Laser-scanning ophthalmoscopy is based on the confocal principle (Fig. 10.1B). Laser light is transmitted through a pinhole diaphragm to one point of the examined object. A beam splitter separates the reflected laser light from the incident laser beam path. The light is deflected again through a confocal diaphragm before arriving at a photosensitive detector. Light reflected from areas off the focal plane is suppressed. The laser beam scans the sample point by point to build a two-dimensional image perpendicular to the optical axis of the device. By shifting the focal plane, images can be acquired from varying depths of the examined object, thus enabling a three-dimensional data set to be built up in a consecutive sequence.

The confocal laser-scanning microscope for the anterior eye segment is based on a laser-scanning system, the HRT II, which uses the refractive media of the eye to produce images of the posterior segment. The RCM is a microscope lens system adapted to the HRT II, which permits anterior segment depiction (Fig. 10.1C). The acquisition time for a volume sequence of 40 planes is 6 s, covering a depth range of 80 µm with each individual section image picked up in 0.024 s. The distance between two consecutive images is approximately 2 µm. In the sequence mode, up to 100 images can be collected with variable frame rates (1–30/s), which permits the recording of dynamic processes (e.g., blood flow in conjunctival vessels).

The size of the obtained field measures 250×250, 400×400, or 500×500 µm, depending on the applied microscope and additional lenses. Two different short focal length water immersion microscope lenses with a high numerical aper-

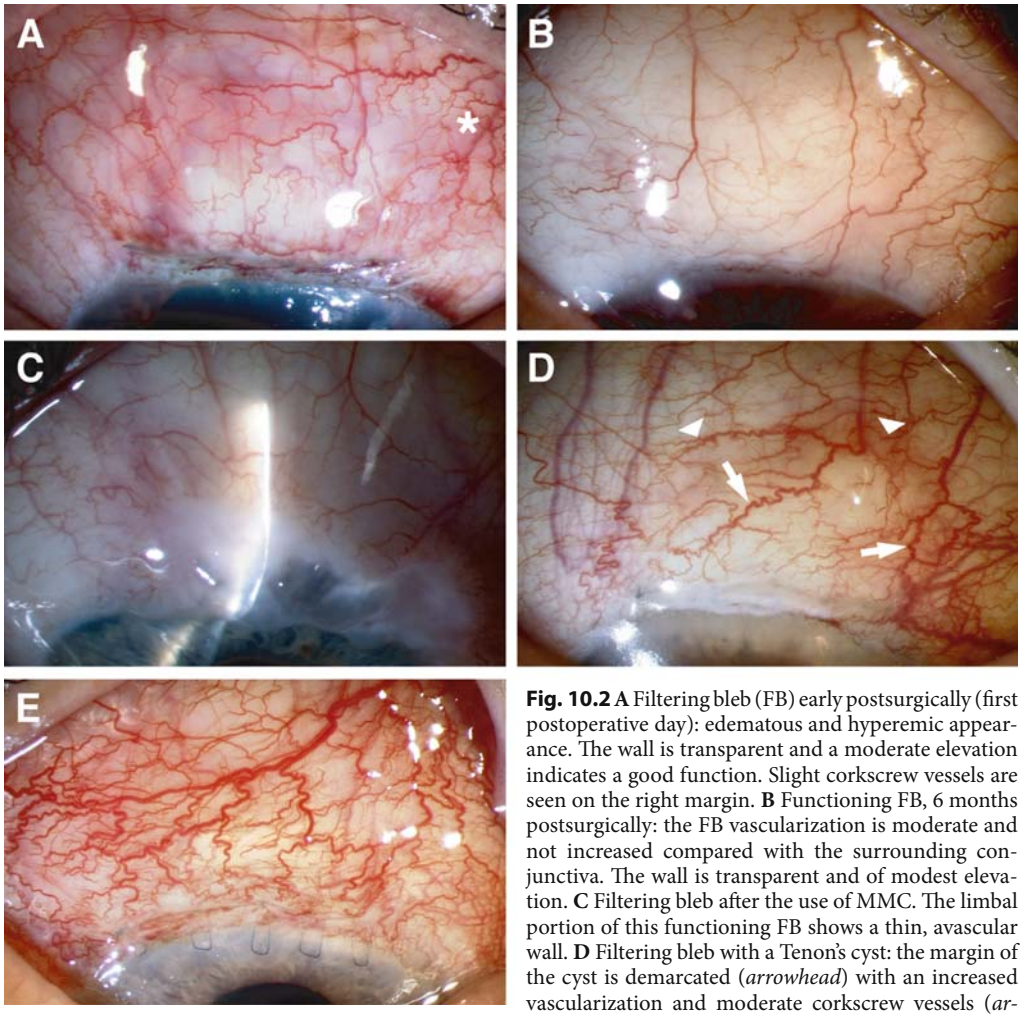


Fig. 10.2 **A** Filtering bleb (FB) early postsurgically (first postoperative day): edematous and hyperemic appearance. The wall is transparent and a moderate elevation indicates a good function. Slight corkscrew vessels are seen on the right margin. **B** Functioning FB, 6 months postsurgically: the FB vascularization is moderate and not increased compared with the surrounding conjunctiva. The wall is transparent and of modest elevation. **C** Filtering bleb after the use of MMC. The limbal portion of this functioning FB shows a thin, avascular wall. **D** Filtering bleb with a Tenon's cyst: the margin of the cyst is demarcated (*arrowhead*) with an increased vascularization and moderate corkscrew vessels (*arrows*). E Failing FB with strong vascularization consisting partly of corkscrew vessels

ture (Achroplan 63× W/ NA 0.95/ AA 2.00 mm, 670 nm, Carl Zeiss or LUMPLFL 60× W/ NA 0.90/ AA 2.00 mm, Olympus) are used to raise the magnification. The distance from the microscope lens to the cornea is kept stable by a thin PMMA cap (TomoCap). The cap is optically coupled to the lens and to the cornea by a protective translucent gel. A video camera, placed next to the microscope, monitors the precise position of the cap during examination.

Summary for the Clinician

- With digital-image-processing technology, quantitative data can be assembled non-invasively, fast, with high resolution, and with low illumination. The RCM/HRT II confocal laser-scanning microscope allows a reliable visualization of the bulbar conjunctiva as well as the FB.

10.3 Biomicroscopic FB Analysis

Frequent biomicroscopy with standardized FB assessments in the very early postoperative course is mandatory in order to intervene with antimetabolites, if necessary. The slit-lamp FB examination should focus particularly on vascularity, corkscrew vessels, microcysts, encapsulation, and elevation.

10.3.1 Early Postsurgical FB Biomicroscopy

In the first 24 postoperative hours, the FB is edematous and hyperemic, representing the extravasation of blood cells and proteins after the surgical trauma (Fig. 10.2A) [3].

10.3.2 Biomicroscopy of Functioning FB with Good or Over-Filtration

Functioning FB can have a variable appearance. They can be diffuse or localized with a non-demarcated margin (Fig. 10.2B). The wall is thin, translucent, and can contain microcysts which are detectable biomicroscopically by indirect illumination. The presence of microcysts is correlated with lower IOP [21]. The elevation over the sclerotomy site is moderate. The wall is avascular or discretely vascularized [19, 24].

Over-filtrating FB are large width extending of two quadrants or more, a marked elevation, and with characteristics otherwise similar to functioning blebs [18].

After the use of MMC or 5-Fluorouracil, the wall over the central portion of the bleb is typically thin, cystic, and avascular (Fig. 10.2C) [19, 24].

10.3.3 Tenon's Cyst

An encapsulated FB (Tenon's cyst) is localized, dome-shaped, monocystic, and tense with vascular engorgement of the overlying conjunctiva (Fig. 10.2D); the latter is movable over the Tenon's capsule. This type appears 2–4 weeks after surgery [19, 24]. A needling procedure with 5-Fluorouracil should be performed.

10.3.4 Scarring FB

Failing FB due to scarring are hyperemic with closely arranged, thick corkscrew vessels (Fig. 10.2E). The surface is often opaque and the FB wall appears thickened [3, 18, 19, 21].

10.3.5 Standardized FB Classification and Bleb Score

Various FB classifications are used to describe the FB to assess the function. Vascularization, corkscrew vessels, microcysts, encapsulation, and bleb elevation are FB features of particular importance for the outcome of FB [18, 19, 21, 25]. These assessment criteria are used for a semi-quantitative FB score for standardized classification to evaluate FB reliably and easily (Table 10.1) [11]. Increased vascularization, corkscrew ves-

Table 10.1 Standardized filtering bleb classification. (From [11])

Vascularization	Corkscrew vessels	Microcysts	Encapsulation
0 = Avascular	0 = Absent	0 = Absent	0 = Absent
1 = Equal to the surrounding conjunctiva	1 = In one third	1 = Above sceral flap	1 = In the first third
2 = Enhanced	2 = In two thirds	2 = At one side	2 = In the second third
3 = Massive	3 = In the whole FB	3 = In the whole FB	3 = In the whole FB

sels, absence of elevation, or increased elevation associated with encapsulation are indicators for failing FB, whereas moderate vascularization and microcysts indicate good function.

Summary for the Clinician

- Intensified postoperative care with standardized FB evaluation is necessary in order to prevent FB failure. The biomicroscopic FB examination should focus on vascularity, corkscrew vessels, encapsulation, and elevation.
- The presence of microcysts in a functioning FB is correlated with lower IOP. An encapsulated FB has a movable conjunctiva over the Tenon's capsule and appears 2–4 weeks after surgery. Failing FB due to scarring typically present strongly vascularized with corkscrew vessels.

10.4 General Anatomical Considerations

10.4.1 Normal Anatomy of the FB Relevant Region

The relevant structures for FB formation include the bulbar conjunctiva, Tenon's capsule, and the episclera; these can easily be investigated by confocal laser-scanning microscopy. The sclera is normally not accessible, presumably due to the highly scattering surface tissues, which diminish the amount of reflected light from the deep situated sclera.

10.4.1.1 Conjunctiva

The bulbar epithelium consists of two or more cylindrical cell layers forming stratified columnar epithelial layer (Fig. 10.3A).

The basal cells with their thin basement membrane are cylindrical with variable numbers of interspersed melanocytes. They are smaller and more densely packed in the limbal region.

The middle and superficial conjunctival epithelium cells appear polygonal and flatten toward the surface. The much larger goblet cells are normally present in the middle and superficial layers and are only occasionally found in the basal layer.

The stroma is composed of a superficial layer with loosely arranged collagen and numerous lymphatic channels and a deeper fibrous layer. While the bulbar stroma is wide and loose, it is thin and dense near the cornea where it merges with Tenon's capsule and the episclera.

Fibroblasts, mast cells, melanocytes, and some inflammatory cells are normally present in the conjunctival stroma. Branches of the anterior ciliary artery supply the bulbar conjunctiva. The bulbar conjunctival veins drain into the episcleral venous plexuses.

10.4.1.2 Tenon

Tenon's capsule is a connective tissue layer of compactly arranged collagen with a few fibroblasts that completely envelops the globe from the limbus to the optic nerve. The anterior portion of Tenon's capsule is thin, merges with the outer portion of the limbal sclera, and is more adhesive to the globe than the posterior portion (Fig. 10.3A). The outer layers of Tenon's capsule are only loosely adherent to the conjunctiva.

10.4.1.3 Episclera

The episclera forms the superficial scleral layer, and consists of loosely arranged collagen bundles interspersed with fibroblasts, elastin fibers, and occasional melanocytes (Fig. 10.3A). The strongly vascularized anterior episcleral portion is supplied by branches of the anterior ciliary arteries. In the deeper portion the connective tissue bundles become firmer and thicker as they merge with the stromal collagen.

10.4.2 Histopathology of FB

The amount of histopathological reports on FB is limited. Naturally, the amount of descriptions of

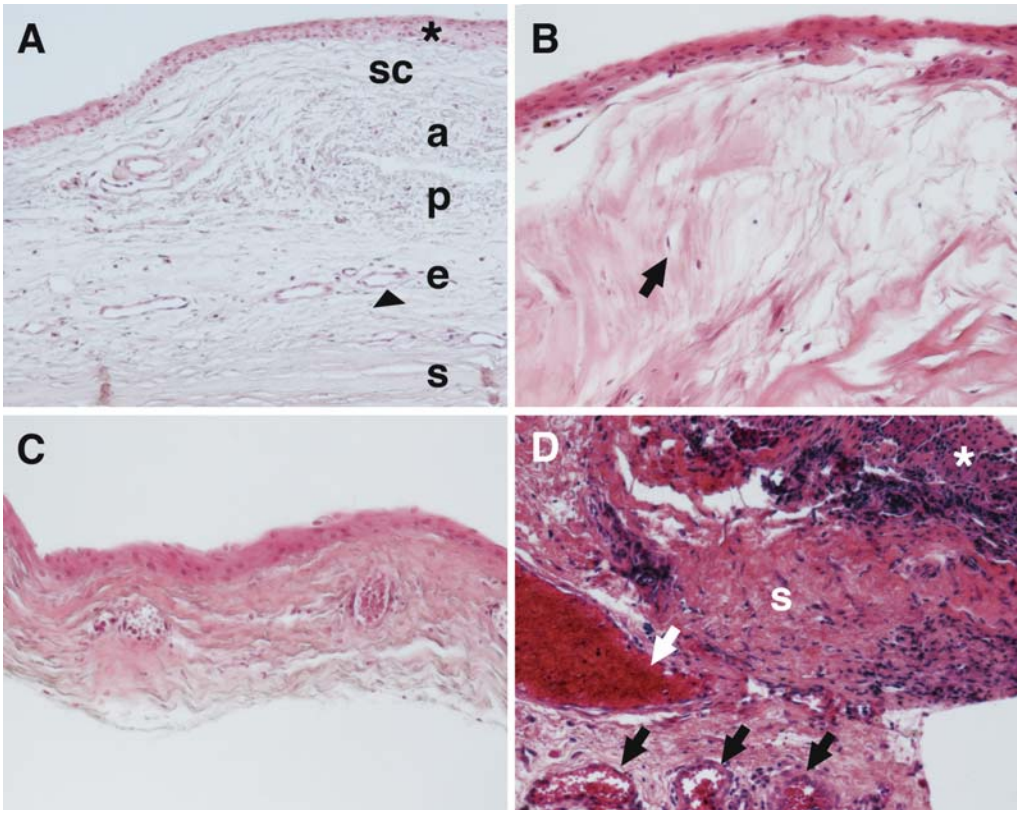


Fig. 10.3 Light microscopy of normal FB-relevant region and FB (hematoxylin–eosin, magnification ×10). **A** Normal bulbar conjunctiva consisting of epithelium (*asterisk*) and loose connective tissue with some vessels (*sc*). Note the anterior (*a*) and posterior (*p*) portion of Tenon's capsule. Beneath, episclera (*e*) with larger vessel (*arrowhead*) and sclera (*s*) is seen. **B** Luxated FB 3 years after trabeculectomy. The stroma is arranged in fine fibers and a few fibroblasts (*arrow*). Vessels are absent. **C** Tenon's cyst from a revised FB. Note the compacted vascularized substantia propria and Tenon's capsule, which represent the FB wall. **D** Failed FB. The excised FB portion shows a thickened epithelium (*asterisk*), a dense collagen-rich stroma (*s*) with a large vessel (*white arrow*). The *black arrows* indicate a corkscrew vessel

functioning FB is smaller than that of scarring, surgically re-treated FB, obtained for further histopathologic examination.

10.4.2.1 Early Postsurgical FB

In the early postoperative course functioning FB treated with MMC contain edematous connective tissue with erythrocytes, blood vessels, and fibrocytes [17].

10.4.2.2 Functioning FB with Good or Over-Filtration

In a functioning or over-filtrating bleb, the central FB portion shows an epithelium with a normal thickness and a few goblet cells (Fig. 10.3B) [1, 7].

The substantia propria is composed of loosely arranged connective tissue with an increased cellularity or only a mild chronic inflammation with lymphocytes, macrophages, and few fibroblasts [2, 4, 6, 12, 20].

After use of Mitomycin C, the epithelium may show irregular thickness [17]. Intraepithelial microcysts and a higher amount of goblet cells is seen sometimes [7, 23, 24].

A prominent hypocellular avascular connective tissue zone may be seen under the thickened epithelial basement membrane [7, 23]. Microcystic spaces are seen within the superficial stroma [1]. The cysts can be lined by epithelium. [8]. The stroma is composed of loosely arranged connective tissue of irregular collagen with a slight or absent subepithelial inflammatory response of lymphocytes, macrophages, and fibroblasts [1, 6, 10, 14, 17, 23, 24].

A small degree of fibrovascular scarring is found in the conjunctival substantia propria [4, 6].

After treatment with 5-Fluorouracil, the corneal epithelium is thinned or absent [4, 23].

The stroma may present moderate scarring with basophilic collagen degeneration with focal distribution of lymphocytes and plasma cells [4].

10.4.2.3 Tenon's Cyst

In late-onset failures within 9 months postoperatively, an encapsulated FB consists of hypocellular fibrous tissue composed of irregular collagen bundles (Fig. 10.3C) [19]. Stromal blood vessels of normal appearance as well as lymphatic vessels may be present in late-onset failure [9]. Mononuclear inflammatory cells may occur.

After use of MMC, areas of proliferating fibroblasts are seen within the connective tissue. In the FB margin, profuse amount of convoluted collagen and fibroblasts are present [13, 17].

10.4.2.4 Scarring FB

In scarring FB the epithelium is thinned or of normal thickness, but may be hyperplastic in failures within the first 6 months (Fig. 10.3D) [1, 13].

The subepithelial stroma is dense and thickened by deposited thin collagen fibrils, which are orientated in an uniform parallel structure [1, 10, 16]. The collapsed FB may stick to the episclera [4]. Numerous spindle-shaped fibroblasts are seen [9, 16]. A marked inflammatory reaction of the stroma and of Tenon's capsule consisting of macrophages and lymphocytes are found [4, 6, 9]. Some of the numerous blood vessels may be leaky [1, 19, 16].

The episcleral fibrocellular tissue of dense collagen is orientated parallel to the scleral lamellae [4].

After MMC treatment, a fibrocellular proliferation is found in the inner stroma [4], which is composed of randomly orientated fibers with large amounts of collagen.

Only a few vessels and spindle cells are seen [16].

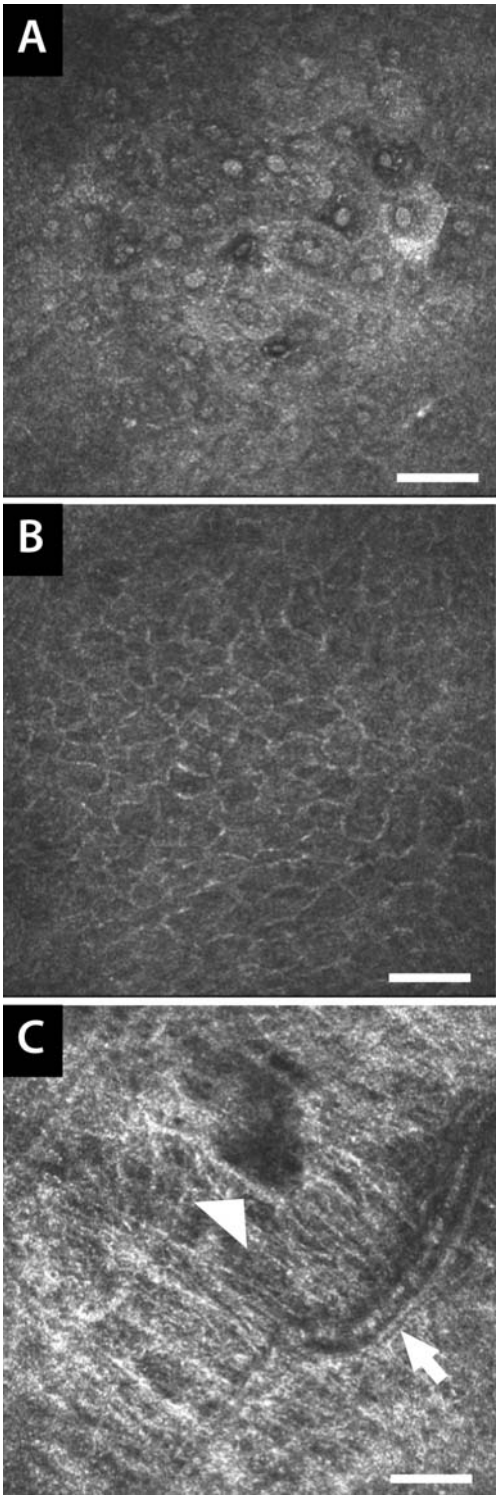
After the use of 5-FU, a thickened epithelium is found. Beneath it a dense layer of hypercellular connective tissue with elongated fibroblasts oriented parallel to the surface is present in Tenon's layer and episclera. Some lymphatic channels and arterioles can be detected [17].

Summary for the Clinician

- In a functioning or over-filtrating bleb, the central FB portion shows an epithelium with a normal thickness and the substantia propria is composed of loosely arranged connective tissue. Within the superficial stroma microcystic spaces are seen. An encapsulated FB consists of hypocellular fibrous tissue composed of irregular collagen bundles. In scarring FB the subepithelial stroma is dense and thickened by deposited thin collagen fibrils, which are oriented in parallel. A marked inflammatory reaction of the stroma and of Tenon's capsule consisting of macrophages and lymphocytes is found. Blood vessels may be leaky.

10.5 FB Confocal In Vivo Laser-Scanning Microscopy

The filtering bleb can be visualized with high contrast using the Rostock Cornea Module (RCM) attachment with the HRT II and, because of the good quality of depth resolution, can be imaged



in optical sections of a few-microns thickness (Fig. 10.1C).

The RCM microscopy of the FB-relevant region is performed under topical anesthesia in down gaze while the upper lid is slightly elevated to expose the 12 o'clock FB area. The conjunctival surface is optically coupled to the acrylic cap of the RCM by a protective, translucent gel. A video camera controls the position.

10.5.1 Normal Anatomy of the FB Relevant Region

10.5.1.1 Conjunctiva

Normal conjunctiva is accessible to a maximal depth of 220 µm by confocal laser-scanning microscopy. The cell membrane and nucleus of superficial epithelial cells are bright, whereas the cytoplasma is hyporeflective (Fig. 10.4A).

The polygonal cells of the intermediate epithelial layers are characterized by a bright nucleus.

The basal cells show a thick bright cell membrane and a polygonal shape (Fig. 10.4B). The nucleus is less demarcated than superficially.

The subepithelial stroma is diffusely hyperreflective. At a greater depth, the substantia propria shows straight, fine to moderately thick fibers of intermediate density which criss-cross parallel to the surface to form a reticular pattern (Fig. 10.4C). Occasionally, small vessels of a diameter up to 60 µm is seen. Stromal cystic spaces, probably representing lymphatic channels, are found.

Fig. 10.4 Confocal in vivo microscopy of normal conjunctiva (*space bars* represent 50 µm). **A** Superficial epithelial cells show round nuclei with scarcely distinguishable cell borders at a depth of 3 µm. **B** Basal polygonal cells at a depth of 25 µm. The nucleoli cannot be differentiated. **C** Conjunctival stroma at a depth of 46 µm presents mainly reticular arranged fibers. Small blood vessel (*arrow*) and lymphatic channels (*arrowhead*) are seen

10.5.1.2 Tenon and Episclera

The Tenon and episclera are not distinguishable from the deep conjunctival stroma.

10.5.2 Filtering Blebs

Filtering blebs can be categorized clinically in functioning or failing blebs according to the standardized classification (see 10.3.5) as follows: functioning FBs include a grade-1 or grade-2 vascularity, the absence of corkscrew vessels, and encapsulation, whereas failed FBs or impending failure enclose a grade-3 vascularity and corkscrew vessels, or encapsulation.

The following parameters assessed in confocal biomicroscopy can be graded semiquantitatively: the presence of epithelial or subepithelial microcysts and cellular infiltrates; width, curvature, and arrangement of stromal fibers in the central FB; as well as the number, width, and curvature of subepithelial vessels.

According to the stromal fiber appearance, connective tissue can be categorized into four types: trabecular; reticular; corrugated; and compact. Trabecular stroma is characterized by wide spaces between fine, straight fibers. In reticular stroma, straight fibers cris-cross closely with small gaps in between. A corrugated pattern consists of short, curved, and randomly arranged fibers. Compacted stroma is characterized by wide, hyperreflective fibers orientated in parallel. Often, mixed types of stromal patterns occur.

10.5.2.1 FB Early Postsurgically

The presence of epithelial cystic spaces is the most striking difference to normal conjunctival epithelium (Fig. 10.5A). In the early postoperative course (within the first 60 postoperative days), we found these cysts in all FB to a different extent, some containing cells. We found an intact epithelium also after MMC treatment.

The conjunctical stroma can show thickened fibers, extravasated red blood cells, and congested blood vessels (Fig. 10.5B). Lymphocytes are found in the epithelium, the epithelial cysts, as well as in the anterior stroma for up to 4 months after surgery.

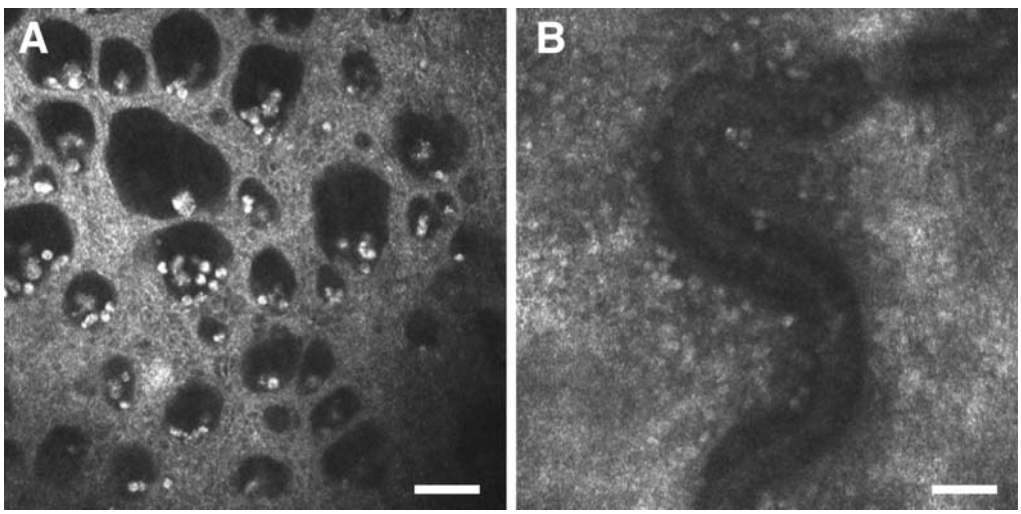


Fig. 10.5 Confocal in vivo microscopy of an FB at the first postoperative day (same patient as in Fig. 2A, *space bars* represent 50 µm). **A** Epithelium with numerous microcysts with a diameter up to 100 µm containing red blood cells. Red blood cells are also seen among epithelial cells. **B** Conjunctival stroma at a depth of 44 µm. Extravasated erythrocytes of contorted vessels reflect the clinical hyperemia and a slight hyposphagma. Edematous stromal fibers appear congested and thickened.

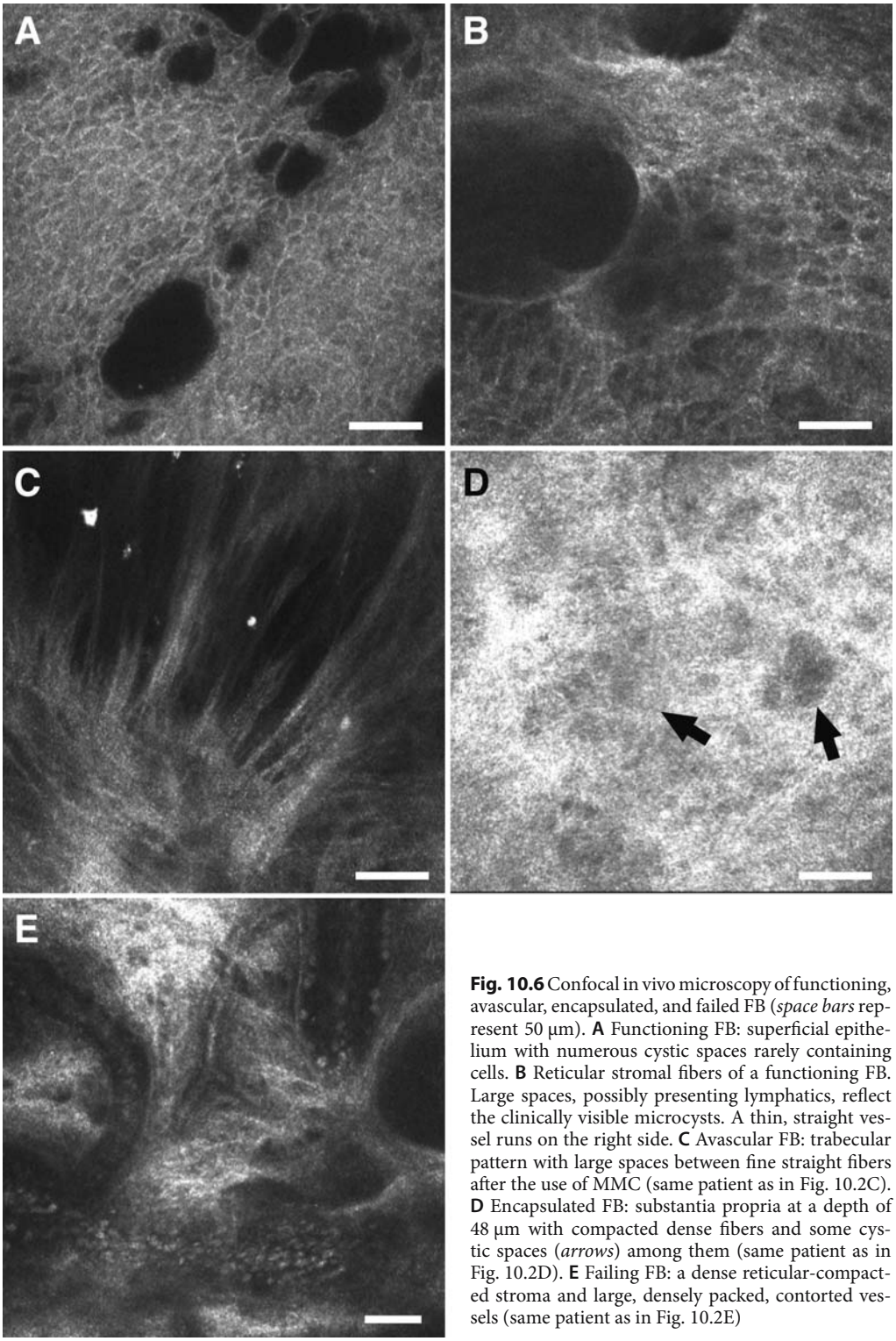


Fig. 10.6 Confocal in vivo microscopy of functioning, avascular, encapsulated, and failed FB (*space bars* represent 50 µm). **A** Functioning FB: superficial epithelium with numerous cystic spaces rarely containing cells. **B** Reticular stromal fibers of a functioning FB. Large spaces, possibly presenting lymphatics, reflect the clinically visible microcysts. A thin, straight vessel runs on the right side. **C** Avascular FB: trabecular pattern with large spaces between fine straight fibers after the use of MMC (same patient as in Fig. 10.2C). **D** Encapsulated FB: substantia propria at a depth of 48 µm with compacted dense fibers and some cystic spaces (*arrows*) among them (same patient as in Fig. 10.2D). **E** Failing FB: a dense reticular-compacted stroma and large, densely packed, contorted vessels (same patient as in Fig. 10.2E)

10.5.2.2 Functioning FB with Good or Over-Filtration

Filtering blebs were clinically evaluated according to the standardized classification and categorized as functioning blebs when the following criteria were fulfilled (see 10.3.5): grade-1 or grade-2 vascularity; the absence of corkscrew vessels; and encapsulation.

Functioning FB often show intraepithelial microcysts (Fig. 10.6A) that rarely contain cells. These cells mainly represent lymphocytes. Some FB contain cystic spaces presumably reflecting the biomicroscopically visible microcysts (Fig. 10.6B). The stromal patterns are mainly trabecular with long filigrane arborescent fibers and wide spaces or reticulo-trabecular with single fibroblasts. In the conjunctival stroma, blebs with good function show either large pores surrounded by collagenous septae or a loose meshwork of collagen fibers with single fibroblasts. Predominantly small (diameter < 60 µm), straight vessels are observed subepithelially and in the deep stroma.

At late stages after surgery functioning blebs rarely show intracystic epithelial cellular infiltrates, subepithelial cysts, or a compacted stromal architecture.

Trabecular and reticular stromal patterns with a diminished collagen network enclosing large spaces without vascularization are found mainly after use of MMC and, to a lesser extent, after 5FU treatment (Fig. 10.6C). In eyes without antimetabolite use, corrugated and compacted stromal patterns predominate.

10.5.2.3 Tenon's cyst

Some microcysts are found in the conjunctival epithelium of FB with Tenon's cyst. The stroma can show a reticular pattern. Deeper, densely packed corrugated–reticular hyperreflective fibers are seen, presumably representing the Tenon's capsule (Fig. 10.6D).

10.5.2.4 Scarring FB

Filtering blebs with grade-3 vascularity and corkscrew vessels according to the standardized classification were clinically categorized as failed FBs or impending failure (see 10.3.5).

Scarring FB show less microcysts, which, if present, often contain cells. Corrugated, compacted, or mixed stromal patterns are common in early-failing blebs as well as contorted and large (diameter > 60 µm) vessels (Fig. 10.6E). Subepithelial cystic spaces and stromal cellular infiltrates are rare. At late stages after surgery, late-failing blebs show intracystic cellular infiltrates, subepithelial cysts, and predominantly a compacted stromal architecture.

Summary for the Clinician

- In all early FB epithelial cystic spaces are seen. In functioning, early postsurgical FB the intraepithelial microcysts are frequent. Mainly trabecular stromal pattern with long filigrane arborescent fibers and wide spaces or reticulo-trabecular indicate good function. The blood vessels are mainly small and straight. Corrugated and compacted stromal patterns predominate in the absence of antimetabolites.
- Tenon's capsule presents as deeper, densely packed corrugated–reticular hyperreflective fibers. The few microcysts of failing FB often contain cells. Corrugated, compacted, or mixed stromal patterns with contorted and large vessels are commonly found in early failing blebs. Late postsurgically, failing blebs show a predominantly compacted stromal pattern.

10.5.3 Clinical Relevance of Confocal In Vivo Laser-Scanning Microscopy in Filtering Bleb Evaluation

The slit-lamp FB evaluation is the main tool to detect early signs of FB scarring and to prevent failure of trabeculectomy. Certain clinical signs, such as moderate vascularity and elevation, as well as the presence of microcysts, indicate a functioning FB. On the other hand, failure or impending FB failure is indicated by strong vascularization with corkscrew vessels, a flat FB, or a marked encapsulation. Standardized FB classifications help to assess the healing stage more precisely [5, 11, 18, 21, 25]. Based on this clinical examination, intensified postoperative care, including the application of 5-Fluorouracil, can substantially increase the success rate of trabeculectomy achieving a target IOP without topical medication [15]. Despite this time-consuming follow-up, the appropriate time for intervention with antimetabolites to prevent FB scarring is easily missed.

Filtering bleb confocal in vivo microscopy with the RCM can give supplementary semiquantitative information about the presence of epithelial or stromal microcysts, the type of cellular infiltrates, and the different arrangement patterns of stromal fibers. The distribution and character of blood vessels is seen more precisely than by regular biomicroscopy. As stromal patterns and infiltrating cells are visualized, this technique holds promise to detect structural alterations before they are accessible to conventional slit-lamp biomicroscopy. With this, confocal in vivo microscopy may help to detect FB scarring. As in the other imaging diagnostics procedures, it is necessary to be familiar with the clinical FB appearance to judge the information obtained by confocal in vivo microscopy. Furthermore, the knowledge of FB histopathology helps to interpret confocal in vivo microscopy surface parallel FB slices.

The exact woundhealing process after trabeculectomy is not clearly understood. Histological and immunohistochemical data about early stage of human FB wound healing are rare. On the other hand, intensive in vitro studies and animal models try to understand FB scarring to prevent delayed FB failure in the future. Confocal in vivo microscopy may augment our understanding as it provides data of this sensitive, early postoperative period.

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Miscellaneous

Chapter 11

Update on Tube-Shunt Procedures for Glaucoma

11

Jeffrey Freedman

Core Messages

- Bleb formation depends on proinflammatory substances in the aqueous, as well as tissue reaction, both of which can be controlled.
- Management of aqueous flow to the plate surface, and elimination of Tenon's capsule from the bleb, can help with the development of a functional bleb.
- Both valved and non-valved implants can be used to control hypotony, the latter by various methods of tube occlusion.
- Plate size does not seem to make a difference in IOP control in long-term studies.
- Supra-Tenon's placement of the implant is a method that can be used to control bleb fibrosis.
- Corneal graft survival is decreased in eyes with glaucoma implants.
- In neovascular glaucoma, while pressure control may be successful early, long-term results are poor as a result of the underlying disease.
- Motility disturbances are more common with Baerveldt glaucoma implants.
- Bleb fibrosis remains the main cause for glaucoma implant failure.

11.1 Introduction

11.1.1 Basics

Present-day glaucoma implants, i.e., long-tube implants, were introduced by Molteno et al. in 1976 [31]. The most commonly used implants include Molteno and Ahmed single- and double-plate implants, and the Baerveldt and Krupin implants. All implants are long-tube implants based on the original Molteno design. The Ahmed and Krupin implants are valved implants. The most recent addition to tube-shunt devices has been the Ex-Press shunt, a non-valved flow restricting implant made of stainless steel, which is discussed later. The basic concept of the long-tube implants is the creation of a filtering bleb over the distal plate.

11.1.2 Bleb Physiology

Epstein [12] showed that when aqueous comes into contact with conjunctiva and Tenon's capsule, an inflammatory reaction occurs, due to the contents of the glaucomatous aqueous. Subsequently, these factors have been identified and amongst other components, such as prostaglandins, and various eicosanoids, tissue growth factor-beta (TGF β) has been shown to occur in glaucomatous aqueous [43]. TGF β is strongly proinflammatory, and when glaucomatous aqueous comes into contact with subconjunctival tissue, it induces an inflammatory reaction, and if excessive, will result in bleb fibrosis and poor functioning of the filtering bleb. High pressure within the bleb results in the secretion of TGF β by the bleb lining [17]. The higher the pressure within the bleb, the greater the amount of TGF β is formed, resulting in inflammation of the bleb wall and subsequent fibrosis and poor bleb function; therefore, the higher the pressure within the bleb, the less likely the development of a good filtering bleb, this having significance when dealing with the hypertensive stage of the bleb which occurs 4—6 weeks after implantation in most cases.

Molteno et al. have described the histopathology of Molteno implant capsules in cases of primary and secondary glaucoma [35]. Without aqueous flow (first stage of a two-stage operation), the episcleral plates of Molteno implants were encapsulated by a very thin (20–60 μm) avascular collagen layer. The second stage of a two-stage insertion, with delayed drainage of aqueous and early temporary postoperative intraocular pressure (IOP) increase to 25–35 mmHg, produced thin (190–250 μm), permeable capsules with fewer fibrovascular than fibrodegenerative components. Insertion of nonligatured implants with immediate aqueous flow produced thicker capsules (300–600 μm) composed of an outer fibrovascular layer and an inner fibrodegenerative layer of approximately equal thickness. Three stage insertion of modified Molteno implants with postoperative IOP not exceeding 12 mmHg produced the thickest, most heavily fibrosed, and impermeable capsules composed entirely of dense fibrovascular tissue without a fibrodegenerative layer. Molteno concluded that without aqueous flow, the episcleral plate of the implant stimulates encapsulation by a thin avascular collagenous layer. With aqueous flow, an immediate inflammatory reaction develops in the episcleral connective tissues that include collagenous and vascular components. After a variable delay, a fibrodegenerative process develops in the deeper layers of the capsule , which is maintained by activation, migration, apoptosis, and production of death messengers by mesodermal cells. The fibrodegenerative process may depend on sufficient increases of IOP for aqueous to displace interstitial fluid from the deeper layers of the capsule. The final thickness of the capsule depends on the timing of these opposing processes which can be influenced by surgical technique and postoperative medications.

The understanding of bleb physiology has important significance as to the ultimate functionality of the bleb.

11.1.3 Therapeutic Options Related to Bleb Physiology

The components of the bleb that can be affected therapeutically are the aqueous and the tissue lining the bleb. This can be achieved by medical or surgical options, or a combination of both.

11.1.3.1 Medical Control of Bleb Fibrosis

Molteno recognized the need to suppress the inflammatory reaction over the plate in order to obtain a functioning bleb, and described the use of both topical and systemic anti-inflammatory medications [32, 33]. The topical regimen consisted of phenylephrine drops 0.5%, topical steroids, and atropine, used for 4–6 weeks. The systemic group consisted of prednisone 5 mg tid, diclofenac 50 mg tid, and colchcine 0.2 mg tid for 4 weeks. The disadvantages of the systemic regimen are potential side effects of the medications used. The use of topically applied mitomycin C, to prevent bleb fibrosis in glaucoma implant surgery, has been shown in most reported studies to be ineffective [2, 25].

11.1.3.2 Surgical Options for Control of Bleb Fibrosis

The surgical options consist of managing the "glaucomatous" aqueous and the tissue over the plate. The initial aqueous contains proinflammatory substances, which must be prevented from reaching the surface of the plate and thereby reacting with the overlying tissue. This can be achieved by blocking the tube with a releasable stent for a period of 10–14 days. During this time the IOP needs to be normalized resulting in the elimination of the "glaucomatous" aqueous and its proinflammatory contents. This lowering of IOP can be achieved by both the effect of the shock of the surgery and the use of anti-glaucomatous medications. Allowing "glaucomatous" aqueous to reach the plate results in a more intense hypertensive phase, and subsequently a less functional bleb, as has been reported with the use of valved implants [36].

The tissue component of the bleb may also be modified surgically. The tissue most responsible for the ultimate formation of the bleb is Tenon's capsule. In patients who have demonstrated a tendency to excessive fibrosis, as seen by previ-

ously failed filtering surgery, or glaucoma implants, Tenon's tissue may be eliminated by the placement of a subsequent glaucoma implant between Tenon's capsule and the overlying conjunctiva [15]. This technique is described later.

Summary for the Clinician

- Understanding bleb physiology plays an important role in achieving a functioning bleb. The discovery of proinflammatory components of the aqueous has highlighted the important role of aqueous control in developing a successful bleb. The combination of topical and systemic anti-fibrotic medication can result in less bleb fibrosis. Management of aqueous flow to the plate surface, and elimination of Tenon's capsule from the bleb, can help with the development of a functional bleb.

11.2 Indications for Implant Use

Initially the implants were used predominantly in those cases where previous glaucoma surgery had failed, as well as in cases known to do poorly with conventional glaucoma surgery. The latter group included: uveitic glaucoma; aphakic and pseudophakic glaucoma; neovascular glaucoma; glaucoma associated with corneal transplants; and congenital glaucoma with iridocorneal dysgenesis. With the advent of the use of antimetabolites in glaucoma surgery, many of the conditions mentioned in this group are now treated with conventional surgery first. Exceptions include neovascular glaucoma, extensive scarring of the conjunctiva, congenital glaucoma with iridocorneal dysgenesis, aphakic glaucoma, and glaucoma associated with corneal transplants, all of which do better with glaucoma implants.

11.2.1 Which Implants to Use

The choices are valved or non-valved, and size. The two implants used that are valved are the Ahmed and Krupin implants. The major advantage of the valved implant is less postoperative hypotony, in most cases. Disadvantages include valve blockage, occurring early or late following implantation. Both circumstances result in a failure of aqueous drainage. The valve systems of the Krupin and Ahmed devices are designed to open at 11 and 8 mmHg, respectively; however, this is not always the case, and hypotony can still occur with these valved implants. Another disadvantage of valved implants is a more intense hypertensive phase and subsequent thicker bleb with less pressure lowering [36].

The Molteno and Baerveldt implants are non-valved. The major disadvantage is hypotony in the immediate postoperative period, but this has been largely eliminated by occluding the tube in the immediate postoperative period. This occlusion has been achieved in a variety of ways, all of which allow the opening of the tube to be facilitated at a later time, when a fine capsule has already formed over the plate, eliminating hypotony when aqueous reaches the plate surface[11, 23, 38]. This also allows normal aqueous to reach the plate surface, resulting in a decreased hypertensive phase and a thinner, more functional bleb.

11.2.2 Significance of Plate Size

The use of double-plate implants and different-size single-plate implants was based on the concept that a larger plate area resulted in greater pressure lowering. This original concept was proposed by Molteno [30], and subsequent reports confirmed this observation [19]. Based on the concept that a larger surface was better, the double-plate implant became more used than the single plate, and larger single plates were developed, such as the various-sized Baerveldt implants. These larger-sized single-plate implants became more popular because surgical implantation is easier when compared with double-plate implants; therefore, the advantages and disadvantages of large single-plate and double-plate implants need to be examined.

The main advantage of the double-plate implant is that egress of aqueous to either plate can be controlled, by ligating the connecting tube;

thus, controlling the flow of aqueous to each plate independently can prevent excessive hypotony. This cannot be done with large-size single plates, and the larger the plate the more likely the occurrence of hypotony and associated complications such as suprachoroidal hemorrhage. This has been reported to occur with the large-surface, 500-mm Baerveldt implant [6]. The disadvantages of the double-plate implants are difficulty of insertion, and if failure occurs, the upper quadrants are no longer available for further drainage surgery or implant use.

The main advantage of the single plate is ease of insertion.

One of the disadvantages of the large single-plate implants is the development of motility problems. Several clinical studies have found that a high incidence of motility problems may occur in patients after implantation of the Baerveldt implant [3, 41, 42].

The question to be asked therefore is whether the pressure lowering obtained by the larger surface implants outweighs the various complications associated with these implants. Britt et al. [6] found no difference in the reduction of IOP between 350- and 500-mm Baerveldt implants, a finding confirmed by Siegner et al. [41]. Molteno et al. reported no significant difference between single- and double-plate implants in the control of pressure in a series of patients followed for 20 years [34].

A recent study comparing the device with the smallest surface area, the single-plate Molteno (surface area 130 mm^2), to the device with the largest surface area, the Baerveldt (350 mm^2), was unable to show any statistical difference in any of the parameters tested [1]. These conclusions were supported by recent studies with long-term follow-up, which included a comparison of single- and double-plate Molteno implants [16, 34].

Mills et al. [29] reported a qualified success rate of 57% at 44 months, using single- or double-plate Molteno implants. They further reported that these implants fail at a rate of 10% per year resulting in a 50% failure rate at 5 years; thus, although some increased reduction of IOP occurs with larger surface implants, certainly in the short term, this advantage seems not to outweigh the potential complications associated with the larger surfaces.

The use of smaller surface implants, i.e., single-plate Molteno implants, with tissue modification, such as supra-Tenon's placement, may achieve a comparable pressure-lowering effect as that obtained with the larger surface implants, but with the advantage of a lesser incidence of complications, and with preservation of one of the upper quadrants for further glaucoma surgery, should it become necessary.

Hong et al. [20] attempted to answer three important questions through a review of the literature:

1. Do all the glaucoma implants lower the pressure, irrespective of their design?
2. Do larger implants lower the IOP more than smaller ones?
3. Does the design of the implant influence the complications, mainly hypotony and diplopia?

Fifty-four articles were included in their final analysis. The overall surgical success rate averaged between 72 and 79% among the five devices, i.e., Molteno single and double plate, Ahmed, Baerveldt, and Krupin implants. No statistical difference was found among the different devices in this meta-analysis. Within the Molteno group, the double-plate Molteno achieved the highest success rate, but this was only over a 12-month follow-up, whereas the other groups were followed for longer durations. All five implants significantly decrease the IOP ($p < 0.001$). The percentage change was between 51 and 62%. The amounts were similar among the five implants after controlling for preoperative IOP ($p = 0.27$). No difference in percent change was found within the Molteno group ($p = 0.58$). There were no statistically significant differences in either the percentage change in IOP or the overall surgical success rate among the five implants, or within the subdivisions of the Molteno group based on the size of the end plate [7].

There were no statistically significant differences among the implants in the overall incidence of transient hypotony in the immediate postoperative period ($p = 0.17$), chronic hypotony ($p = 0.51$), suprachoroidal hemorrhage ($p = 0.47$), or in the decrease of visual acuity after the surgery ($p = 0.90$). The Molteno implant with modified technique to prevent hypotony had the lowest incidence of transient hypotony (12%),

followed by the Ahmed valve (14%) and the Baerveldt (15%). The Molteno implant without any surgical modification to prevent hypotony had a statistically higher rate of hypotony (26%) compared with the Ahmed implant ($p = 0.04$), but this was not statistically different compared with the Krupin implant. All five devices significantly reduced the number of medications in the postoperative period ($p < 0.01$).

The occurrence of diplopia was significantly higher with the Baerveldt implant (9%) compared with the Ahmed (3%), the Molteno implant with ligature (2%), ($p < 0.01$), or the Krupin implant. There was no mention of diplopia in any of the articles with the Molteno implant without the modified technique.

The overall success rate of all the implants appears to be very similar in controlling IOP and preserving vision in intractable cases of glaucoma. The double-plate Molteno had the highest success rate at 91%. This was after a 12-month follow-up, whereas the other groups were followed for a longer period (22–26 months). The success rate would probably have been similar to other devices if the double plate had been followed for a longer period, as was actually reported by Molteno et al. in a study over 20 years [34]. The life-table analysis comparing the double-plate Molteno with the Ahmed implant, by Ayala et al. [1], showed that the success rate decreases by 10–15% every year in the first 3 years. All these findings suggest that a larger end plate does not statistically lower the IOP more than standard-size single plates when followed over a long period, i.e., more than 1 year.

Summary for the Clinician

- Recent studies report that the overall pressure lowering obtained with larger surface implants is not statistically better than pressure lowering from smaller-surface implants in the long term. The ideal size of the plate is unknown but may not be larger than the single-plate Molteno. Single-plate implants are easier to insert and leave an untouched quadrant for further surgery, if necessary.

11.3 Surgical Techniques for Tube-Shunt Implantation

Molteno's original description of implantation of the Tube shunt utilized a subscleral tunnel for the management of the silicone tube [31]. This has been replaced, by and large, by the introduction of the scleral patch graft, and subsequently other materials such as pericardium and dura, to cover the tube without an associated scleral tunnel [5, 13]. The advantage of using a patch was that full-thickness sclera was less likely to erode than a partial-thickness scleral covering obtained with the scleral-tunneling technique. The suturing of the patch over the tube also tends to direct the tube away from the corneal endothelium. The introduction of larger, single-plate implants, such as the Baerveldt and Ahmed implants, has resulted in lesser use of the double-plate implants, which require a more complicated surgical procedure.

One of the more recent surgical modifications of tube-shunt implantation is the placing of the shunt in a supra-Tenon's pocket [15]. This technique is used in patients where there has been a failure of a previous glaucoma procedure or implant insertion, the failure being due to excessive bleb fibosis. These patients have a strong fibrotic reaction to surgery, and need to have Tenon's capsule eliminated from the ultimate bleb formation.

11.3.1 Technique for Supra-Tenon Placement of a Single-Plate Molteno Implant

Conjunctiva and Tenon's capsule are elevated at the limbus by injection of balanced salt solution (Fig. 11.1). A limbal incision through conjunctiva alone is made with a Bard Parker number-15 blade. Conjunctiva is then separated from underlying Tenon's capsule (Fig. 11.2). A small relieving incision is made laterally or medially, depending on the quadrant selected for the insertion, allowing conjunctiva to be dissected posteriorly off the underlying Tenon's capsule. A pocket for the Molteno implant is then made by pushing a Weck cell sponge between conjunctiva and Tenon's capsule (Fig. 11.3). This creates a pocket

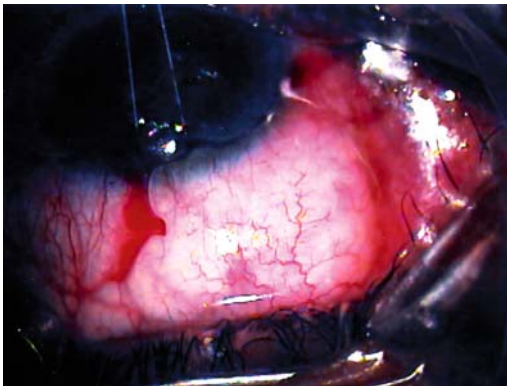

Fig. 11.1 Conjunctiva and Tenon's capsule elevated by subconjunctival injection of balanced salt solution

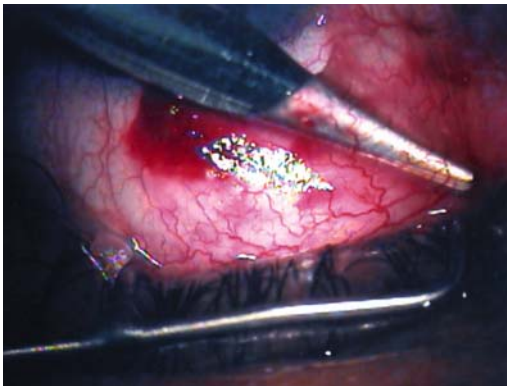

Fig. 11.2 Conjunctiva separated from underlying Tenon's capsule

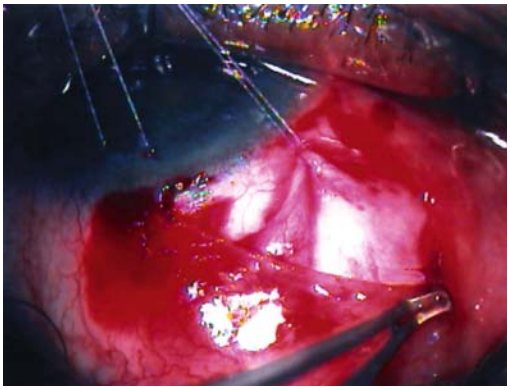

Fig. 11.3 Weck cell sponge being inserted between conjunctiva and Tenon's capsule

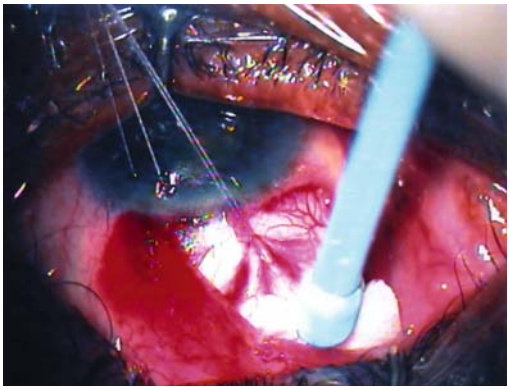

Fig. 11.4 Tenon's capsule being pulled forward by suture

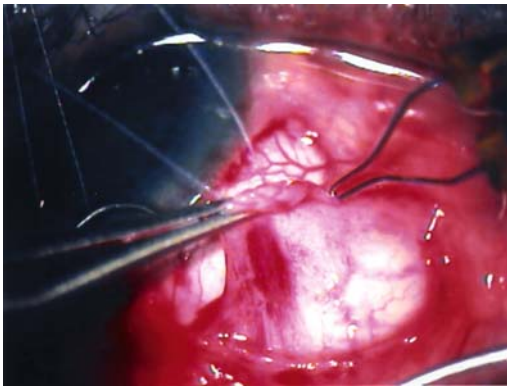

Fig. 11.5 Tenon's capsule being removed by cautery

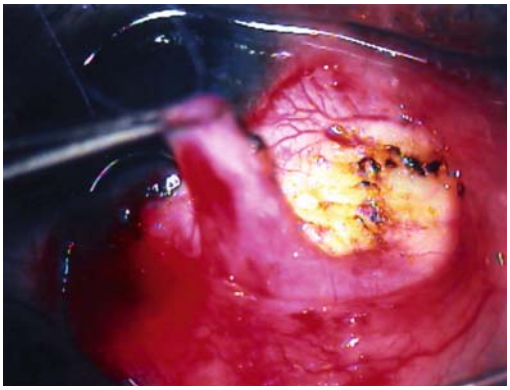

Fig. 11.6 Same as Fig. 5

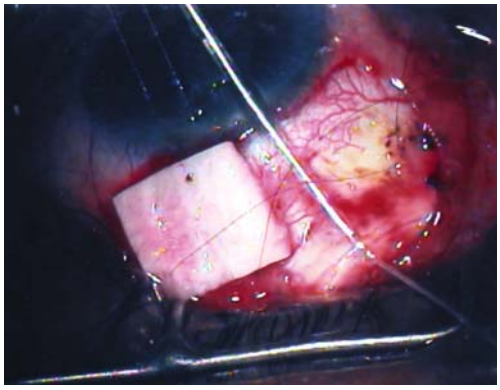

Fig. 11.7 Implant fixated to sclera, with pericardial patch in place to cover tube

for the insertion of the Molteno implant. Tenon's capsule, now lying beneath the implant plate, is dissected off the underlying sclera in front of the plate. A suture is used to pull the dissected Tenon's capsule forward (Fig. 11.4). This Tenon's capsule anterior to the plate is removed with cautery (Figs. 11.5, 11.6). This prevents bleeding and allows for fixation of the plate to the underlying sclera, as well as for the placement of the patch graft over the tube (Fig. 11.7). The remainder of the tube placement is then done in the routinely described manner. Inferior quadrants can be used if both upper quadrants have been scarred by previous surgery.

11.4 The Cornea and Glaucoma Implants

There are two aspects regarding the association of glaucoma implants with the cornea. There is an increased incidence of corneal decompensation in the presence of a tube shunt. Tube shunts are the preferred method of treating glaucoma associated with corneal transplants.

11.4.1 Corneal Decompensation in the Presence of a Pre-existing Tube Shunt

The causes of corneal decompensation in the presence of a pre-existing tube shunt may be multifactorial. Many of the patients exhibiting corneal decompensation are aphakic or pseudophakic. Many patients, in addition, have had previous glaucoma surgery. These multiple surgical procedures are associated with endothelial cell loss. The prolonged use of antiglaucoma medications may also result in endothelial cell loss, as the preservative used in these medications, namely benzalkonium chloride, has been shown to be toxic to rabbit endothelium when topically applied [18]. The presence of the silicone tube in the eye results in a cell loss of two cells per square millimeter per postoperative month [27]. Further endothelial cell loss as a result of the tube may occur as a result of direct tube endothelial touch, either locally or in a diffuse manner, during rubbing of the eye.

Corneal transplants in the presence of a pre-existing tube requires special attention to the tube. If the tube appears to be too close to the endothelium, the options available are as follows:

1. Tube removal and reinsertion away from the endothelium
2. Placing a suture across the anterior chamber, over the tube directing it away from the endothelium [14]
3. Placing the tube via the pars plana, a technique requiring total or subtotal vitrectomy

Of the three options, the suture placed over the tube is the least invasive.

11.4.2 Penetrating Keratoplasty May Result in Glaucoma

Many reasons have been given for the elevation of IOP post-keratoplasty, and this is particularly prevalent in patients receiving transplants for aphakic or pseudophakic bullous keratopathy [21, 37, 44].

Glaucoma implants have become the treatment of choice for the management of medically intractable glaucoma associated with corneal transplants. The incidence of graft rejection, however, remains high in these patients. In an attempt to eliminate the possible effect of the tube as a cause for this failure, a pars plana insertion of the tube has been reported in keratoplasty pa-

tients, but without a significant improvement of graft failure [40].

A unique complication that has been noted to occur with glaucoma implants and penetrating keratoplasty is the development of anterior-segment fibrosis. High pressure within the bleb associated with glaucoma implants has been shown to result in the production of TGFβ. In non-valved implants this TGFβ returns to the anterior chamber and may possibly cause a low-grade inflammation resulting in diffuse anterior segment fibrosis. This complication has not been described with the use of valved implants, where aqueous flow is one way of preventing the TGFβ from reaching the anterior chamber.

11.4.3 Summarized Information from Publications Regarding Success of Glaucoma Implants and Penetrating Keratoplasty

In one study which examined the results of keratoplasty and glaucoma treated with Ahmed or Baerveldt implants the grafts remained clear in 70 and 55% of eyes at 2 and 3 years with glaucoma control of 82% of patients at 3 years [22].

A second study using Ahmed implants in keratoplasty and glaucoma reported successful glaucoma control in 75.4 and 51.5% of eyes at 12 and 20 months, respectively, with 19% having graft failure. This study seemed to imply that graft failure is less with a valved implant [9].

A study reporting results of pars plana insertion of glaucoma implants in glaucoma and keratoplasty reported 12- and 24-month life-table success rates for IOP control and corneal graft clarity to be 85 and 62%, and 64 and 41%, respectively [40].

Other studies reporting graft failure associated with glaucoma implants are:

- McDonnell et al., 41% after 13 months of follow-up [26]
- Beebe et al., 43% after 24 months of follow-up [4]
- Sherwood et al., 22% after 22 months of follow-up [39]

Summary for the Clinician

- Penetrating keratoplasty is associated with an increased incidence of glaucoma, especially in cases of aphakia and pseudophakia. Although not by any means ideal, glaucoma drainage devices are the treatment of choice for medically uncontrolled glaucoma in keratoplasty patients. Glaucoma implants are associated with an increased incidence of corneal decompensation, both prior to and after keratoplasty.

11.5 Neovascular Glaucoma

Neovascular glaucoma remains the one condition in which glaucoma drainage devices are often the primary treatment option. The key to success is the early detection of the neovascular process and its subsequent treatment by pan-retinal photocoagulation before total scarring and closure of the angle has occurred. The use of pan-retinal photocoagulation, if done early, can prevent severe anterior-segment fibrosis and improve prognosis for control of the glaucoma [8].

As a result of progressive peripheral anterior synechiae formation with scarring in the chamber angle, particularly if seen at a late stage, standard glaucoma filtering surgery is less likely to be successful due to closure of the internal filter site. Glaucoma filtering surgery, in order to be successful, requires adequate pan-retinal photocoagulation to be done, followed by a period during which the eye needs to quiet down to prevent intraoperative bleeding. As this is not always possible, glaucoma implants remain the surgical treatment of choice in neovascular glaucoma [38]. The silicone tube is placed well inside the anterior chamber and away from the angle so that any progressive fibrosis will not be able to occlude the tube opening.

Prior to insertion of the glaucoma implant, pan-retinal photocoagulation should be performed to control the neovascular process. This can be done provided that a reasonable level of IOP can be obtained with medical therapy. When

pressure levels are very high and cannot be controlled medically, the treatment of choice is pars plana insertion of the glaucoma implant, coupled with total vitrectomy and laser endophotocoagulation of the retina [24].

Avoiding the neovascular tissue in the angle may necessitate placing the tube of the glaucoma implant slightly more corneal to prevent intraocular hemorrhage from iris vessels. Often when the patient is seen in the acute stage with high IOP, there are posterior synechiae, resulting in pupil block and misdirection of aqueous. Placement of a glaucoma implant in these patients should be associated with a posterior sclerotomy and removal of aqueous/vitreous thereby lowering the IOP, prior to inserting the tube into the anterior chamber. As soon as fluid is removed through the sclerostomy, the anterior chamber needs to be reformed immediately to prevent the occurrence of hyphema from iris vessels. An iridectomy should be done either intraoperatively, if this can be achieved without inducing a hyphema, or postoperatively with a laser.

The reported success rate with the use of glaucoma implants in neovascular glaucoma varies in different studies. A common trend seen in all reported studies is a progressive loss of success with time, with the result often being loss of light perception.

The poor results seen in patients with neovascular glaucoma occurs as a result of the morbidity of the underlying systemic condition associated with severe diabetic retinopathy or central vein occlusion, the main causes of neovascular glaucoma.

Long-term results of glaucoma implants in the treatment of neovascular glaucoma were reported by Mermoud et al. [28]. The success rates reported in that study were 62.5% at 1 year,52.9% at 2 years,43.1% at 3 years, 30% at 4 years, and 10.3% at 5 years. Light perception was lost in 29 of 60 eyes (48%), and phthisis bulbi occurred in 11 eyes(18%). That study highlights the progressive nature of neovascular glaucoma, due predominantly to the underlying progression of the retinal disease.

Summary for the Clinician

- The treatment of choice for neovascular glaucoma is pan-retinal photocoagulation and glaucoma implant.
- Placement of the tube opening distal from the angle prevents closure by fibrous neovascular tissue.
- The overall prognosis for neovascular glaucoma depends on the underlying disease.

11.6 Complications of Glaucoma Implants

Although glaucoma implants may be associated with complications associated with standard glaucoma surgeries, such as hypotony, choroidal effusions, flat anterior chambers, cataract, and infections (although infections are rare), there are a number of complications unique to glaucoma implants, related to the tube and the plate, as well as induced motility problems.

11.6.1 Tube-Related Problems

The tube may be too anterior, resulting in corneal touch, resulting in local or diffuse corneal decompensation. If too posterior, iris or lens damage may occur. Careful positioning of the tube is therefore essential.

Tube exposure may occur as a result of scleral or patch graft erosion, and can result in intraocular infection if not remedied. Tube doubling over of what appears to be a too-thin patch, i.e., pericardium, will prevent this complication in most cases. Recurrent erosion of a patch graft can occur and may be difficult to remedy, and may necessitate tube removal.

11.6.2 Plate-Related Problems

Erosion of conjunctiva and plate exposure can occur. This may be seen if the tube is blocked, allowing conjunctiva to constantly be in contact

with the plate, resulting in erosion. The dehiscence in the conjunctiva may be difficult to close, and if so, the plate will need to be removed to prevent the occurrence of severe hypotony and endophthalmitis, as the exposed surface of the plate is connected to the anterior chamber.

11.6.3 Motility Problems

Due to the large size of the blebs obtained with glaucoma implants, some restriction of eye movement may occur with any of the various implants. Motility disturbances are more likely to occur with inferior placement of the implant due to restricted space in this area, resulting in the disturbing effect of diplopia on downward gaze. Restriction of upward gaze, as may occur with superiorly placed implants, are less likely to produce disturbing diplopia. Superior quadrant placement of implants, if possible, is the procedure of choice to prevent possible diplopia. The reported incidence of motility problems in glaucoma implants appears to be highest with the Baerveldt implant [3, 42]. This may be due to the placement of the implant beneath extraocular muscles, with subsequent scarring and muscle imbalance. The height of the bleb may also play a role in the motility disturbance, and as a result, Baerveldt modified the implant by including fenestrations in the plate, resulting in a lower bleb profile. The overall effect of this fenestration in reducing diplopia has not been documented in a comparative study.

11.6.4 The "Hypertensive Phase"

The "Hypertensive Phase," seen commonly 4–6 weeks after implant surgery, is unique to the use of glaucoma shunts. The IOP may reach very high levels and needs to be lowered both for patient comfort, protection of the optic nerve, and long-term survival of the bleb. This may be accomplished by removing aqueous from the bleb with a 30-G syringe, which may be done in the office under topical anesthesia [16]. This may be repeated as often as necessary, and will help the long-term survival of the bleb.

The hypertensive phase is seen more commonly with Ahmed implant use, and may be due to the early contact of "glaucomatous" aqueous with the tissue overlying the plate [36]. As mentioned previously, this aqueous contains proinflammatory substances, resulting in a more intense reaction in the bleb with the subsequent rise in IOP. Preventing this aqueous from reaching the plate while pressure is normalized will decrease these proinflammatory components and produce less bleb inflammation and subsequently a lower incidence of the hypertensive phase.

Another possible explanation for the development of the hypertensive phase may be related to the plate material. The Molteno and Ahmed plates are made of polypropylene, the differences being that the Ahmed is more rigid and may induce more inflammation by micro-movement of the plate. The Baerveldt implant is flexible and in the rabbit model induces the least amount of inflammation. The Ahmed-designed drainage device recently has been made available in a silicone (and, thus, more flexible) model. It is possible that future studies will show that this change in material and physical properties of the implant positively influences the hypertensive phase.

11.6.5 Bleb Fibrosis

Bleb fibrosis and lack of adequate pressure lowering remains the most important problem associated with glaucoma implants (see 11.1.2). Very low pressures remain difficult to obtain due to this bleb fibrosis. Methods adopted to overcome bleb fibrosis include:

1. The use of systemic antifibrosis medication (Molteno), with good reported results
2. The use of topical antimetabolites (mitomycin C), not very effective
3. The use of supra-Tenon's placement of the implant with encouraging early results

Eliminating bleb fibrosis will require further research to include implant design and tissue-healing properties.

Summary for the Clinician

- Tube or plate exposure may lead to endophthalmitis.
- Motility problems and diplopia are more common with the Baerveldt implant, and with inferior placement of any implant.
- The hypertensive phase is more common with the inflexible Teflon Ahmed implant.

11.7 New Glaucoma Implants

11.7.1 The Ex-Press Glaucoma Shunt

Within the past few years, a new mini-glaucoma shunt, the Ex-Press mini shunt, has been introduced. The device is made of stainless steel, with a 3-mm-long tube with an external diameter of 400 μm and a 50 μm inner diameter. The tube is attached to a disc-like flange at its proximal end to prevent it from being implanted too deeply. The device has a penetrating tip that is inserted into the anterior chamber. Behind the tip is a spur to prevent extrusion of the device. The Ex-Press is used both as a primary procedure and when conventional surgical treatments have failed. Although originally designed to be used subconjunctivally, because of associated complications with this method of implantation, the device is now used predominantly under a scleral flap.

A standard trabeculectomy flap is made and, instead of removing corneal tissue, the Ex-Press shunt is inserted beneath the flap into the anterior chamber, without a peripheral iridectomy. Early results with the shunt placed under a flap have been encouraging. The present author has found the device to be particularly effective in patients with small orbits, where standard implants would be difficult to use. In a recently published report, the Ex-Press was placed into 24 eyes with open-angle glaucoma, 16 with previously failed glaucoma surgery and 8 defined as high risk for failure. The device was placed under a scleral flap. The IOP was significantly reduced from 27.2 mmHg pre-operatively to 14.5 mmHg at 12 months and 14.2 mmHg at 24 months [10]. Future studies, comparing the device to standard trabeculectomy, are required.

11.8 The Future for Glaucoma Implants

The traditional criteria for "successful" IOP control, as reported in the majority of studies, is 21 mmHg, which in advanced glaucoma is currently recognized as too high; thus, a more standardized definition of success with lower IOP and perhaps protection of the visual field needs to be developed.

Will glaucoma implants become the procedure of choice in patients requiring filtering surgery? This question hopefully will be determined by an ongoing study comparing trabeculectomy surgery to glaucoma implants as related to success and complications.

The long tube implant design has stood the test of time for 30 years; nevertheless, changes in implant material, implant size, and methods for reducing fibrosis remain challenges for ongoing research.

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